

Fig. 8.—Cells used for preparing and following iodination experiments.

Before use, cells were washed with cleaning solution and then boiling distilled water.

Kinetic Runs. Cell 1.—Exactly 1.5 cc. of the iodine solution in carbon tetrachloride was syringed into one fork of the cell. The styrene solution then was prepared rapidly in a 5-cc. volumetric flask and 1.5 cc. of this was syringed into the other fork. The cell was attached to the vacuum line (Fig. 8) by its side-arm. The contents of the cell were degassed in the usual way three times and then prepurified nitrogen was bled in. The stopcock on the side-arm was closed and the cell removed from the vacuum line. In the degassing cycles ethanol-Dry Ice mixtures at -78° were used for freezing, room temperature for thawing. The reactants were equilibrated for five minutes in the thermostat, the side-arm was reversed (see Fig. 8), and the cell rapidly mounted in the beam guide. Prior to each reading the cell holder was lifted out of the light beam and the instrument zeroed against tank water. Suitable optical density corrections for the solvent, cells and tank water had already been made. Usually readings were taken initially as rapidly as possible, about every two minutes, and thereafter less often.

Cell 2.—Operation with the second cell was quite similar. Reactants were in turn separately syringed into each fork, degassed several times through the particular joints e and f, and sealed off under vacuum at constrictions a and c, respectively. After the usual temperature equilibrium seal b was broken and the procedure followed as before. In spite of its tedium this method offered several advantages over the first one. It ensured more complete degassing, one could store the filled cell in Dry Ice for several hours before use, and finally it obstructed premature mixing of reactants by distillation as is possible in cell 1. When *inhibitors* were used these were weighed and dissolved in the styrene solution first. In the DPPH run the optical density of the reactants was followed at 6800 and 6600 Å. Because both these compounds absorbed light in this region and since they both obeyed Beer's law separately and when mixed, it was possible to obtain their concentrations by solving simultaneous expressions at each point.

The raw data from all runs were tabulated and plotted on graph paper. Those for the uninhibited runs had to be corrected for the maximum-minimum scale adjustments and then converted from percentage absorption to optical density units. Infinity values were always taken after at least five half-times except in very slow runs, when for mathematical purposes the number could be calculated from the equilibrium constant.

All the inhibited kinetic runs were followed with the Beckman DU spectrophotometer at 6800 Å., except for run 31, with DPPH. Runs 52-72 were recorded on an automatic spectrophotometer built in these laboratories equipped with thermostat and RCA 6217 photomultiplier.³² For concentrations of iodine above 0.001 *M* either of the two Baird interference combination filters 6880 or 6810 Å. were used. Below 0.001 *M* iodine it was necessary to substitute a 5145 Å. Baird interference filter in conjunction with a Kodak Wratten No. 72. This combination gave a very sharp cutoff and transmitted only 1/3% of the incident light intensity at the absorption minimum, 5145 Å., compared to 40% for either of the red filters. For this reason and because the data seemed to be internally consistent, photocatalysis by the light source at 5145 Å was discounted.

Acknowledgments.—It is a pleasure to acknowledge support of this work by the National Science Foundation.

(32) H. Kwart and C. Yang, Technical Report No. 3 to the Office of Naval Research, Project No. NR-056-095, Contract No. N5ori-76, Task XX, Harvard University, Cambridge, Mass., 1949. CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of 2-Substituted Cyclohexanones with Organometallic Compounds

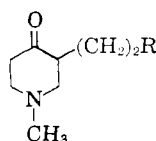
BY S. M. McELVAIN AND RODNEY B. CLAMPITT¹

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The reaction products of a series of 2-substituted cyclohexanones (III) with phenylmagnesium bromide and phenyllithium have been determined. When the 2-substituent is a carbethoxymethyl or a 2-carbethoxyethyl group, a major reaction product is the metal enolate of the original ketone. When this substituent is the dimethylaminomethyl group, normal addition of the organometallic compound to the ketone function occurs. If the amino function is separated from the ring by two or three methylene groups, the enolization reaction is the main or only reaction with phenylmagnesium bromide; with phenyllithium these substituents do not interfere with normal addition to the ketone. With non-polar alkyl groups as 2-substituents, both organometallic compounds give the normal addition reactions. A rationalization of these results is proposed. The propionates of two of the aminocarbinols (XIIIc and d) were prepared and screened for analgesic activity.

In earlier work² in this Laboratory it was found that neither phenylmagnesium bromide nor phenyllithium would add preferentially to the ketonic group of the 3-substituted-4-piperidone Ia. With

the Grignard reagent the main reaction was enoli-



Ia, R is COOEt
Ib, R is CH₂OCOC₆H₅
Ic, R is CONC₃H₁₀
Id, R is CH₂NC₃H₁₀

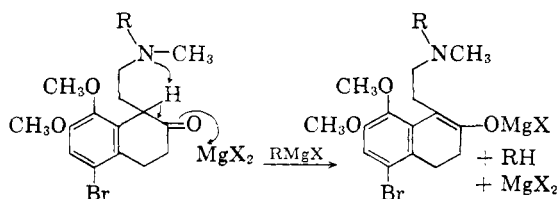
(1) Wisconsin Alumni Research Foundation Research Assistant, 1956-1957; United States Rubber Co. Fellow 1957-1958; E. I. du Pont de Nemours and Co. Summer Research Fellow, 1955.

(2) S. M. McElvain, W. B. Dickinson and R. J. Athey, *THIS JOURNAL*, **76**, 5625 (1954).

zation of the ketone (50%); the only addition

product isolated was the result of addition of the reagent to the ester group. Phenyllithium gave less of the enolization reaction (33%), but addition occurred at both the ketone and ester groups. Similar results were obtained with Ib and c; with Id enolization was the only reaction observed.

Stork and Conroy³ encountered a similar enolization reaction when the aminoethyltetralone IIa was treated with the Grignard reagent prepared from 4-bromobutene-1. They proposed that the amino group, as an internal base, promoted enolization by facilitating the removal of an α -hydrogen through a concerted reaction with the Grignard reagent. This hypothesis was supported by the fact that the non-basic sulfonamide IIb gave much less of the enolization reaction and more of addition of the ketone with this Grignard reagent.



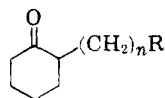
IIa, R is CH₃
IIb, R is SO₂CH₂C₆H₅

It is conceivable that the ring nitrogen of the piperidones Ia-d might function similarly to promote the enolization reaction. Such a scheme, however, would not account for the fact that 1-methyl-4-piperidone⁴ and certain of its 3-alkyl derivatives⁵ add organometallic compounds in good yields to give the corresponding carbinols. It would appear, therefore, that the polar groups of the 3-substituents of the piperidones Ia-d hinder normal addition of the organometallic compound at the ketone group either in a manner similar to that proposed by Stork and Conroy³ or "possibly by interaction of the polar group of the substituent with the carbonyl group."²

The present work was undertaken in order to determine the effect of such polar groups in 2-substituents of cyclohexanone on the course of the reaction of the ketone function with phenylmagnesium bromide and phenyllithium. In these ketones the reaction course would be dependent only on the 2-substituent and not be complicated by any additional factor that might be associated with basic ring nitrogen of the piperidones Ia-d.

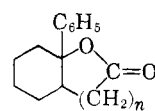
The cyclohexanones used in this study were IIIa-g. The esters IIIa and b were obtained by the reaction of ethyl bromoacetate and ethyl acrylate, respectively, with the anion of 2-carbethoxycyclohexanone followed by decarboxylation and re-esterification. The amine IIIc was obtained from the Mannich reaction with cyclohexanone; the amines IIIId and e were prepared by reduction of the amides resulting from the aminolysis of the ethylene acetals of the esters IIIa and b with dimethylamine. The 2-alkylcyclohexanones (IIIf and g), which were included in order to have steric analogs of IIIId and e, were obtained by alkylation

of the anion of 2-carbethoxycyclohexanone with isoamyl bromide and isohexyl bromide, respectively, followed by decarboxylation of the resulting ketoesters.



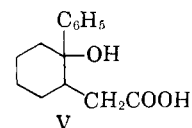
IIIa, *n* is 1; R is COOEt
b, *n* is 2; R is COOEt
c, *n* is 1; R is N(CH₃)₂
d, *n* is 2; R is N(CH₃)₂
e, *n* is 3; R is N(CH₃)₂
f, *n* is 2; R is CH(CH₃)₂
g, *n* is 3; R is CH(CH₃)₂

When an equivalent of phenylmagnesium bromide was added slowly to the ester IIIa in ether, an immediate precipitate formed. Hydrolysis of this reaction mixture with dilute hydrochloric acid and distillation of the reaction products yielded 38% of unchanged IIIa and a higher boiling fraction whose infrared spectrum (phenyl absorption at 6.26, 6.28 and 12.16 μ ; strong γ -lactone carbonyl band at 5.66 μ ; no hydroxyl band) indicated the lactone structure IVa. The yield of this material amounted to 28%. After standing for several weeks this liquid lactone fraction solidified to a crystalline mass from which about 47% of its weight was obtained as colorless needles, m.p. 60–61°. Saponification of the lactone IVa yielded, after acidification, the corresponding hydroxy acid V and reaction with phenylmagnesium bromide gave the diol VI.

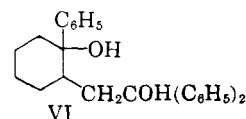


IVa, *n* is 1

IVb, *n* is 2



V



VI

The infrared spectrum of the residue from the distillation of IVa showed the characteristic phenyl bands, a carbonyl band at 5.85 μ and a strong hydroxyl band at 2.89 μ . These bands indicated the presence of 1-phenyl-2-phenacylcyclohexanol, possibly some of VI, and doubtless other more complex reaction products. As this residue could neither be distilled nor crystallized, no further study of it was made.

The lactone IVa appears to have been produced in the reaction from the initially formed carbinol anion and the ester grouping of the 2-substituent. Chatterjee⁶ reported the reaction of IIIa with phenylmagnesium bromide to yield the ethyl ester of V. He hydrolyzed this product to V for which he reported a melting point (129°) corresponding to that of the acid (127–128°) obtained in the present work from the hydrolysis of IVa. The difference in the reaction products of these two experiments doubtless is due to the fact that Chatterjee ran his reaction at ice temperature while in this Laboratory the reaction was carried out at room temperature.

The reaction of the keto ester IIIb with phenylmagnesium bromide was quite similar to that of

(3) G. Stork and H. Conroy, *THIS JOURNAL*, **73**, 4748 (1951).

(4) S. M. McElvain and J. Safranski, *ibid.*, **72**, 3134 (1950).

(5) (a) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947); (b) S. M. McElvain and M. D. Barnett, *THIS JOURNAL*, **73**, 3140 (1956).

(6) N. Chatterjee, *J. Indian Chem. Soc.*, **12**, 591 (1935).

IIIa. Along with a 37% recovery of IIIb, a 38% yield of the δ -lactone IVb was obtained. The residue from the distillation of these products was quite similar to that obtained with IIIa. After several weeks the lactone IVb crystallized and 55% of the material was obtained as colorless crystals, m.p. 74–75°. The hydroxy acid corresponding to this lactone could not be obtained; acidification of a solution of its salt gave the lactone.

The reaction of IIIb with phenyllithium led to the recovery of 59% of the starting ketoester and only a 14% yield of the lactone IVb. The residual material was a pale yellow glass that could not be induced to crystallize.

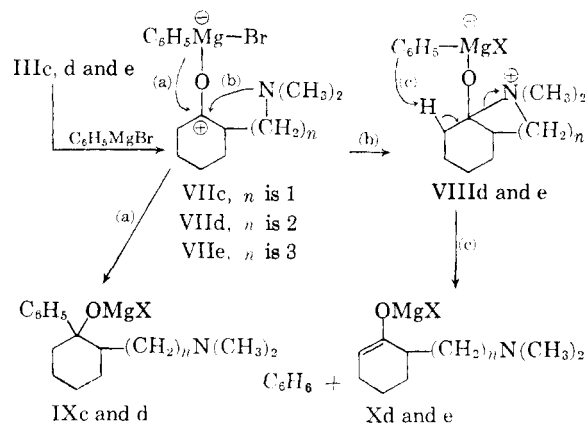
The products of the reactions of the aminoketones IIIc-e and the 2-alkylcyclohexanones IIIf and g with phenylmagnesium bromide and with phenyllithium are summarized in Table I. From these data, it is apparent that with the amino ketones and the Grignard reagent the relative amounts of the addition and the enolization reactions are dependent upon the length of the 2-substituent. However, with phenyllithium high yields in the addition reaction are obtained with each of these amino ketones.

TABLE I
REACTION OF KETONES IIIc-g WITH ORGANOMETALLIC COMPOUNDS

Ketone	Phenylmagnesium bromide		Phenyllithium	
	Recovd. ketone, %	Yield of carbinol, %	Recovd. ketone, %	Yield of carbinol, %
IIIc	8	67	11	75
IIId	50	41	17	72
IIIe	89	0	15	71
IIIf	5	82	14	81
IIIg	13	80

The yields reported in Table I would seem to indicate that there is interaction between the amino group and the ketonic function of certain of the amino ketones, but only after the Grignard reagent has coordinated with the carbonyl oxygen to form the initial complex VII. There is no apparent interaction between the ketone and amino groups before the Grignard reagent is added, as each of the ketones IIIc-e has a normal cyclohexanone band at 5.86 μ in its infrared spectrum. In the complex VII there may be competition between the phenyl (a) and the amino group (b) for the carbonium center. In VIIc path (a) is predominant because path (b) would necessitate the formation of a four-membered ring. However, VIIe appears to follow (b) exclusively to give the quaternary structure VIIIE, which by an internal β -elimination yields benzene and Xe as the only reaction products. The behavior of VIId is intermediate between these extremes; while it mainly follows (b) and (c) to Xd, a considerable amount of the normal addition product IXd is produced *via* (a). This reaction scheme is doubtless an oversimplification, as equilibria and conformational factors are probably important. For example, in order for the enolate Xe to form, VIIIE would preferably have to be in the *cis* configuration with the nitrogen axial.

The relatively high yields of the carbinols from each of the ketones IIIc-e with phenyllithium



most likely are due to the inability of this organometallic compound to coordinate as effectively as the Grignard reagent with the carbonyl oxygen.⁷ In such a case, the formation of a complex of the type of VIII would be minimized.

It is also possible to rationalize the difference in the reaction paths taken with these two organometallic compounds with the aminoketones IIIc-e without assuming a difference in the coordination ability of lithium and magnesium. It may be that lithium does coordinate with the carbonyl oxygen but that the shift of the phenyl group (path a) is able to compete successfully with the attack by the nitrogen (path b) regardless of the length of the side chain. Since phenyllithium is much more reactive than phenylmagnesium bromide,⁸ and the rate-determining step in the normal addition reactions presumably involves either an intramolecular shift of the aryl group or attack by a second molecule of the organometallic compound,^{7,8,9} such a rationalization may not be untenable.

It is not clear, however, why phenyllithium produces a greater amount of the enolization reaction with the keto ester IIIb than does phenylmagnesium bromide. The accompanying lower yield of the lactone IVb doubtless is due to its further reaction with the phenyllithium to give products that comprise the residual material.

It is certain, however, that the polar groups in the side chain have a profound effect on the course of these reactions. The 2-alkylcyclohexanones IIIf and g give high yields of the corresponding carbinols with these organometallic compounds (Table I). In these cases, the sizes of the 2-substituents are quite comparable to those of the amino ketones IIId and e, but the interfering polar group is absent.

If the basic nitrogen of the amino ketones IIIc-e were promoting the enolization reaction by helping to remove an α -hydrogen, as proposed by Stork and Conroy³ to explain the difference in behavior of compounds IIa and b, it is difficult to see why the ketone IIIc should give such a high yield of the

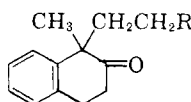
(7) C. G. Swain and L. Kent (THIS JOURNAL, **72**, 518 (1950)) have concluded from kinetic studies that phenyllithium reacts with Michler ketone *via* a preliminary coordination followed by an intramolecular shift of the phenyl group. The carbonyl oxygen of this ketone doubtless has a higher electron density because of resonance effects than the oxygen of an alicyclic ketone. It is possible, therefore, that phenyllithium might coordinate to a greater extent with Michler ketone than with such ketones as IIIc-e.

(8) C. G. Swain, *ibid.*, **69**, 2306 (1947).

(9) C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951).

carbinol with an accompanying small amount of the enolization reaction (Table I). Models of this ketone show that an α -hydrogen (to the carbonyl group) of the methylene group across the ring from the 2-substituent is quite available to the polar amino group of this substituent. Yet this amino ketone shows a negligible amount of the enolization reaction. Hence an intermediate of type VIII, which well explains the differences between IIa and b, seems to be a preferable rationalization of this reaction.

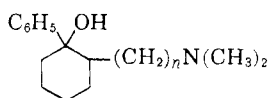
In this connection a recent observation by Fry¹⁰ is of interest. He reported that the ketone XIa failed to add methylmagnesium iodide. No explanation was offered for this behavior other than the statement that it probably was not due to steric factors since the ketone XIb reacted normally with the reagent. An amine carbonyl interaction of the type shown in VIII would seem to be a reasonable interpretation of these results. Indeed it would appear much more likely than abstraction of an α -proton by the amine function as this latter type of interaction would involve a seven-membered ring whereas a complex of type VIII would require the formation of a five-membered ring.



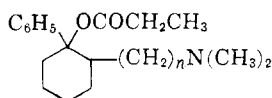
XIa, R is $N(CH_3)_2$
XIb, R is $OCH_2C_6H_5$

The carbinol XIIc, obtained from the reaction of IIIc with either phenylmagnesium bromide or phenyllithium, was a mixture of stereoisomers, which could not be separated by crystallization or by chromatography over alumina or silicic acid. A tedious fractional crystallization of the hydrochlorides of these stereoisomers led to the isolation of two compounds, one of which upon neutralization gave a sharp melting isomer of XIIc.¹¹

The carbinol XIIId, as obtained from both of the organometallic reagents, was also a mixture of stereoisomers. However, one isomer was sufficiently predominant that it could be separated in pure form by recrystallization. The carbinol XIIe, produced by the action of phenyllithium on IIIe, was practically exclusively one stereoisomer.



XIIc, n is 1
XIIId, n is 2
XIIe, n is 3



XIIIc, n is 1
XIIId, n is 2

The propionates XIIIc and d were prepared from the corresponding carbinols in order that they could be screened for analgesic activity; XIIIc previously has been prepared,¹¹ presumably for the same purpose. The carbinol XIIc is readily acylated to XIIIc in 88% yield by treatment with propionic anhydride and sodium propionate at 100° for 8 hours. Acylation of XIIId proved more

difficult; heating this carbinol with propionic anhydride at 115° for 24 hours was required to produce satisfactory yields of XIIId. The corresponding acyl derivative of XIIe could not be prepared. A variety of acylation procedures was utilized and in most cases the carbinol XIIe was recovered unchanged; only when the hydrochloride of XIIe was heated in propionic anhydride at 135° for 24 hours was any evidence of dehydration of the carbinol noted.

The increased difficulty of acylation of XIIId and the failure of XIIe to undergo any acylation are probably due to the steric effects of the 2-substituents, as it was found that the carbinol derived from IIIf (Table I), which contains the non-polar, 2-(4-methylpentyl) substituent, also resisted acylation.

Pharmacological Data.—The amino esters XIIIc and d in the form of their hydrochlorides were screened for analgesic activity by Mr. E. B. Robbins of the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind. Neither of these compounds showed any analgesic activity. Both showed signs of neurotoxicity at 80 mg./kg. dose level in the rat.

Experimental

Ethyl 2-Oxocyclohexaneacetate (IIIa).—A solution of 100 g. of ethyl 1-carbethoxy-2-oxocyclohexaneacetate,¹² prepared from ethyl 2-oxocyclohexanecarboxylate,¹³ in a mixture of 150 ml. of concentrated hydrochloric acid and 150 ml. of glacial acetic acid was refluxed for 17 hours. The hydrochloric and acetic acids were removed under reduced pressure and the crude keto acid was esterified. Distillation of the product gave 54.6 g. (75%) of IIIa, b.p. 85–90° (0.12 mm.), n_D^{20} 1.4580. This material was redistilled; b.p. 79–80° (0.10 mm.), n_D^{20} 1.4572 (lit.¹⁴ b.p. 128–135° (16 mm.)). The infrared spectrum (liquid film) had a strong ester carbonyl band at 5.80 μ and a strong ketone band at 5.88 μ .

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethanol; m.p. 128–129° (lit.¹⁵ m.p. 130.4–131.2°).

Semicarbazone.—After recrystallization from ethanol-water, this derivative melted at 196–196.5° (lit.¹² m.p. 195–196°).

Ethyl 2-Oxycyclohexanepropionate (IIIb).—In a 1-l. flask were placed 85.1 g. (0.5 mole) of ethyl 2-oxycyclohexanecarboxylate¹³ and 400 ml. of dry, thiophene-free benzene. In order to ensure total absence of water, 200 ml. of the benzene was distilled off on the steam-bath. A reflux condenser equipped with a drying tube was attached and 0.6 g. (5 mole %) of sodium hydride was added. After the sodium hydride had all reacted, 50 g. (0.5 mole) of ethyl acrylate (containing 0.25% hydroquinone) was added. The mixture was swirled vigorously and allowed to stand at room temperature for 3 days, after which it was heated on the steam-bath for 1 hour. The benzene solution was washed with two 75-ml. portions of water and dried over anhydrous potassium carbonate. After removal of the benzene under reduced pressure, the product was distilled from a 250-ml. modified Claisen flask. The portion boiling at 123–132° (0.12–0.22 mm.), n_D^{20} 1.4622 (lit.¹⁶ b.p. 150–152° (1.0 mm.), n_D^{20} 1.4633) was taken as ethyl 1-carbethoxy-2-oxocyclohexanepropionate; yield 117.3 g. (87%).

Hydrolysis and decarboxylation of 229.8 g. of this diester in 1:1 concentrated hydrochloric acid–glacial acetic acid mixture followed by esterification gave 141.3 g. (84%) of

(12) F. A. Kuehl, R. P. Linstead and B. A. Orkin, *J. Chem. Soc.*, 2213 (1950).

(13) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

(14) R. Ghosh, *J. Indian Chem. Soc.*, **12**, 601 (1935).

(15) F. Ramirez and J. W. Sargent, *THIS JOURNAL*, **77**, 6302 (1955).

(16) N. J. Leonard and W. J. Middleton, *ibid.*, **74**, 5114 (1952).

(10) E. M. Fry, *J. Org. Chem.*, **22**, 1710 (1957).

(11) A. L. Morrison and H. Rinderknecht (*J. Chem. Soc.*, 1510 (1950); *C. A.*, **43**, P5417 (1949)) have reported the preparation of XIIc in lower yield (50%) from the reaction of phenylmagnesium bromide with IIIc. However, they gave no indication that their product was a mixture of stereoisomers.

IIIb, b.p. 96–100° (0.13–0.15 mm.), n_D^{25} 1.4622 (lit.¹⁷ b.p. 140–143° (12 mm.)). The infrared spectrum (liquid film) contained an ester carbonyl band at 5.81 μ and a ketone band at 5.88 μ .

The 2,4-dinitrophenylhydrazone, after recrystallization from ethanol, melted at 89–91°.

Anal. Calcd. for $C_{17}H_{22}O_6N_4$: C, 53.96; H, 5.86. Found: C, 54.05; H, 5.87.

2-Dimethylaminomethylcyclohexanone (IIIc) was prepared in 70% yield by the method of Mannich¹⁸; b.p. 91–94° (10 mm.), n_D^{25} 1.4633 (lit.¹⁸ b.p. 100° (13 mm.)).

The hydrochloride, after recrystallization from ethanol-ether, melted at 151–152.5° (lit.¹⁸ m.p. 152°).

Ethyl 2,2-Ethylenedioxcyclohexaneacetate.—A mixture of 25.0 g. (0.136 mole) of IIa, 9.3 g. (0.15 mole) of ethylene glycol and 50 mg. of *p*-toluenesulfonic acid in 30 ml. of benzene was refluxed with a water separator until no more water separated (3 hours). The benzene solution was washed with 25 ml. of 5% sodium bicarbonate solution and two 25-ml. portions of water and dried over anhydrous sodium sulfate. After removal of the benzene the remaining pale yellow oil was distilled under reduced pressure; 26.9 g. (87%) of ethyl 2,2-ethylenedioxcyclohexaneacetate, b.p. 87–90° (0.12 mm.), n_D^{25} 1.4645, was obtained. The infrared spectrum (liquid film) contained a sharp ester carbonyl band at 5.80 μ . No other carbonyl band was present.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.62; H, 8.57.

N,N-Dimethyl-2,2-ethylenedioxcyclohexaneacetamide.—A mixture of 15.0 g. of the above ester and 15 ml. of liquid dimethylamine and 0.5 ml. of water was placed in a steel bomb and heated at 175° for 12 hours. The reaction mixture was rinsed out of the bomb with ether, the ether removed under reduced pressure, and the remaining oil distilled under vacuum from a small pear-shaped flask. A fore-run of 1.4 g., b.p. 87–113° (0.06 mm.), and a main fraction of 12.4 g., b.p. 113–125° (0.06 mm.), were collected. The latter fraction represented an 83% yield of crude N,N-dimethyl-2,2-ethylenedioxcyclohexaneacetamide. This amide was redistilled through a 4-inch Vigreux column to give 10.1 g. of pale yellow oil, b.p. 112° (0.05 mm.), n_D^{25} 1.4922. The infrared spectrum (liquid film) had a strong amide carbonyl band at 6.13 μ .

Anal. Calcd. for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31. Found: C, 63.50; H, 9.41.

2-(2-Dimethylaminoethyl)-cyclohexanone (IIIId).—A solution of 10.0 g. (0.044 mole) of the above acetal amide in 75 ml. of dry ether was added over a period of 2 hours to a suspension of 1.67 g. (0.044 mole) of lithium aluminum hydride in 100 ml. of dry ether in a 500-ml. 3-necked flask equipped with a dropping funnel, wire stirrer and reflux condenser. The mixture was stirred for an additional 90 minutes, after which it was decomposed by the cautious addition of 75 ml. of 10% potassium hydroxide solution. The layers were separated and the aqueous layer was extracted with three 30-ml. portions of ether. The ether solutions were combined, the ether was removed on the steam-bath and the remaining pale yellow oil dissolved in 200 ml. of water containing 20 ml. of concentrated hydrochloric acid. This solution was warmed on the steam-bath for 30 minutes after which it was cooled to room temperature, saturated with solid potassium carbonate, and extracted with five 25-ml. portions of ether. The ether extract was dried over anhydrous sodium sulfate. Upon distillation, 6.5 g. (87%) of IIIId, b.p. 106–109° (10 mm.), n_D^{25} 1.4651, was obtained. Although this compound has been prepared previously,¹³ the free base was not analyzed. The infrared spectrum (liquid film) had a sharp ketone carbonyl band at 5.86 μ .

Anal. Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32. Found: C, 70.51; H, 11.14.

The picrate, after recrystallization from ethanol, melted at 119–120° (lit.¹⁹ m.p. 119°).

2-(3-Dimethylaminopropyl)-cyclohexanone (IIIe) was prepared from the keto ester IIIb by a sequence of reactions similar to that described above for the conversion of IIIa to IIIId. The **ethyl 2,2-ethylenedioxcyclohexanepropionate**, obtained in 83% yield, boiled at 99–101° (0.15 mm.), n_D^{25}

1.4663; its infrared spectrum (liquid film) showed a single, sharp carbonyl band at 5.75 μ .

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.79; H, 9.31.

The **N,N-dimethyl-2,2-ethylenedioxcyclohexanepropionamide**, obtained in 92% yield, boiled at 128° (0.06 mm.), n_D^{25} 1.4934; its infrared spectrum (liquid film) had a strong amide band at 6.12 μ .

Anal. Calcd. for $C_{13}H_{23}O_3N$: C, 64.70; H, 9.61. Found: C, 65.03; H, 9.53.

The amino ketone IIIe resulting from the reduction and hydrolysis of this acetal amide was obtained in 94% yield as a colorless mobile liquid, b.p. 70–73° (0.08–0.10 mm.), n_D^{25} 1.4660. This compound rapidly darkened on standing even in an atmosphere of nitrogen. Redistillation of the dark material, however, gave a good recovery of the colorless amine ketone. A sample was redistilled for analysis; b.p. 71° (0.15 mm.), n_D^{25} 1.4656; its infrared spectrum (liquid film) had a sharp carbonyl band at 5.86 μ .

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.55. Found: C, 72.45; H, 11.44.

A picrate was prepared in the usual manner and recrystallized from methanol; m.p. 107–108°.

Anal. Calcd. for $C_{17}H_{24}O_3N_4$: C, 49.51; H, 5.87. Found: C, 49.69; H, 6.21.

2-Isoamylcyclohexanone (IIIIf).—In a 500-ml. three-necked flask equipped with a dropping funnel, wire stirrer, and reflux condenser was placed 4.8 g. (0.20 mole) of sodium hydride. The flask was flushed out with dry nitrogen and a nitrogen atmosphere was maintained throughout the remainder of the reaction. One hundred-fifty ml. of dry xylene was added, stirring started, and 34.0 g. (0.20 mole) of ethyl 2-oxocyclohexanecarboxylate¹³ added from the dropping funnel in 1 hour. The mixture was refluxed for an additional hour. Isoamyl bromide (33.2 g., 0.22 mole) then was added in one portion and the mixture refluxed for 24 hours. The flask was cooled in an ice-bath and 90 ml. of cold 10% sulfuric acid added in 10 minutes. The layers were separated and the xylene layer was washed with 15 ml. of 5% sulfuric acid, 30 ml. of 5% aqueous sodium bicarbonate and 30 ml. of water. After drying over anhydrous magnesium sulfate, the xylene was removed under reduced pressure and the remaining oil distilled to give a small quantity of fore-run and 32.0 g. (67%) of crude alkylated keto ester, b.p. 140–150° (10 mm.), n_D^{25} 1.4571. This material was contaminated with some of the unalkylated keto ester, as it gave a violet color with ferric chloride. The latter was removed by shaking vigorously with 5% aqueous sodium hydroxide for 15 minutes. Distillation of the remaining oil gave pure **ethyl 1-isoamyl-2-oxocyclohexanecarboxylate**, b.p. 93–94° (0.22 mm.), n_D^{25} 1.4558, which gave no color with ferric chloride. The infrared spectrum (liquid film) had ketone and ester carbonyl bands at 5.85 and 5.79 μ , respectively.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.88; H, 9.78.

A solution of 25.0 g. (0.104 mole) of this keto ester in a mixture of 100 ml. of 30% (by weight) sulfuric acid and 200 ml. of glacial acetic acid was heated to reflux. Carbon dioxide was evolved almost immediately as indicated by formation of a precipitate when the evolved gas was passed through a barium hydroxide solution. Reflux was allowed to continue until no more carbon dioxide was evolved (24 hr.). The mixture was cooled to room temperature and solid sodium carbonate was added in small portions until the solution was basic to litmus. Water was added as necessary to keep all the salts in solution. The organic liquid which separated was taken up in 100 ml. of ether and the aqueous solution extracted with 5 additional 50-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, the ether was removed under reduced pressure, and the remaining pale yellow liquid distilled. A small amount of fore-run was collected, followed by 11.6 g. (66%) of IIIIf, b.p. 58–60° (0.6 mm.), n_D^{25} 1.4528. This material was redistilled and a center cut, b.p. 58° (0.3 mm.), n_D^{25} 1.4529, was analyzed. The infrared spectrum (liquid film) contained a strong, sharp, carbonyl band at 5.87 μ .

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.41; H, 11.94.

A 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from absolute ethanol; orange plates, m.p. 123–125°.

(17) F. Lions, C.A., **32**, 5844 (1938).

(18) C. Mannich and R. Braun, *Ber.*, **53B**, 1874 (1920).

(19) R. Grewe, *ibid.*, **76B**, 1072 (1943).

Anal. Calcd. for $C_{17}H_{24}O_4N_4$: C, 58.60; H, 6.94. Found: C, 58.55; H, 6.92.

The semicarbazone crystallized from aqueous ethanol in colorless plates, m.p. 152–154°.

Anal. Calcd. for $C_{12}H_{20}ON_3$: C, 63.96; H, 10.29. Found: C, 63.51; H, 9.98.

2-Isohexylcyclohexanone (IIIg) was prepared in the same manner as IIIf except that isohexyl bromide instead of isoamyl bromide was used in the alkylation step. The isohexyl bromide was prepared from isohexyl alcohol by both the hydrobromic acid-sulfuric acid method and the phosphorus tribromide procedure. The alcohol, which had been prepared by the reaction of isoamylmagnesium bromide with formaldehyde, and its 3,5-dinitrobenzoate had properties corresponding to those reported for these compounds in the literature.²⁰ The isohexyl bromides prepared by the two methods had identical properties: b.p. 146–148°, n_D^{25} 1.4410, d_4^{25} 1.1342; these bromides contained 48% bromine (calcd. 48.4); their infrared spectra were identical and showed no evidence of the presence of any foreign functional groups. Certain of these properties, however, are quite different from those reported in the literature: b.p. 146–147°, n_D^{20} 1.4489, d_4^{20} 1.1683, n_D^{25} 1.4494.²¹

The ethyl 1-isohexyl-2-oxocyclohexanecarboxylate, obtained in 67% yield boiled at 113–115° (0.35 mm.), n_D^{25} 1.4564; its infrared spectrum (liquid film) had carbonyl peaks at 5.79 and 5.86 μ .

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.15; H, 10.65.

The ketone IIIg, obtained in 73% yield from the decarboxylation of this ketoester, boiled at 70–72° (0.07 mm.), n_D^{25} 1.4530. This liquid was redistilled and a center cut, b.p. 70° (0.22 mm.), n_D^{25} 1.4541, was analyzed. The infrared spectrum (liquid film) had a sharp carbonyl band at 5.86 μ .

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found: C, 78.77; H, 12.06.

The 2,4-dinitrophenylhydrazone crystallized from ethanol in orange needles, m.p. 125–126°.

Anal. Calcd. for $C_{18}H_{26}O_4N_4$: C, 59.65; H, 7.23. Found: C, 59.79; H, 7.01.

The semicarbazone was prepared in the usual manner and recrystallized from ethanol-water; m.p. 143–145°.

Anal. Calcd. for $C_{13}H_{22}ON_3$: C, 65.25; H, 10.53. Found: C, 65.24; H, 10.66.

Reaction of IIIa with Phenylmagnesium Bromide.—In a 200-ml. 3-necked flask equipped with a reflux condenser, wire stirrer and pressure-equalized dropping funnel was placed 18.42 g. (0.1 mole) of IIIa in 50 ml. of dry ether. A nitrogen source was attached to the opening of the condenser by means of a T-joint; the other arm of the T was connected to a U-tube which contained just enough mercury to fill the bend. The stopper was removed from the dropping funnel and the system was flushed out with dry nitrogen. The stopper was replaced and a slight positive nitrogen pressure was maintained. In the dropping funnel was placed 67.2 ml. (0.1 mole) of the freshly prepared 1.49 *N* phenylmagnesium bromide solution. The Grignard solution was added to the vigorously stirred solution of IIIa over a period of 1.5 hours. A pale yellow precipitate formed during this addition. Toward the end of the addition the precipitate became sufficiently gummy to make stirring difficult. After completion of the addition, the mixture was refluxed for 30 minutes on the steam-bath, after which it was cooled in an ice-bath and 75 ml. of 10% hydrochloric acid was added from the dropping funnel in 10 minutes. The layers were separated, and the ether layer was washed with 25 ml. of water, 25 ml. of 5% sodium bicarbonate solution and 25 ml. of water, and dried over anhydrous calcium sulfate. The ether was distilled off on the steam-bath and the product was distilled from a small pear-shaped Claisen flask with a Vigreux-type side arm. The following fractions were collected: (1) 3.56 g., b.p. 87–89° (0.25 mm.), n_D^{25} 1.4608; (2) 1.71 g., b.p. 89–90° (0.25 mm.), n_D^{25} 1.4628; (3) 1.85 g., b.p. 90–147° (0.25–0.30 mm.), n_D^{25} 1.4792; (4) 3.78 g.,

b.p. 143–147° (0.22–0.30 mm.); (5) 1.68 g., b.p. 143–153° (0.22 mm.); (6) 0.70 g., b.p. 153–165° (0.33 mm.); (residue) 7.32 g. The infrared spectrum of fraction 5 (liquid film) had a carbonyl band at 5.66 μ and phenyl bands at 6.26 and 13.16 μ .

Fractions 1, 2 and 3 represented a 38.6% recovery of IIIa; fractions 4, 5 and 6 represented a 28.5% yield of 2-hydroxy-2-phenylcyclohexanecetic acid lactone (IVa).

After standing for several weeks, fractions 4, 5 and 6 partly solidified. Four recrystallizations from ether-petroleum ether (40–60°) and one more from petroleum alone resulted in recovery of 47% of this material as colorless needles of IVa, m.p. 60–61°. Further recrystallization did not raise the melting point. The infrared spectrum (solid film) had the characteristic phenyl bands and a strong, sharp carbonyl band at 5.65 μ .

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; sapon. equiv., 216. Found: C, 77.85; H, 7.38; sapon. equiv., 215, 217.

The oil from which crystalline IVa had been separated had the same bands in the infrared as the crystalline material, and in addition had weaker carbonyl bands at 5.82 and 5.88 μ and a weak hydroxyl band at 2.88 μ . After standing for several months, some additional crystalline IVa separated from this material. Attempts to obtain other compounds from this oil failed.

The residue from the original distillation has the phenyl bands, a broad carbonyl band at ca. 5.85 μ , and a strong hydroxyl band at 2.89 μ in the infrared. This material could not be distilled, and could not be induced to crystallize. It did not form derivatives with semicarbazide or 2,4-dinitrophenylhydrazine.

Concentration of the alkaline solutions from the saponification equivalent determinations of IVa followed by careful acidification and extraction with ether resulted in recovery of 2-hydroxy-2-phenylcyclohexanecetic acid (V), m.p. 133–134°. After two recrystallizations from benzene-petroleum ether (60–68°), this substance melted at 127–128° (lit.⁶ m.p. 129°). This acid contained 72.23% carbon and 7.63% hydrogen and the neutral equivalent was 232 (calcd.: C, 71.77; H, 7.74; neut. equiv., 234). The infrared spectrum (mull) contained a hydroxyl band at 2.92 μ and a carbonyl band at 5.85 μ .

To a solution of phenylmagnesium bromide prepared from 0.56 g. (0.023 mole) of magnesium and 3.62 g. (0.023 mole) of bromobenzene in 17 ml. of dry ether was added dropwise 2.16 g. (0.01 mole) of IVa in 10 ml. of dry ether. The reaction mixture became cloudy as the addition progressed, but no voluminous precipitate was formed. After the addition was complete, the reaction mixture was refluxed for 30 minutes on the steam-bath. Hydrolysis was effected by dropwise addition of 15 ml. of 10% hydrochloric acid. The layers were separated and the ether layer was washed with 5 ml. of water, two 5-ml. portions of 5% sodium carbonate solution and 5 ml. of water. The ether solution was dried over anhydrous calcium sulfate. Removal of the solvent left 3.53 g. (95%) of a pale yellow solid, m.p. 113–123°. Three recrystallizations from petroleum ether gave 2.13 g. (57%) of 2-(2-diphenyl-2-hydroxyethyl)-1-phenylcyclohexanol (VI), m.p. 128.5–129.5°. An analytical sample was recrystallized from cyclohexane, m.p. 129.5–130.5°. The infrared spectrum (mull) had hydroxyl bands at 2.81 and 2.95 μ and phenyl bands at 6.28, 6.68 and 13.24 μ .

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.80; H, 7.75.

The Reaction of IIIb with Phenylmagnesium Bromide.—The reaction of 19.86 g. (0.1 mole) of IIIb with 68.2 ml. (0.1 mole) of 1.47 *N* phenylmagnesium bromide solution was carried on as described for the reaction of IIIa. Upon distillation of the product, these several fractions were obtained: (1) 1.12 g., b.p. 95–105° (0.25–0.30 mm.); (2) 2.43 g., b.p. 105–115° (0.30–0.40 mm.); (3) 1.49 g., b.p. 115–130° (0.40–0.25 mm.); (4) 1.13 g., b.p. 130–140° (0.25–0.18 mm.); (5) 3.95 g., b.p. 142–146° (0.18 mm.); (6) 3.90 g., b.p. 146° (0.18 mm.); (7) 2.05 g., b.p. 146–149° (0.18 mm.); (8) 1.17 g., b.p. 149–160° (0.18–0.20 mm.); (9) 0.58 g., b.p. 160–170° (0.20 mm.); and 3.95 g. of residue. Fractions 5, 6, 7, 8 and 9 were combined and re-fractionated. Five fractions were taken: (1) 0.81 g., b.p. 94–100° (0.18–0.20 mm.); (2) 0.42 g., b.p. 100–147° (0.20 mm.); (3) 3.95 g., b.p. 147–149° (0.20 mm.); (4) 3.85 g., b.p. 149–151° (0.20 mm.); (5) 1.05 g., b.p. 151–152° (0.20

(20) (a) A. Buelens, *Rec. trav. chim.*, **28**, 113 (1909); (b) J. F. Norris and F. Cortese, *THIS JOURNAL*, **49**, 2644 (1927); (c) I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, N. Y., 1953, p. 91.

(21) H. A. Shonle, *et al.*, *THIS JOURNAL*, **58**, 585 (1936).

mm.); and 1.52 g. of residue. The infrared spectrum (liquid film) of fraction 4 of the second distillation had the characteristic phenyl bands and a strong carbonyl band at 5.83μ .

Fractions 1, 2, 3 and 4 of the first distillation and fractions 1 and 2 of the second distillation represented a 37% recovery of IIIb. Fractions 3, 4 and 5 of the second distillation represented a 38% yield of 2-hydroxy-2-phenylcyclohexane-propionic acid lactone (IVb). Carbon and hydrogen and saponification equivalent determinations were run on fraction 4.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; sapon. equiv., 230. Found: C, 78.68; H, 7.68; sapon. equiv., 243.

The infrared spectrum of the combined distillation residues had the same peaks as that of the residue from the distillation of IVa. As in the previous case, this residue could not be crystallized or distilled and did not form carbonyl derivatives.

After standing for several weeks, fractions 3, 4 and 5 of the second distillation crystallized. Recrystallization to constant melting point from petroleum ether ($40-60^\circ$) resulted in recovery of 54% of this material as colorless needles of pure IVb, m.p. $74-75.5^\circ$. This material was analyzed: C, 77.96; H, 7.96; sapon. equiv., 228, 230.

The infrared spectrum of the crystalline IVb (solid film) contained the usual phenyl bands and a strong, sharp carbonyl band at 5.82μ . The spectrum of the oil from which crystalline IVb had been separated contained the same bands as the solid material, a weak carbonyl band at 5.92μ and a weak hydroxyl band at 2.91μ . Considerable additional amounts of crystalline IVb separated from this oil after long periods of standing. No other compounds could be isolated from this oil.

Acidification of alkaline solutions which resulted from saponification equivalent determinations on IVb gave only recovered lactone; no hydroxy acid could be isolated.

An ethereal solution of phenyllithium was prepared under nitrogen from 1.94 g. (0.280 mole) of lithium wire and 20.9 g. (0.133 mole) of bromobenzene. The solution was titrated with standard hydrochloric acid.

To a solution of 19.82 g. (0.1 mole) of IIIb in ether was added 94 ml. of 1.064 *N* phenyllithium in the same manner as described for the Grignard reagent. The solution became cloudy during the reaction, but no pasty precipitate formed. The reaction mixture was hydrolyzed with water. The ether layer was washed with six 15-ml. portions of water and dried over anhydrous calcium sulfate. Removal of the ether and distillation of the product gave (a) 11.07 g. (56%) or recovered IIIb, b.p. $87-90.5^\circ$ (0.12 mm.); (b) 1.06 g. of an intermediate fraction, b.p. $105-153^\circ$ (0.20 mm.); (c) 3.26 g. (14%) of IVb, b.p. $153-160^\circ$ (0.20 mm.); and (d) a considerable amount of glassy residue, which could not be induced to crystallize.

Reaction of 2-Dimethylaminomethylcyclohexanone (IIIc) with Phenylmagnesium Bromide.—A solution of phenylmagnesium bromide was prepared under nitrogen from 1.88 g. (0.0773 mole) of magnesium and 12.15 g. (0.0773 mole) of bromobenzene in 50 ml. of dry ether. This solution was siphoned through a glass wool plug, under nitrogen pressure, into a nitrogen filled 500-ml. 3-necked flask equipped with a wire stirrer, dropping funnel and reflux condenser. (A nitrogen atmosphere was maintained as usual throughout the entire reaction.) A solution of 10.00 g. (0.0644 mole) of freshly distilled IIIc in 50 ml. of dry ether was added over a period of 45 minutes. A white precipitate formed immediately upon addition of the amino ketone and did not appear to change during the course of the reaction. This precipitate had a salt-like appearance. The reaction mixture was refluxed on the steam-bath for 30 minutes after addition of the ketone was complete. A saturated aqueous solution of ammonium chloride then was added dropwise until all of the magnesium salts were in solution. The layers were separated and a 20% solution of potassium hydroxide was added dropwise to the aqueous layer until a permanent turbidity resulted, after which the aqueous layer was extracted with six 25-ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the remaining pale yellow oil was distilled. Three main fractions were taken: (1) 0.76 g., b.p. $50-60^\circ$ (0.18 mm.); (2) 0.50 g., b.p. $60-111^\circ$ (0.18 mm.); (3) 10.01 g., b.p. $111-116^\circ$ (0.20 mm.). Fraction 1 was mainly starting material (7.6%); fraction 2 a mixture of starting material and addition product; frac-

tion 3 represented a 67% yield of 2-dimethylaminomethyl-1-aminomethyl-1-phenylcyclohexanol (XIIc) (lit.¹¹ b.p. $108-111^\circ$ (0.5 mm.)). Fraction 3 was redistilled and a middle cut, b.p. 100° (0.07 mm.), n_D^{20} 2.5299, was found to contain 77.37% carbon and 9.99% hydrogen (calcd.: C, 77.20; H, 9.94). The infrared spectrum (liquid film) contained broad hydroxyl absorption in the region $2.88-3.3 \mu$.

The carbinol XIIc so obtained was evidently a mixture of diastereoisomers, as the distilled material on standing partly solidified to a crystalline mush. This material could not be satisfactorily recrystallized, and attempts to separate the isomers by chromatography over alumina or silicic acid failed.

The hydrochloride was prepared by dropwise addition of an ethereal solution of dry hydrogen chloride to an ether solution of 10.0 g. of XIIc until no more precipitate formed. The solid was filtered, washed with dry ether, and dried in a vacuum desiccator; m.p. $166-190^\circ$. Fractional crystallization of this material from acetone gave two different compounds: 5.2 g., m.p. $188-189^\circ$, and 1.4 g., m.p. $189-191^\circ$. Although the melting points of these two salts were quite similar, upon admixture they melted at $177-190^\circ$. The remainder of the material could be obtained in crystalline form, but melted over a wide range.

Anal. Calcd. for $C_{15}H_{24}ONCl$: Cl, 13.1. Found: salt, m.p. $188-189^\circ$, Cl, 13.0; salt, m.p. $189-191^\circ$, Cl, 12.9.

The infrared spectra of these two hydrochlorides (null) were not identical, but both contained sharp hydroxyl bands at *ca.* 2.98μ .

A 3.00-g. sample of the salt, m.p. $188-189^\circ$, was dissolved in 10 ml. of water and a solution of 1 g. of potassium hydroxide in 5 ml. of water was added. An oil separated from the solution which solidified on standing. The resulting white solid was filtered off, washed with several portions of water and dried under vacuum to give 2.56 g. (98%) of XIIc, m.p. $54-56^\circ$. Neutralization of the salt, m.p. $189-191^\circ$, gave a viscous oil which could not be induced to crystallize.

Reaction of IIIc with Phenyllithium.—A solution of phenyllithium was prepared under nitrogen from 1.12 g. (0.163 mole) of lithium wire and 10.6 g. (0.0675 mole) of bromobenzene in 35 ml. of dry ether. The phenyllithium solution was siphoned through a glass wool plug, under nitrogen pressure, into a second nitrogen-filled 3-necked flask equipped with a dropping funnel, wire stirrer and reflux condenser. Stirring was started and 10.00 g. (0.0644 mole) of IIIc in 50 ml. of dry ether was added dropwise over a period of one hour. No precipitate formed during the addition, but the solution became cloudy and heat was evolved. The mixture was refluxed for an additional 30 minutes, after which it was decomposed by the dropwise addition of 25 ml. of water. The layers were separated and the aqueous layer was saturated with potassium carbonate and extracted with three 15-ml. portions of ether. Evaporation of the extracts and the original ether layer under reduced pressure followed by distillation of the remaining oil gave the following fractions: (1) 1.09 g. (10.9%) of IIIc, b.p. $49-50^\circ$ (0.18 mm.); (2) 0.34 g. of an intermediate fraction and (3) 11.26 g. (75%) of XIIc, b.p. $103-109^\circ$ (0.15 mm.). This product was also a mixture of diastereoisomers, as it partly solidified on standing.

Reaction of IIIc with Phenylmagnesium Bromide.—The reaction of 10.00 g. (0.0590 mole) of IIIc with the phenylmagnesium bromide from 1.72 g. (0.0708 mole) of magnesium and 11.12 g. (0.0708 mole) of bromobenzene was carried out as described above with the amino ketone IIIc. After the reaction mixture was worked up as before, the products were distilled. Three fractions were taken: (1) 4.96 g., b.p. $52-55^\circ$ (0.07 mm.); (2) 0.18 g., b.p. $155-166^\circ$ (0.07 mm.); (3) 5.95 g., b.p. $106-130^\circ$ (0.07 mm.). The third fraction was probably superheated, as the temperature of the oil-bath was over 200° when the last part of this fraction was collected.

Fraction 1 was recovered amino ketone IIIc (50%). Fraction 3 was taken as 2-(2-dimethylaminoethyl)-1-phenylcyclohexanol (XIIId); yield 41%. Upon standing overnight fraction 3 completely solidified to a white solid, m.p. $54-66^\circ$. An analytical sample was obtained by vacuum sublimation of a portion of this solid; m.p. $61-70^\circ$.

Anal. Calcd. for $C_{16}H_{26}ON$: C, 77.68; H, 10.19. Found: C, 78.04; H, 10.10.

Recrystallization of this solid carbinol to constant melting point from methanol-water led to recovery of about

50% as colorless needles, m.p. 71–72°. The remainder could easily be recovered in crystalline form from the mother liquors, but melted over a wide range. Evidently this product was a mixture of diastereoisomers, with one isomer predominating. Attempts to separate the isomers by chromatography over alumina or silicic acid failed. A sample of the material melting at 71–72° had the analysis: C, 77.77; H, 9.97.

The infrared spectrum (solid film) contained the characteristic phenyl bands, a weak hydroxyl band at 2.92 μ , and broad absorption in the vicinity of 3.2 μ (probably bonded hydroxyl absorption).

The hydrochloride of the 72° isomer of XIId, after recrystallization from ethanol-ethyl acetate, melted at 200–202° dec. The infrared spectrum (mull) had a strong, sharp, hydroxyl band at 2.98 μ .

Anal. Calcd. for $C_{16}H_{26}ONCl$: Cl, 12.5. Found: Cl, 12.3.

When the hydrochloride was prepared from the mixture of isomers of XIId, 60% could be obtained as colorless prisms, m.p. 200–202° dec., by recrystallization from ethyl acetate-ethanol. The remainder of the material melted at 195–200° dec. Attempts to obtain a second sharp-melting compound were unsuccessful.

Reaction of IIIId with Phenyllithium.—The reaction between 10.00 g. (0.0590 mole) of the amino ketone IIIId and the phenyllithium from 1.03 g. (0.149 mole) of lithium wire and 9.74 g. (0.062 mole) of bromobenzene was carried out and worked up as described for the reaction of IIIC with phenyllithium. Upon distillation of the reaction product, three fractions were obtained: (1) 1.75 g. (17.4%) of recovered IIIId, b.p. 53–54° (0.06–0.05 mm.); (2) 0.20 g. of an intermediate fraction, b.p. 54–106° (0.05 mm.); (3) 10.52 g. (72%) of XIId, b.p. 106–109° (0.05 mm.). Fraction 3 solidified on standing; m.p. 58–70°. A 7.00-g. sample of this material was recrystallized from methanol-water to give 3.93 g. (56% recovery) of colorless needles, m.p. 70–72°. This melting point was undepressed on admixture with a sample of the 72° material obtained from the fraction of IIIId with phenylmagnesium bromide. The remainder of the material could be obtained in crystalline form from the mother liquors, but melted over a wide range.

Reaction of IIIe with Phenylmagnesium Bromide.—The reaction of 7.50 g. (0.0409 mole) of freshly distilled IIIe with the Grignard reagent from 1.21 g. (0.049 mole) of magnesium and 7.70 g. (0.049 mole) of bromobenzene was carried out and worked up as described above. Upon distillation, 6.65 g. (89%) of IIIe, b.p. 70–71° (0.1 mm.), was recovered. The residue (0.70 g.) was a dark gum which could not be induced to crystallize.

This experiment was repeated as follows: 7.30 g. (0.0398 mole) of IIIe in 35 ml. of dry ether was added as usual to the Grignard solution from 1.21 g. (0.049 mole) of magnesium and 7.70 g. (0.049 mole) of bromobenzene. The mixture was refluxed for 30 minutes and allowed to stand until the precipitate had settled. The supernatant ether was siphoned off through a glass wool plug under nitrogen pressure. The precipitate was washed with three 40-ml. portions of dry ether, and the washings removed in the same manner as the original ether. An additional precipitate separated from the combined supernatant ether and washings. This mixture was allowed to stand for 4 days under a dry nitrogen atmosphere after which it was refluxed 4 hours. Upon cooling, the precipitate coagulated and was filtered off. Hydrolysis of this solid yielded 0.15 g. (2%) of the starting amino ketone. The ether solution was fractionated through a 10-inch column packed with stainless steel wire saddles. The distillate was pure ether, b.p. 34°, n_D^{25} 1.3497. The residue from this distillation was distilled from a small pear-shaped flask. A small additional amount of ether was obtained, and then 1.31 g. (42%) of benzene, b.p. 77°, n_D^{25} 1.4817. Since the refractive index was quite low (pure distilled benzene had n_D^{25} 1.4982), the benzene was probably contaminated with some ether. Nitration of this material gave *m*-dinitrobenzene, m.p. 88–89°.

The precipitate from above was suspended in 50 ml. of ether and was decomposed by addition of excess saturated aqueous ammonium chloride. The layers were separated and a 20% solution of potassium hydroxide was added dropwise to the aqueous layer until a permanent turbidity resulted. This aqueous suspension then was extracted with five 25-ml. portions of ether. The combined ether solution was extracted with four 20-ml. portions of 5% hydrochloric

acid, after which it was dried over magnesium sulfate and distilled. Only pure ether, b.p. 34°, n_D^{25} 1.3497, was present; no benzene could be detected. The aqueous acid solution was saturated with solid potassium carbonate and extracted with five 25-ml. portions of ether. The ether solution was dried over magnesium sulfate, the ether removed under reduced pressure, and the residue distilled to give 5.95 g. (81.5%) of recovered IIIe, b.p. 71–73° (0.15 mm.), n_D^{25} 1.4657. No other product could be isolated; only 0.33 g. of tarry residue remained from the distillation.

Reaction of IIIe with Phenyllithium.—The reaction of 10.00 g. (0.0546 mole) of IIIe with the phenyllithium from 0.96 g. (0.138 mole) of lithium and 9.0 g. (0.057 mole) of bromobenzene was carried out and worked up as before. Distillation under reduced pressure gave 1.45 g. (14.5%) of IIIe, b.p. 68–70° (0.07 mm.), and 0.17 g. of an intermediate fraction, b.p. 70–116° (0.07 mm.). The distillation was interrupted at this point since the distillate was very viscous and was beginning to crystallize in the condenser. The residue was removed from the distilling flask with ether, and the ether removed under reduced pressure leaving 10.15 g. of a pale tan crystalline solid, m.p. 98–104°. This amount represented a 71% yield of 2-(3-dimethylaminopropyl)-1-phenylcyclohexanol (XIIe). Recrystallization from petroleum ether (60–68°) gave colorless crystals, m.p. 104.5–106°. Nearly all of the material could be recovered as crystals melting no lower than 103°. The infrared spectrum (solid film) had a strong hydroxyl band at 3.13 μ .

Anal. Calcd. for $C_{17}H_{27}ON$: C, 78.11; H, 10.41. Found: C, 78.44; H, 10.22.

The hydrochloride was prepared in the usual manner and recrystallized from ethanol-ethyl acetate; m.p. 206–208° dec. The infrared spectrum (mull) contained a strong hydroxyl band at 2.98 μ .

Anal. Calcd. for $C_{17}H_{28}ONCl$: Cl, 11.9. Found: Cl, 11.9.

Reaction of 2-Isoamylcyclohexanone (IIIIf) with Phenylmagnesium Bromide.—A solution of phenylmagnesium bromide was prepared under nitrogen from 0.87 g. (0.0357 mole) of magnesium turnings and 5.61 g. (0.0357 mole) of bromobenzene in 30 ml. of dry ether. This solution was siphoned through a glass wool plug under nitrogen pressure into a 250-ml. three-necked flask equipped with a dropping funnel, wire stirrer and reflux condenser. Stirring was started and 5.00 g. (0.0297 mole) of the ketone IIIIf in 30 ml. of dry ether was added dropwise over a period of 1 hour. A nitrogen atmosphere was maintained throughout the entire reaction. No precipitate formed during the addition. The mixture was refluxed on the steam-bath for 30 minutes after addition of the ketone was completed. A saturated aqueous solution of ammonium chloride then was added dropwise until a clean separation to a liquid and a solid phase occurred. The ether was decanted off and the solid washed with three 15-ml. portions of ether. The ether solutions were combined, the ether was removed under reduced pressure, and the remaining oil distilled. Three fractions were collected: (1) 0.24 g., b.p. 59–63° (0.28–0.25 mm.); (2) 0.53 g., b.p. 63–117° (0.25–0.20 mm.); (3) 6.00 g., b.p. 117–118° (0.20 mm.). Fraction 1 was mainly recovered IIIIf (4.8%). Fraction 3, which was a rather viscous liquid, represented an 82% yield of 2-(3-methylbutyl)-1-phenylcyclohexanol. An analytical sample was obtained by redistillation of (3); b.p. 12° (0.30 mm.), n_D^{25} 1.5162. The infrared spectrum (liquid film) had a hydroxyl band at 2.88 μ .

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.00; H, 10.70.

Reaction of IIIIf with Phenyllithium.—To a stirred solution of phenyllithium prepared from 0.52 g. (0.075 mole) of lithium wire and 4.91 g. (0.0312 mole) of bromobenzene in 30 ml. of ether (nitrogen atmosphere). No precipitate formed. The mixture was refluxed for 30 minutes after addition of the ketone was completed, then was cooled to room temperature and decomposed by dropwise addition of 20 ml. of water. The ether layer was washed with three 5-ml. portions of water and dried over anhydrous magnesium sulfate. After removing the ether under reduced pressure, the remaining pale yellow oil was fractionated. Three fractions were taken: (1) 0.70 g. (14%) of IIIIf, b.p. 57–60° (0.30 mm.); (2) 0.12 g. of an intermediate fraction, b.p. 60–113° (0.30–0.15 mm.); (3) 5.89 g. (81%) of 2-(3-methylbutyl)-1-phenylcyclohexanol, b.p. 113–114° (0.15 mm.), n_D^{25} 1.5159.

Reaction of 2-Isohexylcyclohexanone (IIIg) with Phenylmagnesium Bromide.—The reaction of 5.00 g. (0.0274 mole) of IIIg with the Grignard reagent from 0.80 g. (0.0329 mole) of magnesium and 5.17 g. (0.0329 mole) of bromobenzene was carried out as described for IIIf. Distillation of the products gave these various fractions: (1) 0.67 g., b.p. 62–64° (0.11–0.08 mm.); (2) 0.34 g., b.p. 64–120° (0.20 mm.); (3) 5.68 g., b.p. 120–122° (0.08 mm.). Fraction 1 was recovered IIIg (13%); fraction 3 represented an 80% yield of 2-(4-methylpentyl)-1-phenylcyclohexanol. Fraction 3 was redistilled and a middle cut, b.p. 120° (0.08 mm.), n_D^{25} 1.5142, was taken for analysis. The infrared spectrum (liquid film) contained a hydroxyl band at 2.86 μ .

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.62; H, 10.96.

2-Dimethylaminomethyl-1-phenyl-1-propionyloxycyclohexane (XIIIc) Hydrochloride.—A mixture of 2.00 g. (0.0857 mole) of XIIc, m.p. 54–56°, 0.96 g. (0.01 mole) of sodium propionate and 20 ml. of propionic anhydride was placed in a 50-ml. round-bottom flask equipped with a reflux condenser carrying a drying tube. The mixture was heated for 3 hours on the steam-bath, after which it was poured into 50 ml. of water and allowed to stand until the anhydride had all dissolved. The solution was saturated with potassium carbonate and extracted with four 20-ml. portions of ether. The ether solution was dried over anhydrous potassium carbonate and a solution of dry hydrogen chloride in ether was added dropwise until no more precipitate formed. The resulting white solid was filtered off, washed with ether, dried and recrystallized from ethanol–ethyl acetate to give 2.44 g. (88%) of XIIIc hydrochloride, m.p. 182–183.5° dec. A sample was recrystallized two more times for analysis, m.p. 183–185° dec. The infrared spectrum (mull) had a strong carbonyl band at 5.78 μ ; no hydroxyl band was present.

Anal. Calcd. for $C_{18}H_{28}O_2NCl$: C, 66.34; H, 8.66; Cl, 10.9. Found: C, 66.51; H, 8.59; Cl, 10.8

When this preparation was carried out as above, except that heating was continued for only 3 hours, the product consisted largely of unchanged carbinol XIIc.

When the acylation was carried out as above on 13.4 g. (0.0574 mole) of the mixture of isomers of XIIc obtained from the Grignard reaction, 16.3 g. (87%) of XIIIc hydrochloride, m.p. 170–181°, resulted. Fractional crystallization from ethanol–ethyl acetate gave 9.9 g. of colorless prisms, m.p. and mixed m.p. with above product 183–185° dec., and 1.89 g. of colorless needles, m.p. 180–182° dec. The salt, m.p. 180–182°, when mixed with the 185° salt, melted at 170–180° dec. The lower melting salt was analyzed: C, 66.33; H, 8.66; Cl, 10.8. The infrared spectrum (mull) contained a strong carbonyl band at 5.78 μ . This spectrum was similar, but not identical, to the spectrum of the 185° salt.

2-(2-Dimethylaminoethyl)-1-phenyl-1-propionyloxycyclohexane (XIIIId) Hydrochloride.—One gram of XIIId, m.p. 71–72°, 0.48 g. of sodium propionate and 25 ml. of propionic anhydride were placed in a 50-ml. round-bottom flask equipped with a reflux condenser carrying a drying tube.

The mixture was stirred magnetically and heated at 115–120° in an oil-bath for 24 hours, after which it was cooled to room temperature and poured into 50 ml. of water. After the solution had become homogeneous, it was saturated with potassium carbonate and extracted with five 15-ml. portions of ether. After drying over anhydrous potassium carbonate, the ether solution was treated with a solution of dry hydrogen chloride in ether (dropwise addition) until no more precipitate formed. The resulting white solid was washed with ether, dried and crystallized from ethyl acetate, which gave 0.76 g. (55.5%) of XIIIId hydrochloride as colorless plates, m.p. 180–181°. Recrystallization from ethyl acetate resulted in recovery of nearly all of this material as colorless plates, m.p. 181–182° dec. Further recrystallization did not raise the melting point. The infrared spectrum (mull) contained a strong ester carbonyl band at 5.79 μ . No hydroxyl band was present.

Anal. Calcd. for $C_{19}H_{30}O_2NCl$: C, 67.14; H, 8.90; Cl, 10.4. Found: C, 67.31; H, 8.90; Cl, 10.4.

Lower reaction temperatures or shorter heating times gave very little of the ester. Recovered carbinol XIIId was the main product in every case.

The preparation of XIIIId hydrochloride also could be carried out in 46% yield by heating XIIId hydrochloride in propionic anhydride at 115–120° for 24 hours.

Attempted Preparation of the Propionate of XIIe.—Conversion of the carbinol XIIe to this ester was attempted by the following methods: (a) heating XIIe with propionic anhydride and sodium propionate at 115° for 24 hours; (b) same as (a), except heated at 125°; (c) addition of propionyl chloride to a benzene solution of XIIe; (d) treatment of XIIe in ether with one equivalent of phenyllithium to form the lithium salt, followed by addition of propionyl chloride. The main product of each of these reactions was the carbinol XIIe, recovered as the hydrochloride. In no case was any other pure compound isolated.

A fifth method, heating XIIe hydrochloride in propionic anhydride at 135–140° for 24 hours, gave a 9.6% yield of 1 (or 6)-(3-dimethylaminopropyl)-2(or 1)-phenylcyclohexene hydrochloride, m.p. 173–175°, as the only crystalline product. The infrared spectrum had a band of medium intensity at 6.27 μ (probably the conjugated double bond). No hydroxyl or carbonyl bands were present.

Attempted Propionylation of 2-(4-Methylpentyl)-1-phenylcyclohexanol.—A mixture of 3.0 g. (0.115 mole) of this carbinol, 1.1 g. (0.115 mole) of sodium propionate and 30 ml. of propionic anhydride was stirred magnetically and heated at 125° for 24 hours. The excess propionic anhydride was removed under reduced pressure (bath temperature 100°) and the residue was taken up in 40 ml. of dry ether. The ether solution was filtered to remove the sodium propionate, the ether removed under reduced pressure, and the product distilled to give 2.0 g. (67%) of recovered carbinol, b.p. 121–124° (0.1 mm.), n_D^{25} 1.5130. The remainder of the reaction was a brown gum which would not distill.

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

Cyclic Dienes. XXIV. 1,2-Dimethylenedecalin¹

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The cyclic diene 1,2-dimethylenedecalin was synthesized in five steps from 3,4-dihydro-1,2-naphthalic anhydride in an over-all yield of 61%. In the final step, a diacetate was pyrolyzed to give the desired diene. The structure of the 1,2-dimethylenedecalin was proved by analysis, vapor phase chromatography, infrared and ultraviolet absorption spectra and conversion to solid Diels–Alder adducts with maleic anhydride and benzoquinone. The structure of the maleic anhydride adduct was further proved by hydrolysis to the corresponding diacid and by simultaneous dehydrogenation and decarboxylation to phenanthrene.

In a previous article in this series³ a general method for the synthesis of linear condensed poly-

(1) Previous paper in this series, *THIS JOURNAL*, **81**, 5393 (1959).

(2) National Cancer Institute Fellow (U. S. Public Health Service), 1955–1957.

(3) W. J. Bailey and M. Madoff, *THIS JOURNAL*, **75**, 5603 (1953).

nuclear aromatic hydrocarbons was described. For example, pentacene was prepared from 1,2-dimethylenecyclohexane and heptacene and hexacene from 2,3-dimethylenedecalin.⁴ An interest-

(4) W. J. Bailey and C.-W. Liao, *ibid.*, **77**, 992 (1955).