

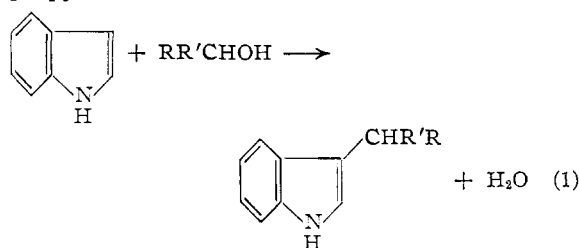
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Disproportionative Condensations. IV. The 3-Alkylation of Indoles by Primary and Secondary Alcohols¹BY ERNEST F. PRATT AND LAURENCE W. BOTIMER²

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A facile process for the 3-alkylation of indoles has been developed. A modification of the method which required heating the indole with a large excess of an alcohol and alkoxide in a sealed tube, the new process is conducted in an open reflux system with much smaller proportions of alcohol and alkoxide. Alkylated indoles have been prepared in good yield employing a variety of primary and secondary alcohols. A reaction course closely analogous to that for several other base-catalyzed alkylations by alcohols has been proposed and evaluated.

The classical alkylation of substituted pyrroles by prolonged heating in a sealed tube at over 200° with a manifold excess of an alcohol and the corresponding alkoxide³ has in recent decades been extended to the alkylation of 2-methylindole⁴ and 2-carboxyindole⁵ (which undergoes spontaneous decarboxylation) and in the cases of methyl and isopropyl alcohols⁵ to indole itself. The need for a



closer investigation of this reaction has been pointed out⁶ and the probable relation to other base-catalyzed alkylations by alcohols has been recognized.^{7,8}

It was apparent that the value of the reaction would be significantly enhanced if it could be carried out in an open system under reflux as described for related reactions in preceding papers of this series.^{1,9} Such a modification would allow the reaction to be accelerated and followed by removing the by-product water as it formed. Drastic reduction in the proportions of alcohol and alkoxide required might also be possible.

It was found that a good yield of 3-benzylindole was obtained readily (expt. 7, Table I) under the conditions previously established for the N-benylation of aniline.⁹ The benzylation of indole, which proceeded only about one-tenth as fast as that of aniline, was accelerated nearly twenty-fold by carrying out the reaction in refluxing *p*-cymene (expt. 1) in place of refluxing xylene; even with the *p*-cymene the reaction temperature is significantly below that used heretofore. The potassium alkoxides were advantageously prepared by volatilizing the by-product water from the reaction of potassium

hydroxide with the alcohols before adding the indole.¹⁰

TABLE I

THE 3-ALKYLATION OF INDOLE

Standard conditions: 0.125 mole of indole, 0.210 mole of alcohol, 0.04 mole potassium alkoxide, 1.0 g. of U.O.P. nickel with *p*-cymene to give 125 ml.

Expt.	Variable	Time, ^a hr.	Temp., °C.	Water, %	Prod., ^b %
Benzyl alcohol and indole under various conditions					
1	Std. cond.	3.8	182-183	99	76
2	0.125 mole C ₆ H ₅ CH ₂ OH	.. ^c	182-183	82	47
3 ^d	0.010 mole C ₆ H ₅ CH ₂ OK	8.4	183-185	91	37
4	0.125 g. U.O.P. nickel	8.6	183-184	102	74
5	No U.O.P. nickel	14.7	182-184	102	78
6 ^e	No U.O.P. nickel plus 0.025 mole C ₆ H ₅ CHO	2.7	181-183	97	68
Indole plus various primary alcohols					
7 ^f	C ₆ H ₅ CH ₂ OH	70.0	145-147 ^f	92	71
8 ^f	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂ OH	52.0	145-147 ^f	94	57
9 ^f	<i>p</i> -CH ₂ OC ₆ H ₄ CH ₂ OH	46.0	145-147 ^f	115	26
10	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OH	10.5	186-188	148	41
11	CH ₃ (CH ₂) ₆ CH ₂ OH	17.8	184-188	152	58
12	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	29.0	180-184	107	76
13	CH ₃ CH ₂ CH ₂ CH ₂ CH(C ₆ H ₅)CH ₂ OH	73.0	182-185	112	71
Indole plus various secondary alcohols					
14	C ₆ H ₅ CHOHCH ₃	5.7	185-186	148	45
15	(C ₆ H ₅) ₂ CHOH	10.0	190-191	105	67
16	CH ₃ (CH ₂) ₃ CHOHCH ₃	37.5	180-188	152	68
17 ^g	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CHOH	64.0 ^g	174-185	148	54
Benzyl alcohol plus substituted indoles					
18	<i>o</i> -C ₆ H ₄ CH=C(CH ₃)NH	1.0	181-183	102	74
19	<i>o</i> -C ₆ H ₄ CH=C(C ₆ H ₅)NH	1.1	184-187	114	49

^a This is the time required for a 90% yield of water to collect. ^b Yield of pure product; product of sufficient purity for most purposes was usually isolated in 10 to 15% higher yield. ^c An 82% yield of water was collected in 8.5 hr. ^d 0.240 mole of alcohol used here to give the standard 0.250 mole of alcohol plus alkoxide. ^e Only 0.185 mole of alcohol used here to compensate for the added aldehyde. ^f Xylene replaced the *p*-cymene. ^g Since only 5% water collected in 3 hr., 0.02 mole of cyclohexanone was added to accelerate the reaction.

In the 3-benylation of indole, as in the N-benylation of aniline,⁹ a decrease in the amount of benzyl alcohol, potassium benzyrate or U.O.P. nickel¹¹ markedly decreased the rate (expts. 1-5). In both benzylation a good yield of product could be obtained in the absence of nickel and, in its ab-

(1) For the preceding paper in this series see E. F. Pratt and A. P. Evans, *THIS JOURNAL*, **78**, 4950 (1956).

(2) From the Ph.D. thesis of L. W. Botimer.

(3) H. Fischer and E. Bartholomäus, *Z. physiol. Chem., Hoppe-Seyler's*, **80**, 6 (1912), and other papers in the same series.

(4) B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933).

(5) R. H. Cornforth and R. Robinson *J. Chem. Soc.*, 680 (1942).

(6) A. H. Corwin, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 307.

(7) J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 682 (1942).

(8) K. L. Schoen and E. I. Becker, *THIS JOURNAL*, **77**, 6030 (1955).

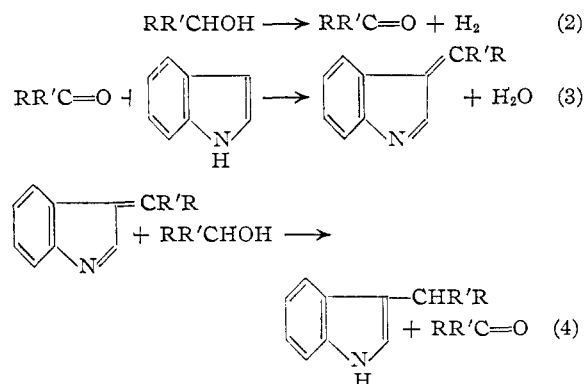
(9) E. F. Pratt and E. J. Frazza, *ibid.*, **76**, 6174 (1954).

(10) T. K. Walker, *J. Soc. Chem. Ind. (London)*, **40**, 172T (1921).

(11) Universal Oil Products Co., 310 S. Michigan Ave., Chicago 4, Ill.

sence, the rate was increased by the addition of a small proportion of benzaldehyde (expts. 5 and 6).^{9,12} Small amounts of hydrogen and benzoic acid were formed in the benzylation of both indole and aniline and, if no excess alcohol was used, the yields of the desired product decreased in both cases (*cf.* expts. 1 and 2). The results of expts. 7, 8 and 9 show that electron-releasing *para* substituents in the benzyl alcohol speed up the rate as they did in the reaction of aniline⁹ and in both studies the "rate curves" obtained upon plotting the volume of water collected *versus* time had similar elongated "S" shapes.

Since the 3-benylation of indole has so many characteristics in common with the N-benylation of aniline as well as with several other base-catalyzed alkylations by alcohols,^{7,8,13,14} an analogous reaction route is indicated.



The fact that only a small proportion of hydrogen is evolved suggests that, as in the alkylation of aniline,⁹ reaction 2 is needed only to initiate the process which proceeds chiefly *via* 3 and 4 the sum of which gives reaction 1. Ketone to initiate the process may also arise by atmospheric oxidation as has been suggested previously.⁸ It was found that water was evolved very rapidly from benzaldehyde and indole under these conditions (equation 3) and this together with other pertinent analogies with the benzylation of aniline⁹ indicates that reaction 4, which may proceed by 1,4-addition or by 1,2-addition followed by tautomerization, is rate controlling during most of the process. Like certain other reactions of indole, this alkylation apparently proceeds *via* the tautomeric indolenine intermediate. As demanded by this interpretation, alkylation occurs exclusively at the 3-position; benzyl and γ -phenylpropyl alcohols (expts. 1 and 10) gave products which melted at the reported temperatures for the 3-alkylated indoles,^{5,15} and the product obtained from methanol using the sealed tube method did not depress the melting point of authentic 3-methylindole.⁵ As expected 3-methylindole failed to undergo benzylation under the conditions of expt. 1, and *t*-butyl alcohol failed to alkylate indole in the sealed tube method.⁵

(12) In ref. 9 benzalaniline rather than benzaldehyde was added. It has been shown¹⁴ that benzaldehyde, which was doubtless immediately converted to benzalaniline, acts similarly.

(13) E. F. Piatt and D. G. Kubler, *THIS JOURNAL*, **76**, 52 (1954).

(14) M. Avramoff and Y. Sprinzak, *ibid.*, **78**, 4090 (1956).

(15) H. R. Snyder, E. L. Eliel and R. E. Carnahan, *ibid.*, **78**, 970 (1951).

Among the primary alcohols it is apparent, in spite of the fact that temperature variations are not always negligible, that saturating the aromatic ring of benzyl alcohol greatly decreases the rate (expts. 1 and 12), while cleaving the saturated ring to give a β -ethyl group (expt. 13) further lowers the rate. Although the rate for *n*-octyl alcohol (expt. 11) can be compared in only approximate fashion because of the large excess of water evolved (*cf.* Discussion below), there is little doubt that it alkylates indole faster than cyclohexylcarbinol and slower than benzyl alcohol.

Replacement of an α -hydrogen of a primary alcohol by a methyl group approximately halves the reaction rate (*cf.* expt. 1 with 14 and 11 with 16), but the results of expts. 15 and 17 emphasize that at least in these latter cases steric hindrance about the carbinol carbon is not the primary rate-controlling factor. The unusually rapid rates obtained with 2-methyl- and 2-phenylindoles (expts. 18 and 19) show that for these compounds an increase in the steric hindrance in the region of the 3-position does not decrease the rate.

The approximately 50% of excess water produced from both primary and secondary alcohols which have a β -methylene group (expts. 10, 11, 14, 16 and 17) suggests that these alcohols are self-condensing *via* Guerbet reactions.¹³ Omission of the indole in an experiment otherwise identical with number 11 resulted in the formation of 2-hexyldecanol-1 in 65% yield. In a similar experiment after the self-condensation of *n*-hexyl alcohol was completed, indole was added to the reaction mixture whereupon water continued to be evolved and a satisfactory yield of 3-(2-butyloctyl)-indole was isolated.

Experimental^{16,17}

Standard Procedure.—The U.O.P. nickel¹¹ was identical with that previously employed^{9,13}; the pellets, which contain 50 to 55% nickel as the metal and metal oxides, were ground to pass a 100-mesh sieve. A single lot of Mallinckrodt A.R. potassium hydroxide was used; calculations were based on the assay value of 85%. The xylene was a commercial mixture of isomers which was redistilled. All other starting materials were purified by standard methods until their melting points or refractive indices agreed closely with the literature values.

The procedure for expt. 1 will be described in detail; the required modifications are indicated by the tabulated data. One-fourth mole of benzyl alcohol was diluted with *p*-cymene to 125 ml., less 14.6 ml. to allow for the 14.6 g. of indole to be added later. This solution together with 0.04 mole of potassium hydroxide was placed in a 250-ml. flask fitted with a thermometer well and surmounted by an asbestos wrapped, 5-ml. Dean-Stark trap, calibrated in 0.1-ml. units, and reflux condenser. Upon application of heat by means of a hemispherical mantle, about 0.04 mole of water collected within 1.5 hr. One-eighth mole (14.6 g.) of indole and 1.0 g. of U.O.P. nickel were then added to the slightly cooled reaction mixture. As refluxing was continued at a rate just below that which would flood the condenser, frequent readings of water volume, time and temperature were taken. The tabulated figures for total yield of water are of semi-quantitative significance only since in many cases heating was stopped while very slow evolution of water was continuing. The number of hours required for the production of a 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 99% yield of water were: 0.08, 0.35, 1.2, 1.9, 2.4, 2.7, 3.2, 3.5, 3.6, 3.8 and 4.5.

(16) All melting points are corrected.

(17) We wish to thank Professor Kathryn Gerdeman and Miss Jane R. Swan for the carbon, hydrogen and nitrogen determinations.

After the catalyst was filtered off about 25 ml. of ether was added to the filtrate which was then washed with two 50-ml. portions of water and dried over calcium chloride. An 81% yield of 3-benzylindole (m.p. 105–106°) was filtered from the cooled solution. Recrystallization from methylcyclohexane and then from methanol raised the m.p. only to 106.5–107° and lowered the yield to 76%. Further recrystallization failed to change the m.p.; lit. values are 103–105°¹⁶ and 111°.⁵ The picrate melted at 114° (lit.⁵ m.p. 113°).

The foregoing isolation and recrystallization procedure was used unless otherwise noted for all solid products. For liquids and a few low-melting solids the ether was volatilized from the washed and dried solution at the water-pump and the crude product isolated by distillation through a vacuum jacketed still-head at about 0.2 mm. pressure. The pure product for which yields are tabulated was obtained by redistillation through an 8-in. Vigreux column.

New Compounds.—Five of the seven products obtained with primary alcohols are new. The 3-(*p*-methoxybenzyl)-indole isolated in the standard fashion was obtained in 36% yield with m.p. 84.0–84.5° and in 26% yield with m.p. 87.0–88.0°. *Anal.* Calcd. for C₁₈H₁₈NO: C, 80.98; H, 6.37. Found: C, 80.90, H, 6.14. The 3-(*p*-methylbenzyl)-indole melted at 95.0–95.5°. Since results of analysis for carbon were erratic, the picrate was prepared. *Anal.* Calcd. for C₁₈H₁₈N·C₈H₈N₃O₇: C, 60.03; H, 4.03. Found: C, 59.75; H, 3.86. The standard distillation procedure for liquids was used for the 3-octylindole. It boiled at 125–127° (0.2 mm.) and solidified in the receiver (m.p. 33–34°). *Anal.* Calcd. for C₁₈H₂₃N: C, 83.78; H, 10.11. Found: C, 83.24; H, 10.18. The 3-(cyclohexylmethyl)-indole distilled at 140–149° (0.1 mm.). Recrystallization of the solidified distillate from methanol gave 20.2 g. (76%) which melted at 70.5–71.5°; further recrystallization raised the m.p. to 72.0–72.5°. *Anal.* Calcd. for C₁₅H₁₉N: C, 84.45; H, 8.97. Found: C, 84.11; H, 8.70. Under the standard distillation conditions 3-(2-ethylhexyl)-indole was obtained at 138–142° (0.5 mm.). The *n*^{25D} value of 1.5415 was raised to 1.5422 upon redistillation to obtain the analytical sample. *Anal.* Calcd. for C₁₈H₂₃N: C, 83.78; H, 10.11. Found: C, 84.13; H, 9.65. The 3-(2-butyl-octyl)-indole described in the following section is also new.

All four of the alkylated indoles obtained with the secondary alcohols are new. The 3-(1-phenylethyl)-indole was isolated by rapid distillation (up to 170° at 0.1 mm.) followed by two recrystallizations from methylcyclohexane. The m.p. of the product, obtained in 45% yield, was raised from 75.5–76.0° to 76.5–77.5° by further recrystallization. *Anal.* Calcd. for C₁₈H₁₉N: C, 86.84; H, 6.83. Found: C, 86.90; H, 6.53. From benzhydrol an 89% yield of 3-(diphenylmethyl)-indole which melted at 120–124° was obtained upon recrystallization from methanol; the yield fell to 67% and the m.p. rose to 127–128° upon recrystallization from methylcyclohexane. *Anal.* Calcd. for C₂₁H₁₇N: C, 89.01; H, 6.05; N, 4.95. Found: C, 89.07; H, 6.11; N, 4.65. The 3-(2-octyl)-indole which distilled at about

148–153° (0.3 mm.) had *n*^{25D} 1.5329. *Anal.* Calcd. for C₁₈H₂₃N: C, 83.78; H, 10.11. Found: C, 83.83; H, 10.39. Distillation up to 145° (0.5 mm.) followed by recrystallization from methyl alcohol gave the pure 3-cyclohexylindole which melted at 92.0–92.5°. *Anal.* Calcd. for C₁₄H₁₇N: C, 84.36; H, 8.60. Found: C, 84.26; H, 8.36.

The tabulated data suffice for the 3-benzyl-,^{5,16} the 3-(3-phenylpropyl)-,⁵ the 2-methyl-3-benzyl-¹⁸ and the 2-phenyl-3-benzylindoles,¹⁹ all of which are known compounds melting very close to the reported temperatures.

Guerbet Condensations.—In order to determine the extent of interference of the Guerbet reaction, expt. 11 was repeated, except the indole was omitted. A 90% yield of water collected in about 19 hr. and a 101% yield in about 25 hr. at 181–185°. The reaction mixture was washed free of base, dried and distilled through an 8-in. Vigreux column to give a 66% yield of 2-hexyldecanol-1 at 133–137° (0.8 mm.); *n*^{25D} was 1.4476 as compared to the lit. value of 1.4472.¹³

In a similar experiment in which 0.50 mole of *n*-hexyl alcohol was used in place of the 0.25 mole of *n*-octyl alcohol, water evolution practically ceased after 80 hr. of refluxing at 165–188° at which time a 90% yield had collected. One-eighth mole of indole was then added and refluxing continued. Since only 0.40 ml. of water collected after 46 hr. at 193–194°, another 0.04 mole of potassium hydroxide was added. After refluxing for 80 hr. more at 191–192°, water evolution ceased at 121%, calculated for complete alkylation of the indole by the 2-butyloctanol-1. After washing the reaction mixture with water, it was dried and distilled through an 8-in. Vigreux column. A 60% yield of 3-(2-butyloctyl)-indole distilled at about 155–170° (0.3 mm.), *n*^{25D} 1.5180. The *n*^{25D} for an analytical sample (b.p. 170° at 0.3 mm.) was 1.5214. *Anal.* Calcd. for C₂₀H₃₁N: C, 84.11; H, 10.95. Found: C, 84.49; H, 11.11.

Supplementary Experiments.—The standard expt. 1 was repeated with a gas buret connected to the top of the reflux condenser. On the assumption that the gas collected throughout the reflux period was a mixture of hydrogen and air it was calculated, from the volume and density, that 0.035 mole of hydrogen was evolved. By acidification of the 100 ml. of aqueous extracts of the reaction mixture, obtained in the standard isolation procedure, 1.2 g. of a white solid was obtained which melted at 121–122° both alone and when mixed with authentic benzoic acid.

In an expt. identical with no. 11 except that no excess of *n*-octyl alcohol was used a 98% yield of water was obtained in 75 hr. The yield of 3-octylindole was 37% showing that here, as with benzyl alcohol, an excess of alcohol markedly improves the yield.

(18) T. Hoshino, *Ann.*, **500**, 40 (1932).

(19) P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, *This Journal*, **67**, 1210 (1945).

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[CONTRIBUTION FROM McNEIL LABORATORIES, INC.]

Dihydroergot Analogs. 1-(3-Indolylmethyl)-piperidinecarboxamides¹

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The preparation of *N*-mono- and *N,N*-disubstituted-1-(3-indolylmethyl)-isonipecotamides, nipecotamides and pipecolamides, structural analogs of the hydrogenated ergot alkaloids, is described. Many of the new compounds when administered intravenously cause a decrease in blood pressure at about 2–16 mg./kg. in dogs anesthetized with α -chloralose. Several of the indolylmethyl nipecotamides and pipecolamides, but not the 4-isomers, also cause a typical apnea. The synthesis of a series of 1-alkyl-, 1-alkyl- and 1-acyl-*N,N*-diethylisonipecotamides, prepared for a study of the effects of alterations in structure of the 1-indolylmethyl compound upon hypotensive activity, is also described.

As part of a search for new synthetic hypotensive agents we have prepared a number of substituted piperidinecarboxamides of formula I. Compounds

in which R₃ is an indolylmethyl group (II) resemble amides of dihydrolysergic acid (III).

Stoll has reviewed the chemistry and pharmacology of the ergot alkaloids.² The most potent hypotensive agents of this group are the dihydro-

(1) Presented before the Division of Medicinal Chemistry at the 126th Meeting of the American Chemical Society, New York, September 17 1954.

(2) A. Stoll, *Chem. Revs.*, **47**, 197 (1950).