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.* ($C_{10}H_{15}NO_3H_2O$) 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.

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The Preparation of Substituted N-Carbamoylpyrazinecarboxamides

J. WILLIAM HANIFIN, ROSEMARY CAPUZZI, AND ELLIOTT COHEN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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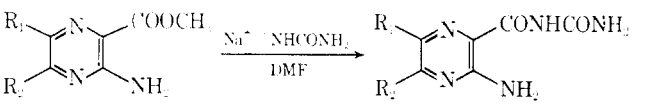
A kaliuretic response is a well-recognized undesirable pharmacologic effect produced by most diuretics. A hypokalemic alkalosis which often accompanies drug-induced natriuresis is found with the use of many of the diuretic compounds currently available. Recently, some pyrazine derivatives have been reported 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.[9] 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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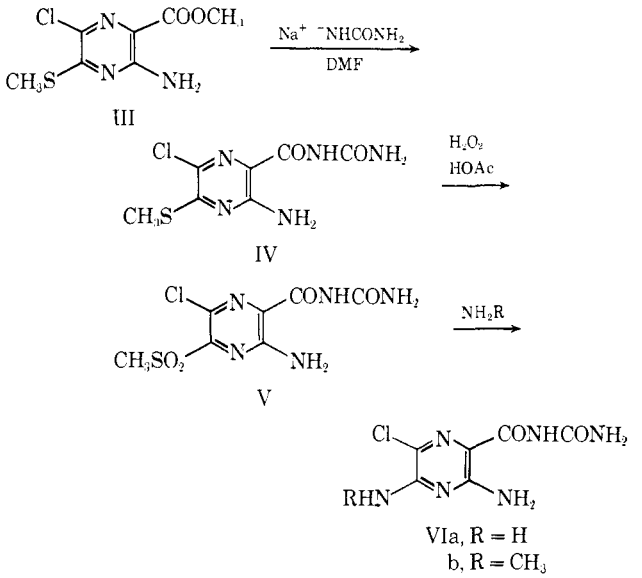
azinecarboxamide (IV). Oxidation of IV with H_2O_2 gave the 5-mesyl derivative V, which is then easily converted to VIa by treatment with NH_3. The 5-methylamino compound VIb was also prepared in this manner.



Pharmacology.—All of these compounds were tested for diuretic activity in both normal rats and hydrated dogs. The normal rats and hydrated dogs were given several doses according to the procedures of Cummings, *et al.*,[10] and Little and Cooper,[11] respectively. Compounds IIa–f and VIa,b were found to be active in the rat. They increased the total urine volume and enhanced the excretion of Na^+ and Cl^-. However, only one of the compounds, IIa, showed antikaliuretic activity. When coadministered with quinethazone, N-carbamoyl-3-aminopyrazinecarboxamide (IIa) showed a slight potentiation of the quinethazone-induced natriuresis. All of the compounds were tested in the dog and found to be inactive. IIa at low doses in combination with quinethazone again showed a natriuretic effect, but it was too small to be significant.

Experimental Section[12]

Methyl 3-aminopyrazinecarboxylate (Ia) was prepared from 3-aminopyrazine-2-carboxylic acid by the method of Ellingson, Henry, and McDonald.[13]

Substituted methyl 3-aminopyrazinecarboxylates (Ib–i, III) were prepared following the procedure of Cragoe, *et al.*[1]

General Procedure for the Substituted N-Carbamoylpyrazinecarboxamides (IIa–i).—To 15 ml of dry DMF was added 0.9 g (0.015 mole) of urea. To the stirred solution cooled to −15° was added 0.7 g (0.015 mole) of NaH (50% in oil). The mixture was left to stir for 1 hr. To the cooled mixture was then added 0.004 mole of the methyl substituted 3-aminopyrazinecarboxylate. This was left to stir for 2 hr. The reaction mixture was then poured onto 25 g of ice–H_2O made slightly acidic with AcOH. The mixture was stripped to dryness and H_2O was added to precipitate the crude product. The solid was then dissolved in hot 3 *N* HCl, filtered, and precipitated with dilute NaOH. An analytical sample was prepared by crystallizing the product from MeOH.

Table I

Yields, Physical, and Analytical Data

No.	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	Analyses
IIa	32	288[b]	W	$C_6H_7N_5O_2$	C, H, N
IIb	16	240	M	$C_6H_6ClN_5O_2$	C, H, N, Cl
IIc	28	218	M	$C_8H_{11}ClN_6O_2$	C, H, N, Cl
IId	29	198	M	$C_{10}H_{15}ClN_6O_2$	C, H, N, Cl
IIe	27	165	M	$C_{12}H_{19}ClN_6O_2$	C, H, N, Cl
IIf	16	148	M	$C_{11}H_{17}ClN_6O_2$	C, H, N, Cl
IIg	24	191	M	$C_{10}H_{15}ClN_6O_2$	C, H, N, Cl
IIh	36	168	M	$C_{10}H_{13}ClN_6O_2$	C, H, N, Cl
IIi	54	176	M	$C_{11}H_{17}ClN_6O_2$	C, H, N, Cl
IV	27	225[b]	M	$C_7H_8ClN_5O_2S$	H, N, Cl, S; C[c]
V	41	215[b]	M	$C_7H_8ClN_3O_4S$	C, H, N, Cl, S
VIa	82	260[b]	M	$C_6H_7ClN_6O_2$	C, H, N, Cl
VIb	37	245[b]	M	$C_7H_9ClN_6O_2$	C, H, N, Cl

[a] W = H_2O, M = MeOH. [b] Compound melts with decomposition. [c] C: calcd, 32.1; found, 32.6.

N-Carbamoyl-3-amino-5-methylmercapto-6-chloropyrazinecarboxamide (IV).—To 15 ml of dry DMF was added 0.3 g (0.005 mole) of urea. To the stirred solution cooled to −15° was added 0.25 g (0.005 mole) of NaH (50% in oil). This was left to stir for 1 hr. To the cooled mixture was added 1.0 g (0.004 mole) of methyl 3-amino-5-methylmercapto-6-chloropyrazinecarboxylate and stirring continued an additional 2 hr. The reaction mixture was then poured onto 15 g of ice–H_2O made slightly acidic with AcOH. A yellow solid precipitated from solution was filtered and washed with H_2O to give 0.7 g of crude product. Crystallization from MeOH gave 0.3 g (27%) of product, mp 225° dec, λ_{max}^{KBr} 5.77 and 5.93 μ.

N-Carbamoyl-3-amino-5-mesyl-6-chloropyrazinecarboxamide (V).—A suspension of 1.0 g (0.004 mole) of N-carbamoyl-3-amino-5-methylmercapto-6-chloropyrazinecarboxamide (IV) in 40 ml of AcOH and 10 ml of 30% aqueous H_2O_2 was stirred at room temperature. After 110 hr an additional 3 ml of 30% H_2O_2 was added and stirring was continued for a total of 168 hr. The yellow solid which precipitated was removed by filtration and washed with EtOAc to give a total crude yield of 0.65 g. Recrystallization from MeOH yielded 0.45 g (41%) of product: mp 215° dec; λ_{max}^{KBr} 5.80, 5.88, and 5.97 μ.

N-Carbamoyl-3,5-diamino-6-chloropyrazinecarboxamide (VIa).—A suspension of 0.42 g (0.0014 mole) of N-carbamoyl-3-amino-5-mesyl-6-chloropyrazinecarboxamide (V) in 2 ml of *i*-PrOH was stirred while 0.14 g of NH_3 in 4 ml of *i*-PrOH was added and the mixture was refluxed for 1 hr. The solution was cooled in an ice bath and the yellow product that separated was removed by filtration. Crystallization from MeOH yielded 0.27 g (82%), mp 260° dec, λ_{max}^{KBr} 5.84 and 6.01 μ.

Acknowledgments.—We wish to thank Drs. J. R. Cummings and R. Z. Gussin and associates for the pharmacological data.

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(12) Yields, physical data, and analyses are listed in Table I. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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Potential Antiparkinsonism Agents. Quinuclidinyl Benzhydryl Ethers

J. Lars G. Nilsson, Jörgen Wågermark, and Richard Dahlbom

Department of Organic Chemistry, Faculty of Pharmacy, Box 6804, 113 86 Stockholm, Sweden

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As part of our current study of quinuclidine derivatives of potential pharmacological value,[1] we have

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