Condensations of 2-Dimethylaminomethylbenzyllithium and Related Amino Organolithium Reagents with Aldehydes and Ketones. Cyclizations to Isochromans[1]

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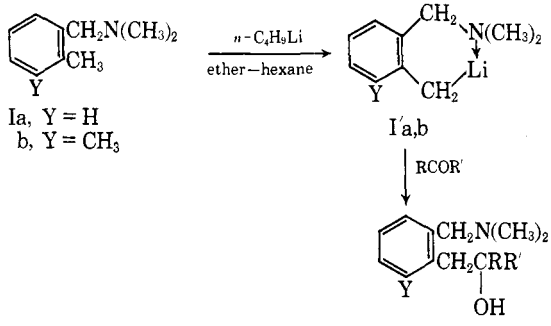
2-Dimethylaminomethylbenzyllithium and some related amino organolithium reagents were prepared by metalation of the appropriate 2-methyl- or 2-benzylbenzyldimethylamines with *n*-butyllithium, and condensed with benzaldehyde and certain ketones to form corresponding amino alcohols. Several of these products were dehydrated to form amino olefins and cyclized through their methiodides to give isochromans. One of the amino alcohols was converted to a cyclic quaternary bromide. One of the amino organolithium compounds was condensed with benzonitrile to form an amino ketone. The adduct of 2-dimethylaminomethylphenyllithium and cyclohexene oxide was cyclized through its methiodide to afford 1,2,3,4,4a,10b-hexahydro-6H-dibenzo[*b,d*]pyran.

2-Dimethylaminomethylbenzyllithium (I'a) and the related amino organolithium reagent I'b have recently[2] been prepared by metalation of 2-methyl- and 2,3-dimethylbenzyldimethylamine (Ia and b) with *n*-butyllithium. The site of metalation was determined by deuteration.[2] We have now condensed these amino organolithium reagents with benzaldehyde and appropriate ketones to form amino alcohols IIa–e (see Scheme A).

SCHEME A

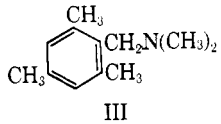


Ia, Y = H
b, Y = CH_3

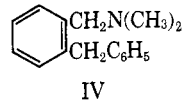
I'a,b

IIa, Y = H; R = H; R' = C_6H_5
b, Y = H; R, R' = C_6H_5
c, Y = H; R, R' = CH_3
d, Y = CH_3; R, R' = C_6H_5
e, Y, R, R' = CH_3

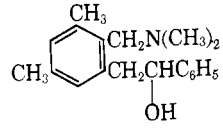
Similarly 2,4,6-trimethylbenzyldimethylamine (III) and 2-benzylbenzyldimethylamine (IV) were metalated and condensed with benzaldehyde and benzophenone to give amino alcohols V and VI, respectively.



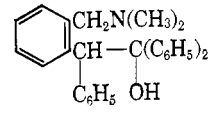
III



IV



V



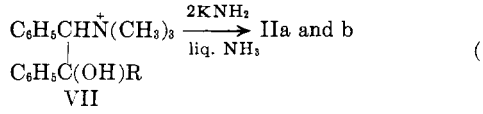
VI

In Table I are summarized the yields of these amino alcohols, in Table II physical data and analyses, and in Table III data for derivatives. Although amino alcohols IIc and IIe contained small amounts of impurities, they afforded pure derivatives.

(1) Supported by Army Research Office, Durham, N. C.

(2) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

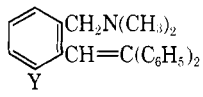
Amino alcohols IIa and b were identified by comparison with samples prepared recently by the *ortho*-substitution rearrangement of appropriate quaternary ion alcohols VII (eq. 1).[3]



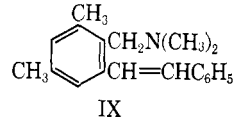
VII (1)

The structures of amino alcohols IId, V, and VI were supported by analyses and infrared spectra, which showed bands in the regions 4000–3000 and 854–837 cm.$^{-1}$ for the hydroxyl[4] and dimethylaminomethyl[5] groups, respectively. Bands designating the appropriate aromatic substitution were present (see Table II).

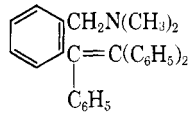
The structures of amino alcohols IIb, IId, V, and VI were further supported by dehydration with 20% sulfuric acid to form amino olefins VIIIa, VIIIb, IX, and X, respectively (Table IV). The formation of these products shows that the amino alcohols were not the possible ring substitution derivatives, for example, XI, which could not undergo such a dehydration.



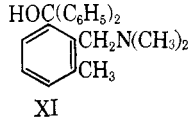
VIIIa, Y = H
b, Y = CH_3



IX



X



XI

Next, the methiodides of certain of the amino alcohols were cyclized thermally to form isochromans and presumably trimethylamine hydroiodide.[6] Thus methiodides XIIa and b afforded isochromans XIIIa and b, respectively (eq. 2).

Similarly, amino alcohol V was cyclized through its methiodide to form isochroman XIV. Methiodide

(3) W. H. Puterbaugh and Charles R. Hauser, *J. Am. Chem. Soc.*, **86**, 1105 (1964); see also *ibid.*, in press.

(4) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958; p. 96.

(5) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

(6) For a related thermal cyclization to form phthalans, see R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 505 (1964).

TABLE I

CONDENSATION OF AMINES WITH ALDEHYDES AND KETONES BY MEANS OF *n*-BUTYLLITHIUM IN ETHER–HEXANE

Amine	Mole of amine	Aldehyde or ketone	Condensation product	Yield,[a] %
Ia	0.08	Benzaldehyde	2-[α-(Dimethylamino)-*o*-tolyl]-1-phenylethanol (IIa)[b]	77
Ia	0.08	Benzophenone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1-diphenylethanol (IIb)[b]	80
Ia	0.15	Acetone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1-dimethylethanol (IIc)[c]	46[d]
Ib	0.05	Benzophenone	2-[2-Dimethylaminomethyl-6-methylphenyl]-1,1-diphenylethanol (IId)	80
Ib	0.086	Acetone	2-[2-Dimethylaminomethyl-6-methylphenyl]-1,1-dimethylethanol (IIe)[e]	61[d]
III	0.10	Benzaldehyde	2-[2-(Dimethylaminomethyl)-3,5-dimethylphenyl]-1-phenylethanol (V)	81
IV	0.06	Benzophenone	2-[α-(Dimethylamino)-*o*-tolyl]-1,1,2-triphenylethanol (VI)	88

[a] The yield is based on the starting amine. The melting point of the product on which the yield is based is slightly lower than those given in Table II. [b] Amino alcohols IIa and b were identified by the mixture melting point method and by comparison of infrared spectra with samples prepared previously.[3] [c] 2-(Dimethylaminomethyl)phenyl-*t*-butyl alcohol. [d] Crude yield, see Experimental. [e] 2-(Dimethylaminomethyl)-6-methylphenyl-*t*-butyl alcohol.

TABLE II

PHYSICAL DATA AND ANALYSES OF AMINO ALCOHOLS

Amino alcohol	Recrystn. solvent	M.p., °C.	Infrared data, cm.$^{-1}$	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IId	95% ethanol	163–164	3356, 855, 775, 760, 709, 700	83.44	7.88	4.05	83.50	7.77	4.27
V	Hexane	120–121	3356, 845, 763, 700	80.52	8.89	4.94	80.49	8.72	5.01
VI	Ethanol–acetone	190–191	3448, 842, 752, 704	85.46	7.17	3.44	85.24	7.35	3.31

TABLE III

DATA FOR DERIVATIVES OF AMINO ALCOHOLS

Amino alcohol	Derivative	Recrystn. solvent	M.p., °C.	Empirical formula	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	Methiodide (XIIa)	Acetonitrile–ether	142.5–143.5	$C_{18}H_{24}INO$	54.41	6.09	3.53	54.44	6.18	3.62
IIb	Methiodide (XIIb)	Ethanol–ether	174–175	$C_{24}H_{28}INO$	60.89	5.96	2.96	60.87	6.18	2.92
IIc	Methiodide	Acetonitrile	176.5–177.5	$C_{14}H_{23}INO$	48.28	6.66	4.03	48.31	6.61	4.25
IIc	Picrate	95% ethanol	170–171	$C_{19}H_{24}N_4O_8$	52.29	5.54	12.84	52.20	5.58	12.99
IId	Methiodide	Acetonitrile	195.5–197.5	$C_{25}H_{30}INO$	61.62	6.20	2.87	61.82	6.05	3.12
IIe	Picrate	95% ethanol	177–177.5	$C_{20}H_{26}N_4O_8$	53.33	5.82	12.44	53.02	5.51	12.58
IIe	Methiodide	Acetonitrile	191–192	$C_{15}H_{26}INO$	49.59	7.21	3.86	49.74	7.10	3.87

TABLE IV

DEHYDRATION OF AMINO ALCOHOLS WITH REFLUXING 20% SULFURIC ACID

Amino alcohol	Reflux time, hr.	Dehydration product	M.p., °C.	Yield,[a] %	Elemental analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIb	18	*o*-(2,2-Diphenylvinyl)-N,N-dimethylbenzylamine (VIIIa)[b]	69–70	78	88.13	7.40	4.47	88.29	7.25	4.54
IId	16	*o*-(2,2-Diphenylvinyl)-N,N,3-trimethylbenzylamine (VIIIb)[b]	68–69	91	88.03	7.70	4.28	88.31	7.66	4.30
V	12	N,N,2,4-Tetramethyl-6-styrylbenzylamine (IX)[c]	70–71.5	54	85.98	8.74	5.28	85.93	8.62	5.27
VI	7	*o*-(1,2,2-Triphenylvinyl)-N,N-dimethylbenzylamine (X)[d]	136–137	97	89.42	6.99	3.60	89.23	7.01	3.56

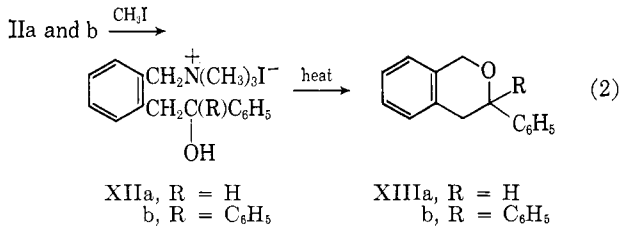
[a] The yield is based on the starting amino alcohol. The melting point of the product on which the yield is based is slightly lower than that given. [b] Recrystallized from hexane. [c] Recrystallized from 95% ethanol. [d] Recrystallized from absolute ethanol.

TABLE V

ISOCHROMANS FROM METHIODIDES OF AMINO ALCOHOLS

Methiodide	Mole of methiodide	Reaction time, hr.	Isochroman	M.p. or b.p., °C.	Yield,[a] %	Infrared data, cm.$^{-1}$	Elemental analysis, % Calcd. C	Calcd. H	Found C	Found H
XIIa	0.012	0.5	3-Phenyl (XIIIa)[b]	76–77.5	68	1093, 767, 744, 698	85.68	6.71	85.47	6.67
XIIb	0.04	1.0	3,3-Diphenyl (XIIIb)[b]	120–121	61	1068, 758, 746, 697	88.08	6.34	87.92	6.50
V[c]	0.05	2.0	6,8-Dimethyl-3-phenyl (XIV)[d]	84.5–86	62	1087, 854, 765, 704	85.67	7.61	85.55	7.49
XV	0.026	6	XVI[e]	101–104 (0.4 mm.)	80	1105, 1030, 957, 742	82.93	8.57	83.06	8.61

[a] The melting points on which these yields are based were slightly lower than the reported values. Yields are based on the methiodides. [b] Recrystallized from absolute ethanol. [c] This methiodide was prepared from amino alcohol V but was not characterized. [d] Recrystallized from 95% ethanol. [e] This compound, which solidified on standing, was indicated to be pure by v.p.c.

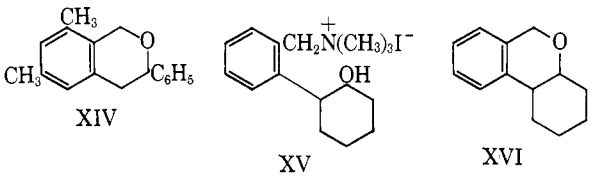


XIIa, R = H
b, R = C_6H_5

XIIIa, R = H
b, R = C_6H_5

(2)

XV[7] was cyclized to give the isochroman-type product XVI, which appears to be the first example and parent compound of the ring system 1,2,3,4,4a,10b-hexahydro-6H-dibenzo[*b*,*d*]pyran.



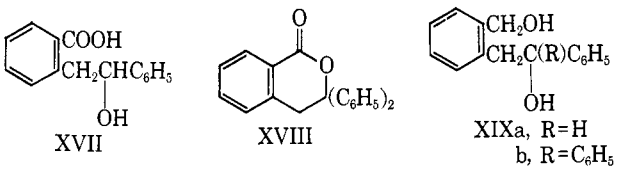
XIV XV XVI

These results are summarized in Table V. The structures of XIIIa and b, XIV, and XVI were supported by analyses and infrared spectra which showed strong peaks in the 1140–1070-cm.$^{-1}$ region indicating a cyclic ether.[8] In the spectrum of XVI, bands appearing at 1030 and 957 cm.$^{-1}$ were attributed to the cyclohexane ring.[9] In the spectra of all four compounds, appropriate aromatic substitution bands were observed (see Table V).

Further evidence supporting structures XIIIa and b, XIV, and XVI was obtained from their n.m.r. spectra. The spectra of XIIIa and XIV were quite similar, both showing a singlet for the C-1 hydrogens at −291 ± 1 and −287 ± 1 c.p.s., respectively, a doublet for the C-4 hydrogens centered at −171 ± 1 and −169 ± 1 c.p.s., respectively, and a triplet for the C-3 hydrogen centered at −275 ± 1 and −272 ± 1 c.p.s., respectively. The spectrum of XIV showed two additional singlets at −123 ± 1 and −133 ± 1 c.p.s. for the two methyl groups. The spectrum of isochroman XIIIb showed singlets for the C-1 and C-4 hydrogens at −276 ± 1 and −204 ± 1 c.p.s., respectively. In each of these three spectra, the coupling constant was 7 c.p.s. and aromatic peaks appeared between −400 and −440 c.p.s.

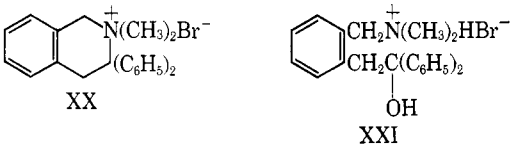
The n.m.r. spectrum of compound XVI was considerably more complex than that obtained for XIIIa and b and XIV. The chemical shift for the isolated $-CH_2-$ was −311 ± 1 cps. The area ratios (obtained by the method of weights) were as follows: C_6H_4/CH_2 = 2.2 (calculated 2.0), cyclohexane/C_6H_4 = 2.5 (calculated 2.5), and cyclohexane/CH_2 = 5.6 (calculated 5.0).

The structures of isochromans XIIIa and b were confirmed by independent synthesis from acid alcohol XVII and lactone XVIII, respectively.[10] These compounds were reduced with lithium aluminum hydride to form diols XIXa and b, which were cyclized with acid to give isochromans XIIIa and b, respectively.



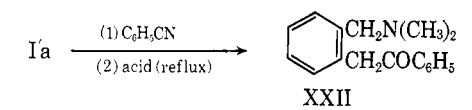
XVII XVIII XIXa, R=H
b, R=C_6H_5

Next, amino alcohol IIb was cyclized by hot 48% hydrobromic acid to form apparently the six-membered ring quaternary ammonium bromide XX.[11] Cold ethanolic hydrobromic acid merely converted IIb to its hydrobromide XXI.



XX XXI

Finally, lithioamine I′a was condensed with benzonitrile to form amino ketone XXII (eq. 3). The structure of this product was supported by analysis and infrared spectrum (see Experimental).



(3)

XXII

Discussion

Most of the reactions described above were realized in good to excellent yields (see Tables I, IV, and V, and Experimental). The conversions of the amino alcohols to their methiodides were almost quantitative. The metalations and condensations, which are readily accomplished, furnish convenient methods for the synthesis of amino alcohols, amino ketones, and presumably other types of compounds. Moreover, the amino alcohols are useful intermediates for the synthesis of amino olefins, isochromans, and cyclic quaternary ions. The present method for the amino alcohols (see Scheme A) is probably preferable to that involving the *ortho*-substitution rearrangement (eq. 1).[3] The method for isochromans involving thermal cyclization of quaternary ion alcohols, which should be quite general, appears superior to that through diols such as XIXa and b, at least for isochromans XIIIa and b. Diol XIXa has previously been prepared by another method and reportedly cyclized to form isochroman XIIIa.[12] However, the melting point given for the latter compound was considerably higher than that observed by us (see Experimental). Apparently the other isochromans presented here have not been described previously, though a number of others have been prepared by other methods.[13]

(7) This compound has recently been prepared by condensation of 2-dimethylaminomethylphenyllithium with cyclohexene oxide followed by methylation [F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963)].

(8) See ref. 4, p. 115.

(9) See ref. 4, p. 31.

(10) The method of preparation of these compounds involved N- and C-metalation of N-methyl-*o*-toluamide with excess *n*-butyllithium and condensation of the resulting dilithio intermediate with benzaldehyde and benzophenone, respectively. The details will be published soon along with a general study of this dilithio reagent.

(11) For a related cyclization to form a five-membered ring quaternary bromide see ref. 7.

(12) S. Siegel and S. Coburn, *J. Am. Chem. Soc.*, **73**, 5494 (1951).

(13) See especially P. Maitte, *Compt. rend.*, **239**, 1508 (1954); E. Schmitz and A. Rieche, *Ber.*, **89**, 2807 (1956); and A. Jacot-Guillarmond, *Helv. Chim. Acta*, **40**, 1639 (1957).

Experimental[14]

Metalations of Amines and Condensations with Aldehydes and Ketones to Form Amino Alcohols (Tables I, II, and III).—To 0.05–0.15 mole of the appropriate amine in a 250-ml. erlenmeyer flask was added a 10% excess of approximately 1.5 *M* *n*-butyllithium in hexane,[15] analyzed as described previously.[16] The flask was filled completely with anhydrous ether, tightly stoppered, and stirred magnetically at room temperature for 6 hr. The resulting metalation mixture was added slowly to a boiling solution of the appropriate aldehyde or ketone (10% excess over the *n*-butyllithium) in 200–300 ml. of anhydrous ether contained in a 1-l. erlenmeyer flask. The reaction mixture was stoppered and allowed to stand at room temperature for 4–8 hr., then hydrolyzed by cautious addition of 200–250 ml. of water. The resulting amino alcohols were isolated as described below.

Amino alcohols IId, V, and VI precipitated on hydrolysis of the reaction mixture. They were removed by filtration, and the organic layer of the filtrate was concentrated to afford second and third crops.

Amino alcohols IIa, IIb, IIc, and IIe remained in solution on hydrolysis of the reaction mixture. The layers were separated. The organic phase was extracted with three 100-ml. portions of 1 *M* hydrochloric acid. The combined acid extracts were cooled and made basic with excess of 6 *M* sodium hydroxide. The basic mixture was extracted with three 100-ml. portions of ether, and the extracts were combined. The ethereal solution was dried over anhydrous magnesium sulfate, and the solvent was removed to leave a light yellow oil. IIb crystallized on standing; IIa was crystallized by addition of one and one-half volumes of hexane. IIc and IIe were distilled *in vacuo* to give fractions boiling at 97–98° at 0.9 mm. and 87–89° at 0.18 mm., respectively. These products were shown by v.p.c. to contain 10 and 3% impurities, respectively. The impurity in the latter product was indicated to be starting amine Ib These products were converted to pure derivatives (see Table III).

The solid amino alcohols were recrystallized from appropriate solvents and derivatives were prepared. Methiodides were made by refluxing the amino alcohol with excess methyl iodide in acetonitrile and adding anhydrous ether to the cooled reaction mixture. Picrates were obtained by addition of saturated ethanolic picric acid to ethanolic solutions of the amino alcohols.

Dehydration of Amino Alcohols to Form Amino Olefins (Table IV).—The amino alcohol (5.0–6.0 g.) was refluxed for several hours with 100 ml. of 20% sulfuric acid. The reaction mixture was cooled and made strongly basic with 6 *M* sodium hydroxide to liberate the amino olefin. Product X, which precipitated, was removed by filtration and recrystallized. Products VIIIa, VIIIb, and IX were taken up in ether and the solution was dried over anhydrous magnesium sulfate. Removal of the solvent afforded oils which were crystallized and recrystallized from appropriate solvents (see Table IV).

Cyclization of Methiodides of Amino Alcohols to Form Isochromans (Table V).—The appropriate methiodide was placed in a round-bottom flask fitted with a two-necked adaptor for gas inlet and condenser. The system was evacuated to 1 mm. and refilled with dry nitrogen three times. After flushing the system for 30 min. with a slow stream of nitrogen (which was continued during the reaction), the flask was immersed in a Wood's metal bath which was preheated to 200–210°.[17] After an appropriate time (see Table V), the mixture was allowed to cool, then boiled with several portions of anhydrous ether to remove the isochroman from the solid residue, presumably trimethylammonium iodide. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The solvent was removed on the steam bath and then *in vacuo* (1 mm.). The residual oils from methiodides XIIa and b and V' crystallized. The oil from methiodide XV'[7] was distilled *in vacuo* (see Table V).

Independent Synthesis of Isochroman XIIIa. Consideration of Earlier Method.—A solution of 2.5 g. (0.011 mole) of 2-(*o*-carboxyphenyl)-1-phenylethanol (XVII)[10] in 250 ml. of anhydrous ether was refluxed overnight with 1.9 g. (0.05 mole) of lithium aluminum hydride.[18] The reaction mixture was worked up[18] to give 2.38 g. (95%) of 2-(*o*-hydroxymethylphenyl)-1-phenylethanol (XIXa), m.p. 85–89°, and 88.5–90° after recrystallization from hexane–ethanol.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.74; H, 7.02.

A solution of 0.8 g. (0.0035 mole) of diol XIXa in 15 ml. of glacial acetic acid containing 0.5 ml. of phosphoric acid was warmed on the steam bath for 20 min., and ice then was added. The resulting thick oil was collected, crystallized, and recrystallized from absolute ethanol to give 0.1 g. (14%) of isochroman XIIIa, m.p. 76–77°, undepressed on admixture with a sample of XIIIa prepared by eq. 2. Also the infrared spectra of the two samples were identical.

An attempt to cyclize diol XIXa with concentrated sulfuric acid in acetic acid, as described in the next section for the cyclization of diol XIXb, afforded an oil which could not be crystallized even when seeded with crystals of isochroman XIIIa.

The earlier method[12] for isochroman XIIIa involved reduction of 3-phenylisocoumarin with lithium aluminum hydride followed by cyclization with concentrated sulfuric acid in glacial acetic acid. In contrast to our results (see above), the intermediate diol XIXa was obtained as a high boiling liquid and isochroman XIIIa was reported to melt at 114–115°. Moreover, the XIIIa was reported to be easily oxidized by air, whereas our XIIIa was not.

Independent Synthesis of Isochroman XIIIb.—A solution of 5.6 g. (0.018 mole) of 3,3-diphenyl-3,4-dihydroisocoumarin (XVIII)[10] in 250 ml. of anhydrous ether was refluxed for 15 hr. with 0.38 g. (0.01 mole) of lithium aluminum hydride.[18] One gram of the resulting crude diol XIXb (m.p. 118–129°) was dissolved in 25 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid was added dropwise. After stirring at room temperature for 5 min., the solution was treated with ice. The resulting solid was collected and recrystallized twice from absolute ethanol to give 0.6 g. (57% based on XVIII) of isochroman XIIIb, m.p. 120.5–122°, undepressed on admixture with a sample of XIIIb prepared by eq. 2. Also, the infrared spectra of the two samples were identical.

Cyclization of Amino Alcohol IIb to Quaternary Bromide XX.—A solution of 5.0 g. (0.015 mole) of IIb in 50 ml. of 48% hydrobromic acid was refluxed for 1.5 hr. The reaction mixture was allowed to cool to room temperature and some ether was added. The resulting solid was collected, washed with water, and dried to afford 5.05 g. (85%) of presumably 2,2-dimethyl-3,3-diphenyl-1,2,3,4-tetrahydroisoquinolinium bromide (XX). After two recrystallizations from absolute ethanol, the product melted at 216–217.5° when placed on a block preheated to 190°.

Anal. Calcd. for $C_{23}H_{24}BrN$: C, 70.05; H, 6.13; N, 3.55. Found: C, 70.07; H, 6.18; N, 3.21.

When a sample of amino alcohol IIb was stirred in 95% ethanol containing some 48% hydrobromic acid (room temperature) and anhydrous ether was added with cooling, the hydrobromide salt XXI was obtained. After two recrystallizations from aqueous ethanol, a sample melted at 132.5–133° dec. when placed in a block preheated to 220°.

Anal. Calcd. for $C_{23}H_{26}BrNO$: C, 66.66; H, 6.42; N, 3.43. Found: C, 66.78; H, 6.20; N, 3.16.

Condensation of Amino Organolithium Reagent I'a with Benzonitrile to Form Amino Ketone XXII.—Amine Ia (11.9 g., 0.08 mole) was metalated for 6 hr. using a 10% excess of 1.5 *M* *n*-butyllithium as described above. To the stirred solution of I'a in a three-necked flask (which had been flushed with dry nitrogen) was added dropwise 10.3 g. (0.10 mole) of freshly distilled benzonitrile in 100 ml. of anhydrous ether. After refluxing 6 hr., the red mixture was cooled in ice and 30 ml. of water was added carefully followed by 6 ml. of glacial acetic acid. The layers were separated, the aqueous layer was washed twice with ether, and the washings were added to the original organic layer. The ethereal solution was dried over anhydrous magnesium sulfate, and the solvent was removed. The oily residue was stirred and refluxed in 250 ml. of 4 *M* hydrochloric acid for 8 hr. and allowed to stand overnight. The mixture was washed with ether, then cooled, and made basic with sodium hydroxide pellets. The liberated oil was taken up in ether, and the solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the oily residue was distilled to afford 13.7 g. (68%)

(14) Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded using Perkin-Elmer Infracords, Models 137 and 237. Nuclear magnetic resonance spectra were obtained on a Varian A-60 NMR spectrometer.

(15) Foote Mineral Company, New Johnsonville, Tenn.

(16) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 115 (1960).

(17) For methiodide XIIa, the temperature was 180–190°.

(18) See R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

of 2-(dimethylaminomethyl)benzyl phenyl ketone (XXII), b.p. 143–146° (0.3 mm.).[19]

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.39; H, 7.64; N, 5.74.

The picrate, recrystallized twice from 95% ethanol, melted at 176–177.5°.

(19) On standing several weeks, this light yellow oil became a red viscous material which resisted attempts at crystallization.

Anal. Calcd. for $C_{23}H_{22}N_4O_8$: C, 57.26; H, 4.60; N, 11.61. Found: C, 57.44; H, 4.67; N, 11.42.

The infrared spectrum of XXII showed a strong peak at 1690 cm.$^{-1}$ for the carbonyl group,[20] at 845 cm.$^{-1}$ for the dimethylaminomethyl group,[5] and at 753, 740, and 690 cm.$^{-1}$ for four and five adjacent aromatic hydrogens.[21]

(20) See ref. 4, p. 132.

(21) See ref. 4, pp. 76–78.

Cyclization of Certain o-Chlorophenyl-β-dicarbonyl Compounds through Dicarbanion–Benzyne Intermediates[1]

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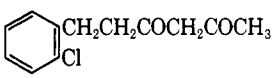
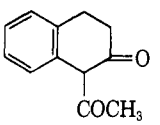
Bunnett's principle of ring closure involving the intramolecular reaction of an anion with the benzyne moiety was adapted to certain cyclizations in which the terminal methyl group of an o-chlorophenyl β-diketone or β-ketoaldehyde was condensed with the aromatic ring through a dicarbanion–benzyne intermediate. The cyclizations, which were effected by means of excess potassium amide in liquid ammonia, afforded five- and six-membered rings. One of these reactions was useful for the synthesis of 3-acetyl-2-tetralone (IX).

Bunnett,[2] Huisgen,[3] and co-workers have effected a number of cyclizations that involve the intramolecular condensation of an anion and the benzyne moiety. Bunnett has formulated this general principle[2a,b] of cyclization and has applied it to the synthesis of homocyclic,[2c] and heterocyclic[2b,d] products. One of these interesting cyclizations was observed with o-chlorophenyl β-diketone I, the methylene group of which was condensed intramolecularly with the aromatic ring to give II.[2c] This reaction was effected by excess potassium amide in liquid ammonia.



I

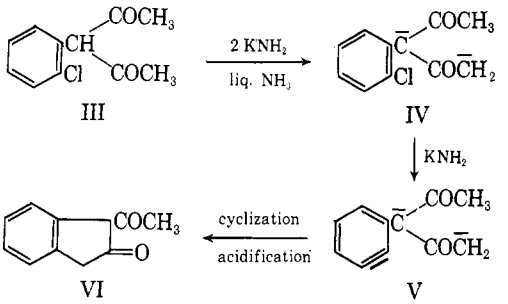


II

In the present investigation Bunnett's principle of ring closure was adapted to certain cyclizations in which a terminal methyl group of a β-diketone or β-ketoaldehyde was condensed intramolecularly with the aromatic ring through the intermediate formation of a dicarbanion and the benzyne moiety. The analogous intermolecular phenylation at the terminal methyl group of acetylacetone had been effected previously through the intermediate formation of benzyne and of the dicarbanion of the β-diketone.[4]

First, the o-chlorophenyl β-diketone III was cyclized to form the five-membered ring β-diketone VI in almost quantitative yield (Scheme A).

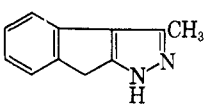
This reaction was effected by the gradual addition of excess[5] potassium amide in liquid ammonia to III in this medium, IV and V presumably being intermediates.



III IV V VI

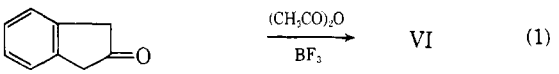
The intermediate formation of dicarbanion IV was indicated by a transient green color similar to that observed with the dicarbanion of 3-phenyl-2,4-pentanedione.[6] Indirect evidence, that the twofold ionization to form IV preceded dehydrohalogenation, was the lack of appreciable amination, which might have been expected if a benzyne were produced first.

Structure VI for the product was supported by analysis, by agreement of its melting point with the reported value,[7] by a positive enol test, and by cyclization with hydrazine to form pyrazole VII.



VII

Structure VI was confirmed by independent synthesis involving acetylation of β-indanone by means of boron trifluoride (eq. 1).



(1)

Similarly, o-chlorobenzyl β-diketone VIII was cyclized to form the six-membered ring β-diketone IX in 65% yield.

That the cyclization product was a carbocyclic derivative, not a heterocyclic derivative such as the

(1) Supported by the National Science Foundation.

(2) (a) B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958); (b) J. F. Bunnett and B. F. Hrutfiord, *ibid.*, **83**, 1691 (1961); (c) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962); (d) J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *ibid.*, **28**, 1 (1963).

(3) R. Huisgen and H. König, *Angew. Chem.*, **69**, 268 (1957); R. Huisgen and H. König, *Ber.*, **92**, 203, 429 (1959); R. Huisgen, H. König, and A. R. Lepley, *ibid.*, **93**, 1496 (1960).

(4) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(5) At least three molecular equivalents of this reagent should be required to effect the reaction since the dicarbanion of product VI would probably be formed.

(6) W. I. O'Sullivan and C. R. Hauser, *J. Org. Chem.*, **25**, 1110 (1960).

(7) M. Konieczny, *Bull. acad. polon. sci., Ser. sci., chim., geol., geograph.*, **8**, 229 (1959).