

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY, DURHAM, N. C.]

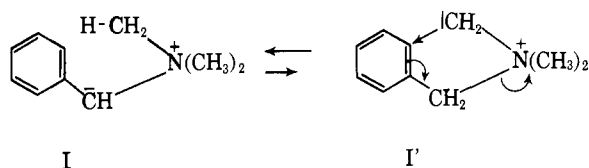
Influence of Basicity of Benzylic Carbanion on the *ortho*-Substitution Rearrangement of Certain α -Carbonyl Benzyltrimethylammonium Compounds¹

BY WALTER H. PUTERBAUGH² AND CHARLES R. HAUSER

RECEIVED SEPTEMBER 9, 1963

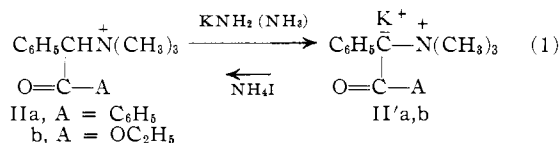
The *o*-substitution rearrangement was realized by means of potassium amide in liquid ammonia with α -carbamoylbzyltrimethylammonium ion (IIIa) and α -(phenylcarbamoyl)-bzyltrimethylammonium ion (IIIb). However, the rearrangement failed with α -benzoylbzyltrimethylammonium ion (IIa) and α -(ethoxycarbonyl)-bzyltrimethylammonium ion (IIb). This difference in behavior of the α -carbonyl bzyltrimethylammonium ions is ascribed to a difference in relative basicity of the corresponding intermediate benzylic carbanions. α -Carboxybzyltrimethylammonium ion (V) reacted with potassium amide in liquid ammonia to form methyl α -dimethylaminophenylacetate (VI) and α -(methoxycarbonyl)-bzyltrimethylammonium iodide (VII).

Evidence has recently been presented that the *o*-substitution rearrangement of the bzyltrimethylammonium ion by alkali amides in liquid ammonia involves the initial formation of the benzylic carbanion I.³ This carbanion is in equilibrium with the more basic methide carbanion I', through which the rearrangement presumably occurs.



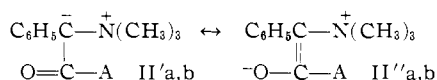
On this basis it seemed possible that rearrangement would fail with certain α -carbonyl bzyltrimethylammonium ions, since their benzylic carbanion might be too weakly basic to enter effectively into equilibrium with the corresponding methide carbanion. This was observed in the present investigation with two carbonyl quaternary ions. However, two other carbonyl quaternary ions still afforded sufficiently basic benzylic carbanions for the rearrangement to be realized.

The two carbonyl quaternary ions that failed to rearrange were IIa,b. These were merely converted by potassium amide in liquid ammonia to their potassium salts II'a,b, from which IIa,b were largely recovered after 6 hr. (eq. 1).



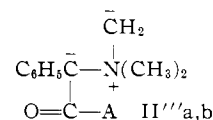
Although the potassium salt of the ester quaternary ion II'b remained in solution, that of the ketone quaternary ion II'a precipitated. The failure of IIa to rearrange cannot be ascribed to precipitation, however, since rearrangement failed even in a mixture of liquid ammonia and tetrahydrofuran, in which medium most of salt II'a dissolved.

As indicated above, the failure to rearrange may be attributed to the weakly basic nature of the benzylic carbanions II'a,b, which would be stabilized by resonance forms II''a,b.



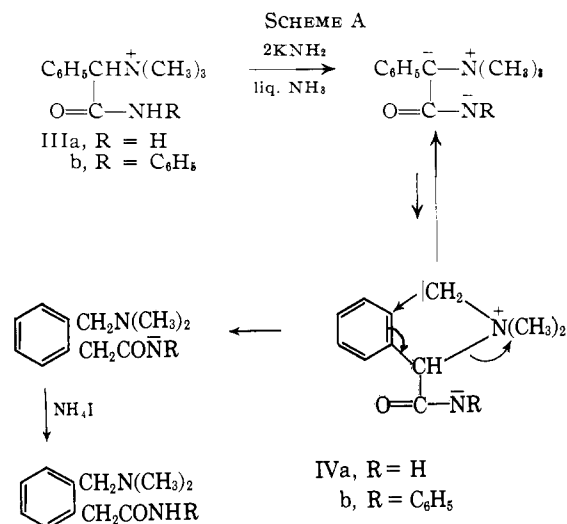
Since excess potassium amide was employed (three molecular equivalents), there was a possibility that

dianions II'''a,b might be formed. If so, however, these too failed to rearrange. This observation sug-



gests that *o*-rearrangement of bzyltrimethylammonium ion likely does not proceed through a corresponding dianion, even when the rearrangement is effected in the presence of excess amide ion.

The two carbonyl quaternary ions that underwent the *o*-substitution rearrangement with excess potassium amide in liquid ammonia were the amide quaternary ions IIIa,b which afforded amino amides IVa,b in yields of 63 and 62%, respectively (Scheme A). These appear to be the first examples of the *o*-rearrangement with an α -substituted carbonyl quaternary ion.



The structures of amino amides IVa,b were supported by analysis and by their infrared spectra which showed amide carbonyl peaks⁴ at 1680–1675 cm.⁻¹, and peaks at 845–840 cm.⁻¹ attributable to the dimethylamino-methyl group.⁵ Compound IVa showed only one peak, at 760 cm.⁻¹, in the 770–680 cm.⁻¹ region, indicative of an *o*-disubstituted rather than a monosubstituted aromatic ring.⁶ Compound IVb also showed such a peak, at 750 cm.⁻¹, but the presence of the additional aromatic ring makes the assignment of the *o*-disubstituted ring less certain.

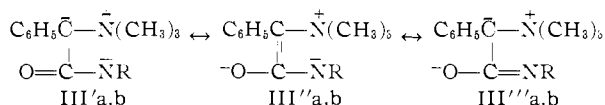
That IVa,b were *o*-rearrangement products was confirmed by oxidation to yield *o*-phthalic acid. Com-

(1) Supported in part by a National Institutes of Health grant.
(2) National Science Foundation Science Faculty Fellow, on leave from Thiel College.
(3) W. H. Puterbaugh and C. R. Hauser, *J. Am. Chem. Soc.*, **86**, 1105 (1964).

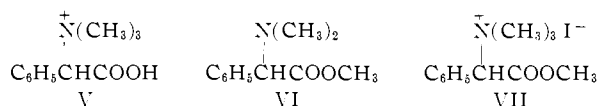
(4) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd. Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 209.
(5) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).
(6) Reference 4, p. 76.

pound IVa was demonstrated to be a primary amide by hydrolysis with potassium hydroxide in aqueous diglyme to yield ammonia. That IVb was an anilide was confirmed by acidic hydrolysis to form aniline. Interestingly, the spectra of both IVa and IVb were unusual in the N-H region (see Experimental).

The success of the rearrangements of IIIa,b may be ascribed to a more favorable equilibrium between their corresponding benzylic and methide carbanions than that between the benzylic and methide carbanions of IIa,b. The more favorable equilibrium with IIIa,b may be attributed to the relatively greater basicities of their benzylic carbanions, which not only bear a double negative charge, but also have additional resonance forms (III''a,b) to contribute to the total structure of the molecules. The net effect of the additional forms would be to increase the electron density at the benzylic carbanions relative to that in the anions derived from IIa,b.



In contrast to the amide quaternary ions IIIa,b, the acid quaternary ion V failed to undergo the *o*-rearrangement with excess potassium amide in liquid ammonia. Instead, there was obtained amino ester VI and the ester methiodide VII in yields of 30 and 34%,⁷ respectively.



That these products were not *o*-rearrangement derivatives was shown by their infrared absorption near 740 and 700 cm^{-1} indicative of a monosubstituted, not a disubstituted, aromatic ring,⁸ and by oxidation of the ester methiodide to form benzoic acid, not *o*-phthalic acid.

The structure of amino ester VI was supported by its hydrochloride whose m.p. agreed with the reported value,⁹ and also by its infrared spectrum which showed carbonyl absorption¹⁰ at 1750 cm^{-1} , and C-O absorption¹¹ at 1220 and 1150 cm^{-1} . This spectrum was very similar to that of the corresponding ethyl ester (see Experimental) from which ester quaternary ion IIb was prepared by quaternization.

The structure of ester methiodide VII was supported by analysis and by its infrared spectrum which showed absorption at 1750 cm^{-1} indicative of the carbonyl group. Compound VII was confirmed as the methiodide of VI by mixture m.p. and identity of its infrared spectrum with that of the product obtained by treating VI with methyl iodide.

The formation of VI and VII under the conditions employed is rather remarkable. Ester VI apparently arose from an intra- or intermolecular displacement, and its methiodide VII by methylation of VI.

The failure of V to undergo the *o*-substitution rearrangement is not necessarily out of line with the theory proposed above. In fact, the benzylic carbanion V' would be expected to be more weakly basic than the benzylic carbanions such as III'a,b since the carboxylate ion is a weaker base than the carbonyl amide ion. Thus,

(7) Presumably an equivalent amount of α -dimethylaminophenylacetic acid was formed, but it was not isolated.

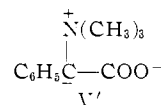
(8) Reference 4, p. 77.

(9) J. Klosa, *Arch. Pharm.*, **285**, 401 (1952); the free ester was reported as an oil.

(10) Reference 4, p. 180.

(11) Reference 4, p. 188.

the *o*-rearrangement may have been retarded enough so that competing reactions could take place.



Experimental¹²

Treatment of IIa with Potassium Amide. (A) In Liquid Ammonia.—To a solution of 0.164 mole of potassium amide in 450 ml. of liquid ammonia¹³ was added 20.8 g. (0.545 mole) of α -benzoylbzyltrimethylammonium iodide (IIa).¹⁴ The mixture, which contained a white precipitate, was stirred for 6 hr. and then neutralized and worked up essentially as described for the rearrangement of IIIa (see below). There was obtained 17.0 g. (82%) of recovered IIa, m.p. 160–164°, and 162–164° on admixture with starting IIa. Only traces of neutral (0.3 g.) and basic (0.1 g.) fractions were found.

(B) In Liquid Ammonia-Tetrahydrofuran.—To a solution of 0.172 mole of potassium amide in 450 ml. of liquid ammonia was added 175 ml. of dry tetrahydrofuran followed, after a few minutes, by 16.4 g. (0.043 mole) of IIa. The resulting mixture, which contained only a very small amount of flocculent gray precipitate, was stirred 5 hr. and then worked up as for (A). There was obtained 15.3 g. (93%) of recovered IIa, m.p. 159–162°. No neutral or basic material was found.

α -(Ethoxycarbonyl)benzyltrimethylammonium Iodide (IIb).—A suspension of 35.4 g. (0.197 mole) of α -dimethylaminophenylacetic acid¹⁵ in 250 ml. of absolute ethanol was saturated with dry hydrogen chloride. After refluxing for 21 hr., the reaction mixture was worked up to give 25.0 g. (61%) of ethyl α -dimethylaminophenylacetate, b.p. 85–97° at 0.8 mm., lit.¹⁶ b.p. 71–78° at 0.6 mm. The infrared spectrum showed principal peaks at 1740, 1455, 1260, 1210, 1150, 1040, 755, and 695 cm^{-1} .

A solution of 20.7 g. (0.10 mole) of the above ester in 100 ml. of acetonitrile was treated with 0.20 mole of methyl iodide to give, within 5 min., 33.4 g. (96%) of IIb, m.p. 172.5–174°, and 173–173.5° after recrystallization from ethanol.

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{INO}_2$: C, 44.71; H, 5.77; N, 4.01. Found: C, 44.72; H, 5.63; N, 3.84.

Treatment of IIb with Potassium Amide.—To a solution of 0.21 mole of potassium amide in 450 ml. of liquid ammonia was added 24.45 g. (0.07 mole) of IIb. After 6 hr., the gray solution was worked up as for IIa to give 24.4 g. (99%) of recovered IIb, m.p. 173.5–174°, undepressed on admixture with starting IIb. The infrared spectra were identical.

α -Carbamoylbzyltrimethylammonium Iodide (IIIa).—A suspension of 17.8 g. (0.10 mole) of 2-(*N,N*-dimethylamino)-2-phenylacetamide¹⁷ in 100 ml. of acetonitrile was treated with 0.20 mole of methyl iodide. After several hours, ether was added to afford 31.6 g. (99%) of IIIa, m.p. 199–200.5°, and 199.5–200.5° after recrystallization from acetonitrile.

Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{IN}_3\text{O}$: C, 41.26; H, 5.35; N, 8.75. Found: C, 41.50; H, 5.36; N, 8.85.

Rearrangement of IIIa to IVa.—To a solution of 0.255 mole of potassium amide in 900 ml. of liquid ammonia was added 27.2 g. (0.085 mole) of IIIa. The lime-yellow mixture was stirred for 6 hr. and then poured into a solution of 37 g. (0.26 mole) of ammonium iodide in 150 ml. of liquid ammonia. The ammonia was evaporated on the steam bath as 250 ml. of ether was added. Water (50 ml.) was added and the layers were separated. The organic layer (containing a suspension) was washed with water and combined with an ether extract of the aqueous layers (previously made alkaline). The combined organic layers were extracted with 2 *M* hydrochloric acid (suspension dissolved) and the acidic extracts were cooled and made basic. The resulting precipitate was removed by filtration to give 9.5 g. (59%) of 2-(*o*-dimethylaminomethylphenyl)acetamide (IVa), m.p. 139–140°. Extraction of the filtrate with ether and removal of solvent from the dried solution gave more (0.7 g., 4%) of IVa, m.p. 136.5–139.5°. Recrystallization from hexane-ethanol afforded the analytical sample, m.p. 140–141°.

(12) Melting points were taken on a Fisher-Johns melting point stage which had been calibrated with standard samples. Analyses by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 237 Infracord using the potassium bromide pellet method for solids, and the neat liquid between sodium chloride plates for liquids.

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

(14) W. H. Putterbaugh and C. R. Hauser, *J. Org. Chem.*, **28**, 3465 (1963).

(15) C. R. Hauser, H. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, **82**, 1786 (1960).

(16) J. A. King and F. H. McMillan, *ibid.*, **73**, 4451 (1951), also observed a wide boiling range for this ester, which they prepared from ethyl α -chlorophenylacetate and dimethylamine.

(17) G. F. Morris and C. R. Hauser, *J. Org. Chem.*, **26**, 4741 (1961).

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.80; H, 8.45; N, 14.40.

Oxidation of 2.6 g. of IVa was effected with excess potassium permanganate in 1 *M* sodium hydroxide (refluxed 20 hr.) to give 1.0 g. (54%) of *o*-phthalic acid, identified by mixture m.p. and infrared spectrum.

Hydrolysis of 5.7 g. of IVa was effected with potassium hydroxide in refluxing water and diglyme. A test of the evolved gas with filter paper moistened with Nessler reagent¹⁸ gave a dark red-brown precipitate identical with that obtained in a blank run with aqueous ammonia. A blank run with aqueous methylamine gave a pale yellow precipitate with this reagent.

The methiodide of IVa (*o*-(carbamoylmethyl)-benzyltrimethylammonium iodide) melted at 212–213° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{19}IN_2O$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.32; H, 5.81; N, 8.17.

The infrared spectrum of IVa showed only a single strong peak, at 3250 cm^{-1} , along with a very weak, broad band, near 3050 cm^{-1} , in the N-H region (3400–3000 cm^{-1}). Primary amides generally exhibit two peaks, near 3350 and 3180 cm^{-1} , in this region.¹⁹ Such peaks were observed in the spectra of quaternary amide 111a and of the corresponding amino amide from which IIIa was prepared by quaternization. The methiodide of IVa did exhibit two normal peaks, at 3380 and 3160 cm^{-1} .

Rearrangement of IIIb to IVb.—To a solution of 0.12 mole of potassium amide in 450 ml. of liquid ammonia was added 15.85 g. (0.04 mole) of α -(phenylcarbamoyl)-benzyltrimethylammonium iodide (IIIb).¹⁴ After 6 hr., the yellow-brown mixture was neutralized inversely with ammonium chloride in ammonia, and the ammonia replaced by ether. The mixture was worked up as described above for the rearrangement of IIIa, except that the mixture obtained on making the acidic extracts basic was extracted with ether rather than separated by filtration. The solvent was removed from the dried ether solution and the residue (10.4 g.) was recrystallized from hexane-ethanol to afford 6.6 g. (62%) of 2-(*o*-dimethylaminomethylphenyl)-acetanilide (IVb), m.p. 129–130.5°, and 129.5–130.5°, after a second recrystallization.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.93; H, 7.65; N, 10.48.

Hydrolysis of 3.7 g. of IVb was effected with refluxing hydrochloric acid to give, after making basic, 1.2 g. (95%) of aniline, identified by v.p.c. (enhancement technique) and infrared spectrum.

Oxidation of IVb was effected by refluxing the basic aqueous extract from the above hydrolysis with excess potassium per-

manganate to give 0.9 g. (40%) of *o*-phthalic acid, m.p. 210–212°, identified by mixture m.p. and infrared spectrum.

The infrared spectrum of IVb failed to show the single secondary amide peak usually observed near 3270 cm^{-1} .²⁰ Instead, it exhibited two weak peaks at 3240 and 3180 cm^{-1} . Unusual absorption in the N-H region was similarly observed with IVa (see above). The amino amide from which quaternary amide IIIb was prepared showed the normal secondary amide peak at 3280 cm^{-1} .¹⁴

α -Carboxybenzyltrimethylammonium Iodide (V).—A suspension of 17.9 g. (0.10 mole) of α -dimethylaminophenylacetic acid¹⁵ in 150 ml. of acetonitrile was treated with 0.20 mole of methyl iodide. After 10 hr. each at 65° and room temperature, ether was added. The tacky solid was rinsed with several portions of ether and recrystallized from ethanol-ether to give 15.6 g. (49%) of V, m.p. 139–141° dec., and 150.5–152.5° dec. after three recrystallizations from ethanol.

Anal. Calcd. for $C_{11}H_{16}INO_2$: C, 41.14; H, 5.02; N, 4.36. Found: C, 41.10; H, 5.25; N, 4.18.

Treatment of V with Potassium Amide to Form VI and VII.—To a solution of 0.21 mole of potassium amide in 450 ml. of liquid ammonia was added 22.5 g. (0.07 mole) of V. After 6 hr., the yellow-brown mixture was neutralized inversely with ammonium iodide and the ammonia replaced by ether. Water was added to dissolve all solid. The layers were separated and the ether layer was washed with water and dried over sodium sulfate. Distillation gave 4.1 g. (30%) of methyl α -dimethylaminophenylacetate (VI), b.p. 69–74° at 0.5 mm. This product was soluble in dilute acid, but insoluble in dilute base or water. The infrared spectrum showed principal peaks at 1740, 1455, 1265, 1215, 1150, 1050, 735, and 695 cm^{-1} . The hydrochloride melted at 177.5–178° dec., lit.⁹ m.p. 177° dec. The methiodide melted at 167.5–168.5° (see below).

The aqueous layer (see above) was adjusted to pH 7 and evaporated under reduced pressure to a volume of about 60 ml. After cooling, the precipitate was collected and dried to give 11.8 g. of solid. The latter was recrystallized from ethanol (filtered from insoluble portion) to give 8.0 g. (34%) of α -(methoxycarbonyl)-benzyltrimethylammonium iodide (VII), m.p. 166–167°, undepressed on admixture with the methiodide of VI (see above). The infrared spectra were identical. A second recrystallization from ethanol gave the analytical sample, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{12}H_{18}INO_2$: C, 42.79; H, 5.37. Found: C, 43.00; H, 5.41.

Oxidation of 2.2 g. of VII was effected by refluxing with excess potassium permanganate in 1 *M* sodium hydroxide to give 0.4 g. (35%) of benzoic acid, m.p. 120–122°, undepressed on admixture with an authentic sample.

(18) M. L. Nichols and C. O. Willits, *J. Am. Chem. Soc.*, **56**, 759 (1934).

(19) Reference 4, p. 206.

(20) Reference 4, p. 207.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF., AND VARIAN ASSOCIATES, PALO ALTO, CALIF.]

The Catalyzed Reaction of Alkylmagnesium Halides with Alkyl Halides. II.¹ The Nature of the Catalyst

BY V. D. PARKER,² L. H. PIETTE, R. M. SALINGER, AND C. R. NOLLER

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An investigation of the colored solutions that result from the reaction of copper, nickel, cobalt, and iron halides with an excess of alkylmagnesium bromide and that markedly catalyze the reaction of alkylmagnesium bromides with alkyl bromides indicates that they are solvated complexes of organometallic compounds with alkylmagnesium bromides.

A reasonably detailed investigation of the catalyzed reaction of ethylmagnesium bromide with ethyl bromide to give ethylene and ethane was reported in 1936.¹ The material added to bring about the reaction was cuprous bromide or cuprous chloride, but it was concluded that the active catalyst was a sol of metallic copper, referred to as colloidal copper. Subsequently, largely because of the work of Kharasch and his associates, the attention of others shifted to the action of cobaltous chloride³

and this trend has continued to the present.⁴ Much of this work has been concerned with whether the active catalyst is colloidal cobalt or a reduced form of cobaltous chloride usually represented as $\cdot CoCl$, and whether the reactions involve free radicals or take place *via* a transition state by either homolytic or heterolytic scission without ever yielding truly free groups.

A few years ago it was decided to repeat and extend the earlier work, making use of the newer techniques and methods of analysis. One phase of this work clearly involves the nature of the catalyst. Most of the present work has been carried out on the red solu-

(1) Paper I: C. B. Linn and C. R. Noller, *J. Am. Chem. Soc.*, **58**, 816 (1936).

(2) American Chemical Society Fellow, 1961–1963.

(3) See M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, Chapters V and XVI.

(4) (a) F. W. Frey, Jr., *J. Org. Chem.*, **26**, 5187 (1961); (b) L. H. Slaugh, *J. Am. Chem. Soc.*, **83**, 2734 (1961); (c) W. B. Smith, *J. Org. Chem.*, **26**, 4206 (1961).