sodium (0.10 mole) in liquid ammonia (300 ml.) was prepared according to the directions of Campbell and Young.[3] The dark red solution was cooled to −76° and 33.2 g. (0.10 mole) of magnesium bromide dietherate was added, with stirring, in small portions. The dark red color of the solution disappeared and an orange precipitate appeared when all the magnesium salt had been added. The ammonia was allowed to evaporate, ether was stirred with the residue and filtered off and the ether evaporated to give 10.5 g. of crude product. Distillation at atmospheric pressure from a Claisen distilling flask gave 9.0 g. of material, b.p. 170–177°, $n^{25}\text{D}$ 1.5460. This represents a 76% recovery of C_9-hydrocarbon; composition 94% propenylbenzene, 6% allylbenzene.

Treatment of the Orange Ammoniated Cinnamylmagnesium Bromide Complex with Oxygen in Liquid Ammonia.—An ether solution (50 ml.) containing 0.040 mole of cinnamylmagnesium bromide was forced, under pressure, through a 0.5-mm. capillary into 400 ml. of stirred liquid ammonia. The temperature of the liquid ammonia was at −76° initially but rose to −70° after the addition of the Grignard solution. A bright orange precipitate formed the instant the Grignard solution came in contact with the liquid ammonia. Oxygen was bubbled through the reaction mixture for 10 to 15 minutes with no perceptible change occurring. The temperature was allowed to rise to about −60°, oxygen addition continuing, and the yellow color of the precipitate changed to greenish-yellow and then to white in about 5 minutes. The ammonia was then allowed to evaporate. Ether and water (75 ml. of each) were added to the reaction mixture and carbon dioxide was bubbled through the stirred mixture for 2 hours. This would decompose the magnesium salts of all alcohols and hydroperoxides which might be present. An easily filterable magnesium salt residue was formed. The reaction mixture was filtered. The ether layer was distilled to remove the ether and the residue was distilled at 20 mm. to give 1.2 g. of material, b.p. 67–73°. (This corresponds to the boiling range for the C_9-hydrocarbons.) The pressure was then reduced to 1 mm. and 0.8 g. of material distilled over between 70 and 100°. This fraction smelled strongly of cinnamaldehyde and gave a positive carbonyl test with 2,4-dinitrophenylhydrazine. There was 2.3 g. of dark residue remaining in the pot. The crude yield of cinnamaldehyde was 15% and of C_9-hydrocarbon, 25%.

The 2,4-dinitrophenylhydrazone had a melting point of 256–257° and was not depressed when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of cinnamaldehyde.

LOS ANGELES 24, CALIF.
CHINA LAKE, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

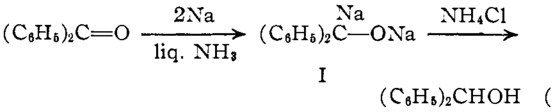
Reductive Metalation of Benzophenone and Benzalacetophenone by Alkali Metals in Liquid Ammonia and Some Condensations of the Resulting Dialkali Salts[1,2]

BY PHILLIP J. HAMRICK, JR., AND CHARLES R. HAUSER

RECEIVED APRIL 7, 1958

Disodiobenzophenone prepared by the reductive metalation of benzophenone with two equivalents of sodium metal in liquid ammonia underwent several types of carbon–carbon condensations including alkylations, addition to the carbonyl group of benzaldehyde and conjugate addition to benzalacetophenone. Similarly, benzalacetophenone was reductively metalated by sodium or potassium in liquid ammonia to form dialkali derivatives. The dipotassio salt produced the corresponding saturated ketone on acidification, and gave the β-benzyl derivative with an equivalent of benzyl chloride. With two equivalents of the halide benzylation occurred at the β- and α-carbon atoms. Also, the dipotassio salt underwent an addition reaction with benzophenone to give the same product that was obtained from the conjugate addition of disodiobenzophenone to benzalacetophenone.

Wooster[3] has shown that benzophenone is reductively metalated by two equivalents of sodium metal in liquid ammonia to form the disodio salt I and that benzhydrol is obtained almost quantitatively on acidification with ammonium chloride (equation 1).



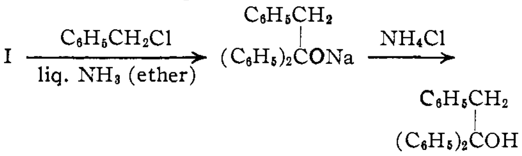
$$(C_6H_5)_2C{=}O \xrightarrow[\text{liq. NH}_3]{2\text{Na}} \underset{\text{I}}{(C_6H_5)_2\overset{\text{Na}}{C}{-}ONa} \xrightarrow{NH_4Cl} (C_6H_5)_2CHOH \quad (1)$$

He also observed that disodio salt I can be alkylated with ethyl bromide to form 1,1-diphenylpropanol-1. The yield was not given, and ethylamine was obtained as a side reaction product.

Schlenk and his co-workers[4] had previously shown that such a reductive metalation of benzophenone and of biphenyl phenyl ketone can be accomplished in ether, and that the resulting disodio salt of the latter ketone can be carbonated to form the corresponding hydroxy-acid. The yield of this acid was not reported.

In the present investigation disodio salt I was found to take part in several carbon–carbon condensations to give good yields of products. More significantly it was shown that benzalacetophenone, which is a vinylog of benzophenone, will form similar dialkali salts and that they will undergo related reactions.

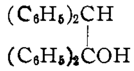
Results with Dialkali Salts of Benzophenone.—Disodiobenzophenone (I) was prepared by means of two equivalents of sodium in liquid ammonia (containing some ether) and benzylated with an equivalent of benzyl chloride to form carbinol II in 76% yield (equation 2).



$$\text{I} \xrightarrow[\text{liq. NH}_3\text{ (ether)}]{C_6H_5CH_2Cl} (C_6H_5)_2\overset{C_6H_5CH_2}{\overset{|}{C}}ONa \xrightarrow{NH_4Cl} \underset{\text{II}}{(C_6H_5)_2\overset{C_6H_5CH_2}{\overset{|}{C}}OH} \quad (2)$$

Evidently this preferential alkylation at the carbanion portion of disodio salt I was not accompanied by appreciable O-alkylation.

Similarly, disodio salt I was benzhydrylated with benzhydryl chloride to give carbinol III in 82% yield.



$$(C_6H_5)_2\overset{(C_6H_5)_2CH}{\overset{|}{C}}OH \quad \text{III}$$

The structure of the latter product was established as III by an independent synthesis from

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(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) Reported before the Regional Meeting of the American Chemical Society at Durham, N. C., November, 1957.

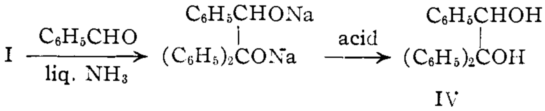
(3) C. B. Wooster, THIS JOURNAL, 50, 1388 (1928).

(4) W. Schlenk, J. Appenrodt, A. Michael and A. Thal, *Ber.*, 47, 473 (1914).

sodium diphenylmethide and benzophenone (equation 3).[5]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. NH}_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow{(C_6H_5)_2C=O} \text{III} \quad (3)$$

A second type of condensation of disodio salt I involved an addition reaction to the carbonyl group of benzaldehyde to form glycol IV in 91% yield (equation 4).

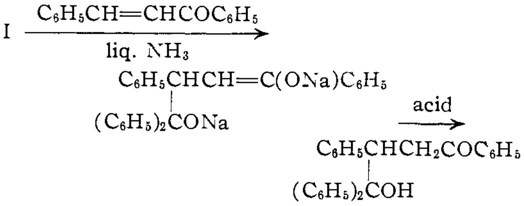


$$\text{I} \xrightarrow[\text{liq. NH}_3]{C_6H_5CHO} \begin{matrix} C_6H_5CHONa \\ | \\ (C_6H_5)_2CONa \end{matrix} \xrightarrow{\text{acid}} \begin{matrix} C_6H_5CHOH \\ | \\ (C_6H_5)_2COH \end{matrix} \quad (4)$$

IV

The structure of the product was established as IV by an independent synthesis from benzoin and excess phenylmagnesium bromide as described by Acree.[6] While this Grignard method may be preferred for glycol IV, the present method should be useful for the preparation of certain substituted glycols from appropriately substituted benzaldehydes.

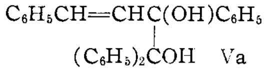
A third type of condensation reaction involved the conjugate addition of disodio salt I to benzalacetophenone to form the keto-alcohol V in 47% yield (equation 5).



$$\text{I} \xrightarrow[\text{liq. NH}_3]{C_6H_5CH=CHCOC_6H_5} \begin{matrix} C_6H_5CHCH=C(ONa)C_6H_5 \\ | \\ (C_6H_5)_2CONa \end{matrix} \xrightarrow{\text{acid}} \begin{matrix} C_6H_5CHCH_2COC_6H_5 \\ | \\ (C_6H_5)_2COH \end{matrix} \quad (5)$$

V

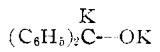
That the product was V and not the possible 1,2-addition derivative Va was supported by the Grignard machine determination which indicated the presence of one hydroxyl group and one carbonyl group. Moreover, the same product was obtained from dipotassiobenzalacetophenone and benzophenone as described in the next section.



$$\begin{matrix} C_6H_5CH=CHC(OH)C_6H_5 \\ | \\ (C_6H_5)_2COH \end{matrix}$$

Va

A fourth type of condensation involved the carbonation of the dipotassiobenzophenone Ib (after replacing the liquid ammonia by ether) to form benzilic acid (50%) and some benzhydrol.

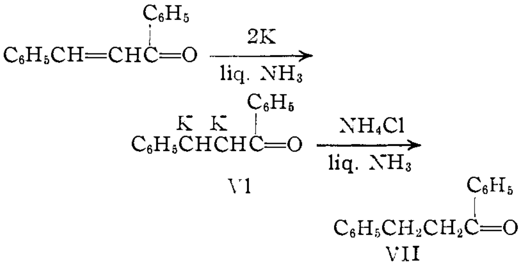


$$(C_6H_5)_2\overset{K}{C}-OK$$

Ib

It should be mentioned that, whereas the reductive metalation of benzophenone by sodium or potassium occurs rapidly (see equation 1), the metalation of the potassio salt of benzhydrol, $(C_6H_5)_2CHOK$, by potassium amide in liquid ammonia is relatively slow. Thus, benzhydrol was evidently not converted appreciably to dipotassio salt Ib on treatment with two equivalents of potassium amide in liquid ammonia during four hours, since the purple color that accompanies the formation of this salt in the reductive metalation method was not observed. Wooster[3] reported the formation of the dipotassio salt Ib by treating benzhydrol with excess potassium in liquid ammonia for 20 hours.

Results with Dialkali Salts of Benzalacetophenone.—Benzalacetophenone was found to undergo rapid reductive metalation with two equivalents of potassium in liquid ammonia to form the dipotassio salt VI[7] which, on acidification with ammonium chloride, gave the corresponding saturated ketone VII in almost quantitative yield (equation 6).

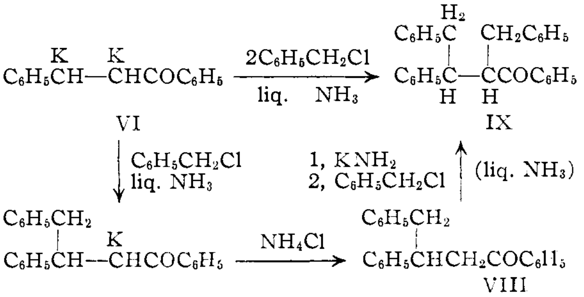


$$C_6H_5CH=CH\overset{C_6H_5}{\overset{|}{C}}=O \xrightarrow[\text{liq. NH}_3]{2K} C_6H_5\overset{K}{C}H\overset{K}{C}H\overset{C_6H_5}{\overset{|}{C}}=O \xrightarrow[\text{liq. NH}_3]{NH_4Cl} C_6H_5CH_2CH_2\overset{C_6H_5}{\overset{|}{C}}=O \quad (6)$$

VI VII

Dipotassio salt VI is of particular interest, since its β-carbon atom underwent preferential benzylation with an equivalent of benzyl chloride to form the monobenzylated ketone VIII in 73% yield. With two equivalents of benzyl chloride, alkylation occurred at the α- as well as the β-carbon atom to form the dibenzylated ketone IX in 76% yield. The monobenzylated ketone VIII was further alkylated with benzyl chloride by means of potassium amide to give the dibenzylated ketone IX in 75% yield. These results are summarized in scheme A (for certain unexplained color changes see Experimental).

SCHEME A



$$\begin{tikzcd} C_6H_5\overset{K}{C}H-\overset{K}{C}HCOC_6H_5 \ (\text{VI}) \arrow[r, "2C_6H_5CH_2Cl", "\text{liq. NH}_3"'] \arrow[d, "C_6H_5CH_2Cl", "\text{liq. NH}_3"'] & C_6H_5\overset{H_2}{C}-\overset{}{C}H(C_6H_5)-CH(CH_2C_6H_5)COC_6H_5 \ (\text{IX}) \\ C_6H_5CH(CH_2C_6H_5)-\overset{K}{C}HCOC_6H_5 \arrow[r, "NH_4Cl"] & C_6H_5CH(CH_2C_6H_5)CH_2COC_6H_5 \ (\text{VIII}) \arrow[u, "1,\ KNH_2;\ 2,\ C_6H_5CH_2Cl", "(\text{liq. NH}_3)"'] \end{tikzcd}$$

The structure of the monobenzylation product was established as VIII not only by its further benzylation to form dibenzylation product IX (see Scheme A), but also by an independent synthesis involving the conjugate addition of benzylmagnesium chloride to benzalacetophenone.

The monobenzylation of dipotassio salt VI presumably involves the introduction of the benzyl group at the β-carbanion without its bonding pair of electrons, whereas the conjugate addition involves the introduction of the benzyl group at the β-carbon with its bonding pair of electrons (as a carbanion), as indicated by mechanisms A and B, respectively. The latter reaction may occur through a cyclic mechanism which is made possible

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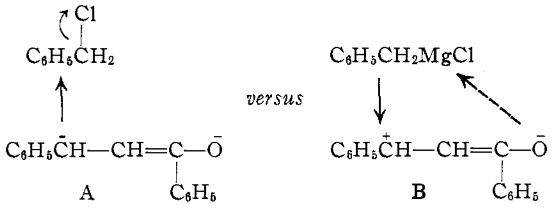
[5] The details of this method will be described later by P. J. Hamrick, Jr., and C. R. Hauser.

[6] S. F. Acree, *Ber.*, **37**, 2753 (1904).

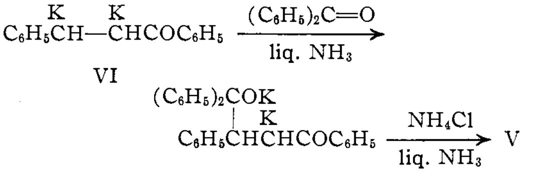
[7] For convenience the dicarbanion resonance sturcture of dipotassio salt VI is indicated, although the dianion would presumably be more like the resonance structure having a negative charge on the oxygen as in mechanisms A and C or as in $C_6H_5\bar{C}HCH=CHC(\bar{O})C_6H_5$.

by the preliminary coördination indicated by the dotted arrow.



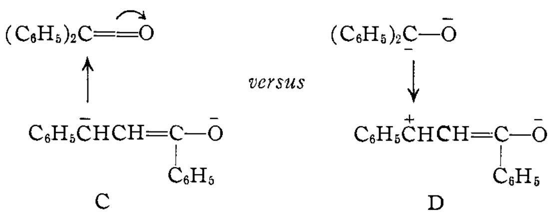
The dibenzylation product IX obtained in good yield in liquid ammonia by either course represented in Scheme A apparently consisted largely of only one of the two possible diastereoisomers, since it melted sharply after one recrystallization. However, when the dibenzylation of dipotassio salt VI was effected with two equivalents of benzyl chloride in a medium containing only ether the product seemed to consist of both isomers (see Experimental). A similar influence of solvent on the proportions of diastereoisomers was recently observed[8] in the α-phenylethylation of potassio phenylacetonitrile with α-phenylethyl chloride.

Another type of condensation of dipotassio benzalacetophenone VI was realized with benzophenone to form hydroxy-ketone V in 56% yield (equation 7).



$$\underset{\text{VI}}{\overset{\text{K}\qquad\text{K}}{C_6H_5CH{-}CHCOC_6H_5}} \xrightarrow[\text{liq. NH}_3]{(C_6H_5)_2C{=}O} \overset{(C_6H_5)_2COK\ \ \text{K}}{C_6H_5CHCHCOC_6H_5} \xrightarrow[\text{liq. NH}_3]{NH_4Cl} \text{V} \quad (7)$$

The condensation occurred at the β-carbon atom and not at the α-carbon atom since this product was the same as that obtained from the conjugate addition of disodiobenzophenone to benzalacetophenone (see equation 5). The mechanisms of these two reactions are contrasted in C and D.



It should be mentioned that disodiobenzalacetophenone was prepared from the α,β-unsaturated ketone and two equivalents of sodium in liquid ammonia and shown to undergo certain of the types of reactions described above for the dipotassio salt VI. In general the yields were lower with the disodio salt.

Experimental[9]

Disodiobenzophenone (I).—To a stirred solution of 4.8 g. (0.2 g. atom) of sodium metal dissolved in 250 ml. of liquid ammonia was added a solution of 18.2 g. (0.1 mole) of benzophenone in 50 ml. of dry ether. The blue solution changed rapidly to purple and finally to black. The resulting solution was assumed to contain 0.1 mole of disodiobenzophenone (I).

Benzylation of Disodio Salt I to Form 1,1,2-Triphenylethanol (II).—To a stirred liquid ammonia solution of 0.1 mole of disodiobenzophenone (I) was added a solution of 12.65 g. (0.1 mole) of benzyl chloride in 50 ml. of dry ether. The reaction mixture became dark green, then yellow. The liquid ammonia was evaporated (steam-bath) while ether (200 ml.) was added to maintain constant volume. The resulting suspension was poured into a solution of 30 ml. of glacial acetic acid in 100 ml. of ether. After washing with saturated sodium bicarbonate solution, the ether layer was dried over Drierite and the ether evaporated (steam-bath). The viscous residue was dissolved in pentane and cooled in an ice-bath to give 22 g. of white crystals, m.p. 85–86°. The product was recrystallized from a 1:4 mixture of benzene and petroleum ether (b.p. 30–60°) to give 21 g. (76%) of carbinol II, m.p. 88°, reported[10] m.p. 89–90° (88°).

Benzhydrylation of I to Form 1,1,2,2-Tetraphenylethanol (III).—To a stirred solution of 0.1 mole of disodiobenzophenone (I) was added 20.3 g. (0.1 mole) of benzohydryl chloride dissolved in 50 ml. of dry ether. The dark solution rapidly turned yellow, and a precipitate formed. The ammonia was removed (steam-bath) while ether (200 ml.) was added gradually. The resulting ether suspension was poured with stirring into 100 ml. of saturated ammonium chloride solution. The insoluble precipitate of carbinol III was collected on a filter funnel, and no additional carbinol III was obtained by evaporating the ether layer. Carbinol III was crystallized from methylene chloride to give 28.7 g. (82%) of white cubic crystals, m.p. 238–239°. This melting point was not depressed on admixture with an authentic sample of the carbinol.[5] The infrared spectra of the two samples were identical in all respects.

Condensation of I with Benzaldehyde to Form 1,1,2-Triphenylethandiol-1,2 (IV).—To a stirred solution of 0.1 mole of disodiobenzophenone (I) in 250 ml. of liquid ammonia was added 10.6 g. (0.1 mole) of benzaldehyde dissolved in 50 ml. of dry ether. The black solution changed to light blue. The ammonia was replaced by ether (200 ml.), and the resulting ether suspension was poured into 100 ml. of an ether solution containing 30 ml. of glacial acetic acid. Water was added and the two layers separated. The ether layer was washed with saturated sodium bicarbonate solution to remove the last of the acetic acid and then dried over Drierite. The solvent was removed on the steam-bath and the residue of crude white solid was taken up in 25 ml. of hot benzene. The benzene solution was diluted with 4 volumes of petroleum ether (b.p. 30–60°) and cooled to deposit 26.5 g. (91%) of IV as white crystals, m.p. 167–168°, reported m.p. 167–167.5°. This melting point was not depressed on admixture with a sample obtained by the method of Acree.[6]

Conjugate Addition of I to Benzalacetophenone to Form β,γ,γ-Triphenyl-γ-hydroxybutyrophenone (V).—Benzalacetophenone (21.8 g., 0.1 mole) dissolved in 150 ml. of dry ether was added to 0.1 mole of disodiobenzophenone in 250 ml. of liquid ammonia. The mixture was stirred rapidly during the addition to produce a yellow mixture containing a heavy precipitate shortly after the addition was complete. The liquid ammonia was removed on the steam-bath, and ether was added to keep the suspension fluid. Saturated ammonium chloride solution (100 ml.) was added with stirring. The remaining solid was collected on a funnel and washed with water and dried. A small additional amount of solid was isolated from the ether layer by evaporating the dried solution. The combined solids were crystallized from benzene to give 18.3 g. (47%) of white crystals of hydroxyketone V, m.p. 222–223°. This melting point was not raised on further recrystallization from benzene.

Anal. Calcd. for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16. Found: C, 85.76; H, 6.16.

A determination in the Grignard machine indicated 1.18 active hydrogen and 0.8 carbonyl group per mole.

Preparation of Dipotassiobenzalacetophenone (VI).—To a stirred solution of 7.8 g. (0.1 g. atom) of potassium metal in 250 ml. of liquid ammonia was added a solution of 20.83 g. (0.1 mole) of benzalacetophenone in 150 ml. of dry ether. The solution turned purple and then black within 5 minutes. This solution was assumed to contain 0.1 mole of dipotassiobenzalacetophenone (VI).

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(8) W. R. Brasen and C. R. Hauser, This Journal, **79**, 395 (1957).

(9) Melting points were taken on a Fisher-Johns melting point apparatus. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(10) I. Heilbron, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, N. Y., 1938, p. 342.

Acidification of Dipotassio Salt VI to Form Dihydrobenzalacetophenone (VII).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) was added cautiously in small portions 12 g. of solid ammonium chloride (black color discharged), and the liquid ammonia was replaced with ether (steam-bath). The resulting ether suspension was cooled, and 100 ml. of water was added with stirring. The ether layer was separated, dried over Drierite, and the solvent evaporated on the steam-bath. The residual yellow oil was dissolved in 25 ml. of hot ethanol, and the solution was cooled in an ice-bath to precipitate 20.4 g. (98%) of slightly yellow ketone VII, m.p. 70–72°. One recrystallization from 95% ethanol raised the melting point to the reported[11] value 72–73°.

Monobenzylation of Dipotassium Salt VI to Form β,γ-Diphenylbutyrophenone (VIII).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) in 250 ml. of anhydrous liquid ammonia was added a solution of 12.66 g. (0.1 mole) of benzyl chloride in 100 ml. of dry ether. The black solution turned red when all the halide had been added. After five minutes the liquid ammonia was replaced with 200 ml. of ether (steam-bath). The resulting suspension in ether was cooled, and 100 ml. of water was added with caution. After stirring to dissolve the suspended solid, the ether layer was separated and dried over Drierite. The solution was concentrated on the steam-bath, and the resulting white solid was taken up in hot 95% ethanol. The hot solution was filtered with suction (Büchner funnel) and cooled to deposit 22 g. (73%) of ketone VIII, m.p. 111–112°. Recrystallization from 95% ethanol gave a white powder, m.p. 112–113°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.51; H, 6.72.

This compound was independently synthesized from 0.1 mole each of benzalacetophenone and benzylmagnesium chloride in ether. The mixture was stirred and refluxed for one hour, then cooled and neutralized with aqueous ammonium chloride to give a 95% yield of crude ketone VIII. After two recrystallizations from 95% ethanol, the ketone melted at 112–113°. This product showed no melting point depression on admixture with a sample of the product prepared as described above. Both samples gave a positive test for the carbonyl function with 2,4-dinitrophenylhydrazine reagent.

Dibenzylation of Dipotassio Salt VI to Form α-Benzyl-β,γ-diphenylbutyrophenone (IX).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) was added a solution of 25.32 g. (0.2 mole) of benzyl chloride in 100 ml. of ether. The red color observed in the monobenzylation (see above) was noticed when approximately half of the halide was added. This became light yellow when the remainder of the halide was added and the mixture was stirred for about 20 minutes. Solid ammonium chloride was then added, and the ammonia removed on the steam-bath. After adding ether, the suspension was cooled and 100 ml. of water added. The solid that failed to dissolve was collected on a funnel, and recrystallized from a 1:1 mixture of 95% ethanol and ethyl acetate to give 30 g. (76%) of ketone IX (white cubic crystals), m.p. 162–163°.

Anal. Calcd. for $C_{29}H_{26}O$: C, 89.35; H, 6.40. Found: C, 89.37; H, 6.26.

Benzylation of Ketone VIII to Form Ketone IX.—To a solution of 0.0334 mole of potassium amide in 250 ml. of liquid ammonia was added a solution of 10 g. of β,γ-diphenylbutyrophenone (VIII) in 100 ml. of ether. The resulting green solution deposited a tan colored precipitate within 10 minutes. To the stirred suspension was added 4.22 g. (0.0334 mole) of benzyl chloride in 50 ml. of ether. A red color was produced which soon faded to yellow. After stirring for one hour, the liquid ammonia was replaced with ether, and the product isolated essentially, as described in the preceding experiment. There was obtained 9.7 g. (75%) of the ketone IX, m.p. 162–163°. This product was shown to be identical with the product obtained in the preceding experiment by mixed melting point and by comparison of their infrared spectra.

Dibenzylation of Dipotassio Salt VI in Ether.—Dipotassio salt VI (0.1 mole) was prepared in liquid ammonia as described above, and the ammonia then replaced with ether. The resulting suspension was cooled, and the mixture treated with a solution of 25.33 g. of benzyl chloride (0.2 mole) in 100 ml. of dry ether. After refluxing for one hour, the reaction mixture was treated with cold aqueous ammonium chloride solution (5 g. in 100 ml. of water). There was obtained 11.9 g. (30%) of ketone IX, m.p. and mixed m.p. 161–162°. Also, an oil was isolated from the ether layer which solidified on cooling in a Dry-Ice acetone-bath but melted on warming to room temperatures. This product appeared to be the second diastereoisomer of ketone IX, but this was not established.

Addition Reaction of Dipotassiobenzalacetophenone (VI) with Benzophenone to Form Hydroxy-ketone V.—To a stirred liquid ammonia solution of 0.1 mole of dipotassiobenzalacetophenone was added 18.2 g. (0.1 mole) of benzophenone in 100 ml. of dry ether. A precipitate formed immediately. After stirring 15 minutes a solution of 12 g. of ammonium chloride in 200 ml. of liquid ammonia was added with stirring. The liquid ammonia was then replaced with ether (steam-bath), and the resulting suspension was shaken with water. The remaining solid was collected on a funnel and dissolved in excess benzene. The solvent was distilled until the condensate was no longer cloudy (water was assumed to be removed), and the clear solution was then cooled to deposit 18.3 g. (47%) of the hydroxy-ketone V, m.p. 222–223°. This melting point was not depressed on admixture with a sample prepared as described above from benzalacetophenone and disodiobenzophenone. The infrared spectra of the two samples were identical.

DURHAM, N. C.

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(11) See ref. 10, Vol. I, p. 139.

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

Synthesis of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines

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RECEIVED JUNE 11, 1958

The preparation of a series of 7-(dialkylaminoalkyl)-benzo[c]phenothiazines is described. Of particular interest is the synthesis of 7-(3-dimethylaminopropyl)-9-chlorobenzo[c]phenothiazine, which is closely related to chlorpromazine (III).

The pharmacological importance of 10-dialkylaminoalkyl derivatives of phenothiazine is well established. Since 1946, when Halpern[1] introduced 10-(2-dimethylaminoethyl)-phenothiazine-HCl (I) and 10-(2-dimethylamino-1-propyl) phenothiazine-HCl or Phenergan (II) as potent antihistamines, the list of useful phenothiazine derivatives has been growing.[2] Phenergan, in addition to its antihistaminic activity, has twice the local anesthetic activity of cocaine.[1] Chloropromazine or 10-(3-dimethylaminopropyl)-2-chlorophenothiazine-HCl (III) has been found effective in suppressing nausea[3] and in the treatment of neuropsychiatric disorders.[4] The tranquilizing activity of Vesprin or 10-(3-dimethylaminopropyl)-2-trifluoromethyl-

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[1] B. N. Halpern, *Compt. rend. soc. biol.*, **140**, 361 (1946).

[2] S. P. Massie, *Chem. Revs.*, **54**, 822 (1954).

[3] D. G. Friend and J. F. Cummins, *J. Am. Med. Assoc.*, **153**, 480 (1953).

[4] J. H. Moyer, *et al.*, *Arch. Internal Med.*, **95**, 202 (1955).