[Contribution from the Department of Chemistry, Duke University, Durham, N. C.]

Ring *versus* Side-Chain Metalation of Benzyldimethylamine with Butylsodium and Phenylsodium. Isomerizations of Metallo Derivatives[1]

By Walter H. Puterbaugh[2] and Charles R. Hauser

Metalation of benzyldimethylamine (I) with *n*-butylsodium or *n*-amylsodium in hexane at 25–30° afforded initially the *o*-sodium derivative IIb, which isomerized to give the α-sodio derivative IVb. These alkali intermediates were condensed with benzophenone to produce the corresponding amino alcohols III and V, respectively. The relative yields of these products were dependent on the time allowed for metalation. However, α-lithiobenzyldimethylamine (IVa), prepared from α-sodio derivative IVb and lithium bromide, underwent the reverse isomerization at 48° to give the *o*-lithio derivative IIa. Metalation of amine I with phenylsodium afforded only the α-sodio derivative IVb.

It has recently been shown that benzyldimethylamine (I) undergoes ring metalation with *n*-butyllithium in ether (solution) at 25–30° to form the *o*-lithio intermediate IIa, which condenses with benzophenone to give amino alcohol III.[3] The possible intermediate formation of the α-lithio derivative IVa was not then excluded.

$$C_6H_5CH_2N(CH_3)_2$$
$$I$$

IIa, M = Li
b, M = Na

III

$$M$$
$$C_6H_5CHN(CH_3)_2$$

IVa, M = Li
b, M = Na
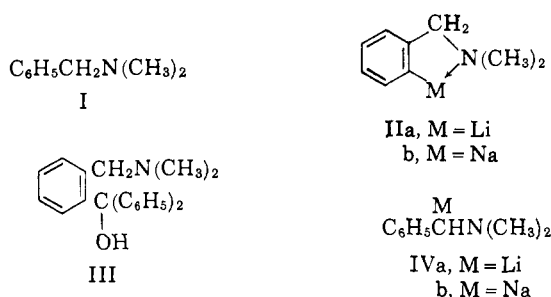
It has now been found that I similarly undergoes ring metalation with *n*-butylsodium and *n*-amylsodium in hexane (suspension) at 25–30°, but that the resulting *o*-sodio derivative IIb then isomerizes to form the side-chain sodio derivative IVb. This was demonstrated by treating the metalation mixture with excess benzophenone after appropriate time intervals and isolating the corresponding condensation products III and V, respectively (Scheme A, Table I).

Scheme A
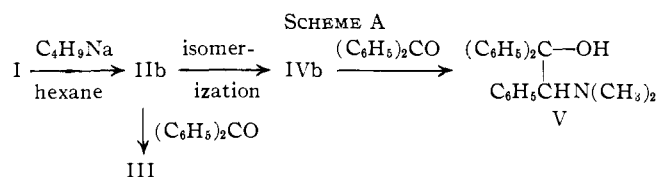
The identity of amino alcohol III was established by comparison with an authentic sample. The structure of amino alcohol V was indicated by agreement of its melting point with the reported value and was confirmed by oxidation and by dehydration and hydrolysis (Scheme B).
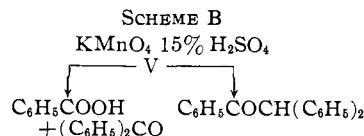
Scheme B

Table I shows that, after 15 min., the total yield of condensation product was 46%, about half of which consisted of the *o*-derivative III. However, after 2 hr., relatively less of this derivative was obtained, and after 20 hr., only the α-derivative V was isolated. Since about as much V as III was obtained after 15

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(2) National Science Foundation Science Faculty Fellow, on leave from Thiel College.

(3) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

Table I

Yields of III and V Obtained According to Scheme A

Reaction time, hr.	Total yield, %	Product distribution,[a] %			Recvd. I, %
		III	V	Unresolved	
0.25	46	40	39	21	49
2.0[b]	75	32	54	14	5
20.0	72	..	87	13	19

[a] These percentages are based on the total yield.   [b] *n*-Amylsodium was used in this experiment.

min., some of the α-sodio intermediate IVb might possibly have been produced simultaneously with the *o*-sodio intermediate IIb.

These results are somewhat similar to those on the metalation of ethylbenzene with *n*-amylsodium by Benkeser and co-workers,[4] who observed recently that this reaction involves initially the formation of ring sodio derivatives, which isomerize to the side-chain sodio derivative. However, their ring sodio derivatives consisted of a mixture of the *m*- and *p*-isomers, whereas ours evidently consisted exclusively of the *o*-isomer (see Experimental). Moreover, their isomerization was effected in the presence of excess ethylbenzene, whereas ours was realized in the presence of a slight excess of metalating agent.

Table II

Yields of III and V Obtained According to Scheme C

Reaction time,[a] hr.	Temp., °C.	Product	Yield, %	Recovd. I, %
1	25–30	V	47	21
23	25–30	V	45	14
45	48	III	40 (35)[b]	35 (39)[b]

[a] After adding lithium bromide.   [b] Duplicate experiment.

Interestingly, the *reverse* isomerization was found to occcur with the α-lithio derivative IV, which was prepared from the corresponding α-sodio intermediate IVb and lithium bromide in ether–benzene–octane. Thus, although IVa was stable at 25–30°, it isomerized at 48° to form the *o*-lithio intermediate IIa. These intermediates were condensed with benzophenone (Scheme C, Table III).

Scheme C
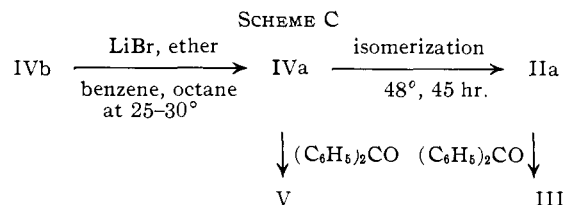
The α-sodio intermediate IVb employed in the preparation of the α-lithio intermediate IVa was prepared by metalation of amine I with phenylsodium, with which only side-chain metalation was observed (see below).

(4) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *J. Am. Chem. Soc.*, **84**, 4971 (1962). This important contribution clarifies certain of the earlier discrepancies on the metalations of alkylbenzenes.

That IVa was formed from IVb and lithium bromide was shown not only by the failure of IVb to isomerize under similar conditions in the absence of lithium bromide (see Experimental), but also by comparative experiments with cyclohexanone. Thus, direct treatment of IVb with this ketone afforded the amino alcohol VI in only 27% yield, whereas prior treatment of IVb with lithium bromide, followed by the ketone, produced VI in 58% yield (Scheme D).

SCHEME D
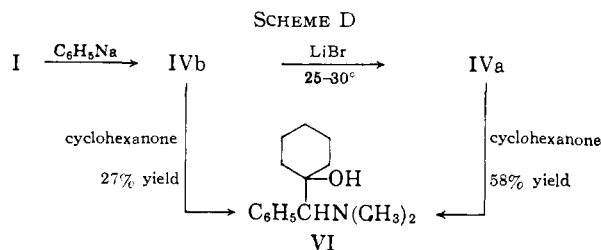
This doubling of the yield of VI by conversion of IVb to IVa is in agreement with the recent observation that the yield of diphenylmethylcarbinol from acetophenone and phenyllithium is much higher than that from this ketone and phenylsodium, with which the α-hydrogen of the ketone mainly undergoes ionization.[5]

Whereas addition of benzophenone to the metalation mixture from amine I and the sodium alkyl after 2 hr. at 25–30° produced both III and V (see Table I), addition of this ketone to the metalation mixture from I and phenylsodium after similar treatment afforded only the side-chain derivative V and recovered I (Table III). Moreover, prolonged refluxing of IVb failed to effect isomerization, and subsequent treatment with benzophenone afforded V in highest yield (see Table III).

TABLE III

YIELDS OF AMINO ALCOHOL V FROM AMINE I AND PHENYL-SODIUM UNDER VARIOUS CONDITIONS

Reaction time, hr.	Temp., °C.	Yield V, %	Recovd. I, %
2	25–30	40	48
18	25–30	48	35
2	85	63	21
24	85	79	11

Similarly, metalation of amine I with phenylpotassium for 18 hr. at 25–30°, followed by treatment with benzophenone, afforded the side-chain derivative V in 73% yield. This metalation evidently occurred more rapidly than that with phenylsodium (see Table III).

However, metalation of I with phenyllithium under these conditions, followed by treatment with benzophenone, produced the o-derivative III, though the yield was low (21%).

Discussion

The o-metalation of amine I with n-butylsodium or n-butyllithium is assumed to involve initial coordination of the metal of the reagent with the free pair of electrons on the nitrogen of I. This coordination and the isomerizations are summarized in Scheme E.
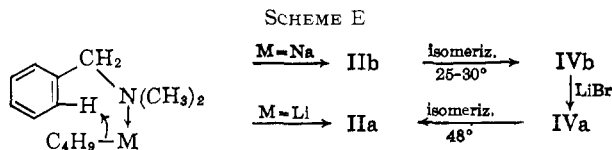
SCHEME E

Some support for the initial coordination shown in Scheme E is the fact that ring metalation of amine I with the sodium reagent is directed to the o-position,

(5) W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, J. Org. Chem., 26, 2306 (1961).

whereas metalation occurs at the m- and p-positions of ethylbenzene,[4] with which no such directive metalation is possible.

The difference in the direction of the isomerizations in Scheme E is rather remarkable. The isomerization of the o-sodio intermediate IIb to the α-sodio intermediate IVb may be ascribed to the formation of the more weakly basic benzylic type of ion, which should be more stable thermodynamically. Notably, α-sodio derivative IVb was stable to prolonged refluxing in benzene–octane (see Table III). However, the reverse isomerization of the α-lithio intermediate IVa to the o-lithio intermediate IIa is presumably due to the greater stabilizing effect of the five-membered ring containing lithium, whose coordinating capacity overcomes the tendency of the potential carbanion to be converted to a weaker base.

Since the α-lithio intermediate IVa isomerizes to the o-lithio intermediate IIa, it might appear that the metalation of amine I with butyllithium could involve initially the formation of IVa. This seems unlikely, however, since IVa failed to isomerize at 25–30° within 23 hr. (see Scheme C, Table II), under which conditions amine I undergoes metalation with butyllithium to form IIa.[3] Moreover, α,α-dimethylbenzyldimethylamine, which has no α-hydrogen, likewise undergoes metalation with n-butyllithium under similar conditions to give the corresponding o-lithio derivative.[6]

Although phenylsodium could similarly coordinate through a complex such as that in Scheme E, we observed no products resulting from abstraction of an o-hydrogen. Instead, the more acidic benzylic hydrogen was ionized. With phenyllithium, the potential phenide ion is apparently able to ionize only the o-hydrogen to which it is directed through coordination, and this ionization occurs at a considerably slower rate than that with n-butyllithium.

Experimental[7]

Metalation of Amine I with Sodium Alkyls. Condensation with Benzophenone (Table I).—A sodium dispersion was prepared from 6.27 g. (0.272 mole) of sodium, 25 ml. of octane, and 3 drops of oleic acid under nitrogen in a 500-ml. Morton flask by means of a high speed stirrer.[8] After adding 100 ml. of hexane, the mixture was cooled to −10°, and a solution of 12.03 g. (0.13 mole) of n-butyl chloride in 25 ml. of hexane was added dropwise during 50 min., maintaining the temperature at −15 to −10° (Dry Ice–acetone bath). After stirring an additional hour at this temperature, the resulting mixture containing n-butylsodium was allowed to warm to room temperature, and a solution of 11.2 g. (0.083 mole) of benzyldimethylamine (I) in 25 ml. of hexane was added during 0.5 min. The resulting orange-red mixture containing the sodio derivative of the amine (IIb and/or IVb) was stirred for the appropriate period (see Table I) at 25–30°, maintained by immersion in water, and a solution of 32.8 g. (0.18 mole) of benzophenone in 80 ml. of ether was added during 6 min. The resultant blue mixture was stirred for 2 hr. and 30 ml. of methanol was added to destroy excess sodium. After stirring for 5 min., the reaction mixture was poured into 150 ml. of cold water. The organic layer was combined with an ether washing of the aqueous layer, and the resulting solution was extracted with five 50-ml. portions of 2 M hydrochloric acid. The acidic extracts were combined and washed with ether. The acidic solution was made basic, and the resulting mixture extracted with ether. The ethereal extract was dried over potassium hydroxide and sodium sulfate, and the solvent removed. The residue in each case was worked up as described below.

In the experiment for 15 min., the semisolid residue (17.9 g.) was dissolved in 25 ml. of hot hexane and allowed to crystallize at room temperature to precipitate 4.0 g. of 2-(dimethylaminomethyl)-triphenylcarbinol (III), m.p. 149–153°, which was separated by decantation. The solution was cooled to deposit 2.5 g. of 2-dimethylamino-1,1,2-triphenylethanol (V), m.p. 99–104°, which was removed by filtration. The filtrate was evaporated and the residue was distilled to remove 5.5 g. (49%) of

(6) F. N. Jones and C. R. Hauser, unpublished results.

(7) Melting points are corrected. Analyses by Dr. Ing. Schoeller, Kronach, W. Germany. Infrared spectra were taken on a model 237 Perkin–Elmer Infracord using the potassium bromide pellet method.

(8) See O. D. Frampton and J. F. Nobis, Ind. Eng. Chem., 45, 404 (1953).

recovered amine I, b.p. 61–63° at 10 mm. The tacky, glassy residue (5.7 g.) was taken up in hexane and chromatographed through an alumina column to give 3.0 g. of solid, m.p. 98–140° (eluted with 20% benzene–80% hexane), and 2.5 g. of hard, glassy material. Recrystallization of the first fraction from hexane gave as first crop at room temperature, 0.7 g. of III, m.p. 151–154°. The filtrate was cooled to deposit 2.1 g. of V, m.p. 100–105°. The infrared spectrum of the hard, glassy material obtained as second eluate from the column showed no appreciable absorptions in the 770–830 cm.⁻¹ region, indicating the probable absence of m- or p-substituted rings.[9] The total amount of products isolated was 11.8 g. (46%), and the product distribution was 4.7 g. (40%) of III, 4.6 g. (39%) of V, and 2.5 g. (21%) of unidentified material. The structures of III and V were proved as described below, and the identity of each crop of III or V was checked by mixture melting point with purified authentic samples.

In the experiment for 2 hr., in which n-amylsodium was used, the residue (22.7 g.) was worked up similarly. There was obtained 0.6 g. (5%) of recovered amine I, and 19.4 g. (75%) of products. The product distribution was 6.2 g. (32%) of III, 10.5 g. (54%) of V, and 2.7 g. (14%) of unidentified material.

In the experiment for 20 hr., the residue (21.3 g.) was worked up simply by recrystallization from hexane to give 16.5 g. (63%) of V, m.p. 102–105.5°. Distillation of the filtrate gave 2.1 g. (19%) of amine I and 2.5 g. of residue. The infrared spectrum of the latter was similar to that of V.

Proofs of Structure. (A) 2-(Dimethylaminomethyl)-triphenylcarbinol (III).—The melting point of the combined products designated as III in the first experiment described above was 149–153°; reported[10] m.p. for 2-(dimethylaminomethyl)-triphenylcarbinol, 153.5–154°. The mixture m.p. with an authentic sample[10] was 150–153°. The infrared spectra were identical. The picrate melted at 169.8–170.4° at a very slow rate of heating, and at 174–174.5° under the usual rate; reported[10] m.p. 168–169°. The m.p. of the picrate was not depressed on admixture with picrate prepared from an authentic sample of III.

(B) 2-Dimethylamino-1,1,2-triphenylethanol (V).—The melting point of the combined products designated as V in the first experiment described above was 100–105°; reported[11] m.p. for 2-dimethylamino-1,1,2-triphenylethanol, 106°. Recrystallization from hexane gave product, m.p. 106–107°. The hydrochloride was prepared by adding 0.5 ml. of concentrated hydrochloric acid to a solution of 1.6 g. of V in 25 ml. of absolute ethanol, followed by precipitation with 100 ml. of ether. There was obtained 1.6 g. (90%) of hydrochloride, m.p. 250–251°, reported[11] m.p. 245–250°.

Oxidation of 3.2 g. of V was effected by refluxing with 13.0 g. of potassium permanganate in 150 ml. of 0.5 M sodium hydroxide for 16 hr. There was obtained 0.6 g. (50%) of benzoic acid, m.p. 120–121.5°, undepressed on mixture with an authentic sample, and 1.0 g. (50%) of benzophenone, m.p. 44–48°, undepressed on mixture with an authentic sample.

Dehydration and hydrolysis of 3.2 g. of V was effected by refluxing with 60 ml. of 15% (by volume) sulfuric acid for 48 hr. The mixture was cooled and the liquid decanted from the residual solid. Recrystallization of this solid from 95% ethanol gave 0.8 g. (30%) of α,α-diphenylacetophenone, m.p. 135–135.5°. The mixture m.p. with an authentic sample[12] was 135–136°. Evaporation of the ethanol filtrate from the recrystallization left a tacky polymer.

Preparation of α-Lithio Derivative IVa.—A 1 M solution of lithium bromide in ether was prepared by the following procedure. To a stirred mixture of 6.5 g. (0.93 mole) of small pieces of lithium wire in 700 ml. of dry ether under nitrogen was added cautiously, during 3.25 hr., 56 g. (0.35 mole) of bromine. After stirring an additional hour, the clear, nearly colorless solution was transferred through a delivery tube under nitrogen pressure to a graduated bottle containing a few pieces of lithium wire. Sufficient ether was added to bring the volume of the solution to 700 ml. and the bottle was tightly stoppered.

A red suspension of α-sodiobenzyldimethylamine (IVb) was prepared by metalation (2-hr. reflux) of 11.9 g. (0.088 mole) of amine I in 20 ml. of benzene with phenylsodium, which was obtained from 5.80 g. (0.252 mole) of sodium and 12.92 g. (0.115 mole) of chlorobenzene in 22 ml. of octane and 50 ml. of benzene (see below). To the stirred suspension of IVb was added 150 ml. (0.15 mole) of the ethereal, 1 M solution of lithium bromide to give an orange-brown mixture containing α-lithiobenzyldimethylamine (IVa).

Isomerization of Lithio Derivative IVa to Form IIa (Table II).—The mixture containing α-lithiobenzyldimethylamine (IVa) in ether–benzene–octane, prepared as described above, was refluxed (48°) for 45 hr., adding ether occasionally to maintain an approxi-

mately constant volume. The mixture was cooled to 30°, and a solution of 27.3 g. (0.15 mole) of benzophenone in 70 ml. of ether was added. After stirring for 4 hr., the mixture was decomposed and worked up as described above for the metalations with n-butylsodium. Recrystallization of the crude amine product from hexane gave 11.1 g. (40%) of amino alcohol III, m.p. 149–153°; mixture m.p. with an authentic sample, 152.5–154°. Evaporation of the solvent from the filtrate and distillation of the residue gave 4.2 g. (35%) of amine I, b.p. 71–73° at 18 mm., and left 2.4 g. of viscous oil which could not be crystallized.

When the suspension of lithio derivative IVa in ether–benzene–octane was stirred at 25–30° for 1 or 23 hr., and the product IIa then added, amino alcohol V (m.p. 102–105°), but not III, was obtained (see Table II).

In a blank experiment, the red suspension of α-sodiobenzyldimethylamine (IVb) in benzene–octane prepared as described above was treated with 150 ml. of dry ether *instead of* the ethereal lithium bromide solution. After refluxing the reaction mixture at 48° for 45 hr. and then adding the benzophenone, 92% of amine I was recovered. Neither of the amino alcohols III or V was obtained. Repetition of this experiment afforded a similar result. Apparently the sodio derivative IVb was decomposed by the ether (presumably by β-elimination) to regenerate amine I, since IVb was found to be stable in benzene–octane at 85° for 24 hr. (see Table III).

Condensations of IVa–b with Cyclohexanone to Form VI. (A). Result with IVa.—α-Lithiobenzyldimethylamine (IVa) was prepared as described above and stirred at 25–30° for 2.5 hr. after adding the ether solution of lithium bromide. A solution of 14.7 g. (0.15 mole) of cyclohexanone in 70 ml. of ether was added over 5 min. while cooling to keep the temperature below 40°. After stirring at room temperature for 2 hr. and then decomposing with methanol, the reaction mixture was worked up as described above for the condensations with benzophenone. Distillation of the amine fraction yielded 3.5 g. (29%) of recovered amine I, b.p. 61–63° at 14 mm., 11.8 g. (58%) of 1-(α-dimethylaminobenzyl)-cyclohexanol (VI), b.p. 124–127° at 1 mm., and 1.1 g. of residue. Redistillation gave an analytical sample of VI, b.p. 117° at 0.7 mm.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 6.00. Found: C, 77.23; H, 9.92; N, 6.16.

The picrate of VI was difficult to crystallize initially. After two recrystallizations from 95% ethanol it melted at 163.5–165°.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.29; H, 5.58; N, 12.34.

The methiodide was prepared by treating 0.05 mole of VI with 0.10 mole of methyl iodide in 50 ml. of acetonitrile for 8 hr. at room temperature, followed by 1 hr. at reflux and another 24 hr. at room temperature. The addition of 100 ml. of ether precipitated a viscous oil which finally crystallized to give a 94% yield of methiodide, m.p. 149–156°. After two recrystallizations from ethanol–ether it melted at 157–158°.

Anal. Calcd. for $C_{16}H_{26}INO$: C, 51.20; H, 6.98; N, 3.73. Found: C, 50.94; H, 6.91; N, 4.01.

(B) Result with IVb.—To a suspension of α-sodio derivative IVb, prepared as described below for the metalation of amine I with phenylsodium (refluxed 2 hr.), was added over 7 min. a solution of 16.7 g. (0.17 mole) of cyclohexanone in 65 ml. of ether. After stirring for 2 hr. at room temperature, the reaction mixture was decomposed and worked up in the usual manner. Distillation of the amine fraction yielded 9.0 g. (67%) of recovered amine I, b.p. 62–65° at 14 mm., 6.4 g. (27%) of VI, b.p. 124–128° at 1 mm., and 0.6 g. of residue.

Metalation of Amine I with Phenylsodium. Condensation with Benzophenone (Table III).—Phenylsodium was prepared in benzene–octane by a modification of an earlier procedure for its preparation in toluene.[13]

To a dispersion prepared from 6.58 g. (0.286 mole) of sodium, 25 ml. of octane, and 3 drops of oleic acid was added 35 ml. of benzene. When the temperature had dropped to 50°, 3 ml. of a solution of 14.62 g. (0.13 mole) of chlorobenzene in 25 ml. of benzene was added. As soon as reaction started, as evidenced by darkening on the surface of the sodium, the stirrer was started and the reaction was cooled to 35° (water-bath) and maintained at 30–40° until the initial reaction had subsided.[14] The remainder of the chlorobenzene solution was then added over 1 hr., keeping the temperature at 30–40°. The resulting black suspension of phenylsodium was stirred an additional hour at room temperature, and a solution of 13.5 g. (0.10 mole) of amine I in 25 ml. of benzene was added rapidly. The mixture was refluxed (85°) for 2 hr., cooled to 30°, and a solution of 30.9 g. (0.17 mole) of benzophenone in 70 ml. of ether was added to the red suspen-

(9) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 78.

(10) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 4389 (1962).

(11) A. Lespagnol and J. Bertrand, *Compt. rend.*, **230**, 658 (1950).

(12) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(13) J. F. Nobis and L. F. Moormeier, *Ind. Eng. Chem.*, **46**, 539 (1964).

(14) Generally these conditions would suffice to initiate the reaction. If the reaction had not started after holding at 50–55° for 5–10 min., the mixture was briefly heated to 70–75° and then quickly cooled to 30–35° as soon as black granules of phenylsodium appeared.

sion. The resulting blue mixture was stirred 4 hr. at room temperature and worked up as described for the metalations with n-butylsodium. Recrystallization of the crude product from hexane gave 20.0 g. (63%) of V, m.p. 105–107°. The solvent was evaporated from the filtrate and the residue distilled to give 2.8 g. (21%) of recovered amine I and 2.6 g. of viscous residue. The infrared spectrum of the latter was similar to that of V.

The other runs listed in Table III were effected similarly, allowing the metalations to proceed under the indicated conditions before adding the benzophenone. No evidences of the presence of o-isomer III could be found in any of the experiments.

Metalation with Phenylpotassium.—To a suspension of phenylpotassium prepared from 15.64 g. (0.40 mole) of potassium sand and 21.6 g. (0.20 mole) of anisole in 165 ml. of heptane[15] was added 13.5 g. (0.10 mole) of amine I in 30 ml. of heptane. The light-red suspension was stirred 18 hr. at room temperature, and a solution of 45.5 g. (0.25 mole) of benzophenone in 125 ml. of benzene was added. After stirring for 4 hr., the reaction mixture

was decomposed with 40 ml. of t-butyl alcohol and then worked up in the usual manner. Recrystallization of the crude amine fraction from hexane gave 23.0 g. (73%) of amino alcohol V, m.p. 106–107°, and distillation of the filtrate afforded 1.9 g. (14%) of recovered amine I.

Metalation with Phenyllithium.—To a solution of phenyllithium prepared from 3.43 g. (0.49 mole) of lithium wire and 36.9 g. (0.235 mole) of bromobenzene in 150 ml. of ether[16] was added 13.5 g. (0.10 mole) of amine I in 60 ml. of ether. The brown solution was stirred for 18 hr. at room temperature, and a solution of 53.5 g. (0.29 mole) of benzophenone in 100 ml. of ether was added. The resulting purple suspension was stirred for 4 hr., then decomposed with methanol and worked up in the usual manner. Removal of solvent from the amine fraction followed by cooling gave 6.7 g. (21%) of amino alcohol III, m.p. 152–153°. The mixture m.p. with an authentic sample of III[10] was 152–153.5°. Distillation of the filtrate gave 9.6 g. (71%) of recovered amine I.

(15) A. A. Morton and E. J. Lanpher, J. Org. Chem., **23**, 1638 (1958).

(16) R. G. Jones and H. Gilman, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

Mass Spectrometry in Structural and Stereochemical Problems. XXVII.[1] Mass Spectral Fragmentation Processes and Hydrogen Transfer Reactions of Amides and Amines[2]

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Numerous deuterated analogs of aliphatic, cycloalkyl and steroidal N-acetylamines have been synthesized and their mass spectra compared with those of the non-labeled parent substances. Such differential labeling has been shown to be of mechanistic significance, clarifying many hydrogen transfer reactions, as well as of analytical consequence by uncovering the composite nature of several mass spectral peaks. The empirical composition of these fragments was such that even high-resolution mass spectroscopy could not have achieved these results. Mechanistic generalizations are feasible and lead to the conclusion that fission of the carbon-carbon bond next to nitrogen is one of the key operations. In amides, if the acyl group can be lost by ketene elimination, such processes occur in order to give rise to the more stable amine ion. In cycloalkylamines and their amides, a single carbon–carbon bond fission cannot fragment the molecule, and subsequent rearrangement results in the formation of a stable, even-electron ion. In amides, this process is accompanied by ketene expulsion to provide the more favored amine ion. Attention is called to a number of competing fragmentation processes and to the differences encountered with the relatively stable nuclear system of the steroids, where rupture of the bond between the ring and the nitrogen takes precedence over ring fission.

The ultimate aim of this series of investigations is to reach that level of sophistication which will permit the prediction (and hence interpretation) of the principal modes of mass spectral fragmentation of fairly complicated organic molecules. For this purpose, it is necessary to study in detail the behavior, upon electron impact, of many common functional groups, often superimposed upon certain fundamental ring systems.[4] In the course of examining the desulfurization of thiazolidines,[5] a number of steroidal amides were obtained and their mass spectra measured. Examination of these spectra prompted us to undertake a detailed study —utilizing deuterated substrates for labeling purposes— of the mass spectral fragmentation behavior of secondary and tertiary amides as well as of certain precursor amines. The experimental results and conclusions constitute the subject matter of the present paper.

Aliphatic Secondary and Tertiary Amides.—The mass spectra of a wide variety of aliphatic amides have

been discussed by Gilpin,[6] who found that two processes predominated.

$$RCO \overset{\xi}{\underset{}{|}} NR' — CH_2 \overset{\xi}{\underset{}{|}} R'' \rightarrow H\overset{+}{N}R' = CH_2 \qquad (2)$$
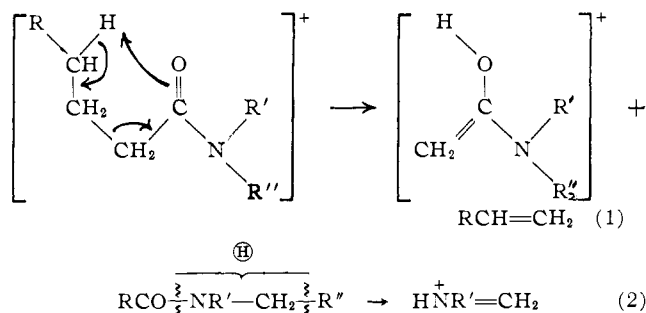
Process 1 occurs when the acyl group contains a hydrogen atom γ to the carbonyl group; it must be the same process which operates in the spectra of various carbonyl compounds[7] and which has been confirmed by labeling experiments in certain esters.[8] Process 2 is less well defined but appears to be analogous to the behavior of amines[9] and ethers.[10] It has not been possible, with the evidence so far published, to determine the origin of the hydrogen atom which is transferred to the ionized fragment.

(1) Paper XXVI: C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. Le Count, A. R. Battersby and H. Schmid, Helv. Chim. Acta, **46**, 742 (1963).

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(3) (a) On leave from the Israel Institute for Biological Research, Ness-Ziona, Israel; (b) Rockefeller Fellow, 1961–1962, on leave from the University of Poznan, Poland.

(4) For examples of our approach toward studying the mass spectral behavior of the carbonyl group in bicyclic (decalin) or tetracyclic (steroid) systems, see E. Lund, H. Budzikiewicz, J. M. Wilson and C. Djerassi, J. Am. Chem. Soc., **85**, 1528 (1963), and D. H. Williams, J. M. Wilson, H. Budzikiewicz and C. Djerassi, ibid., **85**, 2091 (1963), and references cited therein.

(5) C. Djerassi, N. Crossley and M. A. Kielczewski, J. Org. Chem., **27**, 1112 (1962).

(6) J. A. Gilpin, Anal. Chem., **31**, 935 (1959); see also F. W. McLafferty, ibid., **28**, 306 (1956).

(7) F. W. McLafferty, ibid., **31**, 82 (1959).

(8) Ng. Dinh-Nguyen, R. Ryhage, S. Ställberg-Stenhagen and E. Stenhagen, Arkiv Kemi, **18**, 393 (1961).

(9) R. S. Gohlke and F. W. McLafferty, Anal. Chem., **34**, 1281 (1962).

(10) F. W. McLafferty, ibid., **29**, 1782 (1957).