determined using the band at 9.58 $\mu$ and the isovaleramide the band at 11.93 $\mu$ by using the base line technique.

**Pyrolysis of 3-*n*-Propyl-3-methyl-3-isopropyloxazirane.**—The pyrolysis of 25.0 g. of this oxazirane was carried out as described above at 300°. The column was rinsed with 100 ml. of methylene chloride. The solution so obtained was washed with 50 ml. of water and 50 ml. of 10% sulfuric acid. The organic extract was then dried over magnesium sulfate and the volatile solvent evaporated. Distillation of the residual oil in the spinning band column gave 13.9 g. (56%) of mixed amides, b.p. 63–68° (6.0 mm.). Quantitative infrared analysis showed that the mixture consisted of N-*n*-propyl-N-isopropylacetamide (39%) and N-methyl-N-*n*-propylisobutyramide (61%). The acetamide was prepared from acetic anhydride and N-isopropyl-*n*-propylamine, b.p. 68–70° (5.0 mm.), $n^{20}D$ 1.4437.

*Anal.* Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.23; H, 12.17; N, 9.64.

The isobutyramide was prepared from isobutyryl chloride and N-methylpropylamine, b.p. 67° (5.5 mm.), $n^{20}D$ 1.4409.

*Anal.* Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.27; H, 11.65; N, 9.84.

The quantitative analysis was again carried out on the pure amides in a 0.025 mm. cell using the base line technique. The isobutyramide was assayed by its band at 8.43 $\mu$ and the acetamide by its band at 9.74 $\mu$.

**Liquid Phase Pyrolysis of 2-*n*-Propyl-3-methyl-3-isobutyloxazirane.**—A 27.6-g. (0.175 mole) sample of this oxazirane was heated to reflux (168°) under nitrogen. After a 2-hr. period the temperature had dropped to 128°. The effluent gases were passed over aqueous boric acid to remove any ammonia. Titration of the boric acid showed that 0.057 mole (0.33%) of ammonia was obtained. The liquid product was then distilled at atmospheric pressure through a Holzman column[32] to give 16.1 g. (92%) of methyl isobutyl ketone, b.p. 114–116°. The infrared spectrum of this sample was identical with that of an authentic specimen. The residual oil was distilled in a semi-micro spinning band column giving 0.8 g. of unreacted oxazirane, b.p. 43° (3.0 mm.), and 1.0 g. (4%) of mixed amides, b.p. 68–70° (3.0 mm.), very similar in composition to that obtained in the vapor phase pyrolysis of this oxazirane. The identities of these two fractions were based on their infrared spectra. From this distillation a black viscous residue was also obtained which was soluble in acid.

**Liquid Phase Pyrolysis of 2-Isobutyl-3-isopropyloxazirane.**—A 25.0-g. sample of this oxazirane was heated to reflux (165°) under nitrogen. After 3 hr. the pot temperature had dropped to 105°. The mixture was cooled and the aqueous phase was separated. The organic layer was dried over magnesium sulfate and fractionated. There was obtained 8.0 g. (32%) of N-isobutylideneisobutenylamine, b.p. 60° (47 mm.). The infrared spectrum of this compound was identical to that of an authentic sample prepared from anhydrous ammonia and isobutyraldehyde.[18] In addition there were higher boiling products obtained from the pyrolysis reaction but these could not be conveniently separated or characterized.

(32) C. W. Gould, G. Holzman and C. Nieman, *Anal. Chem.*, **20**, 361 (1948).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# Synthetic Hypotensive Agents. VI. 3- and 4-(3′-Aminopropyl)-piperidine Derivatives

BY ARTHUR P. PHILLIPS

RECEIVED JUNE 7, 1957

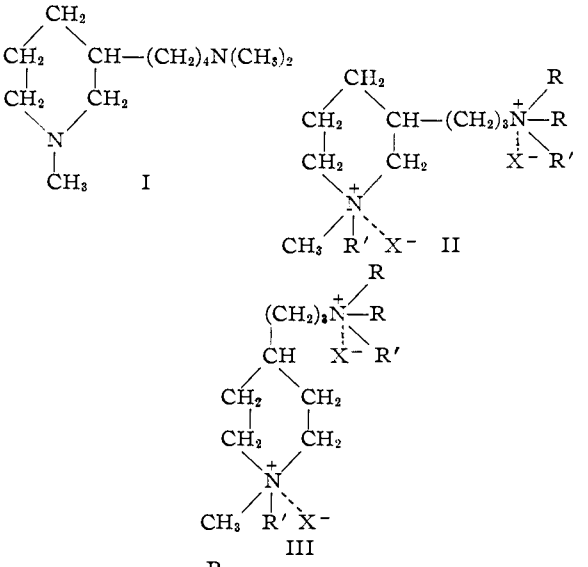
A series of 1-methyl-3(and 4)-(3′-tertiaryaminopropyl)-piperidines and their bis-quaternary ammonium salts have been made for testing as potential hypotensive ganglionic blocking drugs. Several members of this series have shown potencies equal to or greater than hexamethonium as ganglionic blockers in laboratory animals.

In continuation[1] of the investigation of compounds structurally related to 1-methyl-3-(4′-dimethylaminobutyl)-piperidine[2] (I) as potential hypotensive, ganglionic blocking agents, some 1-methyl-3(and 4)-(3′-aminopropyl)-piperidines (II and III) and their bis-quaternary salts have now been made and examined.

Quaternization of the 3-(3′-hydroxypropyl)-pyridine (IV) with methyl iodide gave the methiodide V readily. Attempts to hydrogenate the methiodide catalytically were unsatisfactory because of extremely slow and incomplete hydrogen uptake. After conversion to the chloride VI, catalytic hydrogenation over Adams catalyst proceeded rapidly and quantitatively to give VII.

Chlorination of the 1-methyl-3-(3′-hydroxypropyl)-piperidine hydrochloride (VII) using thionyl chloride gave the chloropropyl compound VIII readily and in excellent yield.

The bis-tertiary amines such as IX were obtained in good yields by heating the chloropropyl-piperidine hydrochlorides (VIII) for several hours with excess of the appropriate secondary amines. The secondary amines used were dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine. Addition of hydrogen chloride or refluxing



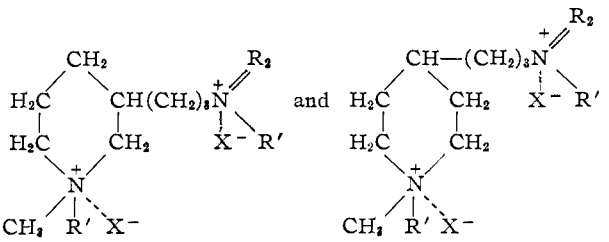
For II and III: $N\langle^{R}_{R}$ = $(CH_3)_2N$, $(C_2H_5)_2N$, pyrrolidino, piperidino and morpholino, etc.
R′X = HCl, $CH_3I$, $C_2H_5I$, etc.

(1) Paper V of this series: A. P. Phillips, THIS JOURNAL, **79**, 2836 (1957).

(2) A. P. Phillips, *ibid.*, **76**, 2211 (1954).

TABLE I

3- AND 4-(AMINOPROPYL)-PIPERIDINES



| Compd. no. | $R_2N$ | R′X | Yield, % | B.p.,[a] °C. | Mm. | M.p., °C. | Crystn.[b] solvent | Formula[c] | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | A. 3-(3′-Aminopropyl)-piperidines | | | | | | | | |
| 1 | $(CH_3)_2N$ | HCl | 95 | 115–116 | 15 | 257–258 | A.E | $C_{11}H_{26}N_2Cl_2$ | 51.4 | 51.3 | 10.2 | 10.2 |
| 2 | $(CH_3)_2N$ | $CH_3I$ | 100 | ..... | | 283–284 | M.Æ | $C_{13}H_{30}N_2I_2$ | 33.3 | 33.3 | 6.5 | 6.7 |
| 3 | $(CH_3)_2N$ | $C_2H_5I$ | 100 | ..... | | 263–264 | M.Æ | $C_{15}H_{34}N_2I_2$ | 36.3 | 36.3 | 6.9 | 6.9 |
| 4 | $(C_2H_5)_2N$ | HCl | 25 | 135–137 | 15 | 245–246 | A.E | $C_{13}H_{30}N_2Cl\cdot H_2O$ | 51.5 | 51.5 | 10.7 | 10.7 |
| 5 | $(C_2H_5)_2N$ | $CH_3I$ | 100 | ..... | | 281–282 | M.Æ | $C_{15}H_{34}N_2I_2$ | 36.3 | 36.4 | 6.9 | 7.1 |
| 6 | Pyrrolidino | HCl | 95 | 153–154 | 17 | 232–233 | A.E | $C_{13}H_{28}N_2Cl_2\cdot{}^1/_2H_2O$ | 53.4 | 53.4 | 10.0 | 10.0 |
| 7 | Pyrrolidino | $CH_3I$ | 100 | ..... | | 294–295 | M.Æ | $C_{15}H_{32}N_2I_2$ | 36.4 | 36.3 | 6.5 | 6.5 |
| 8 | Pyrrolidino | $C_2H_5I$ | 100 | ..... | | 270–271 | A.Æ | $C_{17}H_{36}N_2I_2$ | 39.0 | 38.8 | 7.0 | 7.1 |
| 9 | Piperidino | HCl | 80–90 | 161–163 | 15–16 | 278–279 | A.E | $C_{14}H_{30}N_2Cl_2$ | 56.6 | 56.5 | 10.2 | 10.3 |
| 10 | Piperidino | $CH_3I$ | 100 | ..... | | 283–284 | M.Æ | $C_{16}H_{34}N_2I_2$ | 37.8 | 37.9 | 6.8 | 6.7 |
| 11 | Piperidino | $C_2H_5I$ | 80–90 | ..... | | 245–246 | M.Æ | $C_{18}H_{38}N_2I_2$ | 40.3 | 40.3 | 7.1 | 7.1 |
| 12 | Morpholino | HCl | 50–60 | 173–174 | 15 | 262–263[d] | A.E | $C_{13}H_{28}N_2OCl_2\cdot H_2O$ | 49.2 | 49.4 | 9.5 | 9.3 |
| 13 | Morpholino | $CH_3I$ | 100 | ..... | | 282–283 | Aq.Ac | $C_{15}H_{32}N_2OI_2$ | 35.3 | 35.1 | 6.3 | 6.2 |
| | | | | B. 4-(3′-Aminopropyl)-piperidines | | | | | | | | |
| 14 | $(CH_3)_2N$ | HCl | 100 | 118–120 | 17 | 251–252 | A.Æ | $C_{11}H_{26}N_2Cl_2\cdot 2H_2O$ | 45.0 | 44.9 | 10.3 | 10.3 |
| 15 | $(CH_3)_2N$ | $CH_3I$ | 100 | ..... | | 283–284 | A(M) | $C_{13}H_{30}N_2I_2$ | 33.3 | 33.3 | 6.4 | 6.3 |
| 16 | $(CH_3)_2N$ | $C_2H_5I$ | 100 | ..... | | 255–256 | A.Æ | $C_{15}H_{34}N_2I_2$ | 36.3 | 36.3 | 6.9 | 7.1 |
| 17 | $(C_2H_5)_2N$ | HCl | 80 | 138–140 | 16 | 289–290 | A.Æ | $C_{13}H_{30}N_2Cl_2$ | 54.8 | 54.8 | 10.6 | 10.6 |
| 18 | $(C_2H_5)_2N$ | $CH_3I$ | 100 | ..... | | 292–293 | M.Æ | $C_{15}H_{34}N_2I_2$ | 36.3 | 36.1 | 6.9 | 7.0 |
| 19 | $(C_2H_5)_2N$ | $C_2H_5I$ | 90 | | | 271–272 | M.Æ | $C_{17}H_{38}N_2I_2$ | 38.9 | 38.9 | 7.3 | 7.4 |
| 20 | Pyrrolidino | HCl | 90 | 155–158 | 17 | 255–260 | A.E | $C_{13}H_{28}N_2Cl_2\cdot 2H_2O$ | 48.9 | 49.1 | 10.1 | 10.5 |
| 21 | Pyrrolidino | $CH_3I$ | 95 | | | 304–305 | M.Æ | $C_{15}H_{32}N_2I_2$ | 36.4 | 36.4 | 6.5 | 6.4 |
| 22 | Pyrrolidino | $C_2H_5I$ | 95 | | | 272–273 | A.Æ | $C_{17}H_{36}N_2I_2$ | 39.0 | 39.0 | 7.0 | 7.0 |
| 23 | Pyrrolidino | $C_6H_5CH_2Cl$ | 100 | | | 200–203[d] | A.Æ.E | $C_{27}H_{46}N_2Cl_2$ | 70.0 | 69.5 | 8.7 | 9.0 |
| 24 | Piperidino | HCl | 90 | | | 290–295 | A.E | $C_{14}H_{30}N_2Cl_2$ | 56.6 | 56.3 | 10.2 | 10.2 |
| 25 | Piperidino | $CH_3I$ | 100 | | | 290–295 | M.E | $C_{16}H_{34}N_2I_2$ | 37.8 | 37.9 | 6.8 | 6.8 |
| 26 | Morpholino | HCl | 75 | 172–173 | 17 | 296–298 | A.Æ | $C_{18}H_{38}N_2OCl_2$ | 52.2 | 52.4 | 9.4 | 9.3 |
| 27 | Morpholino | $CH_3I$ | 100 | | | 273–274 | M | $C_{15}H_{32}N_2OI_2$ | 35.3 | 35.3 | 6.3 | 6.7 |
| 28 | Morpholino | $C_2H_5I$ | 100 | | | 216–228 d. | A | $C_{17}H_{36}N_2OI_2$ | 37.9 | 37.6 | 6.8 | 6.9 |

[a] The boiling points (uncor.) are for the bis-tertiary amines. The melting points (uncor.), crystallization solvents and analyses are for the dihydrochlorides and dialkiodide quaternary salts. [b] A = ethanol; Ac = acetone; Æ = ethyl acetate; Aq = water; E = diethyl ether; M = methanol. [c] The dihydrochlorides of the bis-tertiary amines showed a pronounced tendency to form rather stable hydrates from which water could be removed only on careful drying. [d] Hygroscopic.

with the appropriate alkyl halide gave the desired salts, II, from IX.

By aid of an analogous sequence of reactions the 1-methyl-4-(3′-aminopropyl)-piperidines (III) were prepared from 4-(3′-hydroxypropyl)-pyridine.

Physical properties and analyses for all the compounds appear in Table I. It will be noted that the products of type IX have an asymmetric carbon in the 3-position of the piperidine ring. These products are presumably *d–l* mixtures. Upon quaternization of the bis-tertiary amines with *other* than methyl halide a new asymmetric center is created on the 1-nitrogen. Although such products conceivably could be made up of two pairs of racemates, presumably separable by fractional crystallization, so far no evidence has appeared to indicate the existence of more than a single racemate.

**Pharmacology.**—Preliminary examination of these series of 3- and 4-(3′-aminopropyl)-piperidines and their salts for hypotensive effects associated with ganglionic block has been made using cats.

Several of the bis-quaternary salts of the 4-substituted piperidine series (type III) were at least as potent as hexamethonium.[3] The most potent of this series was the bis-methiodide of the dimethylamino compound (no. 15, Table IB) although the bis-methiodide of the morpholino compound (no. 27, Table IB) had a more prolonged duration of action.

According to the current tests none of the bis-tertiary amines of type III showed a potency comparable with the model I or with hexamethonium. Recently McMillan and co-workers[4] have reported on a series of assorted bis-tertiary amines modelled after I. One of their more active compounds was the 1-methyl-4-(3′-dimethylaminopropyl)-piperidine (no. 14, Table IB) which they stated was comparable with I in potency.

The members of the 4-substituted series (type III) are exact chain length analogs of I and of

(3) "Hexameton" brand hexamethonium chloride is supplied by Burroughs Wellcome & Co. (U.S.A.), Inc.

(4) F. H. McMillan, K. A. Kun, C. B. McMillan and J. A. King, THIS JOURNAL, **78**, 4077 (1956).

hexamethonium, as they have six carbons between nitrogens, and they differ from I only in having the three carbon side chain in the 4-position of the piperidine ring.

The products of type II are exact position analogs of I, but having only a three-carbon side chain and thus only five carbons between nitrogens they are also analogs of pentamethonium and of pentapyrrolidinium.

Both the bis-tertiary amines and the derived bis-quaternaries II of the 3-(3′-aminopropyl)-piperidine series were considerably more potent ganglionic blockers with a longer duration of action than the corresponding members of the 4 series III. Here, too, the most potent compounds were all bis-quaternary salts and several of these were equal to or better than hexamethonium. The bis-methiodides and bis-ethiodides of the 3-(3′-aminopropyl) (no. 2 and 3, Table IA) and of the 3-(3′-pyrrolidinopropyl) (no. 7 and 8, Table IA) piperidines were the best compounds of this series and showed potencies up to four times that of hexamethonium in the cat tests.

The pharmacology of these compounds will be reported elsewhere.

**Acknowledgment.**—The author is indebted to Mr. Samuel W. Blackman for the microanalyses and to Dr. Kenneth Colville for the pharmacological data.

## Experimental

**1-Methyl-3- and 4-(3′-chloropropyl)-piperidine Hydrochlorides.**—The 3- and 4-(3′-hydroxypropyl)-pyridines were available commercially.[5] These were transformed into the 1-methyl-3(or 4)-(3′-chloropropyl)-piperidine hydrochlorides using the sequence of reactions outlined above. The methods were modifications of earlier procedures used successfully for related compounds.[6-8]

1-Methyl-3-(3′-chloropropyl)-piperidine hydrochloride melted at 119–120° after recrystallization from ethanol–ether mixtures.

*Anal.* Calcd. for $C_9H_{19}NCl_2$: C, 50.9; H, 9.0. Found: C, 50.8; H, 9.0.

1-Methyl-4-(3′-chloropropyl)-piperidine hydrochloride melted at 131–132° after recrystallization from ethanol–ether mixtures.

*Anal.* Calcd. for $C_9H_{19}NCl_2$: C, 50.9; H, 9.0. Found: C, 50.9; H, 9.0.

**1-Methyl-3-(3′-pyrrolidinopropyl)-piperidine.**—A mixture of 8.5 g. (0.04 mole) of 1-methyl-3-(3′-chloropropyl)-piperidine hydrochloride and 25 cc. of pyrrolidine was heated for 16 hr. at 100°. After removing excess pyrrolidine *in vacuo*, the product base was liberated with 25% aqueous alkali and was taken up in ether. The ether solution was dried over anhydrous potassium carbonate, the ether was evaporated and the residual oil was distilled *in vacuo*. The yield of pure base was 8 g. (95%) boiling at 153–154° at 17 mm.; dihydrochloride salt: m.p. 232–233° from alcohol–ether.

**Dimethiodide.**—A solution of 2.1 g. (0.01 mole) of the above base, 25 cc. of methanol and 5 cc. of methyl iodide was refluxed for 20 hr. After several recrystallizations from methanol–ethyl acetate mixtures the yield of white crystals was 4.9 g. (100%), m.p. 294–295° dec.

(5) These intermediates were purchased from the Reilly Tar and Chemical Co., Indianapolis, Indiana.

(6) A. W. Ruddy and H. W. Bishop, THIS JOURNAL, **74**, 1919 (1952).

(7) R. R. Burtner and J. M. Brown, *ibid.*, **69**, 630 (1947).

(8) T. R. Norton, R. A. Seihert, A. A. Benson and F. W. Bergstrom, *ibid.*, **68**, 1572 (1946).

TUCKAHOE 7, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

# Aliphatic Diazo Compounds. III. Infrared Spectra[1,2]

BY PETER YATES AND BERNARD L. SHAPIRO[3] WITH NAOYA YODA AND JOSEPH FUGGER

RECEIVED MAY 6, 1957

The major bands in the region 2–12 $\mu$ of the infrared spectra of twenty-nine aliphatic diazo compounds are recorded and the relationship between their position and the structure of the diazo compounds is discussed.

Although two recent studies[4,5] of diazonium salts have codified the infrared spectra of many compounds of this type, no similar compilation appears to have been made for aliphatic diazo compounds, apart from the special case of diazoöxides.[5,6] It has been recognized for some time, however, that such compounds consistently show an intense absorption band in the 4.5–5 $\mu$ region, which has been used to confirm the presence of the aliphatic diazo group.[7] In the course of studies of the chemistry of aliphatic diazo compounds we have had occasion to examine their infrared spectra and it is the purpose of the present communication to report some tentative correlations on the basis of these observations.

## Experimental

The diazo compounds were prepared by standard procedures to which references are given in Tables I and II. The spectra of solutions in carbon tetrachloride, dichloromethane or chloroform were recorded with a Perkin–Elmer Model 21 spectrophotometer using an NaCl prism. They were calibrated by the use of atmospheric carbon dioxide and water vapor, and a carbon monoxide gas cell.[8] Representative spectra are illustrated in Fig. 1.

## Results

**Diazohydrocarbons.**—Table I records the bands in the 4.5–5 $\mu$ region for several diazohydrocarbons

(1) For previous papers in this series see P. Yates, THIS JOURNAL, **74**, 5376 (1952); A. K. Bose and P. Yates, *ibid.*, **74**, 4703 (1952).

(2) This work was supported in part by an institutional research grant from the American Cancer Society to Harvard University.

(3) Shell Foundation Fellow, 1955–1956.

(4) M. Aroney, R. J. W. Le Fèvre and R. L. Werner, *J. Chem. Soc.*, 276 (1955).

(5) K. B. Whetsel, G. F. Hawkins and F. E. Johnson, THIS JOURNAL, **78**, 3360 (1956).

(6) R. J. W. Le Fèvre, J. B. Sousa and R. L. Werner, *J. Chem. Soc.*, 4686 (1954).

(7) *Cf.*, for example, S. A. Fusari, T. H. Haskell, R. P. Frohardt and Q. R. Bartz, THIS JOURNAL, **76**, 2881 (1954).

(8) The hand of carbon monoxide at 4.66 $\mu$[9] was used for the calibration of the 4.5–5 $\mu$ region. Since previously published reports of hands in this region in the spectra of individual aliphatic diazo compounds have frequently failed to refer to calibration against a *closelying* standard hand, we have in general not included these hands with the present results.

(9) G. Herzberg, "Molecular Spectra and Molecular Structure. I.