The Indole Grignard Reagents

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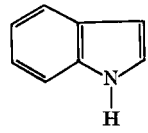
I. Introduction

A decade after Victor Grignard's first publication appeared describing the reagents that bear his name, Oddo reported that indole (**1**),[1,2] like pyrrole,[3] reacted with the simple Grignard reagent, ethylmagnesium iodide, in ether solution to give ethane and indole magnesium iodide.[1,2] The latter compound could be precipitated from ether solution as a pyridine complex.[2]



(**1**)

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[1] B. Oddo, *Ber. Deut. Chem. Ges.* **43**, 1012 (1910).

[2] B. Oddo, *Gazz. Chim. Ital.* **41**, 221 (1911); *Chem. Abstr.* **5**, 2638 (1911).

[3] B. Oddo, *Gazz. Chim. Ital.* **39**, 649 (1909); *Chem. Abstr.* **5**, 686 (1911).

The indole Grignard reagents have been widely employed as intermediates in synthetic work, mainly for the introduction of substituents into the 1- or 3-positions of the indole ring system.

The earlier work on the indole Grignard reagents has been reviewed by Oddo[4] and Mingoia.[5,6] Yoffe and Nesmeyanov have listed all the compounds that were prepared by reactions involving Grignard reagents, including those of indole, prior to January 1948.[7] In 1954, two summaries of the chemistry of the indole Grignard reagents were published (Sumpter and Miller[8] and Kharasch and Reinmuth[9]).

In view of the importance of these compounds in indole chemistry and since there is no adequate modern survey of this field, an attempt has been made to review comprehensively the chemistry of the indole Grignard reagents.

The major portion of the current review consists of a discussion of the reactions of the indole magnesium halides, classified according to the chemical nature of the coreactant species. The authors have endeavored to mention all important papers, that describe reactions involving indole Grignard reagents, which have appeared during the past half century. It is hoped that all major publications on the subject that were available before December 31, 1967 have been cited. A short discussion of the ideas that have been advanced to account for the structure and reactivity of the indole Grignard reagent is included at the end of the chapter.

II. Preparation of the Indole Magnesium Halides

The most widely used procedures for the preparation of the indole magnesium halides are based on the method originally described by Oddo in 1911,[2] and consist of adding a solution of indole or an indole derivative, in dry diethyl ether, to a solution of an alkyl magnesium

[4] B. Oddo, *Mem. Reale Accad. Nazl. Lincei, Classe Sci. Fis. Mat. Nat.* **14**, 510 (1923); *Chem. Abstr.* **19**, 2492 (1925).

[5] Q. Mingoia, *Rev. Brasil. Chim. (Sao Paulo)* **4**, 183 (1937); *Chem. Abstr.* **32**, 549 (1938).

[6] Q. Mingoia, *Boll. Chim. Farm.* **77**, 337 (1938); *Chem. Abstr.* **32**, 7035 (1938).

[7] S. T. Yoffe and A. N. Nesmeyanov, "Handbook of Magnesium Organic Compounds," Vols. I, II, & III. Pergamon, Oxford, 1956.

[8] W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," p. 50. Wiley (Interscience), New York, 1954.
M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances." Prentice-Hall, Englewood Cliffs, New Jersey, 1954.

halide, usually ethyl(or methyl)magnesium iodide(or bromide) in ether. There is, however, a considerable variation in the reported temperatures and times required to complete the reaction, but it was usually assumed that quantitative conversion of the indole to the indole Grignard reagent had occurred.

Anisole and mixtures of diethyl ether with aromatic hydrocarbons have both been widely employed as solvents for these reactions.[10–13] Ethers other than diethyl ether and anisole have also been successfully used (cf. refs. 14–17). Hexamethylphosphorotriamide has recently been used as a solvent for indole Grignard reactions.[18, 19] Young and Mizianty have recently described the use of an aromatic magnesium halide (phenylmagnesium bromide) for the synthesis of indole magnesium bromide.[20–22]

Oddo reported that the organomagnesium derivatives of pyrrole, indole, skatole, and carbazole could be prepared in a single operation by mixing the parent heterocyclic compound with an alkyl halide and magnesium in anhydrous ether.[23] The product formed was reported to be the same as that obtained by the more conventional procedure. However, this approach to the synthesis of the indole Grignard reagents does not seem to have been exploited in subsequent work.

An example of the formation of a Grignard reagent on the benzene ring moiety of the indole nucleus has been described recently. Noland

[10] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **55B**, 3859 (1922).
[11] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **55B**, 3865 (1922).
[12] N. Putochin, *Ber. Deut. Chem. Ges.* **59B**, 1987 (1926).
[13] N. Putochin, *Zh. Russ. Fiz. Chem. Obshchestva* **59**, 761 (1927); *Chem. Abstr.* **22**, 3409 (1928).
[14] G. F. Smith and A. E. Walters, *J. Chem. Soc.* p. 940 (1961).
[15] M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, p. 1183 (1963).
[16] C. R. Ganellin and H. F. Ridley, personal communication, 1967.
[16a] H. F. Ridley, Ph.D. Thesis, University of London, May 1966.
[16b] C. R. Ganellin, D. R. Hollyman, and H. F. Ridley, *J. Chem. Soc.* p. 2220 (1967).
[17] J. C. Powers, W. P. Meyer, and T. G. Parsons, *J. Am. Chem. Soc.* **89**, 5812 (1967).
[18] G. Casnati and A. Pochini, *Chim. Ind. (Milan)* **48**, 262 (1966).
[19] B. Cardillo, G. Casnati, and A. Pochini, *Chim. Ind. (Milan)* **49**, 172 (1967).
[20] T. E. Young, *J. Org. Chem.* **27**, 507 (1962).
[21] T. E. Young and M. F. Mizianty, *J. Org. Chem.* **29**, 2030 (1964).
[22] T. E. Young and M. F. Mizianty, *J. Med. Chem.* **9**, 635 (1966).
[23] B. Oddo, *Gazz. Chim. Ital.* **44**, 482 (1914); *Chem. Abstr.* **8**, 3019 (1914).

and Reich obtained a Grignard reagent from 5-bromo-1,3-dimethylindole which appeared to behave normally on oxidation or carbonation.[24]

III. Reactions of the Indole Magnesium Halides

A. General Comments

In some instances the reactions of the indole Grignard reagents resemble those of simple aryl or alkyl magnesium halides, but in many cases they appear to react anomalously.

A wide variety of reaction temperatures and times have been employed in carrying out these reactions; in an extreme case temteratures of up to ca. 350° were employed. Under these conditions it is quite possible that the actual products isolated were formed as the result of secondary reactions occurring after the primary products had been formed. Standard procedures for the working up of reaction mixtures obtained in Grignard reactions are usually followed.

The structures of the products formed were often ascertained by chemical procedures, which could have led to erroneous conclusions, e.g., the position of the substituent which had been introduced into the indole ring system was sometimes determined by identification of the indole carboxylic acid obtained on alkali fusion. Active hydrogen determinations by the Zerewitinov method and silver derivative formation were two methods widely used for establishing the presence or absence of a substituent on the indole nitrogen atom; both these procedures could possibly have given misleading results. More recently, however, less ambiguous physical methods of structural determination, such as infrared and nuclear magnetic resonance spectroscopy, have been extensively employed.

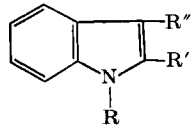
B. Reactions with Organic Halogen Compounds

1. *Alkyl Halides*

Oddo[1, 2] reported over 50 years ago that the interaction of methyl iodide with indole magnesium iodide at the reflux temperature of ether for 12 hours produced 3-methylindole (**2**). Rather surprisingly,

[24] W. E. Noland and C. Reich, *J. Org. Chem.* **32**, 828 (1967).

he stated that 1-methylindole (**3**) and 1,3-dimethylindole (**4**) were obtained when the reaction was carried out under similar conditions but for a shorter time. However, under more vigorous conditions (i.e., heating for 15 hours, in the presence of anhydrous potassium chloride) **2** was definitely obtained.[2] 3-Ethylindole (**5**) was formed more readily than the methyl derivative by the action of ethyl iodide on indole magnesium iodide.[2] More recently, however, Sebastian reported that **2** was essentially the only product obtained in significant amounts by the action of methyl iodide on the indole Grignard reagent when the reaction was carried out in tetrahydrofuran at 23°.[25] A number of other alkyl indoles, including: 3-ethyl-2-methylindole (**6**),[26] 3-ethyl-2-*n*-propylindole (**7**),[26] 3-*n*-butylindole (**8**),[16, 16a, 16b] 3-*tert*-butylindole (**9**),[14] 3-isoamylindole (**10**),[19] and 3-*sec*-octylindole (**11**)[27] have also been prepared by the action of the appropriate alkyl halides on the indole Grignard reagent in question. The reaction of indole magnesium bromide with isoamyl bromide has recently been studied in some detail; it was observed that the reaction was inhibited by increasing the basicity of the solvent and that the use of certain solvents, such as hexamethylphosphorotriamide, resulted in essentially exclusive 1-alkylation occurring[19] (cf. Section IV).

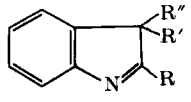


(**2**) R = R′ = H; R″ = CH_3
(**3**) R = CH_3; R′ = R″ = H
(**4**) R = R″ = CH_3; R′ = H
(**5**) R = R′ = H; R″ = C_2H_5
(**6**) R = H; R′ = CH_3; R″ = C_2H_5
(**7**) R = H; R′ = *n*-C_3H_7; R″ = C_2H_5
(**8**) R = R′ = H; R″ = *n*-C_4H_9
(**9**) R = R′ = H; R″ = *tert*-C_4H_9
(**10**) R = R′ = H; R″ = iso-C_5H_{11}
(**11**) R = R′ = H; R″ = *sec*-C_8H_{17}

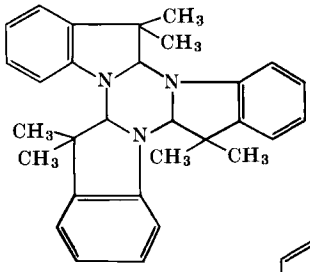
Hoshino reported that a product, described as 3,3-dimethylindolenine (**12**), accompanied by some 1,3-dimethylindole (**4**) and a

[25] J. F. Sebastian, Ph.D. Thesis, University of California, Riverside, 1965.
[26] P. L. Julian and J. Pikl, *Proc. Indiana Acad. Sci.* **45**, 145 (1935); *Chem. Abstr.* **31**, 1026 (1937).
[27] A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968).

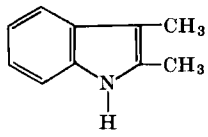
small quantity of an unidentified compound, was obtained by treating skatole magnesium iodide with methyl iodide in benzene at 80°.[28–30] Recently Jackson and Smith[31] have pointed out that several different melting points (i.e., 170°–172°,[32] 152°,[33] and 214°[30,33]) for 3,3-dimethylindolenine (**12**) have been reported. Hoshino reported that the melting point of the compound described as 3,3-dimethylindolenine (**12**) was initially 185°–186°, but this changed to 160°–210° on recrystallization; the change in melting point was accompanied by an apparent increase in molecular weight by a factor of three. However,



(**12**) R = H; R′ = R″ = CH_3
(**15**) R = R′ = R″ = CH_3
(**16**) R = R′ = CH_3; R″ = iso-C_3H_7
(**17**) R = R′ = CH_3; R″ = *tert*-C_4H_9
(**18**) R = H; R′ = R″ = C_2H_5
(**19**) R = H; R′ = CH_3; R″ = C_2H_5
(**20**) R = H; R′ = CH_3; R″ = iso-C_3H_7
(**21**) R = H; R′ = CH_3; R″ = $CH_2C_6H_5$



(**13**)



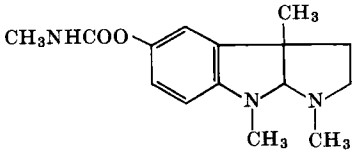
(**14**)

Hoshino further reported that both the melting point and apparent molecular weight of **12** decreased on storage.[28–30] Jackson and Smith, although agreeing that the product in question was 3,3-dimethylindolenine (**12**), reported that the melting point of a purified sample of **12** increased on storage from 172°–176° to more than 200° in 1 week. These authors suggested that polymerization of the monomeric indolenine **12** to the trimeric form **13** was responsible for this and offered spectroscopic evidence to support their contention.[31] Fritz

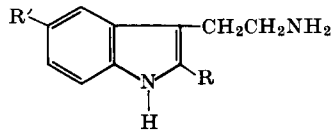
[28] T. Hoshino, *Proc. Imp. Acad. (Tokyo)* **8**, 171 (1932); *Chem. Abstr.* **26**, 4814 (1932).
[29] T. Hoshino, *Abstr. Japan. Chem. Lit.* **6**, 390 (1932); *Chem. Abstr.* **27**, 291 (1933).
[30] T. Hoshino, *Ann. Chem.* **500**, 35 (1933).
[31] A. H. Jackson and A. E. Smith, *Tetrahedron* **21**, 989 (1965).
[32] K. Brunner, *Monatsh. Chem.* **16**, 850 (1895).
[33] R. Robinson and H. Suginome, *J. Chem. Soc.* p. 298 (1932).

and Pfaender recently also reported NMR evidence which shows that **12** exists completely as the monomer at temperatures above 120°, whereas at low temperatures it exists in the trimeric form **13**.[34]

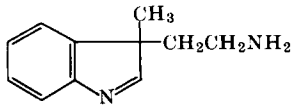
2,3-Dimethylindole (**14**) and 2,3,3-trimethylindolenine (**15**) were obtained by the action of methyl iodide on 2-methylindole magnesium iodide.[28–30] The trisubstituted indolenine derivative **15** was also formed in good yield in a similar manner from 2,3-dimethylindole magnesium iodide.[28–30] Nakazaki and his co-workers have described the preparation of a number of 2,3,3-trisubstituted indolenines,[35, 36] including 2,3,3-trimethylindolenine (**15**), 2,3-dimethyl-3-isopropylindolenine (**16**), and 2,3-dimethyl-3-*tert*-butylindolenine (**17**) by Hoshino's procedure (cf. ref. 30). The synthesis of a number of new 3,3-dialkylindolenines, including 3,3-diethylindolenine (**18**), 3-ethyl-3-methylindolenine (**19**), 3-isopropyl-3-methylindolenine (**20**), and 3-benzyl-3-methylindolenine (**21**) by alkylation of the Grignard derivatives of the appropriate 3-alkylindole has recently been described.[27]



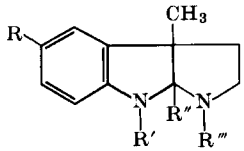
(**22**)



(**23**) R = R′ = H
(**27**) R = CH_3; R′ = H
(**29**) R = H; R′ = OC_2H_5



(**24**)



(**25**) R = R′ = R″ = R‴ = H
(**26**) R = R′ = R‴ = H; R″ = CH_3
(**28**) R = OC_2H_5; R′ = R″ = R‴ = H
(**30**) R = OC_2H_5; R′ = R‴ = CH_3; R″ = H
(**31**) R = OC_2H_5; R′ = R″ = H; R‴ = CH_3

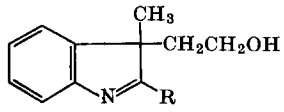
[34] H. Fritz and P. Pfaender, *Chem. Ber.* **98**, 989 (1965).
[35] M. Nakazaki, S. Isoe, and K. Tanno, *Nippon Kagaku Zasshi* **76**, 1262 (1955); *Chem. Abstr.* **51**, 17878 (1957).
[36] M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 838 (1959); *Chem. Abstr.* **54**, 13096 (1960).

A number of synthetic approaches to the pyrrolo[2,3-*b*]indole ring system, present in the physostigmine [i.e., eserine (**22**)] molecule, which involve indole Grignard reagents as intermediates, have been described.

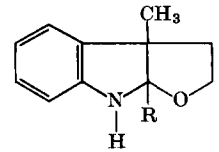
Hoshino and his co-workers reported that treatment of the Grignard reagent obtained from tryptamine (**23**), by the action of a suitable alkyl magnesium halide, with methyl iodide in benzene did not give the expected indolenine derivative **24**; instead dinordeoxyeseroline (**25**) was obtained.[28–30, 37]

Dinordeoxy-9-methyleseroline (**26**) was similarly obtained in high yield, from 2-methyltryptamine (**27**).[28–30, 37] Hoshino and his colleagues obtained dinoreserethole (**28**) by the action of methyl iodide on the Grignard reagent derived from 5-ethoxytryptamine (**29**) in anisole after heating the reaction mixture at 100° for 2 hours.[38, 39] *dl*-Eserethole (**30**) was finally obtained by the methylation of isonoreserethole (**31**), obtained by methylation of the 3-(β-methylaminoethyl)-5-ethoxyindole Grignard reagent with methyl iodide.[38, 40]

Hoshino and Shimodaira observed that the interaction of methyl iodide with the tryptophol Grignard reagent in anisole gave a product, expected to be 3-methyl-3-(β-hydroxyethyl)indolenine (**32**).[41, 42] The relatively weak basic strength of this product was, however, incompatible with an indolenine structure; consequently **32** should probably be formulated in the fully cyclized form (i.e., **33**).[41, 42] Nakazaki has recently shown that the Grignard reagent derived from 2-methyltryptophol undergoes an analogous reaction with methyl iodide; the



(**32**) R = H
(**35**) R = CH_3



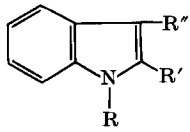
(**33**) R = H
(**34**) R = CH_3

[37] T. Hoshino and K. Tamura, *Ann. Chem.* **500**, 42 (1933).
[38] T. Hoshino and T. Kobayashi, *Ann. Chem.* **516**, 81 (1935).
[39] T. Hoshino and Y. Kotake, *Ann. Chem.* **516**, 76 (1935).
[40] T. Hoshino and T. Kobayashi, *Ann. Chem.* **520**, 11 (1935).
[41] T. Hoshino, *Proc. Imp. Acad. (Tokyo)* **10**, 159 (1934); *Chem. Abstr.* **28**, 5439 (1934).
[42] T. Hoshino and K. Shimodaira, *Ann. Chem.* **520**, 19 (1935).

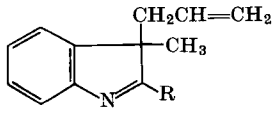
final product in this case being 3*a*,8*a*-dihydro-3*a*,8*a*-dimethyl-3*H*-furo[2,3-*b*]indole (**34**),[43] presumably formed by cyclization of the intermediate indolenine derivative **35**.[43]

2. *Alkenyl Halides*

It is only in relatively recent years that the interaction of indole Grignard reagents with unsaturated aliphatic halogen compounds has



(**36**) R = R′ = H; R″ = $CH_2CH{=}CH_2$
(**38**) R = $CH_2CH{=}CH_2$; R′ = H; R″ = CH_3
(**39**) R = H; R′ = $CH_2CH{=}CH_2$; R″ = CH_3
(**40**) R = $CH_2CH_2CH_3$; R′ = H; R″ = CH_3
(**41**) R = H; R′ = $CH_2CH_2CH_3$; R″ = CH_3
(**43**) R = H; R′ = CH_3; R″ = $CH_2CH_2CH_3$
(**44**) R = H; R′ = CH_3; R″ = $CH_2CH{=}CH_2$,
(**45**) R = $CH_2CH_2CH_2CH_3$; R′ = H; R″ = CH_3
(**46**) R = H; R′ = $CH_2CH_2CH_2CH_3$; R″ = CH_3
(**47**) R = $CH_2CH_2CH(CH_3)_2$; R′ = H; R″ = CH_3
(**48**) R = H; R′ = $CH_2CH_2CH(CH_3)_2$; R″ = CH_3



(**37**) R = H
(**42**) R = CH_3

been studied. 3-Allylindole (**36**) has been obtained by the action of allyl bromide on indole magnesium halides.[18,19,44–46] Using hexamethylphosphorotriamide as solvent Cardillo *et al.* obtained essentially only 1-allylindole in this reaction.[19] Jackson and Smith reported that the skatole Grignard reagent reacted with allyl bromide at 0° in

[43] M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 588 (1959); *Chem. Abstr.* **54**, 7686 (1960).

[44] J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.* p. 3172 (1952).

[45] M. Nakazaki and S. Isoe, *Nippon Kagaku Zasshi* **76**, 1159 (1955); *Chem. Abstr.* **51**, 17877 (1957).

[46] N. Lerner, *Dissertation Abstr.* **24**, 4982 (1964).

benzene–ether solution to give mainly 3-allyl-3-methylindolenine (**37**), accompanied by a mixture of 1-allyl-3-methylindole (**38**) and 2-allyl-3-methylindole (**39**).[31] 1-Allyl-3-methylindole (**38**) and 2-allyl-3-methylindole (**39**), both relatively unstable compounds, were isolated as the corresponding *n*-propyl derivatives **40** and **41** after hydrogenation. The structures of **40** and **41** were confirmed spectroscopically and by alternate syntheses.[31] Nakazaki prepared 3-allyl-2,3-dimethylindolenine (**42**) by the allylation of 2,3-dimethylindole magnesium bromide with allyl bromide in ether.[36]

3-Allyl-3-methylindolenine (**37**) was also synthesized by the action of methyl iodide on 3-allylindole magnesium iodide; however, the yield of **37** was not as good as that obtained in the procedure starting from 3-methylindole.[31]

2-Methyl-3-*n*-propylindole (**43**) was obtained by hydrogenation of the intermediate 2-methyl-3-allylindole (**44**), obtained by the allylation of 2-methylindole magnesium iodide. There were no reports of isomeric products being formed in this reaction.[31]

Jackson and Smith further showed that crotyl bromide reacts with 3-methylindole magnesium iodide to give a mixture of products from which 1-*n*-butyl-3-methylindole (**45**) and 2-*n*-butyl-3-methylindole (**46**) could be isolated after hydrogenation. 3-Methyl-1-isopentylindole (**47**) and 3-methyl-2-isopentylindole (**48**) were similarly obtained by hydrogenation of the initial products obtained when the indole Grignard reagent was allowed to react with 3,3-dimethylallyl bromide in the first instance.[31]

3. *Alkynyl Halides*

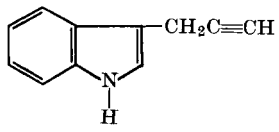
Brown *et al.* were not able to prepare 3-(prop-2-ynyl)indole [i.e., 3-propargylindole (**49**)] by the Grignard reaction[44]; however, Williamson[47] and later Zenitz[48] readily obtained **49** in satisfactory yield by the action of propargyl bromide on indole magnesium bromide in anisole.

4. *Arylalkyl Halides*

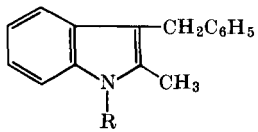
a. *Benzyl Chloride.* In the early 1930's Hoshino showed that 3-benzyl-2-methylindole (**50**) and 3,3-dibenzyl-2-methylindolenine

[47] W. R. N. Williamson, *J. Chem. Soc.* p. 2834 (1962).
[48] B. L. Zenitz, U.S. Patent No. 3,238,215 (1966); *Chem. Abstr.* **65**, 7145 (1966).

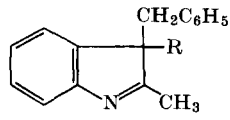
(**51**) were obtained by the action of benzyl chloride on the magnesium derivative of 2-methylindole.[28–30] The indolenine **51** was also produced by the action of benzyl chloride on the 3-benzyl-2-methylindole (**50**) Grignard reagent; in this case some 1,3-dibenzyl-2-methylindole (**52**) was formed as a by-product.[28–30] More recently Nakazaki and his co-workers used essentially Hoshino's procedure for the synthesis of 3-benzyl-2,3-dimethylindolenine (**53**).[35, 36]



(**49**)



(**50**) R = H
(**52**) R = $CH_2C_6H_5$



(**51**) R = $CH_2C_6H_5$
(**53**) R = CH_3

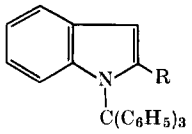
b. *Triphenylmethyl Chloride.* In 1936 Funakubo and Hirotani claimed that 1-triphenylmethylindole (**54**) and 2-methyl-1-triphenylmethylindole (**55**) were obtained when the reaction between triphenylmethyl chloride and indole or 2-methylindole magnesium iodide, respectively, was carried out at the reflux temperature of ether.[49] Two years later Kubota reported the results of an extensive study of the products obtained by the interaction of triphenylmethyl chloride with the Grignard reagents derived from indole and a number of 2-substituted indoles in anisole[50] and concluded that, in contrast to the earlier findings,[49] the products were 3-substituted indoles (cf. ref. 51). In this manner Kubota obtained 3-triphenylmethylindole (**56**), 2-methyl-3-triphenylmethylindole (**57**), 2-phenyl-3-triphenylmethylindole (**58**), 2-(α-naphthyl)-3-triphenylmethylindole (**59**), and 2-(β-naphthyl)-3-triphenylmethylindole (**60**) by the action of triphenylmethyl chloride on the Grignard reagents derived from indole (**1**), 2-methylindole (**61**), 2-phenylindole (**62**), 2-(α-naphthyl)indole (**63**),

[49] E. Funakubo and T. Hirotani, *Ber. Deut. Chem. Ges.* **69B**, 2123 (1936).

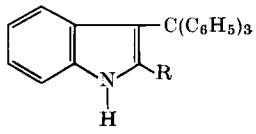
[50] T. Kubota, *Nippon Kagaku Zasshi*, **59**, 399 (1938); *Chem. Abstr.* **32**, 9080 (1938).

[51] It is reported incorrectly in one recent review article (cf. ref. 8) that these products are 2-substituted indoles.

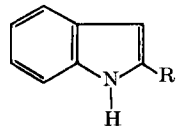
and 2-(β-naphthyl)indole (**64**), respectively.[50] The triphenylmethylindoles **56**, **57**, **58**, **59**, and **60** were formulated a 3-substituted indoles since they all apparently contained one active hydrogen atom and it was assumed that this was in the 1-position. 2,3-Diphenylindole magnesium iodide also reacted with triphenylmethyl chloride in anisole solution; in this case 2,3-diphenyl-3-triphenylmethylindolenine (**65**) was obtained. Kubota observed also that the Grignard reagents derived from the benz[*e*]indoles (**66**) and (**67**) reacted with triphenylmethyl chloride to give the expected 3-triphenylmethyl derivatives;



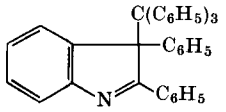
(**54**) R = H
(**55**) R = CH_3



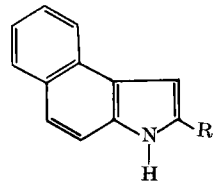
(**56**) R = H
(**57**) R = CH_3
(**58**) R = C_6H_5
(**59**) R = α-naphthyl
(**60**) R = β-naphthyl



(**61**) R = CH_3
(**62**) R = C_6H_5
(**63**) R = α-naphthyl
(**64**) R = β-naphthyl



(**65**)

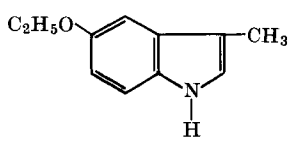


(**66**) R = H
(**67**) R = CH_3
(**68**) R = C_6H_5

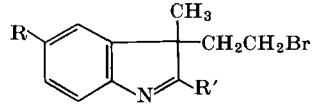
however, no reaction occurred between 2-phenylbenz[4,5]indole (**68**) and triphenylmethyl chloride.[50] In all cases the position of the trityl group was established by the fact that the compounds appeared to contain one active hydrogen atom as determined by the Zerewitinov procedure. Since the hydrogen atom in the 3-position in indole derivatives of this type might also react positively in the Zerewitinov reaction, a completely unambiguous structural evaluation must await further investigation.

5. *Aliphatic Polyhalides*

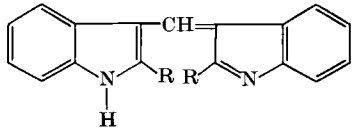
a. 1,2-*Dibromoethane.* In 1939, Kobayashi extended his synthetic approaches to the eserine skeleton to a study of the interaction of 1,2-dibromoethane with the Grignard reagents derived from 3-methylindole (**2**), 2,3-dimethylindole (**14**), and 5-ethoxy-3-methylindole (**69**).[52] In all cases the initial product was probably a 3-(2-bromoethyl)-3-methylindolenine derivative [i.e., **70**, **71**, and **72**, respectively]. The crude products were cyclized by treatment with ammonia at 100°–105° in a sealed tube, giving dinordeoxyeseroline (**25**), dinordeoxy-9-methyleseroline (**26**) and dinoreserethole (**28**), respectively.[52]



(**69**)



(**70**) R = R′ = H
(**71**) R = H; R′ = CH_3
(**72**) R = OC_2H_5; R′ = H



(**73**) R = CH_3
(**74**) R = H

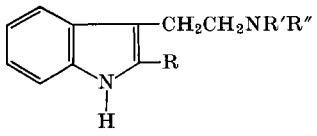
b. *Iodoform and Carbon Tetrachloride.* Iodoform reacts slowly with 2-methylindole magnesium bromide in anhydrous ether to form an orange-yellow solid, probably 2-methyl-3-indolyl-2′-methyl-3′-indoleninylidenemethane (**73**).[53] The same product was obtained by the action of carbon tetrachloride on 2-methylindole magnesium iodide.[54] The related compound, 3-indolyl-3′-indoleninylidenemethane (**74**) was obtained analogously from indole magnesium bromide.[54]

[52] T. Kobayashi, *Ann. Chem.* **539**, 213 (1939).
[53] B. Oddo and F. Tognaschini, *Gazz. Chim. Ital.* **53**, 271 (1923); *Chem. Abstr.* **17**, 2883 (1923).
[54] B. Oddo and G. Sanna, *Gazz. Chim. Ital.* **54**, 682 (1924); *Chem. Abstr.* **19**, 829 (1925).

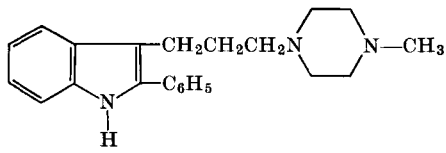
6. *Miscellaneous Alkyl Halide Derivatives*

a. *Ethylene Chlorohydrin.* An early attempt to prepare tryptophol by the action of ethylene chlorohydrin on the indole Grignard reagent was not very successful.[42] However, tryptophol can be readily prepared from the indole Grignard reagent by reaction with ethylene oxide (see Section III, F, 1, a).

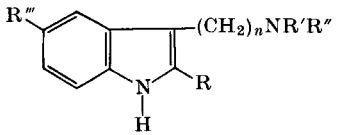
b. *Halogenoalkylamine Derivatives.* The preparation of 3-(β-diethylaminoethyl)-2-methylindole (**75**) by the action of β-diethylaminoethyl chloride on 2-methylindole magnesium bromide in ether solution was first described in 1931.[55] In 1964, Ganellin and Ridley reported that N^{ω},N^{ω}-dimethyltryptamine (**76**), 2,N^{ω},N^{ω}-trimethyltryptamine (**77**),



(**75**) R = CH_3; R′ = R″ = C_2H_5
(**76**) R = H; R′ = R″ = CH_3
(**77**) R = R′ = R″ = CH_3
(**78**) R = C_6H_5; R′ = R″ = CH_3



(**86**)



(**79**) R = H; R′ = H; R″ = CH_3; R‴ = H; $n = 2$
(**80**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = F; $n = 2$
(**81**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = OCH_3; $n = 2$
(**82**) R = 4-FC_6H_4; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 2$
(**83**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 3$
(**84**) R = $CH_2C_6H_5$; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 2$
(**85**) R = H; R′ = C_2H_5; R″ = C_2H_5; R‴ = H; $n = 2$

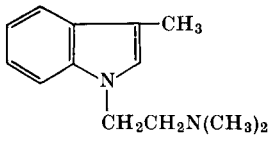
and N^{ω},N^{ω}-dimethyl-2-phenyltryptamine (**78**) were obtained in reasonable yield by the action of β-dimethylaminoethyl chloride on the Grignard reagents derived from indole, 2-methylindole, and 2-phenylindole, respectively, in anisole solution, at low temperatures.[56] The yields of **76**, **77**, and **78** were adversely affected by raising

[55] J. Klarer and F. Mietzsch, U.S. Patent, 1,793,176 (1931); *Chem. Abstr.* **25**, 2153 (1931).

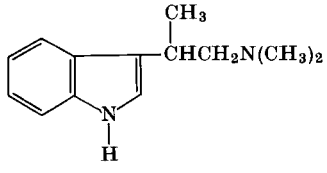
[56] C. R. Ganellin and H. F. Ridley, *Chem. Ind.* (*London*) p. 1388 (1964).

the reaction temperature and none of the desired product was obtained when the reaction was carried out in diethyl ether, tetrahydrofuran,[56] or benzene.[16, 16a, 16b, 56]

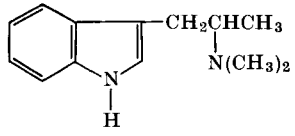
Ganellin and Ridley subsequently showed that this reaction was of wide applicability and could be applied to the synthesis of tryptamine (**23**) itself and a number of indole derivatives with 3-β-mono- or 3-β-dialkylaminoalkyl side chains where the side chain contained two or more carbon atoms.[16, 16a, 16b] A number of compounds of this general type including **79**, **80**, **81**, **82**, **83**, **84**, **85**, and **86** have been prepared by these authors.[16, 16a, 16b] Trace quantities of the corresponding 1-(β-dialkylaminoethyl)indole derivatives were formed at the same time as other isomers. However, only the *N*-substituted product,



(**87**)



(**88**)



(**89**)

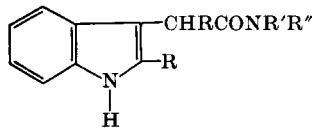
i.e., 1-(2-dimethylaminoethyl)-3-methylindole (**87**) was obtained from the skatole Grignard reagent. Attempts to replace the chlorodialkylamino component by the corresponding bromo compounds in the coupling reaction were not encouraging.[16, 16a, 16b] Kalir and Szara obtained an 8% yield of dimethyltryptamine (**76**) by the action of dimethylaminoethyl chloride, or mesylate, on indole magnesium bromide; however, only traces of the corresponding tryptamine derivatives were obtained using either the diethyl- or diisopropylaminoethyl chlorides.[57]

Ganellin and Ridley obtained a mixture of isomeric products by the action of 2-chloro-1-dimethylaminopropane on indole magnesium iodide. In this case both 3-(2-dimethylamino-1-methylethyl)

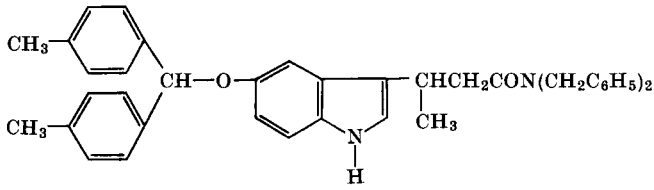
[57] A. Kalir and S. Szara, *J. Med. Chem.* **9**, 341 (1966).

indole (**88**) and 3-(β-dimethylamino-*n*-propyl)indole (**89**) were formed.[16, 16a, 16b] Eiter and Svierak had reported earlier that they were unable to alkylate indole magnesium iodide with 1-chloro-2-dimethylaminopropane in ether.[58]

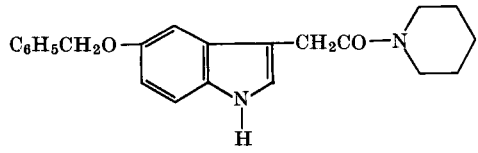
c. *α-Chloro-N-substituted Acetamides.* In 1937 Wegler and Binder reported that *N*,*N*-diethyl-3-indolylacetamide (**90**) could be obtained



(**90**) R = R′ = H; R″ = R‴ = C_2H_5
(**91**) R = H; R′ = R″ = R‴ = CH_3



(**92**)



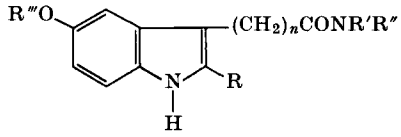
(**93**)

by the action of *N*,*N*-diethyl-α-chloroacetamide on indole magnesium iodide.[59] This reaction has subsequently been shown to be of general utility and a number of substituted 3-indolylacetamides including **91**, **92**, **93**, and the compounds listed in Table I (i.e., **94–102**) have been made by this route.[16, 16a, 16b, 60, 61] The reaction is carried out by heating the chloro compound and the Grignard reagent together in the

[58] K. Eiter and O. Svierak, *Monatsh. Chem.* **83**, 1453 (1952).
[59] R. Wegler and H. Binder, *Arch. Pharm.* **275**, 506 (1937); *Chem. Abstr.* **32**, 939 (1938).
[60] M. E. Speeter, U.S. Patent No. 2,692,882 (1954); *Chem. Abstr.* **49**, 14810 (1955).
[61] R. V. Heinzelman and J. Szmuszkovicz, *Progr. Drug Res.* **6**, 75 (1963).

absence of solvent for several hours. The method was reported to be most successful with disubstituted amides, less successful with monosubstituted amides, and it failed completely with chloroacetamide itself (cf. ref. 61).

TABLE I

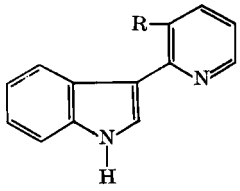


Compound number	R	R′	R″	R‴	n
94	H	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	1
95	H	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	1
96	H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	1
97	CH_3	H	CH_3	$C_6H_5CH_2$ p-$CH_3OC_6H_4$	1
98	H	$C_6H_5CH_2$	$C_6H_5CH_2$	$>CH$ p-$CH_3OC_6H_4$	2
99	H	H	$C_6H_5CH_2$	$(C_6H_5)_2CH$ p-ClC_6H_4	1
100	C_2H_5	CH_3	$C_6H_5CH_2$	$>CH$ p-ClC_6H_4	1
101	H	$(CH_3)_2CH$	$C_6H_5CH_2$	$C_6H_5CH_2$	1
102	H	C_2H_5	C_2H_5	$C_6H_5CH_2$	2

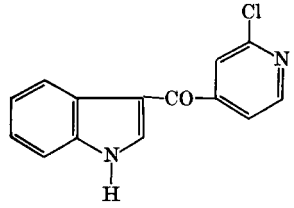
7. *Heterocyclic Halogen Compounds*

Powers reported recently that 3-(2-pyridyl)indole (**103**) is obtained in ca. 17% yield by the interaction of 2-chloropyridine with indole magnesium iodide in a sealed tube at 160° for 12 hours.[62] 3-(3-Cyano-2-pyridyl)indole (**104**) was obtained in 52% yield when the indole Grignard reagent was heated with 2-chloro-3-cyanopyridine at 170° for 3 hours. However, 2-chloro-4-cyanopyridine reacted in a somewhat different manner under similarly vigorous conditions; in this case 3-indolyl 2-chloro-4-pyridyl ketone (**105**) was obtained. This product

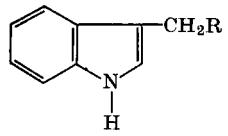
[62] J. C. Powers, *J. Org. Chem.* **30**, 2534 (1965).



(**103**) R = H
(**104**) R = CN



(**105**)



(**106**) R = 2-Pyridyl
(**107**) R = 3-Pyridyl
(**108**) R = 4-Pyridyl

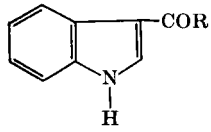
was presumably formed by the initial addition of the Grignard reagent to the nitrile group. The structure of **105** was confirmed by an alternative synthesis.[62]

2-(3-Indolylmethyl)pyridine (**106**), 3-(3-indolylmethyl)pyridine (**107**), and 4-(3-indolylmethyl)pyridine (**108**) have recently been prepared by the condensation of indole magnesium bromide with 2-, 3-, and 4-chloromethylpyridine, respectively.[63]

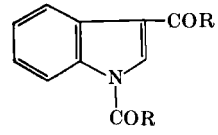
C. Reactions with Derivatives of Organic Acids

1. *Aliphatic Monocarboxylic Acid Chlorides*

a. *Unsubstituted.* In 1911 Oddo and Sessa reported that 3-acetylindole (**109**) was formed readily in a vigorous reaction between indole



(**109**) R = CH_3
(**111**) R = C_2H_5
(**113**) R = n-C_3H_7



(**110**) R = CH_3
(**112**) R = C_2H_5
(**114**) R = n-C_3H_7

[63] J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocyclic Chem.* **3**, 67 (1966).

magnesium iodide and acetyl chloride in ether and that small quantities of the disubstituted product, 1,3-diacetylindole (**110**), were also formed. 3-Propionylindole (**111**) and 1,3-dipropionylindole (**112**) were obtained similarly from propionyl chloride and indole magnesium iodide. These authors concluded that the amount of diacyl derivative formed decreased with the complexity of the acid chloride used. When the reaction was carried out with *n*-butyryl chloride they were able to detect only the 3-acyl derivative (**113**).[64] However, more recently Hishida has obtained both 3-*n*-butyrylindole (**113**) and 1,3-di(*n*-butyryl)indole (**114**) by the action of *n*-butyryl chloride on the indole Grignard reagent, the formation of **114** being favored by low reaction temperatures.[65] In 1922 Majima and Kotake reported the effect of varying the solvent on the yield of 3-acetylindole (**109**), obtained by the action of acetyl chloride on indole magnesium iodide; a 93% yield of **109** was obtained when the reaction was carried out in ether in the cold; however, only a 61% yield was obtained in anisole. They did not, however, report the formation of any of the 1,3-diacetyl derivative **110**.[11] Baker in 1946 also obtained **109** as the main product by this route, when the reaction was carried out at $-20°$ in ether; small quantities of **110** were formed at the same time.[66] In 1952 Saxton reported that good yields of **109** could not be consistently obtained by this procedure.[67] However, more recently Szmuskovicz claimed that the original Grignard procedure for the preparation of **109** was improved if the reaction with the acid chloride was carried out in benzene solution. Szmuskovicz also reported the satisfactory synthesis of 3-propionylindole (**111**) and 3-acetyl-5-benzyloxyindole (**115**) by this procedure, the reactions being carried out in a benzene–ether mixture.[68]

3-Acetyl-2-methylindole (**116**) can readily be obtained by the action of acetyl chloride on the 2-methylindole Grignard reagent in ether.[69–71]

[64] B. Oddo and L. Sessa, *Gazz. Chim. Ital.* **41**, 234 (1911); *Chem. Abstr.* **5**, 2638 (1911)

[65] S. Hishida, *Nippon Kagaku Zasshi* **72**, 312 (1951); *Chem. Abstr.* **46**, 5038 (1952).

[66] J. W. Baker, *J. Chem. Soc.* p. 461 (1946).

[67] J. E. Saxton, *J. Chem. Soc.* p. 3592 (1952).

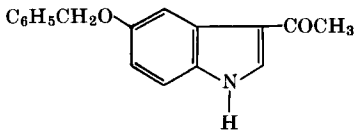
[68] J. Szmuszkovicz, *J. Am. Chem. Soc.* **82**, 1180 (1960).

[69] B. Oddo, *Gazz. Chim. Ital.* **43**, 190 (1913); *Chem. Abstr.* **8**, 85 (1914).

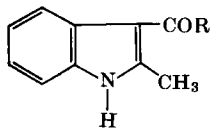
[70] A. H. Salway, *J. Chem. Soc.* **103**, 351 (1913).

[71] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **41**, 2067 (1963).

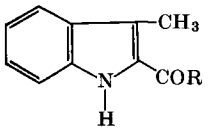
2-Acetyl-3-methylindole (**117**) was obtained when the skatole Grignard reagent was treated with acetyl chloride at 100° in the absence of solvent, but 1-acetyl-3-methylindole (**118**) was obtained when the



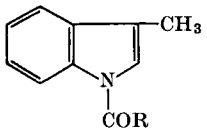
(**115**)



(**116**) R = CH_3
(**121**) R = C_2H_5
(**122**) R = n-C_3H_7



(**117**) R = CH_3
(**120**) R = C_2H_5

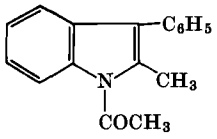


(**118**) R = CH_3
(**119**) R = C_2H_5

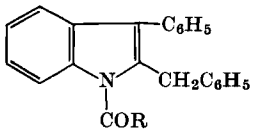
reaction was carried out for 12 days at 0°.[69] Both 3-methyl-1-propionylindole (**119**) and 3-methyl-2-propionylindole (**120**) were obtained analogously by the action of propionyl chloride on the skatole Grignard reagent. 2-Methyl-3-propionylindole (**121**) and 2-methyl-3-n-butyrylindole (**122**) were also prepared by the action of propionyl and n-butyryl chloride on the Grignard reagent from 2-methylindole.[69]

Bruce and Sutcliffe obtained 1-acetyl-2-methyl-3-phenylindole (**123**) by the action of acetyl chloride on 2-methyl-3-phenylindole magnesium iodide in ether.[72] These authors were able to obtain 1-benzoyl-2-benzyl-3-phenylindole (**124**) but not 1-acetyl-2-benzyl-3-phenylindole (**125**) from 2-benzyl-3-phenylindole magnesium iodide by analogous procedures.[72] 3-Acetyl-2-phenylindole (**126**)[16, 16a, 16b, 73] and 3-propionyl-2-phenylindole (**127**)[73] have recently been prepared in fair yield by the acylation of 2-phenylindole magnesium iodide with acetyl and propionyl chloride, respectively. Leete obtained a mixture of 1-acetyl-3-ethylindole (**128**) and 2-acetyl-3-ethylindole (**129**) by the interaction of acetyl chloride with 3-ethylindole magnesium iodide in ether.[74]

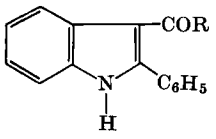
[72] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.* p. 4789 (1957).
[73] G. Buchmann and D. Rossner, *J. Prakt. Chem., Ser. 4*, **25**, 117 (1964).
[74] E. Leete, *J. Am. Chem. Soc.* **83**, 3645 (1961).



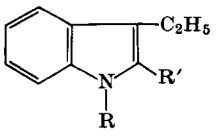
(123)



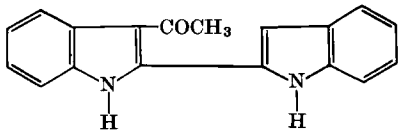
(124) R = C_6H_5
(125) R = CH_3



(126) R = CH_3
(127) R = C_2H_5



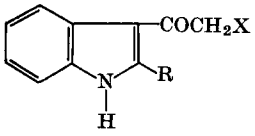
(128) R = $COCH_3$; R′ = H
(129) R = H; R′ = $COCH_3$



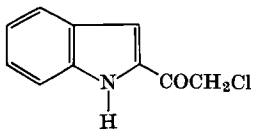
(130)

It has been reported that treatment of the Grignard reagent derived from 2,2′-biindole with acetyl chloride in ether in the cold gives a monoacetyl derivative, probably 3-acetyl-2,2′-biindole (**130**).[75]

b. *Halogen Substituted.* Salway reported in 1913 that 3-chloroacetyl-2-methylindole (**131**) could be obtained by the action of chloroacetyl chloride on 2-methylindole magnesium bromide; however, when the iodide was used in place of the bromide a mixture of approximately equal parts of **131** and 3-acetyl-2-methylindole (**116**) was obtained.[70] The dehalogenated product **116** was formed by the reducing action of the iodide ions, generated during the reaction, on the chloroacetyl



(131) R = CH_3; X = Cl
(132) R = H; X = Cl
(133) R = H; X = Br
(134) R = H; X = I
(135) R = CH_3; X = Br
(136) R = CH_3; X = I



(137)

derivative **131**. Majima and Kotake reported that 3-chloroacetylindole (**132**) was produced by the action of chloroacetyl chloride on indole magnesium iodide in 45% yield when the reaction was carried out at low temperatures in ether, but only in 4.8% yield in anisole.[11]

[75] W. Madelung and F. Hager, *Ber. Deut. Chem. Ges.* **49**, 2039 (1916).

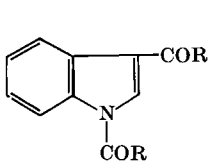
Sanna confirmed that **132** was readily obtained in ether in the cold.[76, 77] Sanna also prepared 3-bromoacetylindole (**133**) and 3-iodoacetylindole (**134**) by the action of bromoacetyl chloride and iodoacetyl chloride, respectively, on the indole Grignard reagent.[76, 77] The corresponding 3-halogenoacetyl-2-methylindole derivatives **131**, **135**, and **136** were obtained analogously from 2-methylindole.[76–78] In 1931 Mingoia claimed that, as well as 3-chloroacetylindole (**132**), a small quantity of an isomeric product, probably 2-chloroacetylindole (**137**), was obtained in the reaction with chloroacetyl chloride.[79] This compound was described as a 2-indolyl derivative since it gave indole-2-carboxylic acid on fusion with potassium hydroxide. It is possible that this conclusion was erroneous since indole-2-carboxylic acid has been obtained on alkaline fusion of other 3-indolyl derivatives (cf. Speeter and Anthony[80]). More recently, however, Ames *et al.* have stated that the main product of the reaction between indole magnesium bromide and chloroacetyl chloride in ether at 0° was 1,3-bis(chloroacetyl)indole (**138**) (m.p. 176°); small quantities of the monochloroacetyl derivative **132** (m.p. 230°) were formed at the same time.[81] They suggest that the melting point (214°) previously reported for **132**[11, 76, 77] was low because these products were essentially impure mixtures of **132** and **138** and that the product (m.p. 230°) obtained by Mingoia[79] and described as the 2-isomer (i.e., **137**) was, in fact, the 3-chloroacetyl derivative **132**.

Mingoia reported that 2-chloroacetyl-3-methylindole (**139**) was obtained by the action of chloroacetyl chloride on the skatole Grignard reagent.[79]

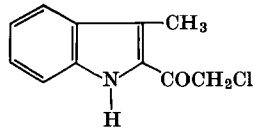
Kalir and Szara obtained 1,3-bis(α-chloropropionyl)indole (**140**) by the action of a 20% excess of α-chloropropionyl chloride on indole magnesium bromide in an ether–toluene mixture.[57] On the other hand, Ganellin and Ridley obtained 3-(α-chloropropionyl)indole (**141**) by the action of a 10% excess of α-chloropropionyl chloride on indole magnesium iodide in anisole.[16, 16a, 16b]

3-Dichloroacetyl-2-methylindole (**142**) and 3-trichloroacetyl-2-

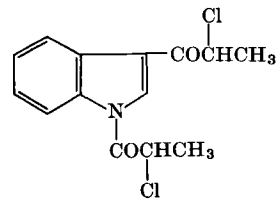
[76] G. Sanna, *Gazz. Chim. Ital.* **59**, 838 (1929); *Chem. Abstr.* **24**, 2127 (1930).
[77] G. Sanna, *Gazz. Chim. Ital.* **59**, 169 (1929); *Chem. Abstr.* **23**, 4215 (1929).
[78] Q. Mingoia, *Gazz. Chim. Ital.* **59**, 105 (1929); *Chem. Abstr.* **23**, 3927 (1929).
[79] Q. Mingoia, *Gazz. Chim. Ital.* **61**, 646 (1931); *Chem. Abstr.* **26**, 1279 (1932).
[80] M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.* **76**, 6208 (1954).
[81] D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.* p. 1984 (1956).



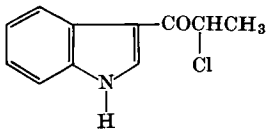
(138) R = CH_2Cl
(147) R = $CHCl_2$
(149) R = CCl_3



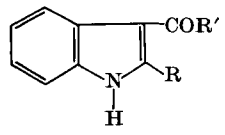
(139)



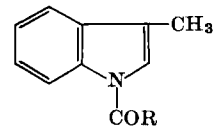
(140)



(141)



(142) R = CH_3; R′ = $CHCl_2$
(143) R = CH_3; R′ = CCl_3
(146) R = H; R′ = $CHCl_2$
(148) R = H; R′ = CCl_3



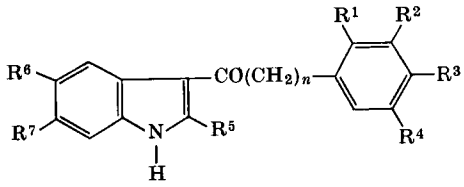
(144) R = $CHCl_2$
(145) R = CCl_3

methylindole (**143**) can be obtained in excellent yield by the action of dichloro- and trichloroacetyl chloride, respectively, on the 2-methylindole Grignard reagent.[82] Sanna and his colleagues later studied the action of dichloroacetyl chloride and trichloroacetyl chloride on the magnesium derivatives of indole and skatole.[83, 84] In the latter case no evidence of 2-substitution was forthcoming, the products being 1-dichloroacetyl-3-methylindole (**144**) and 1-trichloroacetyl-3-methylindole (**145**), respectively. The trichloro compound **145** decomposed in aqueous solution to give skatole, carbon dioxide, and chloroform.[84] In the case of indole, Sanna obtained 3-mono- and 1,3-disubstituted indoles by the action of di- and trichloroacetyl chloride on the Grignard reagent. In the former case 3-dichloroacetylindole (**146**) and 1,3-bis-(dichloroacetyl)indole (**147**) were formed and in the latter case the analogous trichloroacetyl derivatives **148** and **149** were obtained.[83]

c. *Aryl Substituted.* A number of arylalkyl 3-indolyl ketones have been prepared by the coupling of a suitable arylalkyl acid chloride

[82] G. Sanna, *Gazz. Chim. Ital.* **61**, 60 (1931); *Chem. Abstr.* **25**, 2720 (1931).
[83] G. Sanna, *Rend. Seminario Fac. Sci. Univ. Cagliari* **4**, 28 (1934); *Chem. Abstr.* **30**, 6363 (1936).
[84] G. Sanna and F. Athene, *Rend. Seminario Fac. Sci. Univ. Cagliari* **4**, 62 (1934); *Chem. Abstr.* **30**, 6364 (1936).

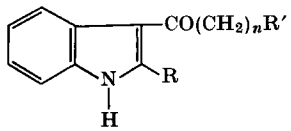
TABLE II



Compound number	R^1	R^2	R^3	R^4	R^5	R^6	R^7
150	H	OCH_3	OCH_3	H	H	H	H
151	NO_2	H	OCH_3	OCH_3	H	H	H
152	H	OCH_3	OCH_3	H	CH_3	H	H
153	NO_2	H	OCH_3	OCH_3	CH_3	H	H
154	H	OCH_3	OCH_3	H	H	Br	H
155	H	$O—CH_2—O$		H	H	H	H
156	H	$O—CH_2—O$		H	H	Br	H
157	NO_2	H	OCH_3	OCH_3	H	Br	H
158	NO_2	H	$O—CH_2—O$		H	H	H
159	NO_2	H	$O—CH_2—O$		H	Br	H
160	CH_3	OCH_3	OCH_3	H	H	H	H
161	OCH_3	OCH_3	H	H	H	H	H
162	H	OCH_3	H	H	H	H	H
163	Cl	OCH_3	OCH_3	H	H	H	H
164	H	OCH_3	OCH_3	Cl	H	H	H
165	Cl	H	OCH_3	OCH_3	H	H	H
166	Br	H	OCH_3	OCH_3	H	H	H
167	H	CH_3	CH_3	H	H	H	H
168	H	Cl	Cl	H	H	H	H
169	H	OCH_3	H	H	H	Br	H
170	H	OCH_3	OCH_3	Cl	H	Br	H
171	Br	H	OCH_3	OCH_3	H	Br	H
172	H	CH_3	CH_3	H	H	Br	H
173	H	$O—CH_2—O$		H	H	$O—CH_2—O$	
174	H	$O—CH_2—O$		H	CH_3	H	H
175	H	CH_3	CH_3	H	CH_3	H	H
176	H	Cl	Cl	H	CH_3	H	H
177	Cl	H	Cl	H	CH_3	H	H

with an indole Grignard reagent,[20–22, 85–87] usually derived from indole or 2-methylindole, although 5-bromoindole magnesium bromide has also been satisfactorily converted into 3-indolyl ketones by this procedure.[21] This reaction is usually carried out either in ether (at 34°)[22, 85–87] or in benzene–ether solutions, at temperatures below

TABLE III



Compound number	R	R′	n
178	H	C_6H_5	2
179	CH_3	C_6H_5	2
180	H	4-ClC_6H_4	2
181	CH_3	4-$CH_3C_6H_4$	2
182	H	6-Tetralyl	2
183	CH_3	4-ClC_6H_4	2
184	CH_3	C_6H_5	3
185	H	4-$CH_3OC_6H_4$	0
186	H	2-ClC_6H_4	0
187	H	4-$C_2H_5C_6H_4$	0
188	CH_3	2-Furyl	0
189	H	1-Naphthyl	0
190	H	2-Naphthyl	0
191	H	1-Naphthyl	1
192	CH_3	2-Thienyl	0
193	CH_3	C_6H_5	1
194	CH_3	1-Naphthyl	1
195	H	4-$NO_2C_6H_4$	1

ambient.[20–22] Nearly 50 different 3-indolyl ketones (i.e., **150–195**) have been prepared in this manner (see Tables II and III). Young and Mizianti reported that the crude products obtained by the action of arylacetyl chlorides on the indole Grignard reagents were usually

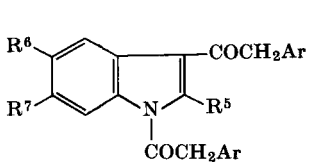
[85] N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *J. Chem. Soc.* p. 3499 (1951).

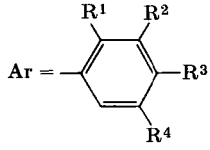
[86] N. P. Buu-Hoï, E. Bisagni, R. Royer, and C. Routier, *J. Chem. Soc.* p. 625 (1957).

[87] S. Takagi, A. Sugii, and K. Machida, *Pharm. Bull.* (*Tokyo*) **5**, 617 (1957); *Chem. Abstr.* **52**, 16331 (1958).

either essentially the 1,3-bis(arylacetyl)indoles **196–200** (see Table IV) or mixtures of these products with the corresponding monoarylacetyl derivative shown in Table II. In the former case the 1,3-disubstituted indoles could readily be obtained in the pure state by recrystallization of the crude product. The five 1,3-bis(arylacetyl)indoles listed in Table IV were prepared in this manner. If this was not

TABLE IV

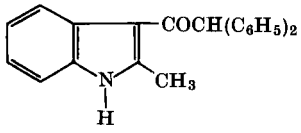




Compound number	R^1	R^2	R^3	R^4	R^5	R^6	R^7
196	H	OCH_3	H	H	H	H	H
197	H	CH_3	CH_3	H	H	H	H
198	H	Cl	Cl	H	H	H	H
199	H	OCH_3	OCH_3	Cl	H	Br	H
200	H	CH_3	CH_3	H	H	Br	H

possible, the crude 1,3-bis(arylacetyl) derivatives were converted into the 3-monoarylacyl derivative by alkaline hydrolysis.[22]

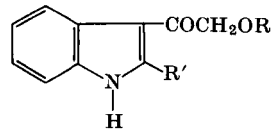
Benzhydryl 2-methyl-3-indolyl ketone (**201**) has been prepared by the action of diphenylacetyl chloride on 2-methylindole magnesium iodide.[88]



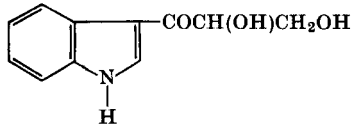
(**201**)

$C_2H_5OCH_2COCl$

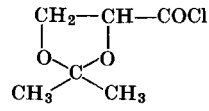
(**202**)



(**203**) R = C_2H_5; R′ = CH_3
(**204**) R = $C_6H_5CH_2$; R′ = H



(**205**)



(**206**)

[88] J. Szmuszkovicz, *J. Org. Chem.* **27**, 511 (1962).

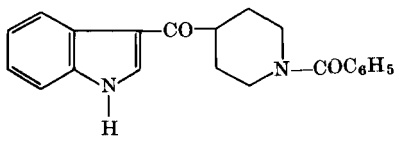
d. *Miscellaneous. i. Ethoxyacetyl chloride* (*o*-ethylglycolyl chloride). Ethoxyacetyl chloride (**202**) reacts readily with 2-methylindole magnesium bromide in ether to give a crystalline product, probably 3-ethoxyacetyl-2-methylindole (**203**).[89]

ii. Benzyloxyacetyl chloride. More recently Suvorov *et al.* have prepared 3-benzyloxyacetylindole (**204**) in an analogous manner by the action of benzyloxyacetyl chloride on indole magnesium iodide.[90]

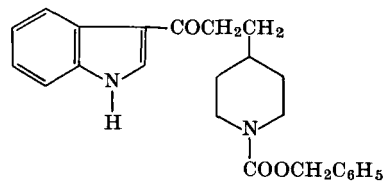
iii. Isopropylideneglyceroyl chloride. 3-(α,β-Dihydroxypropionyl)-indole (**205**) has recently been obtained by hydrolysis of its isopropylidene derivative which, in turn, was produced by the action of isopropylideneglyceroyl chloride (**206**) on indole magnesium iodide in ether.[91]

iv. N-Benzoylisonipecotoyl chloride. 3-(*N*-Benzoylisonipecotoyl)-indole (**207**) can be prepared by the action of *N*-benzoylisonipecotoyl chloride on indole magnesium bromide in ether.[63]

v. β-(1-Carbobenzoxy-4-piperidyl)propionyl chloride. β-(*N*-carbobenzyloxy-4-piperidyl)ethyl 3-indolyl ketone (**208**) was obtained similarly by the condensation of β-(*N*-carbobenzoxy-4-piperidyl)-propionyl chloride with indole magnesium bromide in ether.[92]



(**207**)



(**208**)

2. *Esters of Aliphatic Monocarboxylic Acids*

a. *Simple.* In 1915 Alessandri[93] reported that low yields of what were probably the 3-formyl derivatives of indole and 2-methylindole

[89] A. Sanna and G. Chessa, *Gazz. Chim. Ital.* **58**, 121 (1928); *Chem. Abstr.* **22**, 2562 (1928).

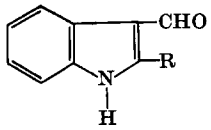
[90] N. N. Suvorov, K. B. Kholodkovskaya, and M. N. Preobrazhenskaya, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 1965 p. 265; *Chem. Abstr.* **63**, 6949 (1965).

[91] M. N. Preobrazhenskaya, K. B. Kholodkovskaya, and N. N. Suvorov, *Sin. Prir. Soedin. Ikh Analogov Fragmentov Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*, 1965 p. 233; *Chem. Abstr.* **65**, 2200 (1966).

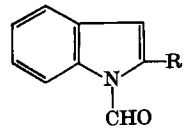
[92] J. I. DeGraw and J. G. Kennedy, *J. Heterocyclic Chem.* **3**, 90 (1966).

[93] L. Alessandri, *Atti Accad. Nazl. Lincei Mem. Classe Sci. Fis. Mat. Nat.* **24**[II], 194 (1915); *Chem. Abstr.* **10**, 1350 (1916).

(i.e., **209** and **210**) were obtained by the action of ethyl formate on the Grignard reagents derived from indole and 2-methylindole. In each case isomeric by-products, probably the corresponding *N*-formyl derivatives (**211** and **212**), were formed in significant yield. A few years later Alessandri and Passerini prepared 1-formyl-2-methylindole (**212**) and 3-formyl-2-methylindole (**210**) by the action of isoamyl formate on 2-methylindole magnesium iodide under mild conditions.[94]



(**209**) R = H
(**210**) R = CH_3



(**211**) R = H
(**212**) R = CH_3

In 1922 Majima and Kotake reported that 3-formylindole (**209**) could be obtained in yields of up to 40% by the action of a fivefold excess of ethyl formate on indole magnesium iodide in anisole at low temperatures. However, they also claimed that only traces of the aldehyde were obtained when the reaction was carried out in ether.[10, 11]

In 1927 Putochin studied the effect of temperature on the nature of the products formed when the formylation reaction was carried out in benzene and observed that 1-formyl derivatives were the major products obtained at low temperatures, whereas the 3-formyl derivatives predominated at higher temperatures.[13] Britton *et al.* in 1947 claimed that the formation of the 3-formylindole derivative is probably favored, relative to the alternate 1-formylation process, by elevated temperatures and pressures.[95] However, it was apparently not possible to suppress completely the formation of the 1-formyl derivatives and yields of the order of 40% of both products were usually obtained.[95]

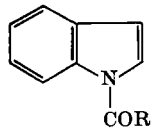
1-Acetylindole (**213**) was obtained by the action of ethyl acetate on indole magnesium iodide at low temperatures; slightly higher yields were obtained when the reaction was carried out in anisole rather than in ether.[96] Putochin subsequently observed that when the reaction was carried out in benzene at 85° both **213** and 3-acetylindole (**109**)

[94] L. Alessandri and M. Passerini, *Gazz. Chim. Ital.* **51**, 262 (1921); *Chem. Abstr.* **16**, 94 (1922).

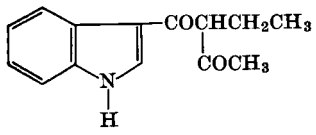
[95] E. C. Britton, J. E. Livak, and J. C. Vander Weele, U.S. Patent No. 2,414,715 (1947); *Chem. Abstr.* **41**, 3129 (1947).

[96] R. Majima and T. Shigematsu, *Ber. Deut. Chem. Ges.* **57B**, 1449 (1924).

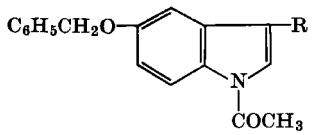
were formed.[13] Horiie reported that **213** was the only product formed when the reaction was carried out in refluxing ether[97]; with ethyl propionate in place of ethyl acetate, 1-propionylindole (**214**) was obtained.[98, 98a]



(**213**) R = CH_3
(**214**) R = C_2H_5



(**215**)



(**216**) R = H
(**217**) R = CH_3

3-(α-Acetyl-*n*-butyryl)indole (**215**) was obtained by the action of ethyl α-ethylacetoacetate on indole magnesium bromide.[65]

Recently two further examples of the 1-acetylation of indoles by this route have been observed by Heacock and Hutzinger. 1-Acetyl-5-benzyloxyindole (**216**) and 1-acetyl-5-benzyloxy-3-methylindole (**217**) were obtained by the action of ethyl acetate on the relevant indole Grignard reagents at low temperatures.[98, 98a]

b. *Halogen Substituted.* The main product obtained from the reaction of indole magnesium iodide with ethyl chloroformate was originally described by Oddo and Sessa in 1911 as 2-ethoxycarbonylindole (**218**).[64] Some years later Majima and Kotake reported that this product was not **218** but the isomeric 3-ethoxycarbonylindole (**219**) which could be obtained in yields of up to 78% under ideal conditions.[11, 99] The Japanese authors further reported that some 1,3-di-(ethoxycarbonyl)indole (**220**) was also invariably formed along with **219** during the course of the reaction and that when the reaction was

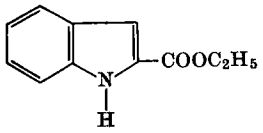
[97] S. Horiie, *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **7**, 143 (1950); *Chem. Abstr.* **45**, 9030 (1951).

[98] R. A. Heacock and O. Hutzinger, unpublished observations, 1965.

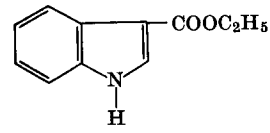
[98a] O. Hutzinger, Ph.D. Thesis, Univ. of Saskatchewan, Saskatoon, Saskatchewan, Canada, 1965.

[99] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **63B**, 2237 (1930).

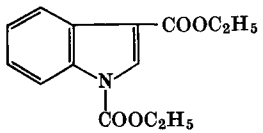
carried out with a 2:1 molecular ratio of ester to indole, significant quantities of the diester **220** were formed.[99] The preparation of **219** by what was essentially Majima and Kotake's procedure has subsequently been described by other workers.[100–102] Brown and Garrison[102] claimed that better results were obtained by carrying out the reaction between $-15°$ and $-5°$ than at the temperature reported by the Japanese workers (i.e., up to 35°) (cf. ref. 99). However, a recent study[103] of the reaction between ethyl chloroformate and indole magnesium iodide has shown that both **219** and 1-ethoxycarbonyl-



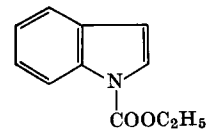
(218)



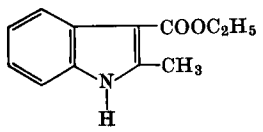
(219)



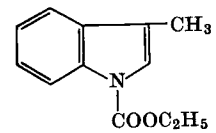
(220)



(221)



(222)



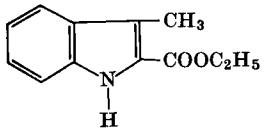
(223)

indole (**221**) are formed when the reaction is carried out with either 1 or 2 moles of ethyl chloroformate. The formation of **221** was favored at low temperatures (e.g., $-10°$), whereas the maximum yields of **219** were obtained at 10°. Significant quantities of the diester **220** were only formed when the reaction was carried out with two equivalents of the chloroformic ester at 35°.[103]

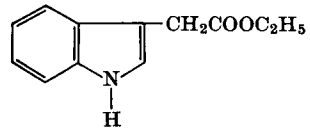
3-Ethoxycarbonyl-2-methylindole (**222**) and 1-ethoxycarbonyl-3-methylindole (**223**) were the main products said to be obtained by the action of ethyl chloroformate on the 2- and 3-methylindole Grignard

[100] E. Leete and L. Marion, *Can. J. Chem.* **31**, 775 (1953).
[101] W. E. Noland and R. D. Rieke, *J. Org. Chem.* **27**, 2250 (1962).
[102] R. K. Brown and R. A. Garrison, *J. Am. Chem. Soc.* **77**, 3839 (1955).
[103] S. Kašpárek and R. A. Heacock, *Can. J. Chem.* **44**, 2805 (1966).

reagents in ether, respectively.[104] The ester **223** was still the main product formed when the latter reaction was carried out at 130°–140°. Under more vigorous conditions (i.e., 240°–250° for 3 hours, after removal of the solvent), a mixture of **223**, a small quantity of a second ester, probably 2-ethoxycarbonyl-3-methylindole (**224**), and their decomposition products were obtained.[104]



(224)



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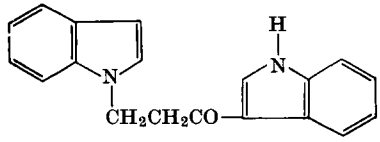


(226)

In an attempt to prepare ethyl 3-indolylacetate (**225**) by the action of ethyl chloroacetate on indole magnesium iodide, only unidentified oily products were obtained under a variety of different experimental conditions.[97] However, when indole magnesium iodide was treated with ethyl β-chloropropionate in ether, a product, identified as 3-[β-(1-indolyl)propionyl]indole (**226**) by its behavior on alkaline hydrolysis and by the number of active hydrogen atoms it contained, was obtained.[97]

3. *Nitriles*

a. *Unsubstituted.* The indole Grignard reagents differ from most other Grignard reagents in their reactivity toward nitriles, in that they do not add to the cyano group in the usual manner.[105] Majima and Hoshino showed that indole magnesium iodide forms a stable addition product with acetonitrile which, although stable at 70°, is readily decomposed by water regenerating indole.[106]

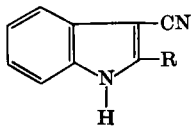
[104] B. Oddo, *Gazz. Chim. Ital.* **42**, 361 (1912); *Chem. Abstr.* **6**, 2234 (1912).

[105] The cyano group in 2-chloro-4-cyanopyridine does, however, appear to react in the expected manner with the indole Grignard reagent (see Section III, B, 7).

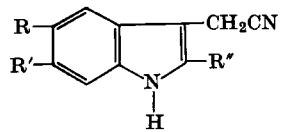
[106] R. Majima and T. Hoshino, *Ber. Deut. Chem. Ges.* **58B**, 2042 (1925).

b. *Halogenonitriles.* In 1924 Majima *et al.* found that cyanogen chloride reacts with the Grignard reagents derived from indole and 2-methylindole to give 3-cyanoindole (**227**) and 3-cyano-2-methylindole (**228**), respectively; these products were readily formed at low temperatures.[107] Only unidentified gummy products were obtained by the action of cyanogen bromide on the indole Grignard reagent.[108]

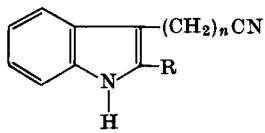
In 1925 Majima and Hoshino reported the formation of 3-indolylacetonitrile (**229**) by the action of chloroacetonitrile on indole magnesium iodide in anisole.[106] 2-Methyl-3-indolylacetonitrile (**230**) was obtained by the action of chloroacetonitrile on 2-methylindole magnesium iodide in ether.[37]



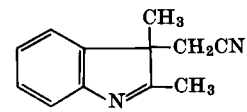
(**227**) R = H
(**228**) R = CH_3



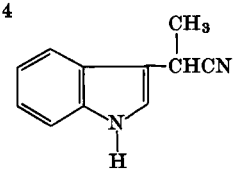
(**229**) R = R′ = R″ = H
(**230**) R = R′ = H; R″ = CH_3
(**231**) R = R″ = H; R′ = OCH_3
(**232**) R = OCH_3; R′ = R″ = H
(**233**) R = $OCH_2C_6H_5$; R′ = R″ = H



(**235**) R = H; $n = 2$
(**236**) R = H; $n = 3$
(**237**) R = CH_3; $n = 3$
(**238**) R = CH_3; $n = 4$



(**234**)



(**239**)

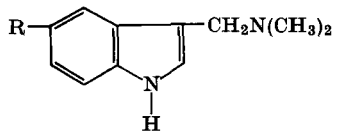
Akabori and Saito obtained 6-methoxy-3-indolylacetonitrile (**231**) from 6-methoxyindole and chloroacetonitrile by the Grignard reaction,[109] and Wieland *et al.* prepared 5-methoxy-3-indolylaceto-

[107] R. Majima, T. Shigematsu, and T. Rokkaku, *Ber. Deut. Chem. Ges.* **57B**, 1453 (1924).
[108] F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.* p. 2853 (1956).
[109] S. Akabori and K. Saito, *Ber. Deut. Chem. Ges.* **63B**, 2245 (1930).

nitrile (**232**) analogously.[110] The preparation of 5-benzyloxy-3-indolylacetonitrile (**233**) by the action of chloroacetonitrile on the 5-benzyloxyindole Grignard reagent in ether has also been described.[111,112] It has been claimed that this reaction is of wide applicability and that many substituted 5-benzyloxy-3-indolylacetonitriles can be prepared by this route.[111,112]

2,3-Dimethylindole magnesium iodide reacts with chloroacetonitrile in ether to give 3-cyanomethyl-2,3-dimethylindolenine (**234**).[37] Majima and Hoshino obtained 3-(2-cyanoethyl)indole (**235**) by the action of β-chloropropionitrile on indole magnesium iodide.[106] The reaction was slower with β-chloropropionitrile than with chloroacetonitrile.[106] 3-(3-Cyano-*n*-propyl)indole (**236**), required as an intermediate in the synthesis of 3-indolyl-γ-*n*-butyric acid, was prepared, but not isolated, by the action of γ-chloro-*n*-butyronitrile on indole magnesium iodide.[113]

Zenitz obtained the analogous compounds **237** and **238** by the action of the corresponding α-cyano-ω-bromo-*n*-alkanes on 2-methylindolyl magnesium bromide in ether.[48] Eiter and Svierak prepared α-(3-indolyl)propionitrile (**239**) by the action of α-bromopropionitrile on indole magnesium iodide in anisole.[58]



(**240**) R = H
(**241**) R = OCH_3

c. *Aminonitriles.* An interesting reaction of a nitrile with the indole Grignard reagent in which the cyano group reacts as a pseudohalogen was described by Wieland and Hsing.[114] Gramine (**240**) was readily obtained by the action of dimethylaminoacetonitrile on indole magnesium iodide in ether. The same authors prepared 3-dimethylaminomethyl-5-methoxyindole (**241**) in an analogous manner.[114]

[110] H. Wieland, W. Konz, and H. Mittasch, *Ann. Chem.* **513**, 1 (1934).

[111] M. E. Speeter, U.S. Patent No. 2,703,325 (1955); *Chem. Abstr.* **50**, 1921 (1956).

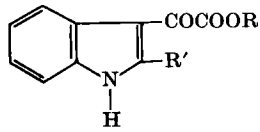
[112] M. E. Speeter, U.S. Patent No. 2,728,778 (1955); *Chem. Abstr.* **50**, 10786 (1956).

[113] S. S. Nametkin, N. A. Dzbanovskii, and A. G. Rudney, *Compt. Rend. Acad. Sci. URSS* **32**, 333 (1941); *Chem. Abstr.* **37**, 3756 (1943).

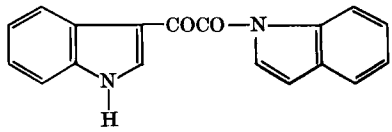
[114] T. Wieland and C. Y. Hsing, *Ann. Chem.* **526**, 188 (1936).

4. *Aliphatic Dicarboxylic Acids*

a. *Ester Acid Chlorides.* Methoxalyl chloride reacts readily with indole magnesium iodide in the cold to give mainly methyl 3-indolylglyoxalate (**242**),[107, 115] accompanied by a small quantity of 1-(3-indolylglyoxalyl)indole (**243**).[107] Ethyl 3-indolylglyoxalate (**244**) and ethyl 2-methyl-3-indolylglyoxalate (**245**) were prepared in an ana-



(**242**) R = CH_3; R′ = H
(**244**) R = C_2H_5; R′ = H
(**245**) R = C_2H_5; R′ = CH_3

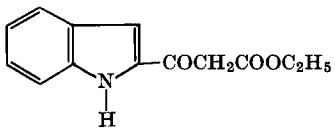


(**243**)

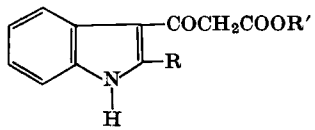
logous manner by the action of ethoxalyl chloride on the relevant indole Grignard reagent in ether.[116] In the case of the 2-methylindolyl derivative some doubt was expressed at that time about the structure of the product as it did not form a silver derivative.[116] The reaction between the indolyl magnesium halides and ethoxycarbonylacetyl chloride has been studied by several workers. Majima *et al.* reported that ethyl β-(3-indolyl)-β-oxopropionate (**246**) [which gave 3-acetylindole (**109**) on alkaline hydrolysis] was readily formed in the cold.[107] Oddo and Albanese confirmed the earlier reports of the Japanese workers that the ester **246** was the main product formed by this interaction, but under the more vigorous reaction conditions employed by the Italian workers a small quantity of a second product, possibly the isomeric 2-indolyl derivative (i.e., **247**) was also formed.[116] Albanese later described the synthesis of the analogous compound derived from 2-methylindole (i.e., **248**) by a similar procedure.[117]

[115] J. W. Baker, *J. Chem. Soc.* p. 458 (1940).
[116] B. Oddo and A. Albanese, *Gazz. Chim. Ital.* **57**, 827 (1927); *Chem. Abstr.* **22**, 1775 (1928).
[117] A. Albanese, *Gazz. Chim. Ital.* **60**, 21 (1930); *Chem. Abstr.* **24**, 4029 (1930).

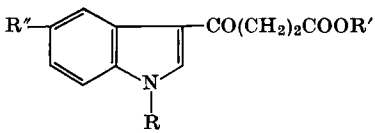
More recently Baker reported that indole magnesium bromide reacts readily in the cold with both methoxycarbonylacetyl chloride and ethoxycarbonylacetyl chloride. In the former case the main product was methyl β-(3-indolyl)-β-oxopropionate (**249**), accompanied by a small quantity of an unidentified substance $(C_{10}H_9ON)_x$; the ethyl ester **246** was the major product in the latter case.[66]



(**247**)



(**246**) R = H; R′ = C_2H_5
(**248**) R = CH_3; R′ = C_2H_5
(**249**) R = H; R′ = CH_3



(**250**) R = R″ = H; R′ = C_2H_5
(**251**) R = R″ = H; R′ = CH_3
(**252**) R = H; R′ = CH_3; R″ = OCH_3
(**253**) R = H; R′ = CH_3; R″ = Br
(**254**) R = R′ = R″ = H
(**255**) R = CH_3; R′ = R″ = H
(**256**) R = R′ = CH_3; R″ = H

Majima *et al.* prepared ethyl γ-(3-indolyl)-γ-oxobutyrate (**250**) in a similar manner by the condensation of the indole Grignard reagent with β-ethoxycarbonylpropionyl chloride.[107] Methyl γ-(3-indolyl)-γ-oxobutyrate (**251**) has been obtained by the action of β-methoxycarbonylpropionyl chloride on indole magnesium iodide in ether.[118,119] Ballantine *et al.* prepared methyl γ-(5-methoxy-3-indolyl)-γ-oxobutyrate **252**[118] and Julia *et al.* obtained methyl γ-(5-bromo-3-indolyl)-γ-oxobutyrate (**253**)[120] by analogous procedures.

In 1966 Eraksina *et al.* obtained γ-(3-indolyl)-γ-oxobutyric acid (**254**) (cf. Section III,E,4,d) on alkaline hydrolysis of the ester **251**,

[118] J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.* p. 2227 (1957).
[119] A. H. Jackson and P. Smith, *Chem. Commun.* p. 264 (1967).
[120] M. Julia, F. LeGoffic, J. Igolen, and M. Baillarge, *Compt. Rend.* **264**, 118 (1967).

prepared by the action of β-methoxycarbonylpropionyl chloride on indole in ether in the presence of anhydrous magnesium bromide at −10°.[121] This interesting reaction is probably mechanistically more similar to the Friedel–Crafts reaction than to a typical indole Grignard reaction. The 1-methyl derivative of the oxoacid **254** (i.e., **255**) was also obtained from the corresponding oxoester **256**, which was prepared analogously from 1-methylindole (**3**).[121]

b. *Diacid Chlorides.* In the early 1920's Oddo and Sanna reported that a number of different products were produced by the action of oxalyl chloride on indole magnesium bromide.[122,123] The various compounds were formulated largely on the basis of the structures of their oxidation and hydrolysis products and on their ability or otherwise to form silver derivatives. Oddo and Sanna[122] initially reported the formation of bis(1,3-dicarbonylindol-1,3-diyl) (**257**), di(3-indolyl)-glyoxal (**258**), and di(1-indolyl)glyoxal (**259**).[124] The product **257** was reported to give **258** and **259** on alkaline hydrolysis. Indole-3-carboxylic acid was obtained on alkaline hydrolysis of the product described as di(3-indolyl)glyoxal (**258**); however, in the case of the isomeric glyoxal derivative **259**, indole-1-carboxylic acid was not isolated, but the hydrolysis products exhibited an odor of indole (**1**).[122] The following year Sanna claimed that, in addition to an unidentified compound (m.p., 163°) and the products described above, di(2-indolyl)glyoxal (**260**), bis(1,2-dicarbonylindol-1,2-diyl) (**261**), and 1-(3-indolylglyoxalyl)indole (**243**) were formed during the course of this reaction.[123]

Majima and Shigematsu later questioned the validity of some of the above structural assignments and claimed that the product described as di(1-indolyl)glyoxal (**259**) is actually 1-(3-indolylglyoxalyl)indole (**243**) since it gives **1** and 3-indolylglyoxalic acid (**262**) on alkaline hydrolysis.[96] The Japanese workers obtained di(1-indolyl)glyoxal (**259**) by the action of diethyl oxalate on the indole Grignard reagent

[121] V. N. Eraksina, A. N. Kost, T. S. Khazonava, and E. V. Vinogradova, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 1966 p. 226; *Chem. Abstr.* **65**, 2201 (1966).

[122] B. Oddo and G. Sanna, *Gazz. Chim. Ital.* **51**, 337 (1921); *Chem. Abstr.* **16**, 1423 (1922).

[123] G. Sanna, *Gazz. Chim. Ital.* **52**, 165 (1922); *Chem. Abstr.* **17**, 1639 (1923).

[124] These products were originally named "indil" derivatives, since they are structurally analogous to the better known compound "benzil" ($C_6H_5COCOC_6H_5$) and its derivatives.

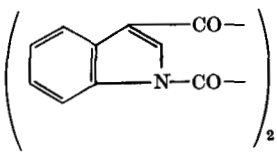
(see Section III,C,4,c) and they further claimed that the compound described as di(1-indolyl)glyoxal (**259**) by Oddo and Sanna[122] is, in fact, the isomeric di(2-indolyl)glyoxal (**260**).[96] In 1958 Millich and Becker[125] confirmed the finding of Majima and Shigematsu,[96] that the product described by Oddo and Sanna[122,123] as di(2-indolyl)-glyoxal (**260**) was, in fact, di(3-indolyl)glyoxal (**258**). Millich and Becker reported that the compound described by the Italian authors was identical to a sample of **258** prepared by the action of 3-indolylglyoxalyl chloride on indole magnesium bromide at room temperature.[125]

The related compounds bis(2-methyl-3-indolyl)glyoxal (**263**)[122,125] and bis(3-methyl-1-indolyl)glyoxal (**264**)[125] have been prepared by the action of oxalyl chloride on the Grignard reagents derived from 2-methylindole and 3-methylindole, respectively, Bis(1-methyl-3-indolyl)-glyoxal (**265**) was prepared by the action of oxalyl chloride on 1-methylindole in ether.[125]

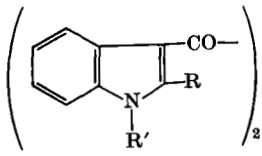
Sanna reported that 1,3-di(3-indolyl)-1,3-dioxo-*n*-propane (**266**) and 1,4-di(3-indolyl)-1,4-dioxo-*n*-butane (**267**) were formed by the action of malonyl chloride and succinyl chloride, respectively, on the indole Grignard reagent in ether, and analogous products could be obtained from 2-methylindole.[126–128]

c. *Diesters.* Majima and Shigematsu observed that three products, namely di(1-indolyl)glyoxal (**259**), 1-(3-indolylglyoxalyl)indole (**243**), and ethyl 3-indolylglyoxalate (**244**), identified by their behavior on alkaline hydrolysis, were obtained by the action of diethyl oxalate on indole magnesium iodide in anisole. No identifiable products were isolated when the reaction was carried out with diethyl malonate instead of diethyl oxalate; however, a product described as 1,4-di(1-indolyl)-1,4-dioxo-*n*-butane (**268**) was isolated from the products obtained by the action of diethyl succinate on the indole Grignard reagent.[96] Several years later Hishida repeated this work using dimethyl oxalate instead of diethyl oxalate and ether as solvent in place of anisole.[65] With a reaction time of 30 minutes the main products were di(1-indolyl)glyoxal (**259**) and 1-(3-indolylglyoxalyl)-indole (**243**), in approximately equal amounts. However, when the

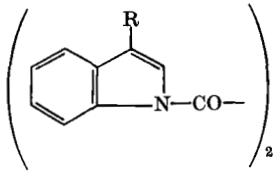
[125] F. Millich and E. I. Becker, *J. Org. Chem.* **23**, 1096 (1958).
[126] G. Sanna, *Gazz. Chim. Ital.* **52**, 170 (1922); *Chem. Abstr.* **17**, 1639 (1923).
[127] G. Sanna, *Gazz. Chim. Ital.* **52**, 177 (1922); *Chem. Abstr.* **17**, 1639 (1923).
[128] G. Sanna, *Gazz. Chim. Ital.* **53**, 177 (1923); *Chem. Abstr.* **17**, 2883 (1923).



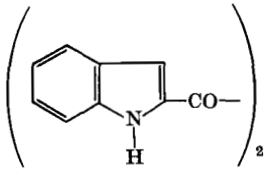
(257)



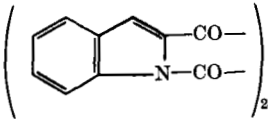
(258) R = R′ = H
(263) R = CH_3; R′ = H
(265) R = H; R′ = CH_3



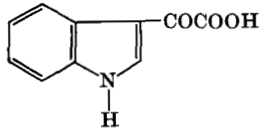
(259) R = H
(264) R = CH_3



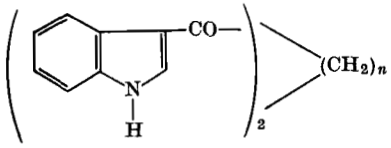
(260)



(261)



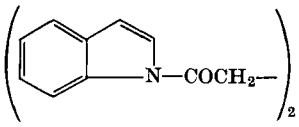
(262)



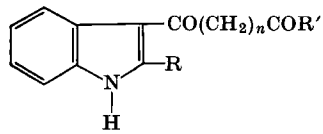
(266) $n = 1$ (267) $n = 2$
(269) $n = 4$ (270) $n = 8$

reaction was carried out for 11 hours, the major product formed was di(3-indolyl)glyoxal (**258**); small quantities of **243** being obtained as a by-product.[65]

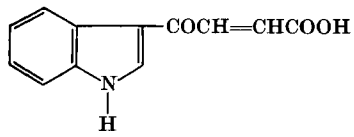
Hishida was unable to obtain any identifiable products when he attempted to extend this work to include the monoesters of several aliphatic dibasic acids. However, definite products (**269** and **270**) were obtained using diethyl adipate and diethyl sebacate, respectively. A second product containing only one indole residue (**271**) was also obtained in the latter case.[65]



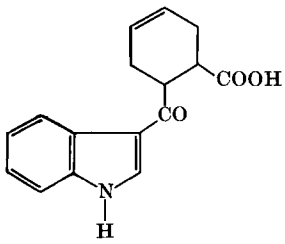
(268)



(271) R = H; R′ = OC_2H_5; $n = 8$
(272) R = CH_3; R′ = OH; $n = 2$
(273) R = C_6H_5; R′ = OH; $n = 2$
(274) R = H; R′ = OH; $n = 3$
(278) R = H; R′ = $NHCH_3$; $n = 2$



(275)



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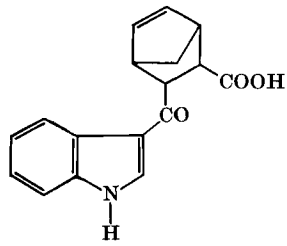


(277)

d. *Anhydrides.* γ-(3-Indolyl)-γ-oxobutyric acid (**254**) has been obtained by the action of succinic anhydride on indole magnesium halides in anisole.[129] The preparation of γ-(2-methyl-3-indolyl)-γ-oxobutyric acid (**272**) and the corresponding 2-phenylindolyl derivative **273** by analogous procedures has been described recently.

Kost *et al.* studied the interaction of indole magnesium iodide with a number of cyclic anhydrides of dibasic organic acids.[130] In addition to **254** the following 3-indolyloxo acids were prepared in this manner; δ-(3-indolyl)-δ-oxovaleric acid (**274**), γ-(3-indolyl)-γ-oxocrotonic acid

[129] A. P. Terent'ev, N. A. Dzbanovskii, and E. M. Urinovich, USSR Patent No. 119,189 (1959); *Chem. Abstr.* **54**, 2358 (1960).

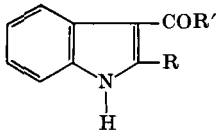
[130] A. N. Kost, V. N. Mitropol'skaya, S. L. Portnova, and V. A. Krasnova, *Zh. Obshch. Khim.* **34**, 2989 (1964); *Chem. Abstr.* **62**, 11761 (1965).

(**275**), *cis*-1-carboxy-2-(3-indolylcarbonyl)cyclohex-4-ene (**276**), and *cis*-2-carboxy-3-(3-indolylcarbonyl)norborn-5-ene (**277**).[130]

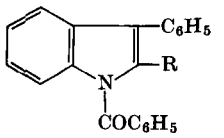
e. *Imides.* γ-(3-Indolyl)-*N*-methyl-γ-oxo-*n*-butyramide (**278**) was obtained when indole magnesium iodide was treated with *N*-methylsuccinimide in benzene.[131]

5. *Aromatic Monocarboxylic Acids*

a. *Acid Chlorides.* Oddo reported that 3-benzoylindole (**279**) was the main product obtained by the reaction of indole magnesium iodide



(**279**) R = H; R′ = C_6H_5
(**280**) R = CH_3; R′ = C_6H_5
(**281**) R = CH_3; R′ = 4-$CH_3C_6H_4$
(**282**) R = CH_3; R′ = 4-$C_2H_5C_6H_4$
(**283**) R = CH_3; R′ = α-naphthyl
(**284**) R = CH_3; R′ = β-naphthyl
(**285**) R = CH_3; R′ = 4-$CH_3OC_6H_4$



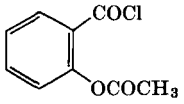
(**286**) R = CH_3
(**287**) R = $CH_2C_6H_5$

with benzoyl chloride.[2,69] More recently Buu-Hoï *et al.* have shown that a large number of simple 3-aroylindoles (i.e., **280–285**) can be readily obtained by the action of aroyl chlorides on indole magnesium bromide in ether.[86,132] Bruce and Sutcliffe obtained 1-benzoyl-2-methyl-3-phenylindole (**286**) and 1-benzoyl-2-benzyl-3-phenylindole (**287**) from the relevant indole Grignard reagents and benzoyl chloride.[72]

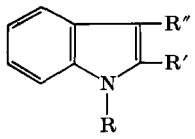
The action of *O*-acetylsalicyloyl chloride (**288**) on the simple indole

[131] Upjohn Co., Netherlands Patent Appl. 6,505,983, Nov. 12, 1965 [U.S. Patent Appl., May 11, 1964]; *Chem. Abstr.* **64**, 12646 (1966).
[132] N. P. Buu-Hoï, N. Hoán, and N. H. Khoi, *J. Org. Chem.* **15**, 131 (1950).

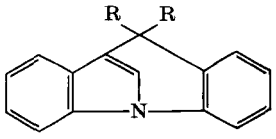
Grignard reagents was studied by Toffoli.[133,134] Two moles of 2-methylindole magnesium bromide and 1 mole of **288** gave mainly



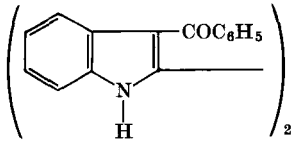
(**288**)



(**289**) R = H; R′ = CH_3; R″ = 2-HOC_6H_4CO
(**290**) R = R′ = H; R″ = 2-HOC_6H_4CO
(**291**) R = R″ = H; R′ = 2-HOC_6H_4CO
(**293**) R = 2-HOC_6H_4CO; R′ = H; R″ = CH_3
(**294**) R = H; R′ = 2-HOC_6H_4CO; R″ = CH_3



(**292**) R = 3-indolyl



(**295**)

2-methyl-3-salicyloylindole (**289**), together with lesser amounts of 3-acetyl-2-methylindole (**116**) and some unidentified by-products.[133,134] In the case where reaction occurred with 2 moles of the indole Grignard reagent the main products obtained were 3-salicyloylindole (**290**) and 3-acetylindole (**109**); smaller quantities of products described as 2-salicyloylindole (**291**) and a substance for which the unlikely structure **292** was proposed were also obtained.[134] Lower yields of the same products were obtained when equivalent quantities of the two reagents were allowed to react.[133,134] In the case of the skatole Grignard reagent the products obtained under analogous circumstances were 1-salicyloylskatole (**293**), 1-acetylskatole (**118**), and 2-salicyloylskatole (**294**).[134]

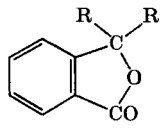
3,3′-Dibenzoyl-2,2′-biindole (**295**) was obtained by the action of benzoyl chloride on the 2,2′-biindole Grignard reagent.[75]

6. *Aromatic Dicarboxylic Acids*

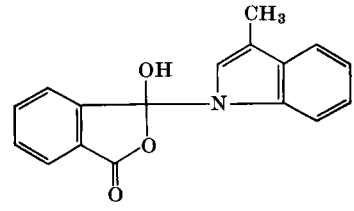
a. *Diacid Chlorides.* The only reactions reported so far between dibasic aromatic acid chlorides and indole Grignard reagents were des-

[133] C. Toffoli, *Gazz. Chim. Ital.* **64**, 364 (1934); *Chem. Abstr.* **28**, 6437 (1934).
[134] C. Toffoli, *Gazz. Chim. Ital.* **65**, 487 (1935); *Chem. Abstr.* **30**, 455 (1936).

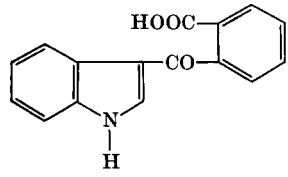
cribed by Oddo over 30 years ago.[135–137] 2-Methylindole magnesium bromide reacts with phthaloyl chloride to give "methylketolphthalein" (**296**) as the main product.[135, 136] An isomeric product, possibly derived from the isomeric (i.e., symmetrical) form of phthaloyl chloride, was formed at the same time.[135, 136] "Indolephthaleine" (**297**) was similarly obtained by the action of phthaloyl chloride on the indole Grignard reagent.[137] This product was possibly accompanied by some



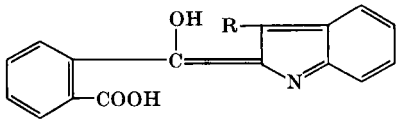
(**296**) R = 2-methyl-3-indolyl
(**297**) R = 3-indolyl
(**298**) R = 3-methyl-2-indolyl
(**299**) R = 3-methyl-1-indolyl



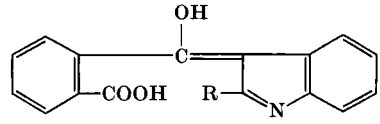
(**305**)



(**300**)



(**301**) R = H
(**304**) R = CH_3



(**302**) R = H
(**303**) R = CH_3

of the dehydrated uncyclized form[137] (cf. Sumpter and Miller[8]). The interaction of the skatole Grignard reagent (2 moles) with phthaloyl chloride gave both **298** and **299**.[138]

[135] B. Oddo, *Atti Accad. Nazl. Lincei Mem. Classe Sci. Fis. Mat, Nat.* **1**[VI], 236 (1925); *Chem. Abstr.* **19**, 2823 (1925).

[136] B. Oddo, *Gazz. Chim. Ital.* **56**, 437 (1926); *Chem. Abstr.* **21**, 241 (1927).

[137] B. Oddo, *Gazz. Chim. Ital.* **58**, 569 (1928); *Chem. Abstr.* **23**, 1634 (1929).

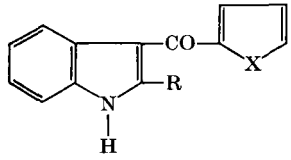
[138] B. Oddo and C. Toffoli, *Gazz. Chim. Ital.* **60**, 3 (1930); *Chem. Abstr.* **24**, 3784 (1930).

b. *Anhydrides.* Kost *et al.* recently reported that 2-(3-indolylcarbonyl)benzoic acid (**300**) (m.p. 196°) was obtained by the action of phthalic anhydride on indole magnesium iodide at 100°.[130] Many years previously Oddo and Toffoli had reported that two compounds, described as 2-carboxyphenyl-(2-indoleninylidene)methanol (**301**) (m.p. 155.5°) and the corresponding 3-indoleninylidene derivative (**302**) (179.5°), were obtained by the action of phthalic anhydride on the indole Grignard reagent.[138] In fact, **302** is merely a tautomeric form of **300**. The structures of these latter two compounds were not rigorously proved by the Italian workers and it is possible that the products **301** and **302** were, in fact, merely somewhat impure versions of **300**.

2-Carboxyphenyl-(2-methyl-3-indoleninylidene)methanol (**303**) was said to be formed by the action of phthalic anhydride on 2-methylindole magnesium bromide.[139] Skatole magnesium bromide, on the other hand, apparently gave 2-carboxyphenyl-(3-methyl-2-indoleninylidene)methanol (**304**) and 3-hydroxy-3-(3-methyl-1-indolyl)-phthalide (**305**) on treatment with 1 mole of phthalic anhydride. The derivative **305** was easily hydrolyzed in alkali, giving skatole and phthalic acid, and was thus formulated as a 1-skatolyl derivative.[138]

7. *Heterocyclic Acids*

a. *Acid Chlorides.* Buu-Hoï *et al.* prepared 3-(2-furoyl)-2-methylindole (**306**) and 2-methyl-3-(2-theonyl)indole (**307**) by the action of



(**306**) R = CH_3; X = O
(**307**) R = CH_3; X = S
(**308**) R = H; X = O

the acid chlorides derived from furan-2-carboxylic acid and thiophene-2-carboxylic acid, respectively, on 2-methylindole magnesium bromide in ether.[86]

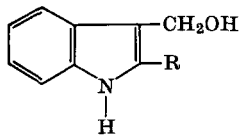
b. *Esters.* 3-(2-Furoyl)indole (**308**) was prepared by the action of 2-ethoxycarbonylfuran on indole magnesium bromide in ether.[65]

[139] B. Oddo and L. Perotti, *Gazz. Chim. Ital.* **56**, 442 (1926); *Chem. Abstr.* **21**, 242 (1927).

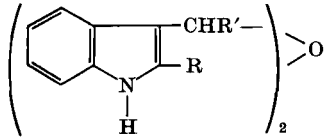
D. Reactions with Carbonyl Compounds

1. *Aldehydes*

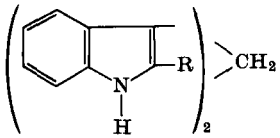
a. *Aliphatic.* Mingoia obtained two products by the action of formaldehyde on the indole Grignard reagent. One of the products had a melting point of 158° and was described as being 3-indolylmethanol (**309**); the second product, which did not melt, was considered to be



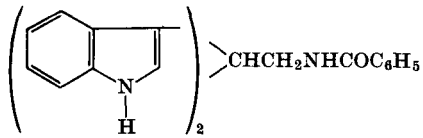
(**309**) R = H
(**312**) R = CH_3



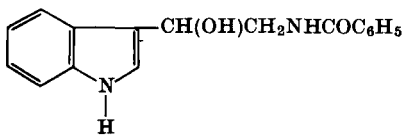
(**310**) R = R′ = H
(**313**) R = H; R′ = CH_3
(**314**) R = R′ = CH_3



(**311**) R = H
(**315**) R = CH_3



(**316**)



(**317**)

bis(3-indolylmethyl) ether (**310**).[140] This author also reported that the analogous 2-methylindolyl compounds were obtained by the action of formaldehyde on 2-methylindole magnesium bromide.[140] In 1953 Leete and Marion reported that repetition of Mingoia's procedure for the preparation of **309** merely gave a glassy solid with an indefinite high melting point.[100] The melting point of an authentic sample of **309**, prepared by an unambiguous route, was 99°–100°.[100] The product (m.p. 158°) obtained by Mingoia was probably di(3-indolyl)methane (**311**) (cf. Bader and Oroshnik,[141] Leete,[142] and

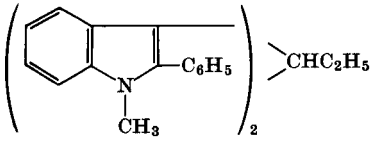
[140] Q. Mingoia, *Gazz. Chim. Ital.* **62**, 844 (1932); *Chem. Abstr.* **27**, 503 (1933).
[141] H. Bader and W. Oroshnik, *J. Am. Chem. Soc.* **81**, 163 (1959).
[142] E. Leete, *J. Am. Chem. Soc.* **81**, 6023 (1959).

Thesing[143]). The melting point (205°–206°) reported [140] for 2-methyl-3-indolylmethanol (**312**) is also higher than would have been expected.

Oddo and Cambieri reported that the interaction of equimolecular quantities of acetaldehyde and indole magnesium bromide and 2-methylindole magnesium bromide, respectively, under fairly vigorous reaction conditions, gave products which did not melt, but which decomposed above 300°, and which were described as bis[1-(3-indolyl)ethyl] ether (**313**) and bis[1-(2-methyl-3-indolyl)ethyl] ether (**314**), respectively.[144] Earlier Oddo and Toffoli had obtained di(3-indolyl)methane (**311**) and bis(2-methyl-3-indolyl)methane (**315**) by the action of 2 moles of the relevant indole Grignard reagents on 1 mole of acetaldehyde.[145] Apart from the different molecular ratios employed, the reaction conditions used (i.e., 1–2 hours under reflux in ether) were considerably milder than those subsequently used by Oddo and Cambieri (i.e., 10 hours at 100°–120°).[144]

In 1956 Ames *et al.* reported that a low yield of 1-benzamido-2,2-di-(3-indolyl)ethane (**316**) was obtained in an attempt to prepare 3-(2-benzamido-1-hydroxyethyl)indole (**317**) by the action of benzamidoacetaldehyde on indole magnesium iodide in ether.[81]

Buchmann and Trautmann reported recently that 1,1-bis(1-methyl-2-phenyl-3-indolyl)propane (**318**) was obtained by the action of propionaldehyde on the Grignard reagent derived from 1-methyl-2-phenylindole.[146] It is implied that a Grignard reagent is formed from the *N*-methylindole derivative in the usual manner. However, fairly vigorous reaction conditions were subsequently employed for interaction with the aldehyde (100°; 6 hours),[146] and the possibility that unchanged 1-methyl-2-phenylindole was the true reacting species, with the magnesium halide merely acting as a catalyst, cannot be excluded.



(**318**)

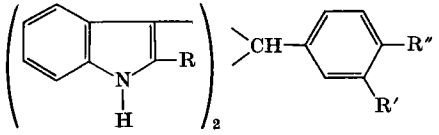
[143] J. Thesing, *Chem. Ber.* **87**, 692 (1954).

[144] B. Oddo and F. Cambieri, *Gazz. Chim. Ital.* **70**, 559 (1940); *Chem. Abstr.* **35**, 1050 (1941).

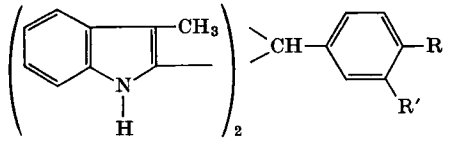
[145] B. Oddo and C. Toffoli, *Gazz. Chim. Ital.* **64**, 359 (1934); *Chem. Abstr.* **28**, 6436 (1934).

[146] G. Buchmann and P. Trautmann, *J. Prakt. Chem., Ser.* 4, **32**, 1 (1966).

b. *Aromatic.* Majima and Kotake obtained di(3-indolyl)phenylmethane (**319**) by the action of benzaldehyde on indole magnesium iodide[11]; later Mingoia reported the ready formation of a number of di(3-indolyl)phenylmethane derivatives by the interaction of several different aromatic aldehydes with the Grignard reagents derived from indole, 2-methylindole, and skatole.[147] The products (i.e., **320** and **321**) obtained from indole and from 2-methylindole (i.e., **322**, **323**, **324**, and **325**) were di(3-indolyl)phenylmethane derivatives, whereas the products derived initially from skatole were described as di(2-indolyl)phenylmethane derivatives (i.e., **326** and **327**).[147]



(**319**) R = R′ = R″ = H
(**320**) R = H; R′ = OH; R″ = OCH_3
(**321**) R = H; R′ + R″ = CH_2O_2
(**322**) R = CH_3; R′ = R″ = H
(**323**) R = CH_3; R′ = OH; R″ = OCH_3
(**324**) R = CH_3; R′ + R″ = CH_2O_2
(**325**) R = CH_3; R′ = H; R″ = NO_2



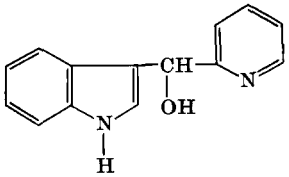
(**326**) R + R′ = CH_2O_2
(**327**) R = H; R′ = NO_2

Recent work by Powers has suggested that in addition to the di-indolylphenylmethane derivatives, 3-aroylindoles are obtained by the action of aromatic aldehydes on the indole Grignard reagents.[148]

c. *Heterocyclic.* The reactions between indole magnesium bromide and several different heterocyclic aldehydes have been studied recently by Bader and Oroshnik.[141] Indole magnesium bromide reacts with 2-pyridinecarboxaldehyde at $-25°$ in an ether–methylene dichloride mixture to give a 50% yield of 3-indolyl-2′-pyridylmethanol (**328**) together with a 5% yield of di(3-indolyl)-2-pyridylmethane (**329**).[141] However, when the reaction was carried out in the same solvent at 0°

[147] Q. Mingoia, *Gazz. Chim. Ital.* **56**, 772 (1926); *Chem. Abstr.* **21**, 1117 (1927).
[148] J. C. Powers, personal communication, 1967.

the yield of **328** dropped to 25%, whereas that of **329** increased to 44%.[141] The reaction with 4-pyridinecarboxaldehyde followed a somewhat similar course. At 0°, in the same solvent, 3-indolyl-4'-pyridylmethanol (**330**) was obtained in 58% yield.[141] However, at 25° with only ether as solvent the yield of **330** dropped to 22%, whilst at 60° the yield of **330** was further reduced to 6.5%.[141] In the higher



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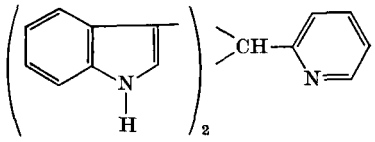

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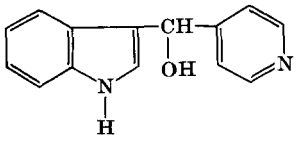

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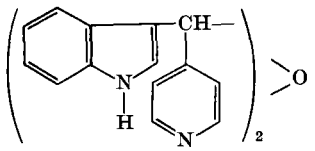

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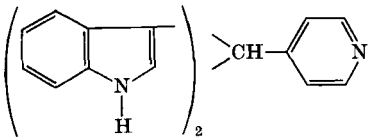

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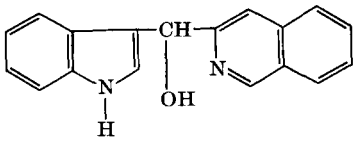

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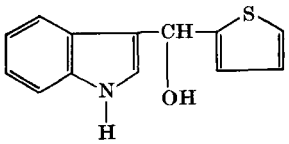

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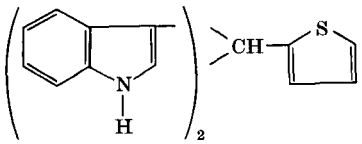


(335)

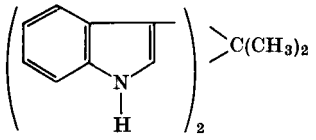
temperature reaction significant quantities of bis(3-indolyl-4'-pyridylmethyl)ether (**331**) (16%) and di(3-indolyl)-4'-pyridylmethane (**332**) (13%) were also obtained.[141]

3-Indolyl-3'-isoquinolylmethanol (**333**) (22%) and a small quantity of an unidentified by-product were formed by the action of 3-isoquinolinecarboxaldehyde on indole magnesium iodide in ether–methylene chloride at room temperature.[141] The expected methanol

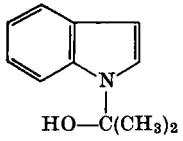
derivative **334** was not produced by the action of 2-thiophenecarboxaldehyde on indole magnesium iodide; however, a 28% yield of di(3-indolyl)-2-thienylmethane (**335**) was obtained.[141]

2. *Ketones*

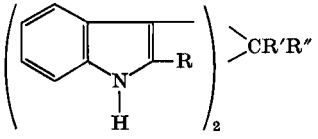
Majima and Kotake prepared 2,2-di(3-indolyl)propane (**336**) by the action of acetone on indole magnesium iodide in ether or anisole.[11] Recently 1-indolyl derivatives have been obtained as primary products by interaction of ketones with indole Grignard reagents[149]; for example acetone gave a 75% yield of 2-(1-indolyl)propan-2-ol (**337**).[149]



(**336**)



(**337**)



(**338**) R = R″ = CH_3
(**339**) R = R′ = CH_3; R″ = C_6H_5
(**340**) R = CH_3; R′ = R″ = C_3H_7
(**341**) R = R′ = CH_3; R″ = p-$CH_3C_6H_4$

Hoshino suggests that the isolation procedure used by Majima and Kotake[11] caused the decomposition of **337** into indole, acetone, and the diindolylpropane derivative **336**.[149]

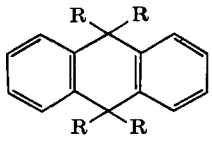
A number of diindolylmethane derivatives including **336**, **338**, **339**, **340**, and **341** have been obtained by the action of the appropriate ketones, under fairly vigorous conditions, on the Grignard reagents derived from indole or 2-methylindole.[150]

3. *Quinones and α-Diketones*

a. *Anthraquinone and Phenanthraquinone.* There are no reports in the literature concerning reactions of indole Grignard reagents with

[149] T. Hoshino, *Chem. Ber.* **85**, 858 (1952).
[150] B. Oddo and L. Perotti, *Gazz. Chim. Ital.* **60**, 13 (1930); *Chem. Abstr.* **24**, 3785 (1930).

simple quinones. However, the reactions of 2-methylindole magnesium bromide with two polycyclic quinones were studied about 40 years ago. 9,9,10,10-Tetrakis(2-methyl-3-indolyl)-9,10-dihydroanthracene



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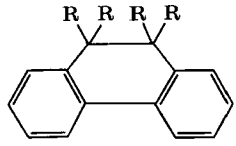
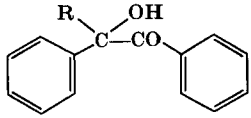
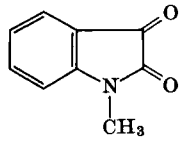


(343)

R = 3-indolyl



(344) R = 3-indolyl
(345) R = 3-methyl-2-indolyl



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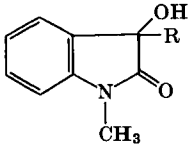
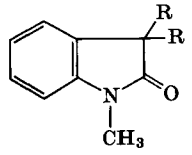


(347) R = 3-indolyl
(349) R = 2-methyl-3-indolyl
(350) R = 3-methyl-2-indolyl



(348) R = 3-indolyl

(342) and 9,9,10,10-tetrakis(2-methyl-3-indolyl)-9,10-dihydrophenanthrene (343) were obtained from anthraquinone and phenanthraquinone, respectively.[151,152]

b. *Benzil and N-Methylisatin.* Benzil reacts with the indole Grignard reagent in ether at room temperature to give α-(3-indolyl)-benzoin (344). The skatole Grignard reagent reacted in an analogous manner to give 345.[153] *N*-Methylisatin (346) reacts with indole magnesium iodide in benzene–ether to give a mixture of 1-methyl-3-(3-indolyl)dioxindole (347) and 1-methyl-3,3-di(3-indolyl)oxindole (348). The dioxindole derivatives 349 and 350 were obtained analogously.[153]

[151] Q. Mingoia, *Gazz. Chim. Ital.* **56**, 446 (1926); *Chem. Abstr.* **21**, 242 (1927).
[152] Q. Mingoia, *Gazz. Chim. Ital.* **58**, 673 (1928); *Chem. Abstr.* **23**, 3465 (1929).
[153] W. Steinkopf and H. Wilhelm, *Ann. Chem.* **546**, 211 (1941).

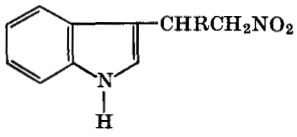
E. Reactions with Nitro Compounds

1. *Aromatic*

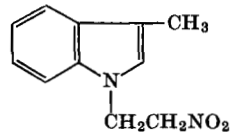
A crystalline addition product of indole with picryl chloride (i.e. 1-chloro-2,4,6-trinitrobenzene), together with an unidentified amorphous substance, were obtained by the action of picryl chloride on indole magnesium iodide, and analogous products were obtained in the reaction between the indole Grignard reagent and 1-chloro-2,4,5-trinitrobenzene.[154]

2. *Aliphatic*[155]

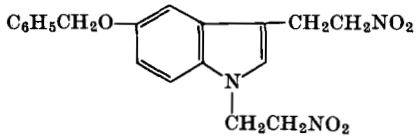
Indole magnesium iodide reacts with nitroethylene to give 3-(2-nitroethyl)indole (**351**) in good yield (Noland and Hartman[156]). Noland *et al.* subsequently showed that this reaction, which is usually carried out in ether at 0°, was of general applicability and reported



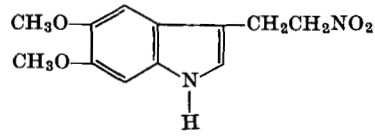
(**351**) R = H
(**352**) R = CH_3
(**353**) R = C_6H_5



(**354**)



(**355**)



(**356**)

that fairly good yields of 3-(1-methyl-2-nitroethyl)indole (**352**) and 3-(1-phenyl-2-nitroethyl)indole (**353**) were formed by the interaction of indole magnesium iodide and 1-nitroprop-1-ene and β-nitrostyrene, respectively.[157]

[154] M. Giua and G. Racciu, *Atti Accad. Sci. Torino, Classe Sci. Fis. Mat. Nat.* **67**, 121 (1932); *Chem. Abstr.* **26**, 5568 (1932).

[155] The reaction of ethyl nitrate with the indole Grignard reagent is discussed in Section III, F, 5, a (miscellaneous organic compounds).

[156] W. E. Noland and P. J. Hartman, *J. Am. Chem. Soc.* **76**, 3227 (1954).

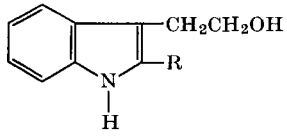
[157] W. E. Noland, G. M. Christensen, G. L. Sauer, and G. G. S. Dutton, *J. Am. Chem. Soc.* **77**, 456 (1955).

In 1961 Acheson and Hands obtained 3-methyl-1-(2-nitroethyl)-indole (**354**) in low yield by the addition of nitroethylene to 3-methylindole magnesium iodide.[158] These authors also obtained 5-benzyloxy-1,3-bis(2-nitroethyl)indole (**355**) and 5,6-dimethoxy-3-(2-nitroethyl)-indole (**356**) by the action of nitroethylene on 5-benzyloxy- and 5,6-dimethoxyindole magnesium iodide, respectively. They excluded the possibility that the products **354**, **355**, and **356** had the isomeric indolenine structures on the basis of their absorption spectra and chemical properties.[158]

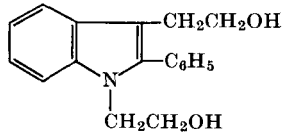
F. Reactions with Miscellaneous Organic Compounds

1. *Oxiranes*

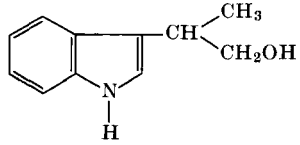
a. *Ethylene Oxide.* Tryptophol (**357**) has been obtained by the action of ethylene oxide on the indole Grignard reagent—first by Oddo and Cambieri[159] and later by Snyder and Pilgrim.[160] The former authors reported that it was necessary to heat the reaction mixture to 100°, after removal of the solvent, in order to obtain the desired



(**357**) R = H
(**358**) R = CH_3



(**359**)



(**360**)

product. 2-Methyltryptophol (**358**) was prepared from 2-methylindole magnesium bromide in a similar manner.[159] In 1966 Buchmann and Trautmann similarly obtained 1,3-bis(2-hydroxyethyl)-2-phenylindole (**359**) from 2-phenylindole.[146]

[158] R. M. Acheson and A. R. Hands, *J. Chem. Soc.* p. 744 (1961).
[159] B. Oddo and F. Cambieri, *Gazz. Chim. Ital.* **69**, 19 (1939); *Chem. Abstr.* **33**, 4239 (1939).
[160] H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.* **70**, 1962 (1948).

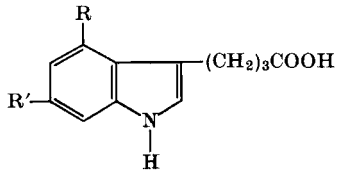
b. *Propylene Oxide.* Kalir and Szara have recently prepared 2-(3-indolyl)propan-1-ol (**360**) by the interaction of indole magnesium bromide with propylene oxide.[57]

2. *Aziridines*

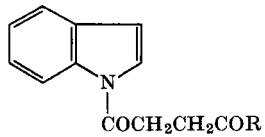
a. *Ethyleneimine.* Tryptamine (**23**) has recently been prepared by the action of ethyleneimine on indole magnesium bromide in boiling xylene.[161]

3. *Lactones*

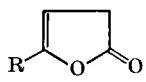
a. *Saturated.* γ-(3-Indolyl)-*n*-butyric acid (**361**) can be obtained by heating indole magnesium iodide with γ-butyrolactone.[162] Shagalov *et al.* have recently obtained γ-(4-chloro-3-indolyl)-*n*-butyric acid (**362**) and γ-(6-chloro-3-indolyl)-*n*-butyric acid (**363**) by analogous procedures.[163]



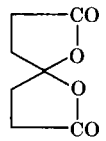
(**361**) R = R′ = H
(**362**) R = Cl; R′ = H
(**363**) R = H; R′ = Cl



(**364**) R = C_6H_5
(**366**) R = CH_3
(**368**) R = CH_2CH_2COOH



(**365**) R = C_6H_5
(**367**) R = CH_3



(**369**)

b. *Unsaturated.* In 1955 Katritzky and Robinson found 1-(β-benzoylpropionyl)indole (**364**) as the only identifiable product from

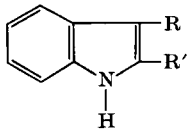
[161] R. Bucourt and M. Vignau, *Bull. Soc. Chim. France* p. 1190 (1961).
[162] F. N. Stepanov, USSR Patent No. 66,681 (1946); *Chem. Abstr.* **41**, 2087 (1947).
[163] L. B. Shagalov, N. P. Sorokina, and N. N. Suvorov, *Zh. Obshch. Khim.* **34**, 1592 (1964); *Chem. Abstr.* **61**, 5596 (1964).

the reaction between 4,5-dihydro-5-oxo-2-phenylfuran (**365**) and indole magnesium iodide.[164] The reaction was carried out under a wide variety of different experimental conditions and in all instances **364** was the major product obtained. 1-Laevuloylindole (**366**) was similarly obtained from α-angelicalactone (**367**). The products **364** and **366** were readily hydrolyzed by warm dilute alkali to indole and the corresponding acids; the absence of any N–H absorption bands in their infrared spectra confirmed that **364** and **366** were 1-indolyl derivatives.[164]

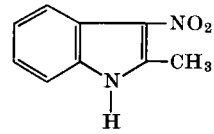
1-(6-Carboxy-4-oxohexanoyl)indole (**368**) was obtained analogously by the action of indole magnesium iodide on the dilactone (**369**) of γ-oxopimelic acid.[164]

4. *Peracids*

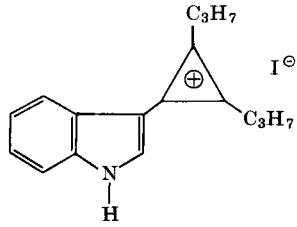
The oxidation of indole magnesium bromide and its 2- and 3-methyl derivatives at room temperature with *p*-nitroperbenzoic acid, in the absence of light and air, results in the formation of 3-bromoindole (**370**), 3-bromo-2-methylindole (**371**), and 2-bromo-3-methylindole (**372**), respectively.[165, 166]



(**370**) R = Br; R′ = H
(**371**) R = Br; R′ = CH_3
(**372**) R = CH_3; R′ = Br



(**374**)



(**373**)

[164] A. R. Katritzky and R. Robinson, *J. Chem. Soc.* p. 2481 (1955).
[165] M. Mousseron-Canet and J.-P. Boca, *Compt. Rend.* **260**, 2263 (1965).
[166] M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. Chim. France* p. 1294 (1967).

5. *Alkoxycyclopropenium Salts*

2-Aza-3,4-benzo-5,6-dipropylpentatriafulvalene hydriodide (**373**) was obtained in 20% yield by the action of 1,2-di-*n*-propyl-3-ethoxycyclopropenium fluoroborate on indole magnesium iodide in a methylene chloride–ether mixture.[167]

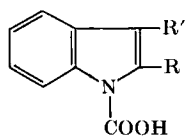
6. *Esters of Inorganic Acids*

a. *Ethyl Nitrate.* A compound described as 2-methyl-3-nitroindole (**374**) was said to be formed in low yield by the action of ethyl nitrate on 2-methylindole magnesium iodide.[4, 93, 94]

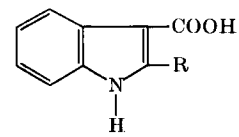
G. Reactions with Carbon Dioxide and Some Carbonic Acid Derivatives

1. *Carbon Dioxide*

Oddo and Sessa claimed that 1-carboxyindole (**375**) was obtained on treatment of indole magnesium iodide with gaseous carbon dioxide.[64] Majima and Kotake later reported that 3-carboxyindole (**376**) and not **375** was the main product obtained in this reaction[11]; improved yields of **376** were obtained when the reaction was carried out in anisole instead of ether.[11] Subsequently, several workers have employed essentially this procedure, for the synthesis of **376**.[108, 168, 169] It has recently been shown, however, that both the acids **375** and **376** are formed in approximately equal amounts by the carbonation of the indole Grignard reagent (Kašpárek and Heacock[170]).



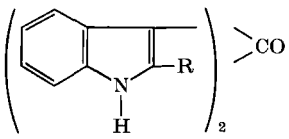
(**375**) R = R' = H
(**377**) R = CH_3; R' = H
(**379**) R = H; R' = CH_3



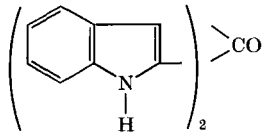
(**376**) R = H
(**378**) R = CH_3

[167] A. S. Kende, P. T. Izzo, and P. MacGregor, *J. Am. Chem. Soc.* **88**, 3359 (1966).
[168] M. S. Melzer, *J. Org. Chem.* **27**, 496 (1962).
[169] A. B. Durkee and J. C. Sirois, *J. Chromatog.* **13**, 173 (1964).
[170] S. Kašpárek and R. A. Heacock, *Can. J. Chem.* **45**, 771 (1967).

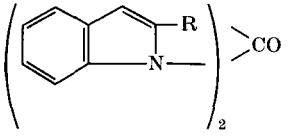
In 1912 Oddo reported the results of an investigation of the products obtained on carbonation of both the 2- and 3-methylindole Grignard reagents.[104] In the former case the relatively unstable 1-carboxy-2-methylindole (**377**) was the main product obtained when the reaction was carried out at temperatures up to 35°; however, at 110° the isomeric 3-carboxy-2-methylindole (**378**) was the major product formed. According to Oddo 1-carboxy-3-methylindole (**379**) is more stable than the corresponding 2-methyl compound (i.e., **377**) and can be obtained by carbonation of the skatole Grignard reagent at 100°.[104]



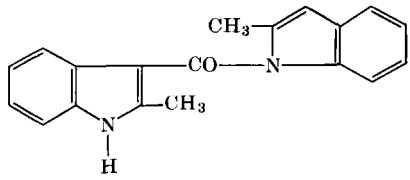
(**380**) R = H
(**383**) R = CH_3



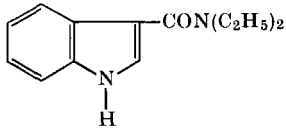
(**381**)



(**382**)



(**384**)



(**385**)

2. *Carbonyl Chloride*

The early literature on the reactions of the indole Grignard reagents with the simple diacid chlorides, in particular with carbonyl chloride and oxalyl chloride (see Section III, C, 4, b), is both conflicting and confusing and much of the work reported warrants repetition since the evidence presented in support of many of the structural assignments made is not entirely convincing.

Oddo and Mingoia reported that di(3-indolyl) ketone (**380**), di(2-indolyl) ketone (**381**), and di(1-indolyl) ketone (**382**) were obtained by

the action of carbonyl chloride on indole magnesium bromide in ether.[171] These authors also reported that carbonyl chloride reacts with the 2-methylindole Grignard reagent to form bis(2-methyl-3-indolyl) ketone (**383**) and 2-methyl-1-indolyl 2′-methyl-3′-indolyl ketone (**384**).[171]

3. *Diethylcarbamoyl Chloride*

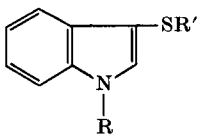
3-(*N*,*N*-Diethylcarbamoyl)indole (**385**) can be prepared by the action of diethylcarbamoyl chloride on indole magnesium iodide.[59]

For reactions with ethyl chloroformate see Section III, C, 2, b.

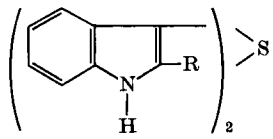
H. Reactions with Sulfur and Sulfur Compounds

1. *Elemental Sulfur and Inorganic Sulfur Compounds*

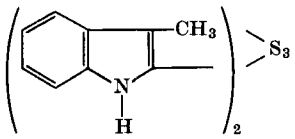
a. *Sulfur.* In an unsuccessful attempt to prepare thioindoxyl (**386**) by the interaction of indole magnesium bromide with sulfur at room temperature, Madelung and Tencer obtained a good yield of a diindolyl sulfide.[172] Although some of the chemical properties of this compound suggested it contained an —*N*—*S*—*N*— linkage, it was assumed that



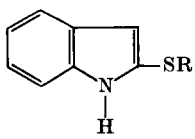
(**386**) R = R′ = H
(**390**) R = H; R′ = COC_6H_5
(**392**) R = R′ = $COCH_3$
(**393**) R = H; R′ = $COCH_3$
(**395**) R = $COCH_3$; R′ = 1-indolyl



(**387**) R = H
(**388**) R = CH_3



(**389**)



(**391**) R = COC_6H_5
(**394**) R = $COCH_3$

[171] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **57**, 473 (1927); *Chem. Abstr.* **22**, 77 (1928).

[172] W. Madelung and M. Tencer, *Ber. Deut. Chem. Ges.* **48**, 949 (1915).

the product was di(3-indolyl) sulfide (**387**) and not the isomeric di(1-indolyl) sulfide (cf. ref. 8, p. 53); this was later confirmed.[173] Bis(2-methyl-3-indolyl) sulfide (**388**) was obtained, in an analogous manner.[172] The interaction of sulfur with the skatole Grignard reagent follows a somewhat different course, giving, initially, bis(3-methyl-2-indolyl) trisulfide (**389**).[174]

3-*S*-Benzoylthioindole (**390**) and 2-*S*-benzoylthioindole (**391**) were obtained together with **387** when indole magnesium bromide was treated successively with sulfur and benzoyl chloride.[175] A similar reaction occurred when acetyl chloride was used in place of benzoyl chloride. In this case 1-acetyl-3-(*S*-acetylthio)indole (**392**) was isolated after further acetylation of the crude products. 3-*S*-Acetylthioindole (**393**) could be obtained by saponification of **392**.[175] With minor modifications in the working-up procedure 2-*S*-acetylthioindole (**394**) and a compound described as 1-acetyl-3-indolyl 1′-indolyl sulfide (**395**) were said to be obtained. A compound described as thioindoxyl (**386**) was obtained on hydrolysis of the acylthio derivatives **390** and **393**.[175] The melting point (235°) reported by Oddo and Mingoia for **386** is much higher than would have been expected for a compound of this type. More recently Grant and Snyder have pointed out that this figure is quite close to that which they and other workers have obtained for di(3-indolyl) disulfide (**396**) prepared by alternate routes.[176–178] Oddo and Mingoia further claimed that thiooxindole (**397**) was obtained on alkaline hydrolysis of the 2-*S*-acylthioindole derivatives **391** and **394**.[175] In this case the melting point reported is close to that obtained for a sample of **397** prepared by the action of phosphorus pentasulfide on oxindole.[179]

By the consecutive action of sulfur and acetyl chloride on the 2-methylindole Grignard reagent Oddo obtained a violet solid (m.p 311°–312°), described as 3-*S*-acetylthio-2-methylindole (**398**), together

[173] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **42**, 2626 (1964).

[174] B. Oddo and L. Raffa, *Gazz. Chim. Ital.* **71**, 242 (1941); *Chem. Abstr.* **36**, 2854 (1942).

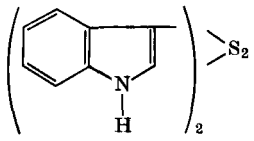
[175] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **62**, 299 (1932); *Chem. Abstr.* **26**, 4603 (1932).

[176] M. S. Grant and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2742 (1960).

[177] W. Carpenter, M. S. Grant, and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2739 (1960).

[178] R. G. Woodbridge and G. Dougherty, *J. Am. Chem. Soc.* **72**, 4320 (1950).

[179] S. Sugasawa, I. Satoda, and J. Yamagisawa, *Yakugaku Zasshi* **58**, 139 (1938); *Chem. Abstr.* **32**, 4161 (1938).



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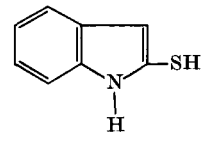

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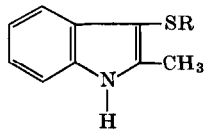
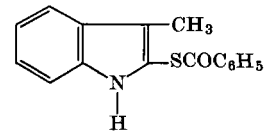
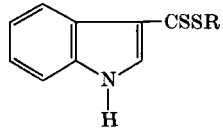


(398) R = $COCH_3$
(399) R = COC_6H_5

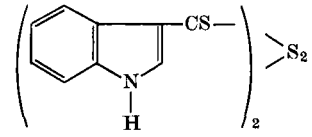


(400)

with some 3-acetyl-2-methylindole (**116**). [The product **116** was probably obtained by the interaction of some unchanged Grignard reagent with acetyl chloride (see Section III,C,1,a)]. The very high melting point and color reported[174] for **398** must throw some doubt on the structure assigned to this compound. Substances described as 3-*S*-benzoylthio-2-methylindole (**399**) and 2-*S*-benzoylthio-3-methylindole (**400**) were obtained in an analogous manner.[174] The reported



(401) R = H
(402) R = NH_4



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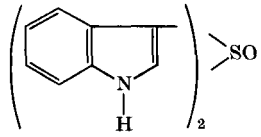

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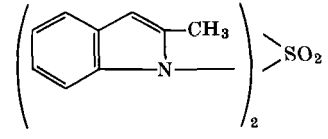

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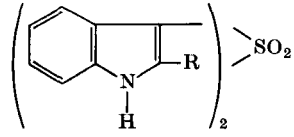


(406) R = H
(407) R = CH_3

melting points for **399** and **400** also seem not to be compatible with the structures originally assigned these compounds.

b. *Carbon Disulfide.* Oddo and Mingoia investigated the action of carbon disulfide on indole magnesium bromide and presumably obtained indole-3-dithiocarboxylic acid (**401**), which could be isolated only as the ammonium salt **402**. The tetrathio derivative **403** was invariably formed at the same time as the salt **402**. Analogous products were obtained from 2-methylindole magnesium bromide.[180]

c. *Sulfur Dioxide.* Di(3-indolyl) sulfoxide (**404**) was the main product obtained under a variety of experimental conditions by the action of sulfur dioxide on indole magnesium bromide.[4, 172, 180] In one instance the formation of di(3-indolyl) sulfide (**387**) as a by-product was also reported.[180] Bis(2-methylindolyl) sulfide (**388**) was the main product obtained analogously from 2-methylindole.[172, 180] Oddo and Mingoia obtained a diindolyl sulfone (possibly **405**) by the action of sulfur dioxide on 2-methylindole magnesium bromide.[180]

d. *Sulfur Dichloride.* Di(3-indolyl) sulfide (**387**) was obtained by the action of sulfur dichloride (SCl_2) on indole magnesium bromide. Di(3-indolyl) disulfide (**396**) could not be obtained in an analogous manner from disulfur dichloride.[172]

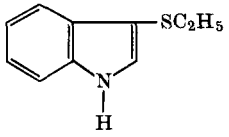
e. *Sulfuryl Chloride.* Di(3-indolyl) sulfone (**406**) and bis(2-methyl-3-indolyl) sulfone (**407**) were obtained by the controlled action of sulfuryl chloride on indole and 2-methylindole magnesium bromides, respectively.[180]

2. *Organic Sulfur Compounds*

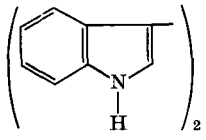
a. *Ethanesulfenyl Chloride.* In 1965 Jardine and Brown reported that a mixture of products including ethyl mercaptan, di(3-indolyl) sulfide (**387**), 3-ethylindole (**5**), diethyl sulfide, 3-ethylthioindole (**408**), 3,3′-biindole (**409**), and di(3-indolyl) disulfide (**396**) was formed by the reaction of indole magnesium bromide with ethanesulfenyl chloride.[181] The mechanisms by which all these products are formed are not clear. 3-Ethylthioindole (**408**) was probably formed by a typical reaction between the Grignard reagent and the halogen compound. Indole (**1**) and diethyl sulfide were most likely obtained by hydrolysis

[180] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **56**, 782 (1926); *Chem. Abstr.* **21**, 1458 (1927).

[181] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **43**, 1298 (1965).



(408)

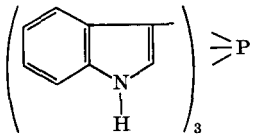


(409)

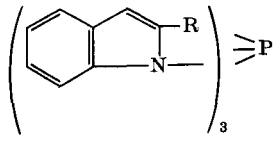
of unreacted starting materials. The 3,3′-biindole (**409**) could have been formed by oxidation of some unreacted Grignard reagent (see Section III,I,4).[181]

I. Reactions with Miscellaneous Inorganic Compounds

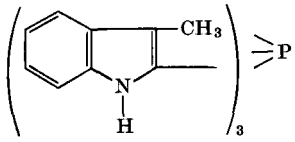
1. *Phosphorus Halides*



(410)



(411) R = H
(412) R = CH_3



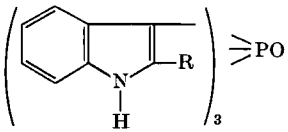
(413)

a. *Phosphorus Trichloride.* Tri(3-indolyl)phosphine (**410**) and tri-(1-indolyl)phosphine (**411**) were obtained from indole magnesium bromide by the action of phosphorus trichloride.[182] Tris(2-methyl-1-indolyl)phosphine (**412**) and tris(3-methyl-2-indolyl)phosphine (**413**) were obtained analogously by the action of phosphorus trichloride on

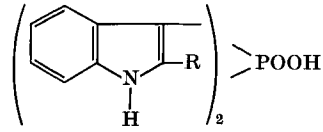
[182] Q. Mingoia, *Gazz. Chim. Ital.* **60**, 144 (1930); *Chem. Abstr.* **24**, 3783 (1930).

2- and 3-methylindole magnesium bromide, respectively. The formation of only one product in each instance was reported in these latter two cases.[182]

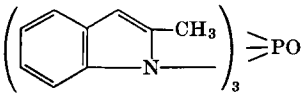
b. *Phosphorus Oxychloride.* Two products tri(3-indolyl)phosphine oxide (**414**) and di(3-indolyl)phosphinic acid (**415**) were formed by treatment of indole magnesium bromide with phosphorus oxychloride.[183] Tris(2-methyl-3-indolyl)phosphine oxide (**416**), tris(2-methyl-1-indolyl)phosphine oxide (**417**), and bis(2-methyl-3-indolyl)-phosphinic acid (**418**) were obtained in a similar reaction from 2-methylindole.[183]



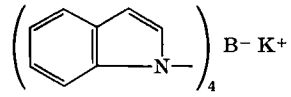
(**414**) R = H
(**416**) R = CH_3



(**415**) R = H
(**418**) R = CH_3



(**417**)



(**419**)

2. *Potassium Fluoroborate*

Potassium tetra(1-indolyl)boron (**419**) was obtained as an infusible white solid by boiling an ethereal solution of indole magnesium bromide with potassium fluoroborate under reflux for 6 hours.[184]

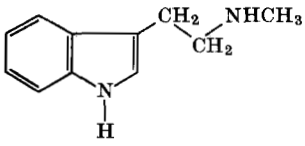
3. *Ferric Chloride*

An early report by Oddo suggested that a product containing two heterocyclic residues and one iron atom per molecule was obtained by the action of ferric chloride on the 2-methylindole Grignard reagent.[185]

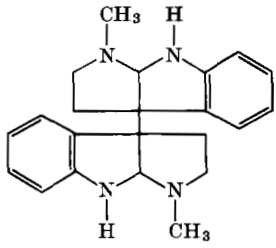
The formation of diphenyl on oxidation of phenyl magnesium bromide by anhydrous ferric chloride has been known for some

[183] Q. Mingoia, *Gazz. Chim. Ital.* **62**, 333 (1932); *Chem. Abstr.* **26**, 4813 (1932).
[184] V. A. Sazonova and V. I. Karpov, *Zh. Obshch. Khim.* **33**, 3313 (1963); *Chem. Abstr.* **60**, 4089 (1964).
[185] B. Oddo, *Gazz. Chim. Ital.* **44**, 268 (1914); *Chem. Abstr.* **9**, 795 (1915).

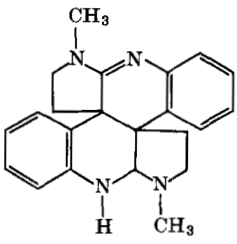
time [186] and this reaction has recently been utilized for biogenetic-type syntheses of some of the calycanthaceous alkaloids.[187] Hall *et al.* showed that treatment of N^{ω}-methyltryptamine (**420**) magnesium iodide with ferric chloride in anhydrous ether resulted in the formation of a number of dimeric products including *rac*- and *meso*-chimonanthine (**421**), *meso*-dehydro-β-calycanthine (**422**), and the isomeric



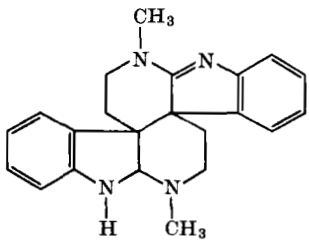
(**420**)



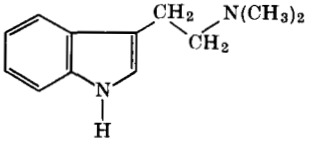
(**421**)



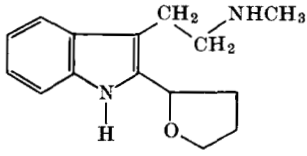
(**422**)



(**423**)



(**424**)



(**425**)

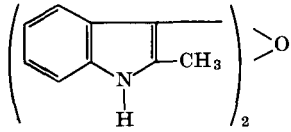
amidine **423**.[187] However, when the reaction was carried out in tetrahydrofuran in place of ether as solvent the yields of dimeric products were markedly reduced; the main products, in this case, were N^{ω},N^{ω}-dimethyltryptamine (**424**) (from excess of CH_3I in the Grignard reagent) and N^{ω}-methyl-2-(α′-tetrahydrofuranyl)tryptamine (**425**).[187]

[186] G. Champetier, *Bull. Soc. Chim. France* **47**, 1131 (1930).
[187] E. S. Hall, F. McCapra, and A. I. Scott, *Tetrahedron* **23**, 4131 (1967).

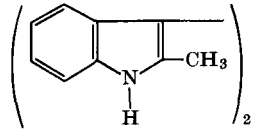
4. *Oxygen*

Toffoli obtained two products when 2-methylindole magnesium bromide was oxidized with oxygen in boiling ether solution, for 45 hours.[188, 189] One was a yellow crystalline substance ($C_{18}H_{16}ON_2$, m.p. 208°), probably the same compound as that previously obtained by Oddo by the autoxidation of 2-methylindole and described as bis(2-methyl-3-indolyl) ether (**426**).[190] The second compound was probably 2,2′-dimethyl-3,3′-biindole (**427**); this latter compound was also obtained by the action of 2-methylindolyl magnesium bromide on the magnesium derivative of ethyl acetoacetate.[188] Toffoli also reported that a small quantity of an unidentified product (m.p., 255°–260°) was obtained on oxygenation of an ethereal solution of indole magnesium bromide for 25 hours.[188] More recently Jardine and Brown obtained chromatographic evidence for the formation of 3,3′-biindole (**409**) and at least nine other unidentified products, when a solution of the indole Grignard reagent was stirred in air at room temperature for 26 hours.[181]

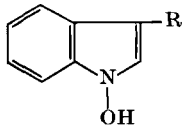
5. *Hydrogen Peroxide*



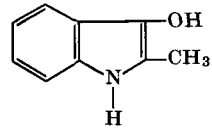
(**426**)



(**427**)



(**428**) R = H
(**429**) R = CH_3



(**430**)

Ingraffia studied the oxidation of the Grignard reagents derived from indole, skatole, and 2-methylindole with hydrogen peroxide and

[188] C. Toffoli, *Rend. Ist. Sanita Publica* **2**, 565 (1939); *Chem. Abstr.* **34**, 4733 (1940).

[189] C. Toffoli, *Atti 10th Congr. Intern. Chim., Rome, 1938* **3**, 369 (1939); *Chem. Abstr.* **33**, 9321 (1939).

[190] B. Oddo, *Gazz. Chim. Ital.* **50**, 268 (1920); *Chem. Abstr.* **15**, 2272 (1921).

reported that in all cases this resulted in the hydroxylation of the indole ring system. *N*-Hydroxylation was reported to occur with indole and skatole; 1-hydroxyindole (**428**) and 1-hydroxyskatole (**429**), respectively, being formed. 3-Hydroxy-2-methylindole (**430**) was formed in an analogous manner from the 2-methylindole Grignard reagent.[191] It should be noted, however, that Mousseron-Canet and Boca were unable to obtain *N*-hydroxyindoles by the oxidation of indole Grignard reagents with peracids.[166]

6. *Deuterium Oxide*

Jardine and Brown reported that the product obtained on treatment of indole magnesium iodide in ether with deuterium oxide in tetrahydrofuran was deuterated to the extent of about 50% in both the 1- and 3-positions of the indole nucleus.[71]

The reaction of the indole Grignard reagent with deuterium oxide has recently been studied in greater detail by Powers and his coworkers.[17,192] These workers observed that, similarly to the alkali metal salts of indole, the indole Grignard reagent undergoes essentially *N*-deuteration in tetrahydrofuran, but the Grignard reagent behaves differently from the other metal derivatives and undergoes 3-deuteration in ether solution. The amount of exchange that occurred in the 3-position was markedly affected by the amount of heavy water used. The optimum conditions for exchange at the 3-position involved the use of a moderate excess of deuterium oxide (ca. 5–7 equivalents). Smaller amounts or a large excess of D_2O gave only low yields of the 3-deuterated product; *N*-deuteration occurred under these conditions. Powers *et al.* explain their results by assuming that a complex between the Grignard reagent and D_2O is formed initially. In the presence of small amounts of D_2O, this complex is believed to be quite stable and exchanges very slowly. Since the conditions of work-up of these reaction mixtures all involved the use of a large excess of water, no *N*-deutero products would be detected and little 3-deuteration would be observed in this case. In the case where a large excess of D_2O was employed, the D_2O would increase the polarity of the medium and increase the dissociation of the N—MgX bond, which would lead to exchange occurring at the nitrogen atom. Where intermediate amounts

[191] F. Ingraffia, *Gazz. Chim. Ital.* **63**, 175 (1933); *Chem. Abstr.* **27**, 3710 (1933).
[192] J. C. Powers and W. P. Meyer, *Abstr. 149th Meeting Am. Chem. Soc., 1965* p. 56P, Abstr. No. 114.

of D_2O were used, a stable complex was assumed to be formed which gave rise to 3-deuteration, because solvation about the nitrogen atom may have prevented reaction at the nitrogen atom. Exchange at the 3-position was then presumed to occur through some form of intermediate indolenine complex.[17,192]

IV. Molecular Structure

In the half-century that elapsed between its discovery in 1910[1] and the early years of the present decade, the structure of the indole Grignard reagent was the subject of sporadic speculation by a few authors. The conclusions reached by these early workers with regard to the structure of the indole magnesium halides were essentially based on the substitution behavior of these compounds. However, as a result of a number of recent systematic chemical and physicochemical investigations, much more is now known about their structure. Nevertheless, a considerable amount of further work will be required to resolve fully the twin problems of the structure and reactivity of the indole Grignard reagent. This is perhaps not too surprising since, as Ashby has pointed out in a recent review, the composition of Grignard reagents, in general, is one of the most fascinating and fundamental problems facing organic chemists today.[193]

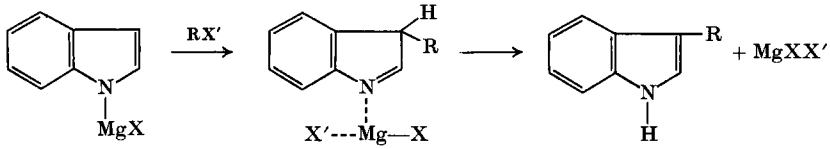
Although Oddo was the initial discoverer of the indole Grignard reagents and despite the fact that Oddo and his collaborators carried out an extensive research program on the chemistry of these compounds between 1911 and 1941, these workers did not propose any particular structure for the indole Grignard reagent. Chelintzev and Tronov were the first workers to comment on the position of the magnesium residue in indole magnesium iodide, prepared from indole and propyl magnesium iodide. These workers suggested that the indole Grignard reagent could be regarded as either a C—MgX or an N—MgX species, but they did not attempt to distinguish between the two possibilities.[194] In 1930 Nenitzescu reported that indole magnesium iodide gave a negative color test with Michler's ketone and considered this fact as evidence that the indole Grignard reagent contained the

[193] E. C. Ashby, *Quart. Rev. (London)* **21**, 259 (1967).

[194] V. V. Chelintzev and B. V. Tronov. *Zh. Russ. Fiz. Khim. Obshchestva* **46**, 1876 (1914); *Chem. Abstr.* **9**, 2071 (1915).

N—MgX grouping.[195] This conclusion was based on the fact that pyrrole magnesium halides, which were regarded at that time as being C—MgX derivatives, gave violet colors with Michler's ketone. This test had been previously developed by Gilman and Schulze for detecting the presence of Grignard reagents containing the C—MgX grouping.[196] Other workers subsequently claimed that Nenitzescu's conclusions could be questioned on several grounds. Kharasch and Reinmuth suggested that pyrrole magnesium halides, regardless of their constitution, are capable of reacting with the carbonyl group of Michler's ketone (cf. ref. 9, p. 76); Gilman and Heck had pointed out earlier that color tests alone could not effectively differentiate between C—MgX and N—MgX structures in the case of the pyrrole Grignard reagent.[197]

In the 1930's a number of workers, including Hoshino,[30] Oddo,[198] and Kubota[50] suggested that indolenine-type intermediates (cf. **431**) were formed during the reaction of the indole Grignard reagents [depicted as N—MgX derivatives (cf. **432**)] with alkyl and arylalkyl halides. Rather surprisingly these were the last reports dealing with



(**432**) (**431**)

the structure and reactivity of the indole Grignard reagents to appear for 30 years. During this period these reagents were alternatively depicted in the literature as C—MgX or N—MgX species (cf. refs. 8 and 199).

In the early 1960's Katritzky and Lagowski[200] and Badger[201] suggested that the indole Grignard reagents were essentially ionic

[195] C. D. Nenitzescu, *Bul. Soc. Chim. România* **11**, 130 (1930); *Chem. Abstr.* **24**, 2458 (1930).

[196] H. Gilman and F. Schulze, *J. Am. Chem. Soc.* **47**, 2002 (1925).

[197] H. Gilman and L. L. Heck, *J. Am. Chem. Soc.* **52**, 4949 (1930).

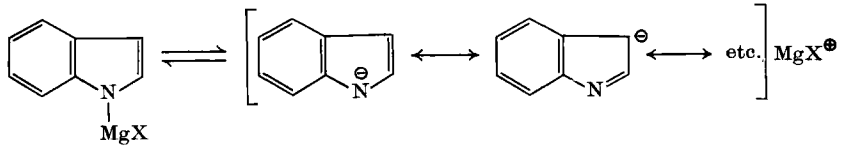
[198] B. Oddo, *Gazz. Chim. Ital.* **63**, 234 (1933); *Chem. Abstr.* **27**, 3933 (1933).

[199] P. L. Julian, E. W. Meyer, and H. C. Printy, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3. Wiley, New York, 1952.

[200] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," p. 174. Wiley, New York, 1960.

[201] G. M. Badger, "The Chemistry of Heterocyclic Compounds," p. 64. Academic Press, New York, 1961.

compounds; the indole anion was depicted as the resonance hybrid (cf. **433**).[201] A structure of this type could easily explain the substitution behavior observed when the indole Grignard reagents reacted with electrophilic reagents. In 1963 Reinecke *et al.* reported certain spectroscopic evidence that supported the ionic formulation.[15] The



(**432**) (**433**)

(**434**) (**435**)

NMR spectrum of indole magnesium bromide in tetrahydrofuran was different from that of indole, but was essentially the same as that obtained from the sodium derivative of indole, a compound in which the nitrogen–metal bond was presumed to be essentially ionic. The similarity of the NMR spectra of these two organometallic indole compounds tended to eliminate the possibility that the essentially covalent N—MgX species **432** made any significant contribution to the overall structure of the indole Grignard reagent. The possibility that the indole magnesium halides existed as either of the C—MgX forms **434** or **435** was also considered unlikely. First signals due to the N—H group could not be detected in either the NMR or the infrared spectra of the indole Grignard reagent; this tended to eliminate structure **434**. The indolenine structure **435** for the indole magnesium halides was also rejected on the grounds that the β-proton resonance observed in the NMR spectrum was not shifted to higher field on formation of the Grignard reagent either from indole or 2-methylindole.[15]

However, the formulation of the indole Grignard reagent as a purely ionic compound appears to be an oversimplification of the picture and is probably incorrect, since several workers have recently described a number of important differences between the behavior of the indole

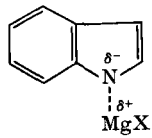
Grignard reagent on the one hand and that of the alkali metal salts of indole on the other. Sebastian reported one significant difference between the NMR spectra of these indole derivatives.[25] An equimolar mixture of indole and indolyl sodium gave the time-averaged spectrum, indicating that rapid exchange was taking place between indole and its sodium derivative. However, the NMR spectrum of a mixture of indole magnesium bromide and indole showed the presence of two distinct sets of resonances due to the presence of both species indicating that no significant exchange was occurring. Temperature had no effect on the NMR spectrum of the mixture.[25] This behavior suggested that the nitrogen–metal bond in the Grignard reagent was of a different character from that in the alkali metal derivatives of indole.

Sebastian also observed that although alkylation of the indole Grignard reagent with methyl iodide in tetrahydrofuran at 23° gave essentially 3-methylindole, variable amounts of 1- and 3-methylindole were obtained on alkylation of the alkali metal salts of indole under similar conditions.[25] Sebastian's results were qualitatively similar to those obtained earlier by Lerner[46] and more recently by Cardillo *et al.*[19] who studied the reaction of a number of organometallic derivatives of indole, including the indole Grignard reagents, with allyl bromide. *N*-Substitution was favored by increasing electropositivity of the cation, i.e., relatively more *N*-substitution was observed in the case of the potassium derivative than in the case of the lithium derivative.[25, 46] Furthermore, factors that tended to facilitate dissociation of the indole salts, such as increasing the polarity of the medium, increased the tendency for substitution to occur at the 1-position (cf. refs. 19, 25, and 46).

Sebastian concluded that all these organometallic indole derivatives were essentially ionic nitrogen–metal species, but with a higher degree of ionic character being present in the nitrogen–alkali metal bond than in the nitrogen–magnesium bond, and that the indol Grignard reagent was best represented by a structure of type shown in formula **436** in which the N—MgX bond has a considerable degree of ionic character but with the possibility of overlap between the nitrogen and magnesium orbitals. He pointed out, however, that his data did not completely eliminate the possibility of an equilibrium of **436** with an ion-pair structure such as **437**.[25]

However, Powers *et al.* concluded, as a result of their investigations of the protonation of the indole Grignard reagent,[17, 192] that in ether

solution, at least, the N—MgX bond of the indole Grignard reagent has a considerable covalent character.[17] In tetrahydrofuran, however, the stronger basicity of this ether, which would coordinate more strongly with the magnesium, would increase the ionic character of the N—MgX bond.[17]



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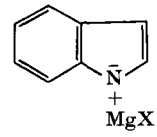

(437)

By virtue of their extensive studies on the interaction of β-dimethylaminoalkyl halides (see Section III, B, 6, b) with some organometallic derivatives of indole, including the indole Grignard reagents, Ganellin and Ridley came to conclusions not too dissimilar to those of Sebastian[25] and Powers *et al.*[17] These workers were able to exclude the possibility of a C—MgX species and concluded that the indole Grignard reagents are essentially N—MgX species in which the N—MgX bond in the indole magnesium halides is formally covalent but is polarized to induce partial anionic character in the indole nucleus, with the consequent increase in electron density at the 3-position, which would facilitate electrophilic substitution at that position.

Foti and Ruff have also reported recently that infrared spectroscopic studies indicate that the magnesium function in indole magnesium iodide is associated with the nitrogen atom of the indole nucleus and not the carbon atom in the 3-position.[202]

Some recent studies have underlined the effect that certain physical properties of the reaction medium have in governing the nature and yields of the products obtained when indole Grignard reagents react with alkyl or alkynyl halides. Such factors include the basicity and dielectric constant of the medium and its ability to solvate any of the reacting species.[18, 19]

In conclusion it appears that the indole magnesium halides are essentially N—MgX species, with the degree of ionic character of the N—MgX bond being markedly affected by external factors, such as

[202] A. Foti and F. Ruff, *Magy. Kem. Folyoirat* **73**, 91 (1967); *Chem. Abstr.* **67**, 11386 (1967).

the polarity of the medium. However, there are still several questions concerning the structure and reactivity of the indole Grignard reagents which are not fully answered by the aforementioned model.

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