[CONTRIBUTION FROM SAHYUN LABORATORIES]

Antispasmodics: Esters of Heterocyclic Alcohols

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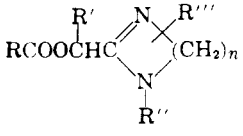
A series of 53 esters of 2-hydroxymethyl-2-imidazoline, 2-hydroxymethyl-1,4,5,6-tetrahydropyrimidine and 2-hydroxymethyl-4,5,6,7-tetrahydro-1,3-diazepine was prepared for testing as anticholinergic agents. Certain of the esters showed outstanding gastric antisecretory activity in the experimental animal.

Compounds whose structures contain the 2-diethylamino thyl group commonly exhibit useful physiological activity, and this group is present in several synthetic drugs, especially local anesthetics, antispasmodics and antihistaminics. Numerous variations of this group have been investigated in searches for improved compounds. One of these variations, the 2-dihydroimidazolylmethyl group ($-CH_2C(=NCH_2CH_2NH)$), has been reported[1] as being approximately physiologically equivalent to the 2-diethylaminoethyl group when attached to an appropriate nucleus. This heterocyclic system has been used to prepare basic ethers[1,2] and substituted ethylenediamines[3] as antihistaminic agents. To the best of our knowledge, its use as the nitrogen-containing moiety of basic esters has not been reported.[4] This paper deals with the preparation of a series of such esters, some of which showed outstanding properties as gastric antisecretory agents in animal studies. The structure of these esters is represented by the generic formula

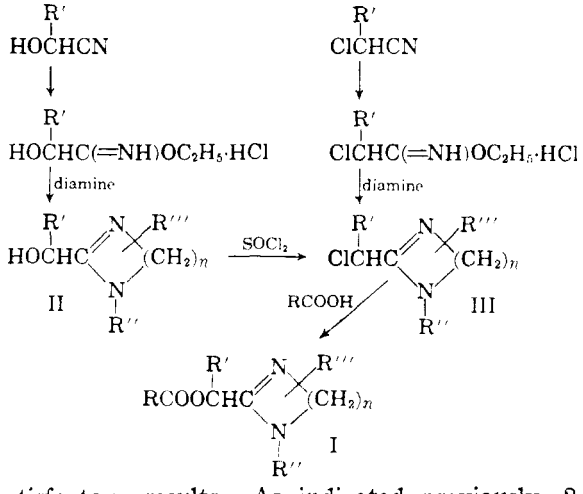


I, R' = H, CH_3
R'' = H, alkyl, aralkyl
R''' = H, OH, CH_3
n = 2,3,4

The general synthesis for these basic esters is outlined in the scheme shown, leading to I, in which the abbreviations are identical to those used for the above generic formula.

The two routes shown for the chloromethyl compounds III have been described for 2-chloromethyl-2-imidazoline derivatives,[5] and both routes were employed by us with approximately equal success. However, because of its greater availability, glycolonitrile rather than chloroacetonitrile was generally used as the starting material. This procedure also was applicable for those compounds in which $R' = CH_3$ by starting with lactonitrile.

The hydroxynitriles were converted almost quantitatively to the corresponding imidic ester hydrochlorides which were then condensed with various diamines to provide good yields of the hydroxymethylheterocycles II, isolated as their hydrochloride salts. These hydroxymethyl compounds tended to be hygroscopic and were somewhat difficult to purify. Three of them could not be obtained crystalline and were used as oils with



satisfactory results. As indicated previously, 2-hydroxymethyl-2-imidazoline hydrochloride and 2-(1-hydroxyethyl)-2-imidazoline hydrochloride are known.[5] 2-Hydroxymethyl-4-methyl-2-imidazoline hydrochloride (II, $R''' = CH_3$, $n = 2$), 2-hydroxymethyl-4,5,6,7-tetrahydro-1,3-diazepine hydrochloride (II, $n = 4$) and the various 2-hydroxymethyl-1,4,5,6-tetrahydropyrimidines (II, $n = 3$) apparently are novel. The 2-hydroxymethyltetrahydropyrimidines are listed in Table I.

The hydroxymethyl compounds II were converted smoothly by the action of thionyl chloride into the hydrochloride salts of the corresponding chloromethylheterocycles III. Certain of the chloromethylheterocycle hydrochlorides, especially those in which the imino nitrogen was substituted ($R''' =$ alkyl) resisted all attempts to obtain them in crystalline form, and the oils were used in subsequent reactions. The bases of these salts were fairly water-soluble, low melting solids or oils, and were relatively unstable; hence the hydrochlorides were neutralized *in situ* just prior to esterification. Except for 2-chloromethyl-4-methyl-2-imidazoline hydrochloride, the 2-chloromethyl-2-imidazolines (III) are known.[5] 2-Chloromethyl-4,5,6,7-tetrahydro-1,3-diazepine hydrochloride (III, $n = 4$) and the 2-chloromethyl-1,4,5,6-tetrahydropyrimidines (III, $n = 3$) listed in Table II have not been reported previously.

The bases of the chloromethylheterocycles III reacted normally in the Horenstein–Pählicke esterification[6] to form the basic ester hydrochlorides

(1) W. B. Wheatley, W. E. Fitzgibbon, L. C. Cheney and S. B. Binkley, THIS JOURNAL, **72**, 4443 (1950).

(2) (a) C. Djerassi and C. R. Scholz, *ibid.*, **69**, 1688 (1947); (b) *J. Org. Chem.*, **13**, 830 (1948); (c) S. B. Binkley and L. C. Cheney, U. S. Patent, 2,703,324, March 1, 1955.

(3) Swiss Patents, 242,839, June 15, 1946; 246,579, Oct. 1, 1947; *C. A.*, **43**, 3979, 6240 (1949).

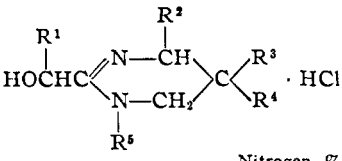
(4) Basic esters of 5-hydroxymethylimidazole have been reported: B. N. Craver, *et al.*, *Arch. Intern. Pharm.*, **87**, 33 (1951); *C. A.*, **46**, 624 (1952); O. K. Nikiforova, *Zhur. Obshchei Khim.*, **24**, 1866 (1954); *C. A.*, **49**, 13224 (1955).

(5) W. Klarer and E. Ureck, *Helv. Chim. Acta*, **27**, 1762 (1944).

(6) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1654 (1938).

TABLE I

DERIVATIVES OF 2-HYDROXYMETHYL-1,4,5,6-TETRAHYDROPYRIMIDINE

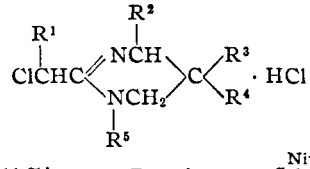


R¹	R²	R³	R⁴	R⁵	M.p., °C.[a]	Yield, %[b]	Formula	Nitrogen, % Calcd.	Found
H	H	H	H	H	100–102	88	$C_6H_{11}ClN_2O$	18.60	17.80
H	CH_3	H	H	H	123–126	66	$C_6H_{13}ClN_2O$	17.02	16.95
H	H	H	H	CH_3	164–165	60	$C_6H_{13}ClN_2O$	17.02	17.05
H	H	H	H	C_2H_5	[c]	74	$C_7H_{15}ClN_2O$	...	...
H	H	H	H	C_4H_9	[c]	65	$C_9H_{19}ClN_2O$	...	...
H	H	H	H	$CH_2C_6H_5$	170–171	85	$C_{12}H_{17}ClN_2O$	11.64	11.37
H	CH_3	H	H	CH_3	[c]	100	$C_7H_{15}ClN_2O$	...	...
H	H	CH	CH_3	CH_3	145–149	68	$C_8H_{17}ClN_2O$	14.54	14.77
CH_3[d]	H	H	H	H	169–173	73	$C_6H_{13}ClN_2O$	17.02	17.08

[a] For analytical samples obtained by repeated crystallization from alcohol or alcohol–ether. The crude materials usually melted over a 5–10° range. [b] Of crude material sufficiently pure for subsequent use. [c] Oil. [d] The ethyl lactimidate used in the preparation of this compound was prepared according to ref. 14.

TABLE II

DERIVATIVES OF 2-CHLOROMETHYL-1,4,5,6-TETRAHYDROPYRIMIDINE



R¹	R²	R³	R⁴	R⁵	Method	M.p., °C.[a]	Yield,%[b]	Formula	Nitrogen, % Calcd.	Found
H	H	H	H	H	A (B)	224–225 d.	86 (47)	$C_5H_{10}Cl_2N_2$	16.57	16.53
H	CH_3	H	H	H	A (B)	173–174	68 (40)	$C_6H_{12}Cl_2N_2$	15.30	15.15
H	H	H	H	CH_3	A	[c]	100	$C_6H_{12}Cl_2N_2$	...	...
H	H	H	H	C_2H_5	A	[c]	73	$C_7H_{14}Cl_2N_2$	...	...
H	H	H	H	C_4H_9	A	[c]	80	$C_9H_{18}Cl_2N_2$	...	...
H	H	H	H	$CH_2C_6H_5$	A	138–142	71	$C_{12}H_{16}Cl_2N_2$	10.81	10.64
H	CH_3	H	H	CH_3	A	[c]	90	$C_7H_{14}Cl_2N_2$	...	...
H	H	CH_3	CH_3	CH_3	A	177–180	77	$C_8H_{16}Cl_2N_2$	13.28	13.24
CH_3	H	H	H	H	A	206–207	78	$C_6H_{12}Cl_2N_2$	15.30	15.16
H	H	OH	H	H	B	171–173	74	$C_5H_{10}Cl_2N_2O$	15.14	14.90

[a] For analytical samples obtained by repeated recrystallization from alcohol or alcohol–ether. The crude materials usually melted over a 5–10° range. [b] Of crude material sufficiently pure for subsequent use. [c] Oil.

TABLE III

IMIDAZOLINE ESTERS RCOOCHC(R¹)=N—CHR²—NH—CH₂ · HCl

RCOO– = acid[a]	R¹	R²	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
Diphenylacetic	H	H	201–202 d.	$C_{18}H_{19}ClN_2O_2$	8.47	8.34	10.72	10.51
Benzilic	H	H	211–212 d.	$C_{18}H_{19}ClN_2O_3$	8.08	7.92	10.24	10.36
α-Cyclohexylphenylglycolic[b]	H	H	207–208 d.	$C_{18}H_{25}ClN_2O_3$	7.94	7.84	10.05	9.82
α-Cyclohexylphenylglycolic[b]	H	CH_3	166–167	$C_{19}H_{27}ClN_2O_3$	7.64	7.70	9.66	9.50
α-Cyclohexylphenylglycolic[b]	CH_3	H	235–236 d.	$C_{19}H_{27}ClN_2O_3$	7.64	7.54	9.66	9.66
α-Cyclopentylphenylglycolic	H	CH_3	192–193	$C_{18}H_{25}ClN_2O_3$	7.94	7.81	10.05	10.25

[a] All compounds were recrystallized from alcohol or alcohol–ether. [b] E. D. Venus-Danilova and A. I. Bolshukin, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2823 (1937).

I listed in Tables III and IV. In addition to these, two tetrahydroazepinylmethyl esters were prepared in the same manner using 2-chloromethyl-4,5,6,7-tetrahydro-1,3-diazepine, $ClCH_2C{=}N(CH_2)_4NH$. While potassium iodide was routinely added to the esterification reaction to generate, by metathesis, the more reactive iodomethyl compounds, its presence was not always necessary for a satisfactory rate of esterification.

The novel α-cyclopentyl-, α-(2-pentyl)- and α-hexylphenylglycolic acids were prepared by the action of the appropriate Grignard reagent on benzoylformic acid. The other acids employed in the esterification are known, and literature references to them are listed in the tables in which they appear.

Those diamines having no N-substituent which were condensed with the imidic ester hydrochlorides were obtained from commercial sources. Most of the N-substituted 1,3-diaminopropanes were prepared by the reduction of N-substituted aminopropionitriles obtained by the condensation of acrylonitrile and the corresponding amines. The reductions of the nitriles were effected by means of

TABLE IV

TETRAHYDROPYRIMIDINE ESTERS RCOOCHC(R¹)=NCH(R²)CH(R³)C(R⁴)NCH₂(R⁵)·HCl

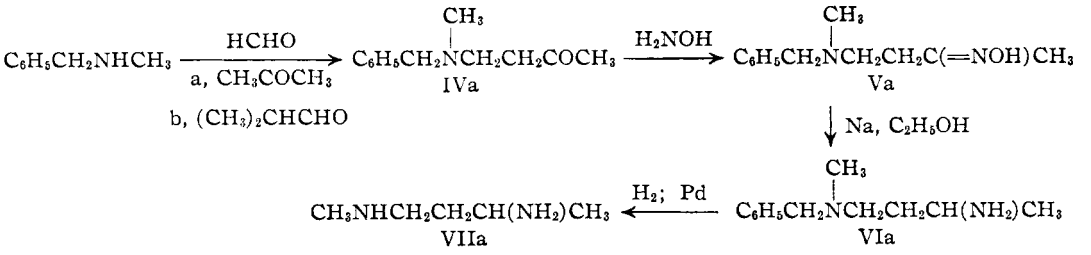
R¹	R²	R³	R⁴	R⁵	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
					Esters of diphenylacetic acid					
H	H	H	H	H	237–238 d.	$C_{19}H_{21}ClN_2O_2$	8.13	7.99	10.28	10.23
					Benzilic acid					
H	H	H	H	H	218–219 d.	$C_{19}H_{21}ClN_2O_3$	7.76	7.59	9.83	9.79
H	CH_3	H	H	CH_3	204–205 d.	$C_{21}H_{25}ClN_2O_3$	7.22	7.11	9.12	8.90
H	H	H	H	CH_3	219–220 d.	$C_{20}H_{23}ClN_2O_3$	7.48	7.47	9.46	9.33
CH_3	H	H	H	H	231–232 d.	$C_{20}H_{23}ClN_2O_3$	7.48	7.42	9.46	9.35
					α-Cyclohexylphenylacetic acid[a]					
H	H	H	H	H	234–235	$C_{19}H_{27}ClN_2O_2$	7.99	7.81	10.10	10.10
H	CH_3	H	H	H	235–236 d.	$C_{20}H_{29}ClN_2O_2$	7.68	7.52	9.72	9.84
H	CH_3	H	H	CH_3	171–172	$C_{21}H_{32}N_2O_6S$[b]	6.36	6.27	..[c]	...
H	H	OH	H	H	189–190	$C_{19}H_{27}ClN_2O_3$	7.46	7.49	9.66	9.66
H	H	CH_3	CH_3	CH_3	201–202 d.	$C_{22}H_{33}ClN_2O_2$	7.13	7.33	9.02	8.89
CH_3	H	H	H	H	174–175	$C_{20}H_{30}N_2O_6S$[b]	6.57	6.56	...[d]	...
					α-Cyclohexylphenylglycolic acid[e]					
H	H	H	H	H	237–238 d.	$C_{19}H_{27}ClN_2O_3$	7.64	7.59	9.66	9.79
H	CH_3	H	H	H	244–245 d.	$C_{20}H_{29}ClN_2O_3$	7.36	7.33	9.31	9.33
H	CH_3	H	H	CH_3	217–218 d.	$C_{21}H_{31}ClN_2O_3$	7.10	7.10	8.98	8.98
H	H	CH_3	CH_3	CH_3	227–228 d.	$C_{22}H_{33}ClN_2O_3$	6.85	6.67	8.67	8.86
H[m]	H	H	H	CH_3	231–232 d.	$C_{20}H_{29}ClN_2O_3$	7.36	7.39	9.31	9.23
H	H	H	H	C_2H_5	202–203 d.	$C_{21}H_{31}ClN_2O_3$	7.10	6.93	8.98	8.96
H	H	H	H	C_4H_9	175–176	$C_{23}H_{35}ClN_2O_3$	6.62	6.44	8.38	8.20
H	H	H	H	$CH_2C_6H_5$	218–219 d.	$C_{26}H_{33}ClN_2O_3$	6.13	6.00	7.76	7.86
CH_3	H	H	H	H	206–208	$C_{20}H_{29}ClN_2O_3$	7.36	7.21	9.31	9.26
H	H	OH	H	H	183–185	$C_{19}H_{27}ClN_2O_4$	7.32	7.18	9.26	9.14
					α-Cyclopentylphenylacetic acid[f]					
H	CH_3	H	H	H	227–228	$C_{19}H_{27}ClN_2O_2$	7.99	8.07	10.10	10.01
H	H	H	H	CH_3	187–188	$C_{19}H_{27}ClN_2O_2$	7.99	7.83	10.10	10.00
					α-Cyclopentylphenylglycolic acid					
H	H	H	H	H	234–235 d.	$C_{17}H_{25}ClN_2O_3$	7.94	7.94	10.05	10.34
H	CH_3	H	H	CH_3	184–185	$C_{20}H_{29}ClN_2O_3$	7.36	7.36	9.31	9.28
H	H	CH_3	CH_3	CH_3	180–181 d.	$C_{21}H_{31}ClN_2O_3$	7.10	7.03	8.98	9.04
H	H	OH	H	H	202–203	$C_{18}H_{25}ClN_2O_4$	7.60	7.57	9.61	9.73
H	CH_3	H	H	H	239–240 d.	$C_{19}H_{27}ClN_2O_3$	7.64	7.39	9.68	9.40
H	H	H	H	CH_3	217–218 d.	$C_{19}H_{27}ClN_2O_3$	7.64	7.52	9.68	9.66
H	H	H	H	C_2H_5	177–178 d.	$C_{20}H_{29}ClN_2O_3$	7.36	7.32	9.31	9.40
H	H	H	H	$CH_2C_6H_5$	197–198 d.	$C_{24}H_{31}ClN_2O_3$	6.33	6.15	8.00	7.88
					α-Butylphenylglycolic acid[g]					
H	H	H	H	H	198–199	$C_{17}H_{25}ClN_2O_3$	8.22	8.03	10.40	10.31
H	CH_3	H	H	H	199–200	$C_{18}H_{27}ClN_2O_3$	7.90	7.90	9.99	10.12
H	H	H	H	CH_3	194–195	$C_{18}H_{27}ClN_2O_3$	7.90	7.94	9.99	10.18
					Phenyl α-(2-thienyl)-glycolic acid[g]					
H	H	H	H	H	213–214 d.	$C_{17}H_{19}ClN_2O_3S$	7.64	7.63	9.67	9.83
H	H	H	H	CH_3	210–211 d.	$C_{18}H_{21}ClN_2O_3S$	7.36	7.18	9.31	9.56
					α-Cyclopentyl-α-(2-thienyl)-glycolic acid[h]					
H	H	H	H	CH_3	214–215 d.	$C_{17}H_{25}ClN_2O_3S$	7.51	7.31	9.51	9.42
					α-(2-Pentyl)-phenylglycolic acid					
H	H	H	H	H	218–219 d.	$C_{18}H_{27}ClN_2O_3$	7.90	7.80	9.99	9.85
H	H	H	H	CH_3	217–218	$C_{19}H_{29}ClN_2O_3$	7.60	7.61	9.61	9.75
					α-Hexylphenylglycolic acid					
H	H	H	H	CH_3	171–172	$C_{20}H_{31}ClN_2O_3$	7.32	7.27	9.26	8.99

TABLE IV (*Continued*)

R^1	R^2	R^3	R^4	R^5	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine Calcd.	Chlorine Found
					Fluorene-9-carboxylic acid[i]					
H	H	H	H	H	259–260 d.	$C_{19}H_{19}ClN_2O_2$	8.17	8.30	10.34	10.10
H	H	H	H	CH_3	217–218 d.	$C_{20}H_{21}ClN_2O_2$	7.85	7.85	...	...
					Bicyclohexyl-1-carboxylic acid[j]					
H	H	H	H	H	212–213 d.	$C_{18}H_{31}ClN_2O_2$	8.15	8.06	10.34	10.25
H	H	H	H	CH_3	145–147	$C_{19}H_{34}N_2O_6S$[b]	6.70	6.44	...[k]	...
					Xanthene-9-carboxylic acid[l]					
H	H	H	H	H	217–218 d.	$C_{19}H_{27}ClN_2O_3$	7.64	7.70	9.66	9.80

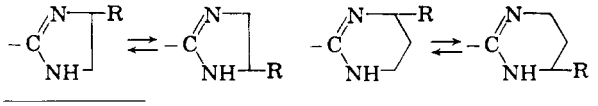
All compounds were recrystallized from alcohol or alcohol–ether. [a] Ref. *a*, Table III. [b] Sulfate. [c] Calcd.: $SO_4^=$, 21.80. Found: $SO_4^=$, 22.00. [d] Calcd.: $SO_4^=$, 22.51. Found: $SO_4^=$, 22.40. [e] K. Hoffmann and H. Schellenberg, *Helv. Chim. Acta*, **30**, 292 (1947). [f] G. Vasiliu, V. Dumitrascu and H. Vulcan, *Soc. Chim. Romania Sect. romane Stiinte, Bul. chim. pura apl.*, [2] **3A**, 54 (1941–1942); *C. A.*, **38**, 5493 (1944). [g] F. F. Blicke and M. V. Tsao, THIS JOURNAL, **66**, 1645 (1944). [h] F. F. Blicke, U. S. Patent 2,541,634 (Feb. 13, 1951). [i] H. J. Richter, *Org. Syntheses*, **33**, 37 (1953). [j] M. Kopp and B. Tchoubar, *Bull. soc. chim. France*, 84 (1952). [k] Calcd.: $SO_4^=$, 22.94. Found: $SO_4^=$, 22.98. [l] R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 1582 (1943). [m] Compound no. 16.

lithium aluminum hydride as well as by catalytic hydrogenation previously used.[7] The synthesis of N-methyl-1,3-diaminobutane[8] is illustrated by the sequence of reactions

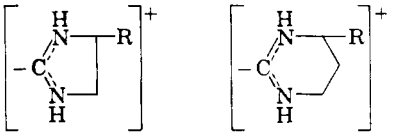


The hitherto unreported N-methyl-1,3-diamino-2,2-dimethylpropane was obtained in a similar fashion by substituting isobutyraldehyde for acetone in the Mannich step of the above scheme. However some difficulty was encountered in the reduction of the oxime. The reduction product was the desired benzylamine derivative contaminated with an unknown basic substance possibly resulting from a rearrangement of the oxime. Catalytic debenzylation of the crude product yielded a mixture of amines from which N-methyl-1,3-diamino-2,2-dimethylpropane dihydrochloride was obtained by fractional crystallization.

The reaction between imidic esters and unsymmetrical diamines could be expected to afford a mixture of two isomers of 2-imidazoline bases or 1,4,5,6-tetrahydropyrimidine bases containing an imino hydrogen. In fact, it has been stated that tetrahydropyrimidine bases derived from 1,3-diaminobutane were mixtures, presumably of the 4- and 6-methyl isomers.[9] These isomeric pairs of bases differ only in the position of a hydrogen atom, and the mixtures would therefore appear to be virtually tautomeric



However, as has been discussed with the similar imidazole system,[10] the addition of a proton to the pyridine nitrogen leads to the formation of an ion in which the possibility for isomerism is lost, and both forms, as salts, are identical



The 4- and 5-positions of the imidazoline salts are therefore equivalent, as are the 4- and 6-positions of the tetrahydropyrimidine salts. In the conventional formulas of the tables, which show a pyridine nitrogen, we have assigned the lower number to the position of the substituent.

Pharmacology.—The pharmacologic evaluation of the basic esters was carried out in the Department of Pharmacology and Toxicology, University of Texas—Medical Branch, under the direction of Drs. G. A. Emerson and J. B. Nash. A digest of their findings has been reported.[11] Some of the more active compounds of this series also were studied by Dr. S. Y. P'an in the Department of Pharmacology of Chas. Pfizer and Co., Inc. A report of the studies of the latter investigator on compound no. 16, Table IV, is soon to be published.

In general, the most effective compounds of this series were shown to be N-alkylated tetrahydropyrimidine esters of α-cycloalkylphenylglycolic acids. While the antispasmodic potencies of the

(7) D. S. Tarbell, N. Shakespeare, C. J. Claus and J. F. Bunnett, THIS JOURNAL, **68**, 1217 (1946).

(8) T. B. Johnson and A. W. Joyce, *ibid.*, **38**, 1854 (1916).

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most active compounds are in the order of one-half to one-fourth that of atropine, they are considerably more potent as antisecretory agents and their action is more prolonged. Moreover the toxicities and side effects are generally much less than those of atropine. Three of the compounds, 12, 16 and 29, (Table IV) are undergoing clinical testing. A clinical report on compound 12 has appeared in the literature.[12]

Experimental[13]

N-Benzylmethylaminomethylacetone (IVa).—A cooled solution of 121 g. (1 mole) of benzylmethylamine in 500 ml. of acetone was acidified with a mixture of 86 ml. (1 mole) of 36% hydrochloric acid in 100 ml. of acetone. To the mixture, from which benzylmethylamine hydrochloride had separated, was added 45 g. (1.5 moles) of paraformaldehyde and 100 ml. of isopropyl alcohol. The mixture was refluxed for 6 hours and distilled to an oily residue which was dissolved in 100 ml. of water. The solution was made strongly alkaline with sodium hydroxide, and the liberated oily base was extracted with ether. Fractionation of the dried ether solution yielded 146 g. (77%) of a water-white distillate, b.p. 124–128° (2.5–3 mm.).

Anal. Calcd. for $C_{12}H_{17}NO$: neut. equiv., 191. Found: neut. equiv., 188.

N-Benzylmethylaminomethylacetone Oxime (Va).—A solution of 19.1 g. (0.1 mole) of the Mannich base IVa in 25 ml. of isopropyl alcohol was combined at room temperature with a solution of 7 g. (0.1 mole) of hydroxylamine hydrochloride in 25 ml. of water. After 1.5 hours at room temperature, the mixture was distilled to remove the alcohol. An aqueous solution of the residue was made alkaline with sodium hydroxide, the oxime base was extracted with ether, and the dried ether solution fractionated; yield, 17 g. (83%), b.p. 161–164° (2.5–3 mm.).

Anal. Calcd. for $C_{12}H_{18}N_2O$: neut. equiv., 206. Found: neut. equiv., 209.

N-Benzylmethyl-1,3-diaminobutane (VIa).—Sodium (150 g., 6.6 g. at.) was added to a refluxing solution of 114 g. (0.55 mole) of the oxime Va in 1.5 l. of ethanol during a 45-minute period. As soon as the sodium had reacted, a liter of water was added, and the solution was distilled to a volume of approximately one liter. The oil which separated was extracted with ether, the ether solution dried over potassium hydroxide pellets and fractionated; yield 54 g. (51%), b.p. 114–116° (2.5 mm.).

The reduction of the oxime was also accomplished with lithium aluminum hydride in about the same yield. Potentiometric titration showed inflection points at *p*H 7.5 and 3.9.

Anal. Calcd. for $C_{12}H_{20}N_2$: equiv. wt., 96. Found: equiv. wt., 99.

N-Methyl-1,3-diaminobutane (VIIa).—A solution of 27 g. (0.14 mole) of the diamine VIa in 150 ml. of ethanol containing 30 ml. of glacial acetic acid was hydrogenated at an initial pressure of 48 lb. per square inch over 5% palladium-on-charcoal. The calculated amount of hydrogen was absorbed in about 2 hours at room temperature. Two such charges were run, combined and filtered to remove the catalyst. Removal of the solvent left an oily residue which was dissolved in water. The solution was made strongly alkaline and the liberated amine base was steam distilled from the mixture and collected in hydrochloric acid. About 2 liters of distillate was collected and concentrated to an oil, the last stages of the concentration being done under vacuum. The oily residue, after being dried by distilling fresh portions of isopropyl alcohol from it, became a solid and was recrystallized from methanol. A second crop was obtained by dilution with acetone; total yield 33 g. (72%), m.p. 182–183° (analytical sample, recrystallized from methanol–ether).

Anal. Calcd. for $C_5H_{16}Cl_2N_2$: N, 16.00; Cl^-, 40.49. Found: N, 15.87; Cl^-, 40.34.

The monohydrochloride of this diamine, prepared by a different series of reactions, is reported to melt at 223°.[8]

N-Benzylmethylaminomethylisobutyraldehyde (IVb).—A mixture of 143 g. (0.9 mole) of benzylmethylamine hydrochloride, 65 g. (0.9 mole) of isobutyraldehyde, 60 g. (2 moles) of paraformaldehyde and 400 ml. of isopropyl alcohol was refluxed for 8 hours. After the alcohol had been removed by distillation, the residue was dissolved in water, and the solution made strongly alkaline. The insoluble oil was extracted with ether, and the dried ether solution was fractionated to yield 135 g. (73%) of product boiling at 142–147° (16 mm.). On redistillation it boiled at 144–146° (16 mm.).

Anal. Calcd. for $C_{13}H_{19}NO$: neut. equiv., 205. Found: neut. equiv., 208.

N-Benzylmethylaminomethylisobutyraldehydeoxime (Vb).—A solution of 68 g. (0.33 mole) of the amino-aldehyde IVb in 100 ml. of isopropyl alcohol was combined with a solution of 23 g. (0.33 mole) of hydroxylamine hydrochloride in 30 ml. of water. The warm solution was allowed to remain at room temperature for 1 hour and then was distilled to remove most of the alcohol. The residual solution was made alkaline, the oily base was extracted with ether, and the dried ether solution was fractionated; yield 69 g. (95%), b.p. 143–147° (2 mm.). On redistillation it boiled at 145–147° (2 mm.).

Anal. Calcd. for $C_{13}H_{20}N_2O$: neut. equiv., 220. Found: neut. equiv., 218.

N-Benzylmethyl-1,3-diamino-2,2-dimethylpropane (VIb).—Sodium (161 g., 7 g. at.) was added to a refluxing, stirred solution of 147 g. (0.67 mole) of the oxime Vb in 1.6 liters of ethanol over a period of 1 hour. After all the sodium had reacted, a liter of water was added, and the solution was distilled to a volume of approximately 1 liter. The oil which had separated was extracted with ether, and the ether solution was dried and distilled. The fraction boiling at 90–155° (1.5 mm.) weighed 86.5 g., and was redistilled through a 6-inch Vigreux-type column. The fraction boiling at 118–121° (2 mm.) and weighing 47 g. was redistilled and a small middle cut, b.p. 107–108° (0.7 mm.), was taken for analysis.

Anal. Calcd. for $C_{13}H_{22}N_2$: neut. equiv., 103; N, 13.59. Found: neut. equiv., 122; N, 12.81.

The analytical data, titration curves and subsequent results indicate that this material is the desired diamine, N-benzylmethyl-1,3-diamino-2,2-dimethylpropane, contaminated with an unknown basic product.

N-Methyl-1,3-diamino-2,2-dimethylpropane Dihydrochloride (VIIb).—A solution of 20.6 g. (0.1 mole) of the crude N-benzylmethyl-1,3-diamino-2,2-dimethylpropane (VIb) in 100 ml. of ethanol was acidified with 20 ml. of glacial acetic acid and hydrogenated at room temperature at an initial pressure of 44 lb. per square inch, using 5% palladium-on-charcoal as the catalyst. About 130% of the calculated amount of hydrogen was absorbed in 1.5 hours, after which absorption ceased. After being filtered, the solution, which smelled strongly of toluene, was dried. The oily residues from three such runs were combined, dissolved in water, made strongly alkaline and steam distilled into hydrochloric acid, 4–5 liters of distillate being collected. The distillate was concentrated to a sirup which upon trituration under isopropyl alcohol solidified to a soft solid weighing 49 g. Repeated crystallization of this mixture from methanol yielded 24.5 g. of the desired diamine dihydrochloride, m.p. 223–224°. Potentiometric titration showed a sloping inflection point at *p*H 8.8.

Anal. Calcd. for $C_6H_{18}Cl_2N_2$: neut. equiv., 95; N, 14.81; Cl^-, 37.49. Found: neut. equiv., 97; N, 14.79; Cl^-, 37.49.

There was also obtained 1.7 g. of a crystalline substance, m.p. 213–214°, the identity of which has not been established. Its analysis (N, 12.34; Cl^-, 32.12) indicates a unit molecular weight of 114, which is in fair agreement with the value of 110 obtained from its titration curve that showed one sharp inflection point at *p*H 7.5.

In addition, 12.5 g. of the unresolved mixture was recovered as a crystalline solid.

2-Hydroxymethyl-1,4,5,6-tetrahydropyrimidine Hydrochloride.—Seventy grams (0.5 mole) of ethyl glycolimidate hydrochloride,[14] prepared in 86% yield from glycolonitrile,[15]

(12) A. B. M. Sison, E. P. Namin and L. S. Villadolid, *J. Philippine Med. Assoc.*, **33**, 389 (1957).

(13) All melting points are corrected for stem-emergence.

(14) J. Houben and E. Pfankuch, *Ber.*, **59B**, 2397 (1926).

(15) Obtained by fractional distillation of commercial 70% aqueous glycolonitrile.

ethanol and hydrogen chloride in chloroform solution, was added in portions to a stirred solution of 50 g. (0.5 mole) of 1,3-diaminopropane in 400 ml. of ethanol maintained at 0–5°. The suspension was stirred at 5–10° for 2 hours, and the resulting homogeneous solution was distilled to remove the ammonia. The solution was acidified with 30 ml. of 6.5 *N* ethanolic hydrogen chloride, filtered, concentrated to approximately 200 ml., and refrigerated. The solid which separated was collected on a filter and dried in a vacuum desiccator. A second crop was obtained as a soft solid by concentration of the mother liquor. The total yield (crude) was 66 g. (88%), m.p. 100–102° after two recrystallizations from ethanol. It is quite hygroscopic.

2-Chloromethyl-1,4,5,6-tetrahydropyrimidine Hydrochloride.—The following procedures are representative for the chloromethyltetrahydropyrimidine hydrochlorides listed in Table II.

Method A.—2-Hydroxymethyl-1,4,5,6-tetrahydropyrimidine hydrochloride (37.5 g., 0.25 mole) was added in portions to 119 g. (1 mole) of thionyl chloride. The solution was refluxed for 2 hours. The excess thionyl chloride was removed by vacuum distillation, and the solid residue was recrystallized (charcoal) from 100 ml. of ethanol. A second crop was obtained by concentration of the mother liquor, yield 36.5 g. (86%), m.p. 224–225° dec.

The base was obtained by alkalizing a cold solution of 6.8 g. (0.04 mole) of the hydrochloride in 10 ml. of water with 5 ml. of 50% sodium hydroxide. The precipitated solid was filtered off and dried in a vacuum over phosphorus pentoxide, yield, 4.7 g. (89%), m.p. 85–86° dec. It is unstable and decomposes after a few hours at room temperature.

Method B.—A stirred solution of 7.5 g. (0.1 mole) of 1,3-diaminopropane in 90 ml. of ethanol was cooled to 0–5° and 15.8 g. (0.1 mole) of ethyl chloroacetimidate hydrochloride, prepared[2a] from chloroacetonitrile, ethanol and hydrogen chloride in ether solution, was added in portions. The mixture was stirred for 1 hour at 0–5°, and acidified at this temperature with ethanolic hydrogen chloride. The mixture was filtered and the filtrate was vacuum-distilled to a solid residue which was recrystallized from alcohol; yield 8 g. (47%).

2-Hydroxymethyl-4-methyl-2-imidazoline hydrochloride was prepared in 78% yield (crude) by the condensation of equimolar quantities of ethyl glycolimidate hydrochloride and commercial 1,2-diaminopropane as described above for the hydroxymethyltetrahydropyrimidines. It was an amber oil which was not obtained crystalline.

2-Chloromethyl-4-methyl-2-imidazoline Hydrochloride.—To a cooled solution of 59 g. (0.39 mole) of the oily 2-hydroxymethyl-4-methyl-2-imidazoline hydrochloride in 150 ml. of chloroform was added slowly 70 ml. (0.94 mole) of thionyl chloride. After the initial reaction had subsided, the dark solution was distilled to an oil which was dissolved in ethanol and treated with decolorizing charcoal. The addition of ether precipitated a total of 18 g. (27%) of crystalline product, m.p. 148–149°.

Anal. Calcd. for $C_6H_{10}Cl_2N_2$: N, 16.57. Found: N, 16.41.

2-Hydroxymethyl-4,5,6,7-tetrahydro-1,3-diazepine Hydrochloride.—A stirred suspension of 16.1 g. (0.1 mole) of commercial 1,4-diaminobutane dihydrochloride in 200 ml. of alcohol was neutralized with two equivalents of alcoholic sodium methylate and refluxed for 5 hours. It then was filtered and the cooled filtrate containing the diamine base was treated with 13.9 g. (0.1 mole) of ethyl glycolimidate hydrochloride in essentially the manner described above for the hydroxymethyltetrahydropyrimidine; yield 10 g. (61%), m.p. 133–135° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_6H_{13}ClN_2O$: N, 17.02. Found: N, 16.74.

2-Chloromethyl-4,5,6,7-tetrahydro-1,3-diazepine Hydrochloride.—A solution of 9 g. (0.055 mole) of the 2-hydroxymethyl-4,5,6,7-tetrahydro-1,3-diazepine hydrochloride in 25 ml. of thionyl chloride was refluxed for 0.5 hour and diluted with ether. The precipitated solid was recrystallized from a mixture of ethanol and ether; yield 6.5 g. (65%), m.p. 255–257° dec.

Anal. Calcd. for $C_6H_{12}Cl_2N_2$: N, 15.30. Found: N, 15.02.

α-Cyclopentylphenylglycolic Acid.—A Grignard reagent, prepared from 4.8 g. (0.2 mole) of magnesium, 29.8 g. (0.2 mole) of cyclopentyl bromide and 150 ml. of ether, was stirred at 0–5° and treated dropwise with a solution of 13 g. (0.09 mole) of benzoylformic acid[16] in 125 ml. of benzene. After the mixture had stirred for an additional hour at ice-bath temperature, it was allowed to remain at room temperature overnight. Dilute hydrochloric acid was added and the mixture was stirred until two clear layers were obtained. The ether layer was separated, and the ether was removed. The residue was dissolved in dilute sodium carbonate solution, and the solution was filtered and acidified to precipitate the solid acid which was recrystallized from acetic acid; yield 5.1 g. (27%), m.p. 148–149°.

Anal. Calcd. for $C_{13}H_{16}O_3$: neut. equiv., 215. Found: neut. equiv., 214.

α-(2-Pentyl)-phenylglycolic acid, m.p. 115–116° (neut. equiv. calcd. 222, found 220), and α-hexylphenylglycolic acid, m.p. 97–98° (neut. equiv. calcd. 236, found 238), were obtained in 27 and 53% yields, respectively, following the same general procedure.

Preparation of Basic Esters.—A suitable quantity, usually 0.03 mole, of the chloromethylheterocycle hydrochloride (III) was dissolved in 30–50 ml. of isopropyl alcohol, and the solution was neutralized with an equimolar amount of standardized methanolic sodium methylate. The solution was filtered to remove the precipitated sodium chloride, and the filtrate was added immediately to a solution of an equimolar quantity of the acid dissolved in 30–50 ml. of isopropyl alcohol. A small amount of powdered potassium iodide (0.1–0.2 g.) was added, and the solution was refluxed for a minimum of 4 hours, the last half-hour of which was in the presence of decolorizing charcoal. In some instances, the ester hydrochloride separated from the filtered, cooled solution and was further purified by recrystallization from an appropriate solvent. In others, it was necessary to concentrate the solution and dilute with ether. Whenever crystallization proved to be difficult, the solvent was removed completely, and the oily residue was partitioned between water and ether. The aqueous solution then was made alkaline, and the ester base was extracted with ether. Treatment of the dried ether solution with ethereal hydrogen chloride precipitated the ester hydrochloride as an oil which was dissolved in alcohol and diluted with ether to effect crystallization.

In those cases in which the ester hydrochloride separated directly from the cooled reaction mixture, the yields were as high as 65%. The other methods of isolation resulted in much lower yields, some as low as 10%. It should be pointed out, however, that conditions leading to optimum yields were not established in our experiments.

The melting points of the ester hydrochlorides were ordinarily over 200° and most of them decomposed. It was noted that the melting points varied with the rate of heating and also depended upon the initial temperature of the bath. All melting points recorded were determined by inserting the tube into a stirred bath below 100° and elevating the temperature quite slowly, especially near the melting point. Consistent values were obtained in this manner.

4,5,6,7-Tetrahydro-2-(1,3-diazepinyl)-methyl-α-cyclohexylphenylglycolate hydrochloride was prepared in 39% yield by the esterification of α-cyclohexylphenylglycolic acid with 2-chloromethyl-4,5,6,7-tetrahydro-1,3-diazepine; m.p. 232–233° dec.

Anal. Calcd. for $C_{20}H_{29}ClN_2O_3$: N, 7.36; Cl^-, 9.31. Found: N, 7.44; Cl^-, 9.18.

4,5,6,7-Tetrahydro-2-(1,3-diazepinyl)-methyl α-cyclopentylphenylglycolate hydrochloride was prepared in 30% yield by the esterification of α-cyclopentylphenylglycolic acid with 2-chloromethyl-4,5,6,7-tetrahydro-1,3-diazepine; m.p. 219–220° dec.

Anal. Calcd. for $C_{19}H_{27}ClN_2O_3$: N, 7.64. Found: N, 7.75.

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(16) T. S. Oakwood and C. A. Weisgerber, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 114.