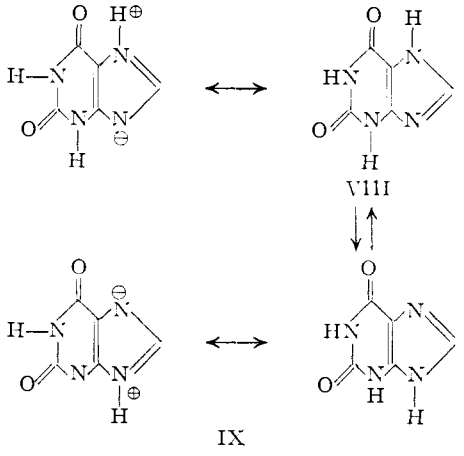


VIII

IX

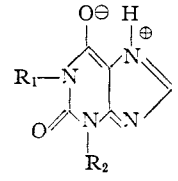
TABLE I

Compound	pK_{a1} Spectral[a]	pK_{a1} Potentiometric[11]	pK_{a2} Spectral	pK_{a2} Potentiometric[b]
Xanthine	7.53	7.7	11.63	...
1-Methylxanthine	..[c]	7.7	...[c]	12.05
3-Methyl-	8.32	8.5 (8.10)[b]	11.9	11.3
7-Methyl-	8.33	8.5 (8.30)[b]	~13	...
9-Methyl-	..	6.3 (6.25)[b]	...	...
1,3-Dimethyl-[d]	8.81	8.6	...	...
1,7-Dimethyl-	8.71	8.5	...	...
3,7-Dimethyl-	9.97	9.9	...	...
Xanthosine	5.50	6.0	~13	...

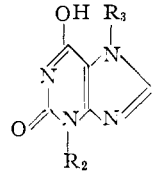
[a] pK_a ± 0.05. [b] H. F. W. Taylor, *J. Chem. Soc.*, 765 (1948). [c] Due to the impurity of our sample, these pK_a's were not determined. [d] J. K. Wood, *J. Chem. Soc.*, 1839 (1906), has determined the pK_a values of xanthine and a number of methylated xanthines by observing the rate of saponification of methyl acetate in the presence of the various sodium salts.

In 7-methylxanthine only forms of type VIII can contribute to the state of the molecule. Since the seat of the negative charge is at the 9-nitrogen atom, ionization of the 3-hydrogen will occur at higher pH values. The reverse obtains with 9-methylxanthine. This explanation is also consistent with the relationship between the pK_a values of 1,7-dimethyl- and 1,9-dimethylxanthine and with the fact that pK_{a1} for xanthine lies between those for 7- and 9-methylxanthines.

On the basis of a similarity among the pK_a values of the various methylated xanthines and the ΔpK_a for water *vs.* 90% ethanol, Ogston[11] assigned zwitterionic structures for the neutral forms of most of the compounds investigated. For example, 1,3-dimethylxanthine was written as X while 3,7-dimethylxanthine (XI) was not considered to be a dipolar ion.



X



XI

The present results show that this hypothesis need not be invoked. We have shown experimentally that 1,3-dimethylxanthine cannot exist to any appreciable extent as a dipolar ion since its apparent molar volume is 143.6 ± 0.1 cc. as compared to 143.2 ± 0.1 cc. for 3,7-dimethylxanthine both at a molar concentration of 0.007590. If the former existed as a dipolar ion its partial molar volume would be significantly less than the latter due to electrostriction.[15] However, the zwitterionic hypothesis cannot be discarded on this basis alone since the dipolar ions could exist in minute and undetectable amounts.

Acknowledgment.—The authors wish to express their gratitude to Dr. George Bosworth Brown for helpful discussions and continued interest.

(15) E. Cohn and J. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 155.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

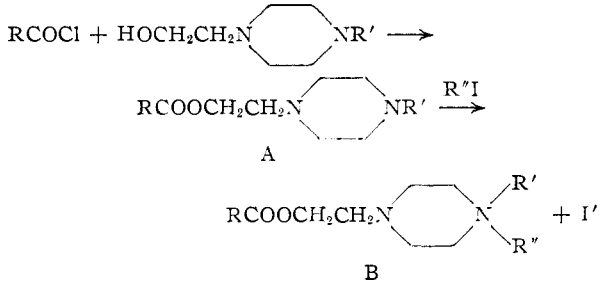
Unsymmetrically N-Substituted Piperazines. VI. Ester Derivatives as Spasmolytics[1]

BY WALTER S. IDE, EMIL LORZ AND RICHARD BALTZLY

RECEIVED JULY 27, 1953

The preparation of a series of piperazino esters, mainly derived from N-methyl-N'-hydroxyethylpiperazine, is described.

Some piperazine derivatives reported in the first paper of this series[2] exhibited a degree of spasmolytic activity. It seemed desirable therefore to examine the properties of piperazine derivatives constructed on the model of typical ester type spasmolytics. The greater part of the compounds so prepared were esters of N-β-hydroxyethyl-N'-alkyl piperazines. Data on these and on a number of the derived quaternary salts are presented in Table I. The synthetic methods involved were conventional and involved the sequence



A

B

The reactions of the acid chlorides with the aminoalcohols were conducted in inert solvents and the products isolated through their solubility in dilute

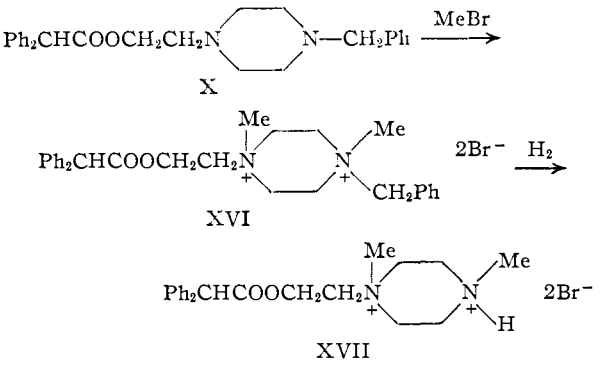
(1) The work here reported is part of a joint project with the Pharmacology Department of these laboratories.

(2) R. Baltzly, J. S. Buck, E. Lorz and W. Schoen, THIS JOURNAL, **66**, 263 (1944).

acid and their substantial insolubility in water. In the preparation of compounds XI and XII, diphenylchloroacetyl chloride was employed and the chlorine of the ester base was allowed to hydrolyze in dilute hydrochloric acid to form the desired esters of benzilic acid. The secondary base VIII was obtained by catalytic debenzylation of X.

The spasmolytic activity of these compounds was not sufficiently high to provoke further interest and the monoquaternary salts were not significantly more active. As measured by the classical method employing guinea pig ileum, none of these compounds had an anti-acetylcholine activity over 5% that of atropine. It appeared possible that for this purpose quaternization was at the wrong nitrogen atom since in the familiar ester spasmolytics only one nitrogen is present and this is removed by two or three atoms only from the ester function. That quaternization should affect first the nitrogen bearing the simple alkyl rather than that having the acyloxyethyl substituent is to be expected both because of electronic and steric influences. Experimental confirmation was obtained through the isolation of 4-hydroxyethyl-1,1-dimethylpiperazinium iodide, as a by-product during the purification of certain of the quaternary salts.[3]

Accordingly an example of a "hither" quaternary salt (compound XVII) was prepared by the following sequence of reactions

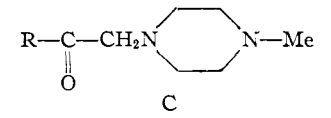


The first experiments involved the use of methyl iodide to prepare a diquaternary salt (the iodide of XVI). This could not be reduced directly since iodide ion is a strong poison for palladized charcoal[4] and conversion to the chloride with silver chloride failed probably because of hydrolysis and ester exchange. The bis-metho-bromide (XVI) proved satisfactory and XVII was obtained and tested. As it also exhibited no exemplary properties no further analogs were prepared.

Certain other types of ester derivative corresponding to Formulas C and XXI were also prepared. The syntheses were conventional and are discussed in the experimental section, None of these compounds showed marked spasmolytic activity.

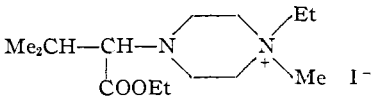
(3) While the bivalent cations are relatively resistant to acid-catalyzed ester exchange, this is not true of the mono-cations of formula B. For these compounds isopropyl alcohol would theoretically be preferable as a crystallizing solvent but in practice most of these salts were too insoluble in isopropyl alcohol for convenience.

(4) R. Baltzly, THIS JOURNAL, **74**, 4586 (1952).



C

XVIII, R = Ph_2CHO
XIX, R = $PhC_6H_{11}CHO$, methiodide
XX, R = α-$C_{10}H_7NH$



XXI

Experimental

Of the piperazino-alcohol bases, N-benzyl-N'-hydroxyethylpiperazine and N-ethyl-N'-hydroxyethylpiperazine have been reported previously.[2] While a number of alternative lines of preparation are possible, the following procedures are given as being satisfactory either because of yield or through convenience in isolation of a pure product.

N-Benzyl-N'-hydroxyethylpiperazine.—One-fifth of a mole each of N-benzylpiperazine[2] (35.2 g.) and ethylene oxide (8.8 g.) were added to 100 cc. of absolute ethanol contained in a distilling flask. The reaction mixture was cooled to 0° in an ice–salt-bath during addition and was allowed to warm up to room temperature gradually. After standing five days, the alcohol was distilled off at atmospheric pressure and the residue was distilled *in vacuo*. There was obtained 42.6 g. (97%) of base boiling at 142–143° at 2 mm. pressure.

N-Ethyl-N'-hydroxyethylpiperazine.—One mole (159 g.) of piperazine dihydrochloride was dissolved in warm methanol and a sodium methylate solution prepared from 23 g. of sodium was added. One mole (109 g.) of ethyl bromide was then added and the solution was allowed to stand overnight. After a one-hour reflux period the solution was cooled. A sodium methylate solution containing two moles of base (from 46 g. of sodium) was added and the precipitate was filtered. The sodium halide precipitate was washed with methanol and the washings added to the filtrate. Fifty-two grams (1.2 moles) of ethylene oxide was added and the solution was allowed to stand three days at room temperature. Solvent was then removed *in vacuo*, and the residue was transferred to a distilling flask after removal of a little more sodium halide. On distillation there was obtained 58 g. (37%) of base boiling at 125–130° at 25 mm. On redistillation, this boiled sharply at 128° at 21 mm. pressure.

N-Methyl-N'-hydroxyethylpiperazine.—One mole (159 g.) of piperazine dihydrochloride and 84 g. (1 mole) of sodium bicarbonate were heated in one l. of methanol until the evolution of carbon dioxide had stopped. The flask was cooled and 50 g. (1.13 moles) of ethylene oxide was added. The solution was allowed to stand four days at room temperature and was then filtered off from the precipitated sodium chloride. The filtrate and washings were evaporated *in vacuo* on the steam-bath. To the residue was added 53 g. of sodium carbonate and 250 cc. of water. The solution was warmed on the steam-bath and again evaporated *in vacuo*. The residue was dissolved in a minimum of water and 100 cc. of 37% formalin solution and 150 cc. of 98% formic acid were added. After the reaction had subsided the reaction mixture was heated four hours on the steam-bath. Two hundred and fifty cc. of concentrated hydrochloric acid was then added and the solution was evaporated *in vacuo*. The residue was suspended in methanol and the solution was saturated wtih ammonia. The resultant precipitate corresponded to the calculated amount of sodium chloride plus only a part of the expected ammonium chloride from which it was deduced that the product still was largely mono-cationic. Sodium methylate (0.77 mole) was added, salts were filtered off and the filtrate was evaporated and distilled *in vacuo*. The yield was 66 g. (0.5 mole); b.p. 103–105° (9 mm.).

N-Hydroxyethyl-N'-*p*-anisylpiperazine.—This compound was obtained by a modified Wallach reaction.[5] The base boils at 182–183° at 2 mm. and the dihydrochloride melts at 238°.

(5) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

TABLE I: ESTERS OF HYDROXYETHYLPIPERAZINE

Cpd. no.	R	R′	Dihydrochlorides, RCOOCH₂CH₂N(CH₂CH₂)NR′·2HCl: M.p., °C.[a]	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Compound No.	Quaternary Iodides, RCOOCH₂CH₂N(CH₂CH₂)N(R″)R′I⁻: R″	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	$(C_5H_{11})_2CH$	Me	210[b]	$C_{19}H_{40}Cl_2N_2O_2$	57.1	57.4	10.0	10.3	Ia	Me	194[b]	$C_{20}H_{41}IN_2O_2$	51.3	51.2	8.8	9.0
II	$(C_6H_{13})_2CH$	Me	207[b]	$C_{21}H_{44}Cl_2N_2O_2$	59.0	58.9	10.3	10.5[h]								
III	$(CH_2)_5CPh$	Me	258[c]	$C_{20}H_{32}Cl_2N_2O_2$	59.5	59.8	8.0	8.1	IIIa	Me	198[c]	$C_{21}H_{33}IN_2O_2$	53.4	53.4	7.1	7.2
									IIIb	n-C_4H_9	142[d]	$C_{24}H_{39}IN_2O_2$	56.0	55.9	7.6	7.8
IV	$(CH_2)_5CPh$	Et	230[b]	$C_{21}H_{34}Cl_2N_2O_2$	60.4	60.0	8.2	8.3								
V	$C_6H_{11}CHPh$	Me	215[b]	$C_{21}H_{34}Cl_2N_2O_2$	60.4	60.1	8.2	8.2								
VI	$C_6H_{11}CHPh$	Et	201[e]	$C_{22}H_{36}Cl_2N_2O_2$	61.3	61.5	8.4	8.7								
VII	$(C_6H_{11})_2CH$	Me	237[b]	$C_{21}H_{40}Cl_2N_2O_2$	59.6	59.2	9.5	9.6	VIIa	Me	222[b]	$C_{22}H_{41}IN_2O_2$	53.7	53.9	8.3	8.6
VIII	Ph_2CH	H	179[f]	$C_{20}H_{26}Cl_2N_2O_2$	60.5	60.4	6.6	7.0								
IX	Ph_2CH	Me	218[f]	$C_{21}H_{28}Cl_2N_2O_2\cdot(H_2O)^1/_2$	60.0	60.1	6.9	7.2								
X	Ph_2CH	CH_2Ph	235[b]	$C_{27}H_{32}Cl_2N_2O_2$	66.5	66.0	6.6	6.7[i]	Xa	Me	182[b]	$C_{28}H_{33}IN_2O_2$	60.4	60.4	5.9	5.9
XI	Ph_2COH	Me	208[c]	$C_{21}H_{28}Cl_2N_2O_3$	59.0	59.1	6.6	6.9								
XII	Ph_2COH	p-$CH_2C_6H_4OMe$	218[b]	$C_{28}H_{34}Cl_2N_2O_4$	63.0	62.7	6.4	6.3								
XIII	$Ph_2CH\cdot CH_2$	Me	208[c]	$C_{22}H_{30}Cl_2N_2O_2$	62.1	61.8	7.1	6.8	XIIIa	Me	142[c]	$C_{23}H_{31}IN_2O_2$	55.9	55.7	6.3	6.4
									XIIIb	Et	81[b]	$C_{24}H_{33}IN_2O_2$	56.7	56.7	6.5	6.9
XIV	$C_{13}H_9$[j]	Et	234[g]	$C_{22}H_{28}Cl_2N_2O_2$	62.4	62.2	6.6	6.7								
XV	$C_{13}H_9O$[k]	Me	227[c]	$C_{21}H_{26}Cl_2N_2O_3$	59.3	59.6	6.1	5.9	XVa	Me	191[b]	$C_{22}H_{27}IN_2O_3$	53.4	53.2	5.5	5.7

[a] Melting points below 220° are corrected. [b] Crystallized from absolute ethanol–ether mixture. [c] Crystallized from absolute ethanol. [d] Crystallized from acetone. [e] Crystallized from absolute ethanol–ethyl acetate–ether mixture. [f] Crystallized from isopropyl alcohol. [g] Crystallized from aqueous ethanol. [h] Analysis corrected for loss of weight on drying in high vacuum. [i] N, calcd. 5.8; found 5.8. [j] 9-Fluorenyl. [k] Xanthydryl.

Anal. Calcd. for $C_{14}H_{24}Cl_2N_2O_2$: C, 52.0; H, 7.4. Found: C, 51.8; H, 7.4.

Carboxylic Acids.—Diamyl- and dihexylacetic acids, diphenylacetic, β,β-diphenylpropionic acids and benzilic acid were obtained from commercial sources. Dicyclohexylacetic acid,[6] phenylcyclohexylacetic acid,[7] 1-phenylcyclohexanecarboxylic acid[8] and fluorene-9-carboxylic acid[9] were prepared by literature methods. For xanthene-9-carboxylic acid[10] a preparation that seems more convenient than those previously reported was developed. This depends on the tendency of xanthydrol to become cationic under acid conditions. Under suitably chosen conditions it is to be presumed that xanthydrylcarbonium ion reacts reversibly with such reagents as acetic acid but irreversibly with cyanide ion, or perhaps with hydrogen cyanide.

Xanthene-9-carboxylic Acid.—In a chilled glass-lined steel bomb were placed 19.8 g. (0.1 mole) of freshly made xanthydrol, 10.4 g. of sodium cyanide (*ca.* 0.2 mole) and 80 cc. of cold glacial acetic acid. The bomb was closed and heated at 100° for 24 hours. It was then cooled and opened. The largely-solidified reaction mixture was transferred to a beaker containing 500 cc. of ice-water and the solid that separated was filtered off and washed thoroughly with cold water. The solid (18 g. dry) was refluxed in 200 cc. of 75% methanol containing 20 g. of potassium hydroxide for 24 hours, by which time the evolution of ammonia had ceased. After one-half hour of refluxing a bulky precipitate (amide) separated and largely dissolved in the next five to six hours. At the end of the reflux period, the bulk of the methanol was boiled off and water was added to give a volume of 300 cc. A small amount of solid was filtered off and the filtrate was extracted twice with ether. The cold aqueous layer was then acidified strongly with hydrochloric acid and the precipitated solid was taken into ether and dried over sodium sulfate. After removal from the desiccant, 100 cc. of hexane was added and the mixture was evaporated. The residual acid weighed 15.5 g. (68–69% of the calculated yield) and melted at 218–220°. The alkali-insoluble solid removed earlier was largely xanthone which may have been present as an impurity in the xanthydrol.

This preparation is not especially sensitive to minor changes in conditions, especially as the reaction mixture is in effect heavily buffered. In an earlier run in which 0.05 mole of xanthydrol, 0.06 mole of cyanide and 0.1 mole of sulfuric acid were employed in 40 cc. of glacial acetic acid, the yield was 20%. Since in this case there was a considerable amount of free sulfuric acid, it seems reasonably certain that quantities of mineral acid less than equivalent to the alkali cyanide would not affect the reaction significantly.

Preparation of the Esters.—The carboxylic acids were converted to the chlorides, usually with thionyl chloride. Benzilic acid was converted to α-chlorodiphenylacetyl chloride by the method of Billman and Hidy.[11] In the preparation of compounds I and II, the acid chlorides were distilled *in vacuo;* in the other cases, excess thionyl chloride was removed *in vacuo* on the steam-bath and the residual material was used directly. The acid chlorides were treated with 2 equivalents of the appropriate amino-alcohol base in inert solvents (ether, benzene) at room temperature or under gentle reflux in some cases. As a rule a quantity of amino-alcohol hydrochloride close to the calculated amount separated as a solid and could be filtered off. The ester base was further purified by partitioning between ether and carbonate solution, dried over potassium carbonate and converted to

(6) R. Willstätter and E. Waldschmidt-Leitz, *Ber.*, **54**, 1422 (1921).

(7) E. D. Venus-Danilova and A. J. Bosschukin, *Chem. J. (Ser. A.) J. Allg. Chem.*, **7**, (69) 2823 (1937); *Chem. Zentr.*, **109**, II, 3391 (1938).

(8) C. H. Tilford, M. G. VanCampen, Jr., and R. S. Shelton, THIS JOURNAL, **69**, 2902 (1947).

(9) R. R. Burtner and J. W. Cusic, *ibid.*, **65**, 262 (1943).

(10) R. R. Burtner and J. W. Cusic, *ibid.*, **65**, 1582 (1943); J. B. Conant, *ibid.*, **49**, 2085 (1927).

(11) J. H. Billman and P. H. Hidy, *ibid.*, **65**, 760 (1945).

the dihydrochloride or in some cases, a portion of the solution was treated directly with methyl iodide. In earlier experiments, an excess of methyl iodide was avoided but it was later found that at or near room temperature and with ether or acetone as solvent there was little or no tendency to formation of a diquaternary salt. The following preparations are given as typical.

β-(N'-Methylpiperazinoethyl) Xanthene-9-carboxylate (XV).—Xanthene-9-carboxylic acid (3.6 g., 0.016 mole) was warmed with 6 g. of thionyl chloride under reflux until the evolution of gas had ceased. The flask was evacuated on the steam-bath and the residue was dissolved in dry ether. To it was added 6 g. of N-methyl-N'-hydroxyethylpiperazine also in ether. There was some evolution of heat; after that had subsided the solution was refluxed four hours and allowed to stand overnight. The precipitated solid was filtered off, washed with ether and the filtrate and washings were partitioned against water until the aqueous layers were neutral. The ethereal layer was then extracted with *N* hydrochloric acid. The aqueous layer was basified with sodium bicarbonate and the base was taken into ether and dried over potassium carbonate. On evaporation, the base weighed 4.4 g. (0.0125 mole). It was dissolved in dry ether and the solution was divided into two equal parts. One was converted to the dihydrochloride by addition of excess ethanolic hydrogen chloride while the second reacted with methyl iodide in ether to give compound XVa.

β-(N'-Benzylpiperazino)-ethyl Diphenylacetate (X).—To 11 g. of N'-benzyl-N-hydroxyethylpiperazine in 15 cc. of dry benzene was added 5.5 g. of diphenylacetyl chloride also in benzene. The solution warmed up and a gelatinous precipitate separated. Fifty cc. more benzene was added, the precipitate was broken up and the reaction mixture was heated on the steam-bath. After five minutes, refluxing was stopped because of excessive bumping. The reaction mixture was allowed to stand two hours and was then partitioned between ether and dilute alkali. The ethereal layer was washed with water until the *p*H of the washings was 8. From the combined aqueous layers 5 g. of N'-benzyl-N-hydroxyethylpiperazine was later recovered. The ethereal layer was dried over potassium carbonate and evaporated. The residue weighed 10 g.; a portion was converted to the dihydrochloride (X), and another to the methiodide (Xa).

β-(N'-Benzylpiperazino)-ethyl Diphenylacetate Bismethobromide (XVI).—Twenty-one grams of ditertiary base obtained as above dissolved in 100 cc. of cold benzene was placed in a steel bomb, 20 g. of cold methyl bromide was added and the bomb was closed. The bomb was heated at 100° (steam-bath) for 25.5 hours, cooled and opened. The contents were removed and the dirty-white precipitate was washed with benzene. It was recrystallized from absolute ethanol in which it was sparingly soluble, m.p. 208°.

Anal. Calcd. for $C_{29}H_{36}Br_2N_2O_2$: C, 57.6; H, 6.0. Found: C, 57.1; H, 6.2.

The corresponding bis-methiodide was obtained by refluxing the monomethiodide (Xa) with excess methyl iodide in isopropyl alcohol. It forms yellow crystals from methanol–ether mixture and decomposes at 199°.

Anal. Calcd. for $C_{29}H_{36}I_2N_2O_2$: C, 49.9; H, 5.2. Found: C, 49.5; H, 5.6.

1,4-Dimethyl-1-(β-diphenylacetoxy)-ethylpiperazinium Bromide Hydrobromide (XVII).—The bis-methobromide (XVI), 5.2 g., was dissolved in aqueous methanol and hydrogenated with Adams catalyst[12] at room temperature. The solution, after removal of the catalyst, was evaporated *in vacuo* below 60°. The colorless, crystalline residue melted at 116° as did several other samples. The melting point, which was unchanged by recrystallization from methanol–ether is presumably that of a hydrate. Analysis was difficult even for a piperazine derivative. When dried in high vacuum, the compound on exposure to air rapidly became sticky, wet and finally became again a dry solid.

Anal. Calcd. for $C_{22}H_{30}Br_2N_2O_2 \cdot 2.5H_2O$: C, 47.2; H, 6.3. Found: C, 47.4; H, 6.2.

On drying a larger quantity (118 mg.) in high vacuum, the loss in weight was intermediate between that calculated for $2H_2O$ and for $2.5H_2O$. A sample kept in a vacuum desiccator for two weeks gave analytical values slightly high for a monohydrate (Calcd.: C, 49.6; Found: C, 50.0). The analytical evidence is consistent with the existence of a monohydrate of very high and a higher hydrate of relatively low stability.

Benzhydryl-N'-Methylpiperazinoacetate (XVIII).—Four grams of N-methylpiperazine and 5.2 g. of benzhydryl chloroacetate[13] were dissolved in 15 cc. of benzene. The temperature of the solution rose spontaneously to 40–50°. After refluxing two hours it was allowed to stand overnight and partitioned between ether and water. The ethereal layer was dried over potassium carbonate, filtered and evaporated; weight of residue, 6.5 g. A portion was converted to the dihydrochloride, m.p. (unchanged on recrystallization from absolute ethanol) 186–187°.

Anal. Calcd. for $C_{20}H_{26}Cl_2N_2O_2$: C, 60.5; H, 6.6. Found: C, 60.6; H, 6.6.

Phenylcyclohexylcarbinyl-N'-methylpiperazinoacetate Methiodide (XIX).—Methylpiperazine was treated with phenylcyclohexylcarbinyl chloroacetate[13] as in the previous preparation. The dihydrochloride was not obtained analytically pure but the methiodide, which melted at 207–208°, gave correct analytical figures.

Anal. Calcd. for $C_{21}H_{33}IN_2O_2$: C, 53.4; H, 7.0. Found: C, 53.5; H, 7.3.

α-(4-Methylpiperazino)-N-1-naphthylacetamide (XX).—Four grams of N-methylpiperazine was added to a solution in warm benzene of 4.4 g. of chloroacetyl-α-naphthylamine[14] and the solution was refluxed 20 minutes on the steam-bath. After cooling and addition of absolute ether, the precipitated methylpiperazine hydrochloride was filtered off and the filtrate was washed with water. The ethereal layers were dried over potassium carbonate, filtered and evaporated. The residual oil weighed 4.2 g. and crystallized on standing, m.p. 122°. It was converted to the dihydrochloride which decomposes at 233°.

Anal. Calcd. for $C_{17}H_{23}Cl_2N_3O$: C, 57.3; H, 6.5. Found: C, 57.1; H, 6.1.

N-Methyl-N-ethyl-N'-(α-carbethoxyisobutyl)-piperazinium Iodide (XXI).—Eight grams of methylpiperazine and 8.4 g. of ethyl α-bromoisovalerate were refluxed in benzene 32 hours. The reaction mixture was partitioned between ether and water and the ethereal layer, after drying, was acidified with ethanolic hydrogen chloride. The resultant dihydrochloride, which was very deliquescent, gave poor analytical results. It was dissolved in water, basified with sodium carbonate and the base was taken into ether and dried over potassium carbonate. After removing the desiccant an excess of ethyl iodide was added. The resultant quaternary salt was recrystallized from ethanol–ether mixtures, m.p. 137–138°.

Anal. Calcd. for $C_{14}H_{29}IN_2O_2$: C, 43.7; H, 7.6. Found: C, 43.9; H, 7.5.

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(12) Palladized charcoal, usually to be preferred in debenzylations, proved disadvantageous in this instance due to its adsorbing tendencies. The time required for adequate washing prolonged the desired rapid manipulations.

(13) Prepared by the method of J. W. Cusic, U. S. Patent 2,543,764.

(14) Tommasi, *Bull. Soc. Chem.*, [2] **20**, 21 (1873.)