11.7 g., m.p. 256–258° dec. Analysis indicated contamination by tartaric acid so that the above transformation through the free base was repeated once more to give 8.44 g. of *d*-II **dihydrochloride**, m.p. 266° dec., $[\alpha]^{25}D$ +6.2° (*c* 0.05 g./ml., H_2O) (Table I).

To isolate the *l*-isomer, the mother liquor, remaining after isolation of the second crop from the original crystallization, was evaporated to dryness at room temperature to give a yellow semi-solid residue. This was taken up in a minimum quantity of boiling methanol and refrigerated for several days after seeding with *d*-II bis-*d*-tartrate. The precipitated material was removed by filtration and the filtrate was concentrated to a volume of 75–100 ml. This was refrigerated again for several days, but only a trace of solid precipitated. After filtering, the filtrate was evaporated to dryness to yield a semi-solid product which was extracted four times by decantation with boiling isopropyl alcohol. The combined extracts were filtered and concentrated to give 29.4 g. of a viscous yellow oil which consisted largely of *l*-II **bis-*d*-tartrate**. This material was treated in exactly the same way as described above for the 24 g. of *d*-II bis-*d*-tartrate. There was obtained, in this way, 3.05 g. of *l*-II-**dihydrochloride**, m.p. 266° dec., $[\alpha]^{25}D$ −6.2° (*c* 0.05 g./ml., H_2O) (Table I).

Treatment of the free base obtained from *d*-II dihydrochloride with dimethyl sulfate in methyl ethyl ketone in the usual manner (method A) gave *d*-II **methomethyl sulfate**, m.p. *ca.* 190° dec., $[\alpha]^{22}D$ +4.42° (*c* 0.05 g./ml., H_2O).

Similarly, from *l*-II dihydrochloride was obtained *l*-II **methomethyl sulfate**, m.p. *ca.* 190° dec., $[\alpha]^{22}D$ −4.45° (*c* 0.10 g./ml., H_2O) (see Table I).

Acknowledgment.—The authors wish to thank Dr. G. M. Everett, Dr. K. Hwang, Mr. L. E. Blockus and Miss I. M. Shepperd for the pharmacological data. Extended and more detailed results will be published by them elsewhere. The infrared determinations were carried out by Mr. W. Washburn and the microanalyses under the direction of Mr. E. F. Shelberg.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

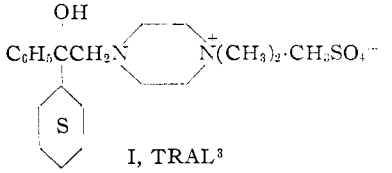
Tertiary Carbinols of the Piperazine Series. II. The Site of Quaternization

BY HAROLD E. ZAUGG AND RAYMOND J. MICHAELS

RECEIVED DECEMBER 16, 1957

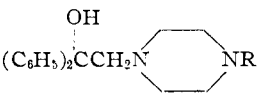
By a system of alternate introduction of benzyl and methyl groups, by hydrogenolytic removal of benzyl from a methylated 1-benzyl-4-piperazine-ethanol derivative, and by unequivocal synthesis of the alternate position isomer, it has been demonstrated that 1-(2′,2′-diphenyl-2′-hydroxyethyl)-4-methyl(and benzyl)-piperazine (II and III) and the cyclohexyl analog quaternize at the 4-position. The possibility of the occurrence of geometric isomerism in 1,4-substituted piperazines is discussed. An incidental anomaly indicating a cationic influence on anionic exchange with IR-45 resin is noted.

In the first paper of this series[1] the preparation was reported of a number of monoquaternary salts of unsymmetrically 1,4-disubstituted piperazines. The ambiguity arising from the uncertain position of the quaternary center remained unresolved. Baltzly, Ide and Lorz,[2] in a study of benzylhydrylpiperazines, assumed, on the basis of steric and known electronic effects, that quaternization of their compounds occurred at the nitrogen atom (called terminal, in this discussion) not attached to the benzhydryl group. Their assumption was reinforced by the inability of their compounds to form diquaternary salts. However, in our series of piperazinecarbinols,[1] the demonstrated capacity to form diquaternary salts shows that the nitrogen atom (called central, in this discussion) attached to the bulkier group can quaternize. Because one of our quaternary salts I has shown clinical usefulness, it seemed desirable to identify unequivocally the particular nitrogen atom involved in salt formation even though the assumptions of the previous workers[2] seem quite reasonable.



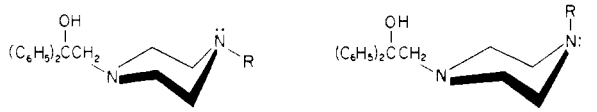
I, TRAL[3]

In the accompanying paper[1] it was reported (see Tables I and II) that the quaternary salt obtained from II by the action of methyl bromide melted at 223–224°, whereas the quaternary salt obtained from III by the action of benzyl bromide melted at 219–220°. Although their mixed melting point was intermediate between these two values and their infrared spectra (KBr pellet) were essentially identical, thus indicating terminal quaternization,



II, R = $CH_2C_6H_5$
III, R = CH_3

there still remained the possibility that this small difference in melting point could be due to the presence of a different ratio of two possible geometric isomers in the two salts. If, in II and III, different equilibria between the two possible conformations, a and b, were to result from the difference in bulk between methyl and benzyl, then different ratios of the two possible geometric isomers of the salts obtained by terminal quaternization would be expected, provided that the large group on the central nitrogen were to maintain a stable conforma-



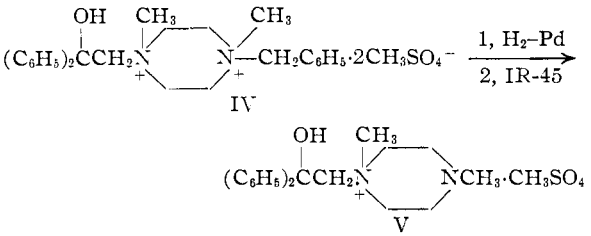
tion with respect to the ring. That such isomerism about the nitrogen atom actually does occur in the more rigid tropine ring system, has been shown by Zeile and Schulz.[4] However, their stereoisomeric

(1) H. Zaugg, *et al.*, THIS JOURNAL, **80**, 2763 (1958).
(2) R. Baltzly, W. Ide and E. Lorz, *ibid.*, **77**, 4809 (1955).
(3) Registered trademark of Abbott Laboratories, North Chicago, Ill.
(4) K. Zeile and W. Schulz, *Ber.*, **88**, 1078 (1955).

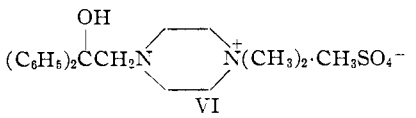
quaternary salts showed more than our 4° divergence in melting point and exhibited gross differences in their infrared spectra. Because of these confusing factors, more definitive evidence for terminal quaternization in our series of piperazines was sought.

When the N-benzyl derivative II was quaternized with an equivalent quantity of dimethyl sulfate and the benzyl group was subsequently removed by catalytic hydrogenolysis, a 58% yield of III was obtained, showing that in this particular case, terminal methylation had occurred. However, the generality of this evidence is subject to criticism on the grounds that the terminal nitrogen in II is probably more basic than the terminal nitrogen in III and hence would be expected to undergo quaternization more readily. Since it is the mode of quaternization of a terminally *methyl* substituted piperazine that we are primarily concerned with still further evidence was desired.

Treatment of II with an excess of dimethyl sulfate gave a very hygroscopic diquaternary salt IV. Catalytic hydrogenolysis of the benzyl group, followed by removal of the methylsulfuric acid by passage through a column of basic ion exchange resin,



gave the monoquaternary salt V. Compound V melted 20° lower than the isomeric salt VI obtained by treatment of III with an equivalent of dimethyl sulfate. Furthermore, the infrared spectra of the two salts showed gross differences. The structure



VI for the normal product of quaternization can therefore be regarded as reasonably well established.

In order to relate the corresponding cyclohexyl compound I with VI, the latter was catalytically hydrogenated. However, in order to achieve saturation of one of the phenyl rings, an acidic medium was required. When the reduced solution was passed through a column of IR-45 resin to remove the excess sulfuric acid originally added, only the corresponding chloride of I could be isolated (as the monohydrate) even though the resin previously had been very carefully washed with alkali. Therefore compound I itself was treated similarly with IR-45 resin and a chloride identical with the one resulting from hydrogenation of VI was obtained. The structure of I was thereby established.

It is interesting to note that, whereas the methyl sulfate anion of the terminally quaternized compound I exchanges readily with the chloride ion of IR-45 resin, the same anion of the centrally quaternized compound V does not.

Experimental

Hydrogenolysis of the Methomethyl Sulfate of Compound II.—A solution of 7.6 g. (0.152 mole) of 1-(2′,2′-diphenyl-2′-hydroxyethyl)-4-benzyl-4-methylpiperazinium methyl sulfate (see Table II of reference 1) in a mixture of 75 ml. of ethanol and 10 ml. of water was treated with 1.5 g. of 5% palladium–charcoal catalyst and hydrogenated at 60° under 20 pounds pressure. Hydrogen uptake appeared to be complete in 1 hr., but reaction was continued for 3 hr. in all. The catalyst was removed by filtration and the filtrate was concentrated to dryness. Addition of 75 ml. of benzene to the residue followed by concentration once more to dryness to remove last traces of water gave a residue which solidified (m.p. 120–123°) on trituration with dry ether. Two recrystallizations of this crude salt from dry ethanol gave 3.6 g. (58%) of the tertiary methyl sulfate salt of III, m.p. 143–144°.

Anal. Calcd. for $C_{20}H_{28}N_2O_5S$: C, 58.80; H, 6.91; N, 6.85. Found: C, 58.82; H, 7.22; N, 7.16.

Conversion of this salt to the free base gave a product, m.p. 83–84°, identical with III prepared by an unequivocal method.[1]

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.46. Found: C, 77.11; H, 8.27; N, 9.36.

The dihydrochloride of III was also prepared, m.p. 226–227°, identical with an authentic specimen.[1]

Hydrogenolysis of the corresponding methobromide of II by the above procedure also led to a 53% yield of III isolated as the dihydrochloride, m.p. 226–227°.

Preparation of the Diquaternary Salt IV and Subsequent Hydrogenolysis to the Monoquaternary Salt V.—A solution of 9.3 g. (0.025 mole) of II in 75 ml. of methyl ethyl ketone was allowed to stand overnight at room temperature with 7.6 g. (0.06 mole) of dimethyl sulfate. The resulting crude monoquaternary salt, m.p. 180–187°, was collected by filtration and recrystallized once from absolute ethanol. The purified monoquaternary salt, m.p. 187–188°, was then taken up in 75 ml. of hot absolute ethanol and refluxed for 16 hr. with 6.3 g. (0.05 mole) of dimethyl sulfate. On cooling, nothing crystallized so the crude diquaternary salt IV (10.5 g., m.p. 75–85°) was precipitated by the addition of dry ether. Attempts to purify this salt were hampered by its extreme hygroscopicity. Therefore, the entire 10.5 g. (0.0168 mole) was taken up in 100 ml. of 50% aqueous ethanol, treated with 2.0 g. of 5% palladium–charcoal catalyst and hydrogenated at 25 pounds pressure for 1 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness under reduced pressure. The liquid residue was taken up in 125 ml. of water and stirred for 45 minutes with IR-45 resin. The *p*H of the solution changed from 1.2 to 3.8. The solution was filtered from the resin and then run through a column containing about 50 ml. of the same resin. Including subsequent wash water, four 50-ml. fractions were taken. The *p*H of these fractions varied between 8.9 and 9.4, but concentration of them to dryness gave only a slight trace of dissolved material. The resin column was then washed with 200 ml. of a 70% ethanol–water mixture. The eluate was concentrated to dryness on the steam-bath under reduced pressure and the liquid residue was taken up in 50 ml. of absolute ethanol and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the alcoholic solution was treated with dry ether to precipitate a crystalline solid, m.p. 131–148°. After decolorizing with charcoal during two recrystallizations from an isopropyl alcohol–ether mixture, there was obtained 0.3 g. of pure V, m.p. 142–143°.

Anal. Calcd. for $C_{21}H_{30}N_2O_5S$: C, 59.69; H, 7.16; N, 6.63. Found: C, 59.69; H, 7.14; N, 6.61.

A mixture of V with compound VI,[1] m.p. 160–162°, melted at 125–130°. The infrared spectra of the two substances were quite dissimilar.

The low yield of product undoubtedly was due to the unexpected tenacity with which it was held to the IR-45 resin.

Hydrogenation of a Phenyl Ring in VI.—A solution of 4.22 g. (0.01 mole) of VI in 200 ml. of methanol containing 2.0 ml. of concentrated sulfuric acid was treated with 2.0 g. of prehydrogenated platinum oxide catalyst and reduced at 30 pounds pressure for 3 hr. at room temperature. During this time a column of about 100 ml. of IR-45 resin was washed, over a period of 4 hr., with 500 ml. of a 4% aqueous sodium hydroxide solution until the eluate gave no positive

test for chloride ion. This was followed by washing with distilled water until the eluate became neutral. After removal of catalyst by filtration, the hydrogenation mixture was diluted with 100 ml. of water and passed through the washed column. Six fractions of 40 ml. each, ranging in *p*H from 9.2 to 10.9, were saved and combined. Concentration on the steam-bath under reduced pressure yielded an oil which was taken up in 100 ml. of absolute ethanol and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated to 30 ml. and treated with dry ether to precipitate the crude quaternary salt, m.p. 198–201°. Three recrystallizations from an isopropyl alcohol–ether mixture gave 0.2 g. of the monohydrate of the methochloride analog of I, m.p. 208–209°. When mixed with a sample of I, m.p. 211–212°, the resulting melting point was depressed to 187–191°.

Anal. Calcd. for $C_{20}H_{33}ClN_2O \cdot H_2O$: C, 64.75; H, 9.51; N, 7.55; Cl, 9.56. Found: C, 64.28; H, 9.60; N, 7.70; Cl, 9.07.

Conversion of I to the Corresponding Chloride by IR-45 Treatment.—A solution of 3.2 g. (0.008 mole) of I in 200 ml. of 50% aqueous methanol was passed through a 100-ml. column of IR-45 resin at a rate of about one drop per second. The eluate was concentrated to dryness under reduced pressure and the semi-solid residue was taken up in 100 ml. of absolute ethanol. After drying with anhydrous sodium sulfate and removing the drying agent by filtration, the solution was concentrated to 30 ml., cooled and treated with dry ether to precipitate the crude quaternary salt. Two recrystallizations from isoproyl alcohol–ether gave 1.7 g. of the methochloride monohydrate, m.p. 208–209°. A mixture of this material with the product obtained from the hydrogenation of VI melted at 208–209°, and the infrared spectra (mull) of the two samples were qualitatively identical.

Anal. Calcd. for $C_{20}H_{33}ClN_2O \cdot H_2O$: C, 64.75; H, 9.51; N, 7.55; Cl, 9.56. Found: C, 64.89; H, 9.62; N, 7.47; Cl, 9.22.

Acknowledgment.—The authors wish to thank Mr. M. Freifelder and Mr. G. R. Stone for their technical help in the hydrogenations and Mr. William Washburn for the infrared spectra. Helpful suggestions were received from Dr. M. A. Spielman. The microanalyses were carried out under the direction of Mr. E. F. Shelberg.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

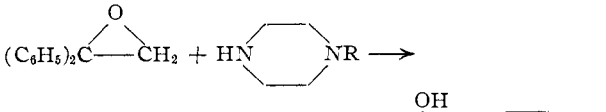
Tertiary Carbinols of the Piperazine Series. III. Reaction of 1,1-Diphenylethylene Oxide with Piperazines and Other Polyamines

BY HAROLD E. ZAUGG AND RAYMOND J. MICHAELS

RECEIVED DECEMBER 16, 1957

1,1-Diphenylethylene oxide reacts with piperazine and 1-methylpiperazine to give good yields of the carbinols I and II, respectively. A minor by-product of the reaction with piperazine is the dicarbinol III. This reaction has been extended to include several other substituted piperazines and a number of mono-primary and mono-secondary di- and triamines. Although diethylaminoethyl mercaptan gave the expected aminohydroxy thioether, tertiary aminoalkanols could not be made to yield the analogous O-ethers. A modified method for the preparation of 1,1-diphenylethylene oxide is reported.

During the search for a more convenient method for the preparation of certain of the pharmacologically interesting piperazinecarbinols previously reported,[1] the reaction of 1,1-diphenylethylene oxide with piperazines was examined. Gilman and Wanser[2] had shown that N-methylethanolamine attacked this epoxide at the 2-carbon atom. In the present work it was found that piperazine and 1-methylpiperazine reacted analogously to give 82 and 90% yields, respectively, of the carbinols I and II, identical with the compounds previously obtained by other methods.[1] As an expected by-



I, R = H; II, R = CH_3
III, R = $(C_6H_5)_2C(OH)CH_2$

product of the reaction with piperazine, the symmetrically disubstituted product III was obtained in 14% yield when a 3:1 molar excess of piperazine was employed. Lowering this ratio led to higher yields of III at the expense of I. A recent work[3] reports the reaction of 1-*n*-butyl-1-ethylethylene oxide with piperazine to give a 52% yield of the symmetrical N,N′-disubstituted piperazine as the only isolated product. Methylation of I with formaldehyde and formic acid gave an 80% yield of II, thus providing a route to II utilizing piperazine in place of the more costly 1-methylpiperazine.

The extension of this reaction to other substituted piperazines is summarized in Table I. Of the three methylated piperazines used, in which both nitrogens were unsubstituted, only 2,5-dimethylpiperazine gave any isolable disubstituted by-product. The carbinols derived from 2-methyl and 2,6-dimethylpiperazine are structurally ambiguous. However, since it was found that 2,3,5,6-tetramethylpiperazine would not react with diphenylethylene oxide under the conditions used, and since only one product was obtained in each case, the structures indicated in Table I, arising from attack by the less hindered nitrogen, have been assigned to them.

Table II lists the products obtained by the reaction of 1,1-diphenylethylene oxide with a number of di- and triamines. The yields reported are lower than those obtained in the preparation of the carbinols I and II. However, it is felt that most of these yields could be improved by a more careful study of conditions for each reaction. As indicated in Table II a low yield of product, not obtainable analytically pure, was secured from the reaction

(1) H. Zaugg, *et al.*, THIS JOURNAL, **80**, 2763 (1958).
(2) H. Gilman and C. Wanser, *ibid.*, **73**, 4030 (1951).
(3) L. Dedussenko and M. Mowssumsade, *Chem. Zentr.*, **127**, 13126 (1956).