

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

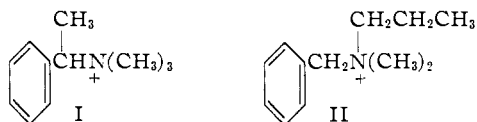
A Novel Ring Enlargement Involving the *ortho* Substitution Rearrangement by Means of Sodium Amide in Liquid Ammonia¹

BY DANIEL LEDNICER AND CHARLES R. HAUSER

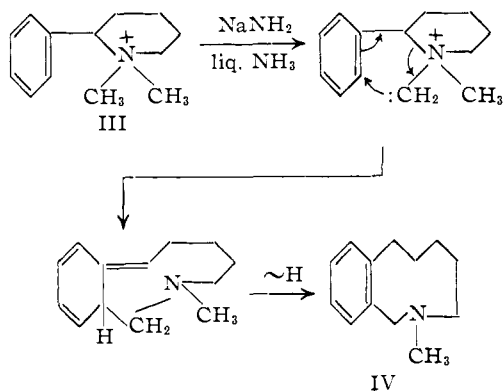
RECEIVED MARCH 28, 1957

The *ortho* substitution rearrangement was realized with the 1,1-dimethyl-2-phenylpiperidinium ion, the piperidine ring of which underwent ring enlargement to form a new nine-membered nitrogen-containing ring system. The structure of the product was established by independent synthesis. The success of the rearrangement appears to be dependent on a favorable conformation of the molecule, in which a methyl group is near to the *o*-position of the aromatic ring, since similar open-chain quaternary ammonium ions exhibit considerable β -elimination.

The *ortho* substitution rearrangement by means of sodium amide in liquid ammonia has been especially characteristic of benzyl-type quaternary ammonium ions having no β -hydrogen such as the benzyltrimethylammonium ion.² The rearrangement has been realized, however, in fairly good yields with quaternary ions I and II which do have β -hydrogens.³ For example, the former ion underwent the rearrangement to 2-ethylbenzyltrimethylamine in 42% yield. This reaction was accompanied by β -elimination to give styrene in 14% yield as well as some dimerization and trimerization.



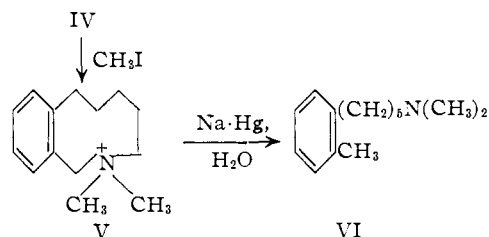
Since the quaternary ion III has some of the structural features of both I and II, it might be expected to undergo the rearrangement to some extent involving the novel ring enlargement shown below. Actually this reaction was realized in 83% yield to form tertiary amine IV, which has a new nine-membered nitrogen-containing ring system. No appreciable β -elimination was observed.



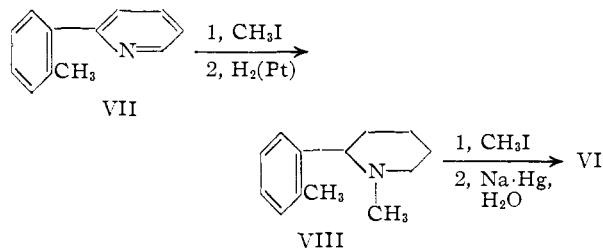
The starting quaternary ion III (as iodide) was prepared by the hydrogenation of the methiodide of 2-phenylpyridine followed by treatment with methyl iodide. This is a modification of the route described in the literature⁴ in which 2-phenylpyridinium chloride was hydrogenated, the product then methylated and finally quaternized.

The reaction of III with sodium amide in liquid ammonia was carried out in the usual manner. The

colorless amine product boiled over a narrow range. On exhaustive oxidation with permanganate, *o*-phthalic acid was obtained in 55% yield, showing that the rearrangement had indeed involved substitution into an *o*-position of the aromatic ring. That ring enlargement had occurred to form amine IV was established by an Emde reduction of the methiodide of the product V which gave amine VI in 80% yield.



The structure of the latter amine VI was confirmed by an independent synthesis from 2-*o*-tolylpyridine (VII),⁵ the structure of which seems well established.



Each of four steps of this independent synthesis appears unequivocal. Thus, the hydrogenation of the methiodide should not be expected to cause structural changes, while the Emde reduction is known to cleave only benzyl-type quaternary salts. The over-all yield from VII to VI was 54%.

It was shown, incidentally, that the product from the *ortho* substitution rearrangement of quaternary ion III was not tertiary amine VIII⁶ which is isomeric with tertiary amine IV. Thus, the methiodides of these two amines not only melted seventeen degrees apart, but a considerable depression of the melting points was observed on mixing the two

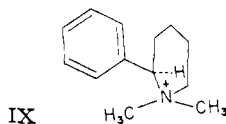
(5) We are indebted to Dr. C. K. Bradsher and Mr. Kenneth B. Moser for a generous sample of this compound which was prepared from *o*-tolylithium and pyridine, by the method for the preparation of 2-phenylpyridine; J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

(6) This product might have arisen by the migration of a methyl group from nitrogen to the ring by a mechanism that has earlier been discarded; see ref. 2.

(1) Supported by the Office of Ordnance Research, U. S. Army.
 (2) S. W. Kantor and C. R. Hauser, *THIS JOURNAL*, **73**, 4122 (1951).
 (3) C. R. Hauser and A. J. Weinheimer, *ibid.*, **76**, 1264 (1954).
 (4) R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951).

derivatives. Moreover, the two amines showed different infrared absorption bands in the 10–15 μ region.

The fact that quaternary ion III underwent the *ortho* substitution rearrangement unaccompanied by an appreciable amount of β -elimination may be due in part to the closeness of the methyl groups to the aromatic ring as indicated in IX. All conformations of the molecule have at least one of the methyl groups in a favorable position for the attack of its carbanion on the ring. On the other hand, the quaternary ions I and II have conformations which appear to place the methyl groups in less favorable positions for rearrangement; hence, even though they have fewer β -hydrogens than quaternary ion III, they exhibit relatively more β -elimination.



An attempt to effect further rearrangement of methiodide V to produce a *meta*-bridge was unsuccessful. Although an appreciable amount of fairly constant boiling amine product was obtained, it was judged to be a mixture because of the wide melting range of its picrate. In line with the argument cited above, the only conformation of methiodide V that allows the approach of a methyl group to the aromatic ring appears to involve a strained ring. It is possible that a *meta*-bridge might be realized if a larger nitrogen-containing ring were employed. Studies along these lines are now being carried out.

Experimental⁷

1,1-Dimethyl-2-phenylpiperidinium Iodide (III).—A solution of 62 g. (0.40 mole) of 2-phenylpyridine and 88 g. of methyl iodide was allowed to stand at room temperature for three days. The solid which had formed was broken up, washed with ether and recrystallized from acetonitrile-ether to yield 113.8 g. of the quaternary salt, m.p. 141–144°.

A suspension of 56.9 g. of the methiodide and 1.0 g. of platinum oxide⁸ in 250 ml. of ethanol was shaken under 50 p.s.i. of hydrogen until a pressure drop of 40 p.s.i. had occurred (1.5 hr.).⁹ The remainder of the quaternary salt was treated in the same manner and the two reaction mixtures combined. The catalyst was removed by filtration and the amber filtrate reduced to about 100 ml. under vacuum. The residual oil was taken up in water and the solution saturated with sodium bicarbonate. The alkaline suspension was then extracted with ether and the organic layer dried over sodium sulfate. The yellow oil which remained behind when the solvent was removed *in vacuo* was distilled to afford 41.8 g. of 1-methyl-2-phenylpiperidine, b.p. 103–109° at 9 mm.

The solid which came out when a solution of the tertiary amine in 100 ml. of acetonitrile was treated with methyl iodide (65 g.) followed by ether was recrystallized from acetonitrile-ether to yield 74.1 g. (68% from 2-phenylpyridine) of III, m.p. 178–179.5°, lit.⁴ 180°.

Rearrangement of III to IV.—Over a period of 10 minutes 74.1 g. (0.234 mole) of the solid methiodide III was added to 0.46 mole of sodium amide (from 10.6 g. of sodium metal) in 900 ml. of liquid ammonia. The light orange-tan suspension was stirred for an additional hour and then neutralized with 23 g. of solid ammonium chloride. The residue

(7) Boiling points are uncorrected; melting points are recorded as obtained on a Fisher-Johns melting point block. The microanalyses are by Calbraith Laboratories, Knoxville, Tenn.

(8) American Platinum Works, Newark, N. J.

(9) In a preliminary run it was noted that if the reaction is not stopped when one equivalent of hydrogen has been taken up, considerable overreduction probably in the form of ring cleavage occurs.

which remained after the ammonia had evaporated was washed thoroughly with about 1 l. of ether; these extracts were washed with water and dried over anhydrous sodium sulfate. The light yellow oil which remained after the ether was removed afforded 38.5 g. (83%) of IV, b.p. 104–106° at 4 mm.

The analytical sample, n_D^{20} 1.5380, distilled at 95.5° at 3 mm.

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.67; H, 9.92; N, 7.33.

The picrate of IV was formed from 0.5 g. of the amine and 10 ml. of saturated ethanolic picric acid and recrystallized to a constant m.p. of 169–170°.

Anal. Calcd. for $C_{10}H_{22}N_4O_7$: C, 54.54; H, 5.31; N, 13.38. Found: C, 54.61; H, 5.20; N, 13.35.

Exhaustive Oxidation of IV.—The tertiary amine IV (2.5 g., 0.013 mole) was added to a solution of 0.5 g. of potassium hydroxide and 6.25 g. of potassium permanganate in 100 ml. of water. The suspension was brought to reflux and, over a period of 48 hr., an additional 18.75 g. of permanganate was added in portions. The cooled suspension was filtered and reduced in volume to 30 ml. This solution was cooled in ice, saturated with hydrogen chloride and extracted with 120 ml. of ether. The solid which remained (1.2 g., 55%) on removing the ether was recrystallized from water. The m.p. of this acid, 216° dec., was not depressed by admixture with *o*-phthalic acid. The infrared spectrum of the oxidation product was superposable on that of an authentic sample of the dibasic acid.

Reaction of Amine IV with Methyl Iodide.—Forty ml. of methyl iodide was added to a solution of 38.5 g. (0.205 mole) of IV in 200 ml. of acetonitrile, with occasional cooling in an ice-bath; colorless crystals were observed to separate from the solution. The mixture was cooled for an additional hour and the crystals collected on a filter to afford 65.0 g. (96%) of colorless powdery needles, m.p. 211–214°.

A sample was crystallized from acetonitrile to give the analytical sample as heavy colorless prisms, m.p. 223–225°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 50.68; H, 6.58; N, 4.31.

Emde Reduction of the Methiodide V to VI.—Over a period of 50 minutes 276 g. of 5% sodium amalgam was added to a hot stirred solution of 10.5 g. (0.034 mole) of the quaternary salt in 200 ml. of water. The mixture was then heated (with stirring) on a steam-bath for 24 hr. The oily layer which separated when the reaction cooled was taken up in ether and the extract washed with water and dried over anhydrous sodium sulfate.

The oil which remained when the solvent was removed was distilled at 5 mm. to afford 5.53 g. of the amine, b.p. 126–128°.

The picrate, m.p. 108–109°, was obtained by reaction of 0.5 g. of the amine with 10 ml. of saturated ethanolic picric acid, followed by recrystallization of the resulting bright yellow crystals from ethanol.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.12; H, 6.07; N, 12.93.

The remainder of the product (5.03 g.) in 10 ml. of acetonitrile was treated with 6.5 ml. of methyl iodide. The reaction was extremely exothermic, resulting in some loss of material. The quaternary salt thus obtained, m.p. 124–126°, was recrystallized from acetonitrile to a constant m.p. of 125–126°.

Anal. Calcd. for $C_{15}H_{26}NI$: C, 51.87; H, 7.55; N, 4.03. Found: C, 51.24, 51.33; H, 7.57, 7.46; N, 4.21.

Independent Synthesis of the Tertiary Amine VI. 1-Methyl-2-*o*-tolylpyridinium Iodide.—Thirty grams (0.21 mole) of methyl iodide was added to 20 g. (0.12 mole) of 2-*o*-tolylpyridine in an ice-cooled flask. The orange solid thus obtained was dissolved in chloroform and treated with activated charcoal. Yellow to orange crystals came out on the addition of ether. The yield of methiodide, m.p. 182–187°, was 34.7 g. (94%). This material was used in the next step without further purification.

A sample, m.p. 199–200°, was obtained by repeated recrystallization from acetonitrile-ether.

Anal. Calcd. for $C_{13}H_{14}NI$: C, 50.18; H, 4.53; N, 4.55. Found: C, 50.14; H, 4.56; N, 4.55.

1-Methyl-2-*o*-tolylpiperidine (VIII).—A suspension of 34.2 g. (0.109 mole) of the above methiodide and 0.5 g. of

platinum oxide in 200 ml. of ethanol was shaken under 60 p.s.i. of hydrogen. The pressure drop was less than 1 p.s.i.; 3.5 hours after an additional 0.5 g. of catalyst had been added, the theoretical amount (23 p.s.i.) of hydrogen had been taken up. The reaction was worked up in the same manner as described for the reduction of 1-methyl-2-phenylpyridinium iodide. Distillation of the residual oil afforded 15.6 g. (75%) of yellow liquid, b.p. 103–105° at 4.5 mm. This was redistilled through a short Vigreux column to yield 14.8 g. of yellowish oil, n_D^{25} 1.5280, b.p. 98–99° at 3.5 mm.

Anal. Calcd. for $C_{13}H_{13}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.30; H, 9.93; N, 7.29.

1,1-Dimethyl-2-*o*-tolylpiperidinium iodide was obtained as colorless fine crystals, m.p. 190–195°, from the reaction of 10.0 g. (0.053 mole) of the tertiary amine in 25 ml. of acetonitrile with 15 ml. of methyl iodide. The yield was 17.4 g. (99%).

A sample of this quaternary salt was recrystallized from acetonitrile-ether to a constant melting point of 206–208°. The mixed melting point of this with the methiodide V (223–225°) was 179–185°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.78; H, 6.70; N, 4.23. Found: C, 50.65; H, 6.72; N, 4.24.

1-Dimethylamino-5-*o*-tolylpentane (VI).—To a well-stirred hot solution of 16.4 g. (0.050 mole) of the above methiodide

in 300 ml. of water there was added over 1 hr. 400 g. of 5% sodium amalgam. After an additional 26 hr. heating on steam, the reaction mixture was worked up as in the Emde reduction described above to afford 7.80 g. (77%) of the tertiary amine, b.p. 122–125° at 4.8 mm.

The picrate, m.p. 108–109°, and the methiodide, m.p. 125–126°, were prepared in the same manner as described above. A mixed m.p. of each of these derivatives with those of the amine obtained by reduction of V failed to show any depression.

Attempted Rearrangement of V.—The methiodide (20 g., 0.0605 mole) was added to 0.122 mole of sodium amide (from 2.8 g. of sodium metal) in 200 ml. of liquid ammonia. After 40 minutes stirring, the reaction was neutralized with 12 g. of solid ammonium chloride. The oil which was obtained when the reaction mixture was worked up in the usual manner was distilled through a short Vigreux column. At 2 mm., 2.72 g. of colorless liquid, b.p. 96–100°, was obtained; this was followed by 1.0 g., b.p. 100–110°; the residue (5.07 g.) had not yet come over when the bath temperature was 250°. The first fraction formed a picrate of m.p. 110–165°, which could not be recrystallized readily.

Substantially the same result was obtained with a reaction time of 5 hr. In this case, however, some ether-insoluble, rubber gum was obtained as well.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. X. α, α -Diphenyl- γ -amino Amides¹

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED MARCH 25, 1957

A number of α, α -diphenyl- γ -amino amides, their salts and intermediate nitriles have been prepared and tested for anticholinergic activity. In several cases the same tertiary amino groups that previously gave highly active anticholinergics in the ester series also gave very active compounds when introduced into the γ -position of these amides. The effects of substitution or replacement of one of the phenyl groups and of branching the alkyl chain were also explored.

The reports of Bockmühl and Ehrhart² in which certain α, α -diphenylamino amides were shown to be powerful antispasmodic agents have stimulated considerable work³ on this interesting type of compound. In our study of the relationship between structure and anticholinergic activity it seemed of interest to introduce, in the γ -position of these amides (I), some of the amino groups that gave good results in the ester type of anticholinergics⁴ (II).

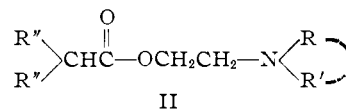
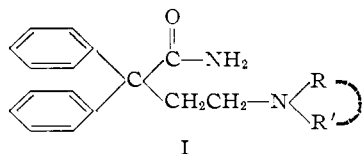


Table I lists the compounds tested in this study with their toxicities and antispasmodic and gastric antisecretory activities. For comparison the activities of atropine, Pamine,⁵ and a few previously reported amides have also been included.

It would hardly be expected that any correlation would exist between the anticholinergic activity and the type of amino groups in molecules so fundamentally different, and indeed no close correlation was found. For example, esters containing dimethylamino and piperidyl groupings have not been very effective, whereas at least one amide with each of these groupings has been outstanding enough to market.⁶ On the other hand, some pyrrolidine-containing amides are no better than the corresponding pyrrolidine-containing esters. However, the methyl-substituted pyrrolidine-containing esters III, IV and V had atropine indexes (in Thiry-vella dogs) of 2, 1 and 1, and antisecretory ED₅₀'s of 0.4, 0.5 and 0.1, respectively, while the

(5) Pamine Bromide is the Upjohn brand of scopolamine methyl bromide.

(6) α, α -Diphenyl- γ -dimethylaminovaleramide hydrogen sulfate is being marketed by Bristol Laboratories as Centrine; α, α -diphenyl- γ -piperidylbutyramide methobromide is marketed by Farbwerke Hoechst as Resantin.

(1) Presented in part before the Division of Medicinal Chemistry, A.C.S., at Miami, Florida, April, 1957, abstracts p. 19-N.

(2) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943); *Ann.*, **561**, 52 (1943).

(3) (a) J. B. Hoekstra and H. L. Dickison, *J. Pharmacol. Exptl. Therap.*, **98**, 14 (1950); R. J. Cozort, *ibid.*, **100**, 325 (1950). (b) O. Schaumann and E. Lindner, *Arch. Exper. Path. Pharmacol.*, **214**, 93 (1951). (c) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952); W. B. Wheatley, *ibid.*, **19**, 434 (1954); W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, M. E. Speeter, L. C. Cheney and S. B. Binkley, *ibid.*, **19**, 794 (1954). (d) P. Janssen, D. Zivkovic, P. Demoen, D. K. deJongh and E. G. von Proosdij-Hartzema, *Arch. intern. pharmacodynamie*, **103**, 82 (1955).

(4) R. B. Moffett, B. D. Aspergren and F. E. Visscher, *THIS JOURNAL*, **77**, 1565 (1953), and preceding papers.