Anticholinergic Esters of 2,6-Bis(methoxymethyl)piperid-4-ol

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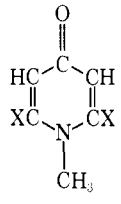
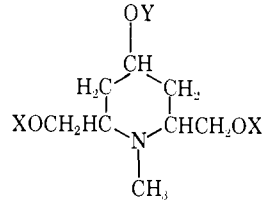
Received May 2, 1969

Some of the pharmacological properties of atropine are shared by relatively simple piperidol esters, *e.g.*, eucatropine, and we considered whether suitable oxygenation of such bases would lead to changes in their pattern of activity comparable for example with the well-known differences in the actions of atropine and scopolamine.

Esters of carbinol **8a** met some of the criteria we envisaged and we have devised a synthesis of it by the route depicted (**1** → **8**). N-Methylchelidamic acid (**1**), which is readily prepared[1] from chelidonic acid, promised to be a convenient starting material. Conversion to its ethyl ester **2** by conventional Fischer–Speier or azeotropic techniques proceeded in only relatively poor yield because of the ease with which decarboxylation took place. The yield was much enhanced when the bisethoxyformic anhydride (**3**) was allowed to decompose in the presence of Et_3N or, better, when a salt of the acid was treated with triethyloxonium tetrafluoroborate.[2]



1, X = COOH
2, X = $COOC_2H_5$
3, X = $COOCOOC_2H_5$
4, X = CH_2OH
5, X = CH_2Cl
6, X = CH_2OMe



7, X = Y = H
8a, X = CH_3; Y = H
b, X = CH_3; Y = $CONHCH_3$
c, X = CH_3; Y = $COCH(C_6H_5)_2$
d, X = CH_3; Y = $COCHOHC_6H_5$
e, X = CH_3; Y = $COCHOAcC_6H_5$

Suitable conditions could not be found for the selective reduction of **2** to **4** with $LiAlH_4$ but with $LiBH_4$ in THF this was readily accomplished in good yield. $NaBH_4$ in MeOH also appeared effective but we have not given attention to the isolation procedure which is complicated by the change of cation.

Treatment of diol **4** with $SOCl_2$ converted it to the corresponding dichloro derivative **5** which in turn reacted with methanolic NaOMe to give the bis(methoxymethyl) derivative **6**.

There remained the task of reducing the pyrid-4-one system to a piperid-4-ol. A preliminary experiment had shown that diol **4** could be hydrogenated in high yield to give **7** which was characterized as its tri-N-methylcarbamic ester. The bimethoxy derivative **6** was similarly hydrogenated to **8a**, from which the crystalline hydrochloride and N-methylcarbamate **8b** were obtained. The OCH_3 protons of the free base gave rise to a single peak at τ 6.7 in the nmr spectrum and the OCH_2 protons a doublet at 6.55 which indicated that the CH_3OCH_2 groups were symmetrically disposed and therefore *cis*.

Carbinol **8a** was converted to its diphenylacetate **8c**, its mandelate **8d** (*via* the phenyl glyoxylate), and its acetylmandelate **8e**. These esters had only a very weak anticholinergic action (Table I).

TABLE I
PHARMACOLOGICAL EVALUATION

Compound	Preliminary general observation in mice (dose 400 mg/kg)	Dose (μg) causing 25% reduction of acetylcholine spasm in gp ileum
8a	Inactive	1
8b	Weak depressant (ip)	>10
8c	Weak depressant (*po*)	
	Convulsant, respiratory depressant (ip)	5
8d	Weak depressant (ip)	>10
8e	Weak depressant (ip)	5
		50% reduction
Atropine sulfate		0.0025
Scopolamine hydrobromide		0.0001

Experimental Section[3]

Diethyl N-Methylchelidamate. (**a**) N-Methylchelidamic acid (18.5 g) was heated under reflux for 20 hr in dry EtOH (500 ml) saturated with HCl. The solution was concentrated and basified with Na_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried ($MgSO_4$) extract left an oil (10.7 g, 45%) which soon crystallized. For analysis, a portion was recrystallized from benzene (charcoal) to give needles, mp 46–47°. *Anal.* ($C_{12}H_{15}NO_5$) C, H, N.

(**b**) A solution of triethyloxonium tetrafluoroborate (225 g) in CH_2Cl_2 (500 ml) was added slowly with stirring over 1.5 hr to a solution of N-methylchelidamic acid (95 g) and Et_3N (72.5 ml) in CH_2Cl_2 (950 ml). Next morning the solvent was removed under reduced pressure and H_2O (1 l.) was added, followed by K_2CO_3 to render the mixture alkaline. The ester (80.5 g, 66%) was isolated as before.

(**c**) EtOCOCl (47.5 ml) was added to an ice-cold solution of N-methylchelidamic acid (50 g) and Et_3N (70 ml) in $CHCl_3$ (500 ml). After 15 min, more Et_3N (25 ml) was added and the mixture was kept at room temperature for 48 hr. The solution was washed with H_2O and evaporated leaving the ester as an oil (35 g, 55%) which soon crystallized.

2,6-Bis(hydroxymethyl)-1-methylpyrid-4-one.—$LiBH_4$ (11.2 g) was added in small portions over 1.5 hr to a stirred ice-cooled solution of diethyl N-methylchelidamate (95 g) in dry THF (950 ml). After 16 hr at room temperature, H_2O (200 ml) was added slowly to decompose the excess borohydride, and the solution after neutralization with HCl was evaporated to dryness under reduced pressure. A solution of the residue taken up in EtOH slowly deposited the crystalline diol (63 g) which was sufficiently pure for the next stage. Recrystallization from aqueous EtOH afforded the pure product (70% yield) as prisms, mp 242–243°, λ_{max} 213 and 267 mμ (ε 16,900 and 18,145). *Anal.* ($C_8H_{11}NO_3$) C, H, N.

2,6-Bis(hydroxymethyl)-1-methylpiperid-4-ol Tris-N-methylcarbamic Ester.—2,6-Bis(hydroxymethyl)-1-methylpiperid-4-one (3 g) in EtOH (800 ml) was hydrogenated over Raney Ni W7 at 70 kg/cm² and 150° for 5 hr. The gummy residue from the evaporation of the filtered solution was redissolved in C_5H_5N (30 ml) and methyl isocyanate (4 ml) was added. After 3 hr at 80°, excess reagents were evaporated under reduced pressure and the residue was recrystallized from Me_2CO–isopropyl ether to give prisms (3.2 g, 35%), mp 146°. *Anal.* ($C_{14}H_{26}N_4O_6$) C, H, N.

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2,6-Bis(chloromethyl)-1-methylpyrid-4-one.—$SOCl_2$ (150 ml) was added to the preceding diol (44 g) with ice-cooling and stirring. After the initial reaction had subsided, the mixture was refluxed for 30 min and the excess $SOCl_2$ was then evaporated. The residue crystallized from MeOH in prisms (39 g, 60%), mp 200° dec, λ_{max} 219.5 and 278 mμ (ε 18,520 and 16,070). *Anal.* ($C_8H_9Cl_2NO \cdot HCl$) C, H, N, Cl.

2,6-Bis(methoxymethyl)-1-methylpyrid-4-one.—The preceding chloro compound (55 g) was refluxed overnight with NaOMe (from 15.5 g of Na) in MeOH (1300 ml). After filtration the resulting solution was evaporated to dryness and the residue was recrystallized from CCl_4 to afford prisms (37 g, 76%). *Anal.* ($C_{10}H_{15}NO_3 \cdot H_2O$) C, H, N.

2,6-Bis(methoxymethyl)-1-methylpiperid-4-ol.—The preceding bismethoxymethyl derivative (8 g) in EtOH (800 ml) was hydrogenated over Raney Ni W7 at 150° and 105 kg/cm² for 3 hr. The filtered solution was evaporated under reduced pressure and the residue in dry Et_2O was treated with dry HCl. The product, which initially separated as a gum, crystallized from 2-PrOH–isopropyl ether to afford the hydrochloride (5.3 g, 55%), mp 173–174°. *Anal.* ($C_{10}H_{21}NO_3HCl$) C, H, N.

2,6-Bis(methoxymethyl)-1-methylpiperid-4-yl N-Methylcarbamate.—A mixture of the preceding piperidol hydrochloride (2 g), methyl isocyanate (2 ml), and dry C_5H_5N (20 ml) was kept at room temperature overnight and then refluxed for 5 hr. After the removal of reagents under reduced pressure, H_2O was added and the product was collected in C_6H_6. The residue from evaporation of the dried solution was taken up in dry Et_2O and treated with HCl. The resulting hydrochloride (0.7 g, 30%), recrystallized from Me_2CO–Et_2O had mp 159–161°. *Anal.* ($C_{12}H_{24}N_2O_4 \cdot HCl \cdot H_2O$) C, H, N.

2,6-Bis(methoxymethyl)-1-methylpiperid-4-yl Diphenylacetate. The piperidol hydrochloride (1 g) and diphenylacetyl chloride (2 g) were refluxed together in dry C_5H_5N (20 ml) overnight. The C_5H_5N was removed under reduced pressure, Na_2CO_3 solution was added to the residue, and the product was extracted into EtOAc. The residue after removal of the solvent was converted to the hydrochloride (0.7 g, 43%) which, recrystallized from CCl_4, had mp 143–145°. *Anal.* ($C_{24}H_{32}NO_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2,6-Bis(methoxymethyl)-1-methylpiperid-4-yl Mandelate.—A mixture of the piperidol hydrochloride (2.4 g), phenylglyoxylyl chloride (2.0 g), and C_6H_6 (50 ml) was kept at room temperature for 16 hr and then refluxed for 0.5 hr. The resulting crude phenyl glyoxylate (3.1 g), isolated in the usual way, was refluxed in wet Et_2O (50 ml) with Al–Hg (0.3 g of Al washed with 1% $HgCl_2$ solution) for 2 hr. Evaporation of the filtered solution left the oily mandelate base which was converted by ethereal HCl to its hydrochloride (2.4 g), mp 80°, after crystallization from 2-PrOH. *Anal.* ($C_{18}H_{27}NO_5 \cdot HCl \cdot H_2O$) C, H, N.

2,6-Bis(methoxymethyl)-1-methylpiperid-4-yl Acetylmandelate.—A mixture of the piperidol hydrochloride (1.5 g), acetylmandelyl chloride (1.5 g), C_5H_5N (15 ml), and C_6H_6 (30 ml) was refluxed for 16 hr. The residue from evaporation of the H_2O-washed solution was redissolved in dry Et_2O and treated with hydrogen chloride. The resulting hydrochloride (1.3 g), mp 138–141°, recrystallized from Me_2O–Et_2O. *Anal.* ($C_{20}H_{29}NO_6 \cdot HCl$) C, H, N.

Acknowledgment.—We thank Mr. Peter Southgate for the pharmacological evaluation of the above-mentioned esters.

The Preparation of Substituted N-Carbamoylpyrazinecarboxamides

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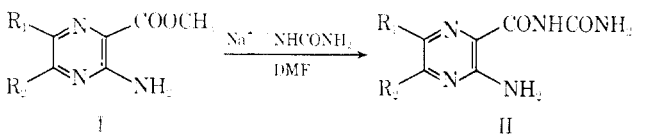
Received May 19, 1969

A kaliuretic response is a well-recognized undesirable pharmacologic effect produced by most diuretics. A hypokalemic alkalosis which often accompanies drug-induced natriuresis is found with the use of many of the diuretic compounds currently available. Recently, some pyrazine derivatives have been reported as diuretic agents which spare potassium.[1,2] The most promising of these was N-amidino-3,5-diamino-6-chloropyrazinecarboxamide hydrochloride dihydrate (amiloride hydrochloride). Of additional interest are reports that this drug exhibits a synergistic effect when given in combination with other diuretic agents such as acetazolamide or the thiazides.[3] This antikaliuretic effect has also been demonstrated in a number of clinical studies.[4-7]

Chemistry.—We wish to report here the synthesis and activity of several substituted N-carbamoylpyrazinecarboxamides, a related series of compounds. Reaction of the appropriate ester with monosodium urea[8] in DMF was found to be a good method for preparing the desired compounds.[8] Following this procedure, the substituted N-carbamoylpyrazinecarboxamides IIa–i were prepared.



I II

	R_1	R_2
a	H	H
b	Cl	H
c	Cl	$N(CH_3)_2$
d	Cl	$N(CH_3)(i\text{-}C_3H_7)$
e	Cl	$N(C_2H_5)(n\text{-}C_4H_9)$
f	Cl	$N(C_2H_5)(n\text{-}C_3H_7)$
g	Cl	$N(CH_3)(n\text{-}C_3H_7)$
h	Cl	$N(CH_3)(CH_2CH{=}CH_2)$
i	Cl	$N(CH_3)(n\text{-}C_4H_9)$

While the procedure readily produced the 5-dialkylamino derivatives, reaction of the related 5-amino or 5-methylamino ester with monosodium urea gave only starting material. This reaction was repeated unsuccessfully several times varying the ratio of ester to monosodium urea. It is of interest to speculate why the 5-dimethylamino ester (Ic) should react while the 5-amino ester is unreactive. In the case of the latter, it seems quite possible that a proton-exchange reaction is involved between the ester and the monosodium urea to produce urea and the sodium salt of the ester. The sodium salt of the ester is then unreactive to any additional amounts of monosodium urea.

After several unsuccessful approaches, the synthesis of N-carbamoyl-3,5-diamino-6-chloropyrazinecarboxamide (VIa), the direct analog of amiloride, was accomplished using the following synthetic scheme. Reaction of methyl 3-amino-5-methylmercapto-6-chloropyrazinecarboxylate (III) with monosodium urea yields N-carbamoyl-3-amino-5-methylmercapto-6-chloropyr-

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