Pyrazine Diuretics. V. N-Amidino-3-aminopyrazinecarboxamidines and Analogous 2,4-Diaminopteridines

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Received June 29, 1967

The synthesis of a series of N-amidino-3-aminopyrazinecarboxamidines, principally by the reaction of a 3-aminopyrazinecarbonitrile with an appropriate guanidine, is described. Cyclization of selected members of this series afforded the analogous 2,4-diaminopteridines. The required 3-aminopyrazinecarbonitriles were prepared from the corresponding carboxamides; 3-amino-5,6-dichloropyrazinecarbonitrile yielded a variety of 5-substituted derivatives by nucleophilic displacement of the 5-chloro group. The N-amidino-3-aminopyrazinecarboxamidines exhibited diuretic activity as measured by several assay methods in rats and dogs. These compounds were generally less active than the corresponding 2,4-diaminopteridines which, in turn, were less potent than the corresponding N-amidino-3-aminopyrazinecarboxamides.

The discovery of the interesting diuretic–saluretic properties of the N-amidino-3-aminopyrazinecarboxamides[1] prompted the investigation of the corresponding N-amidino-3-aminopyrazinecarboxamidines (VII). Some related N-amidinoalkanamides have been reported by Birtwell[2] who described two synthetic routes. However, application of either of these methods to the pyrazine series was unattractive because of the poor yields and the inaccessibility of many of the required Grignard reagents.

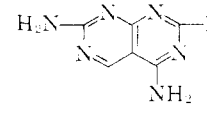
During the present investigation, three other synthetic methods were employed; these methods involved the reaction of a guanidine with the appropriate (A) imino ether (V), (B) imino thioether (VI), or (C) 3-aminopyrazinecarbonitrile (IV). These synthetic routes are illustrated graphically by Scheme I which summarizes the salient points concerning the preparation of four compounds of type VII (*i.e.*, a–d). Also, they are exemplified in the Experimental Section as methods 4A, 4B, and 4C, respectively.

N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamidine (VIIb) was produced in 84% yield from the reaction of 3-amino-5-dimethylamino-6-chloropyrazinecarbonitrile (IVj) and guanidine in methanol at room temperature. However, conducting the reaction at reflux caused cyclization to the corresponding pteridine (VIIIi). The reaction of 3-amino-5-diethylamino-6-chloropyrazinecarbonitrile (IVk) (or one of several analogous nitriles) with guanidine in an alcohol at ambient temperature gave a mixture of the acyclic (VII) and cyclized (VIII) products. In some instances, cyclization was so facile that, although the solid N-amidinopyrazinecarboxamidine could be isolated momentarily, spontaneous cyclization precluded its characterization. Early in this study it became apparent that many of the N-amidinopyrazinecarboxamidines (VII) were rather unstable and generally quite modest in their biological activity. Therefore, the reaction of the pyrazinecarbonitriles (IV) with guanidine was usually carried out under conditions expected to produce only the pteridine (VIIIa–h, j, k).

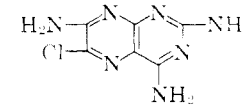
Only one of the pteridines obtained in this study, 2,4-diamino-6-methylpteridine (VIIIa), has been reported previously;[3] it has been prepared in 31% yield from 2,4,5,6-tetraaminopyrimidine and methylglyoxal in the presence of sodium bisulfite.

It is noteworthy that 2,4-diamino-6-chloro-7-isopropoxypteridine (VIIIk) was produced in 52% yield from the reaction of 3-amino-5,6-dichloropyrazinecarbonitrile (IVa) with guanidine in *i*-PrOH. Thus, in addition to condensation with guanidine and cyclization, displacement of the 5-chloro by isopropoxy occurred in this strongly basic environment.

Taylor, *et al.*,[4] has reported the synthesis of an isomeric heterocycle, 2,4,7-triaminopyrimido[4,5-*b*]-pyrimidine (XI) from guanidine and 2,4-diamino-5-cyanopyrimidine. However, the condensation is not as facile as that involving the subject pyrazinecarbonitriles (IV) and guanidine. Since some pteridines have been reported[5] to have diuretic activity, it was of interest to



XI



VIIIe

examine the novel pteridines of type VIII for their diuretic properties.

The intermediate 3-aminopyrazinecarbonitriles (IV) were prepared by dehydration of the corresponding 3-aminopyrazinecarboxamides (II). Ellingson, *et al.*,[6] have described the preparation of 3-aminopyrazinecarbonitrile from 3-aminopyrazinecarboxamide and P_2O_5 in pyridine. However, we obtained erratic results and very poor yields in an attempt to apply this reaction to 3-amino-6-chloropyrazinecarboxamide.

A method of dehydrating simple benzamides using $SOCl_2$ or $POCl_3$ in DMF[7,8] was adapted to the present series; best results were obtained when $POCl_3$ in DMF was employed. The intermediate formamidines (III) were easily isolated and purified, and dilute acid hydrolysis afforded the corresponding IV in excellent yields

(1) J. B. Bicking, J. W. Mason, O. W. Wohlersdorf, Jr., J. H. Jones, S. F. Kwong, C. M. Robb, and E. J. Cragoe, Jr., *J. Med. Chem.*, **8**, 638 (1965), paper I of this series.

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(5) (a) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowski, and P. J. Larsen, *Federation Proc.*, **20**, 409 (1961); (b) V. D. Wiebelhaus, J. Weinstock, A. R. Maas, F. T. Brennan, G. Sosnowski, and T. Larson, *J. Pharmacol. Exptl. Therap.*, **149**, 397 (1965).

(6) R. C. Ellingson, R. L. Henry, and F. S. McDonald, *J. Am. Chem. Soc.*, **67**, 1711 (1945).

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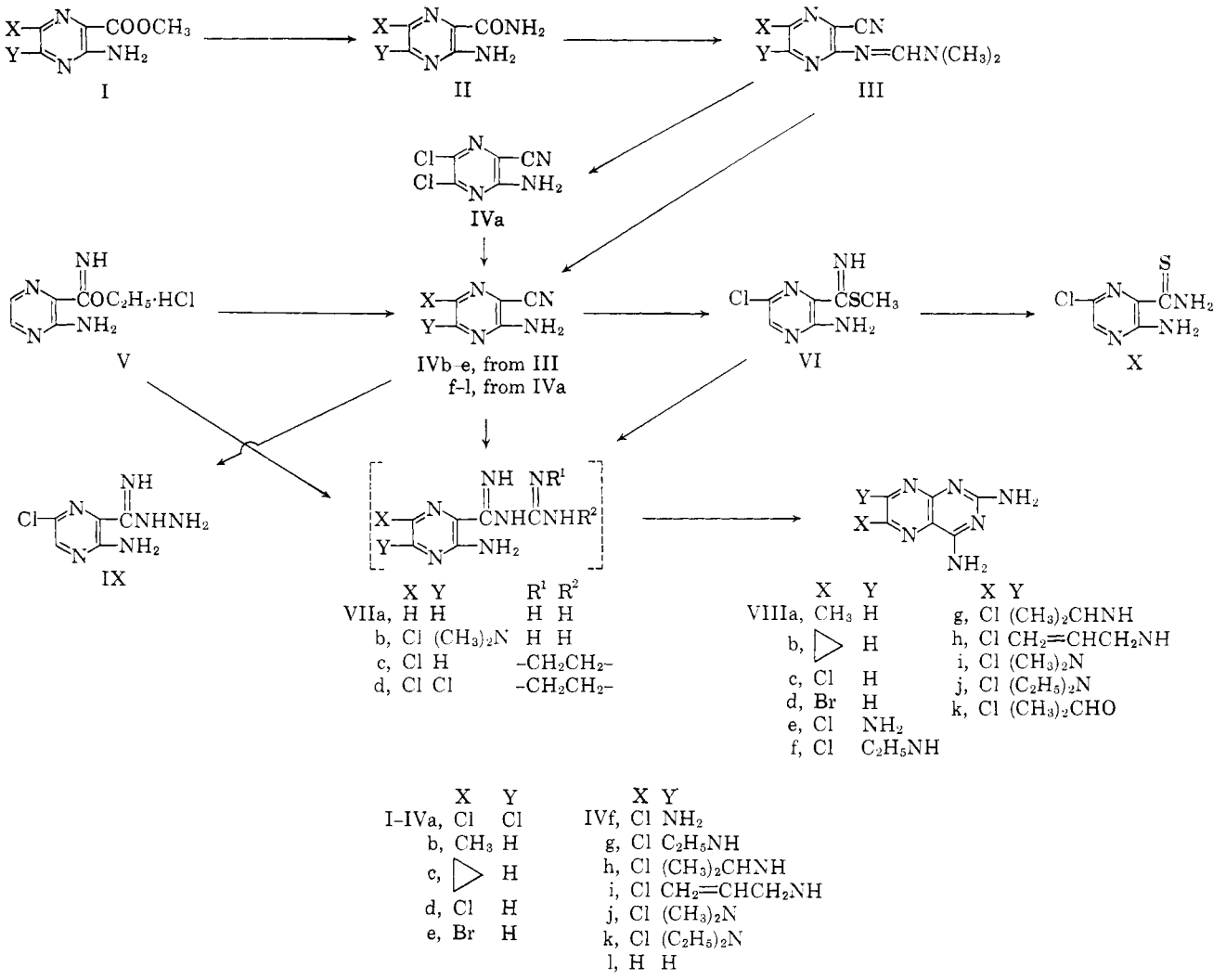
SCHEME I



(see method 3A, Experimental Section). The preparation of 3-amino-5,6-dichloropyrazinecarbonitrile (IVa) provided a versatile intermediate which was used to synthesize a number of 5-substituted pyrazinecarbonitriles (IVb–e); nucleophilic displacement of the 5-chlorine atom occurred in a fashion analogous to that observed with the corresponding ester[9] (see method 3B).

The intermediate methyl pyrazinecarboxylates (I) and pyrazinecarboxamides (II) shown in Scheme I have been described in previous papers[9-11] of this series, except for IId and IIe which were prepared by standard methods.

Methyl 3-amino-6-chloropyrazinethiocarboximidate (VI) was synthesized from the corresponding nitrile (IVd) and methyl mercaptan in the presence of a small amount of base. Under acidic conditions, no reaction occurred. Compound VI readily reacted with 2-amino-2-imidazoline to give the desired compound (VIIc). Treatment of VI with H_2S in pyridine, in an attempt to prepare the dithio ester by the method of Marvel,[12] resulted in the formation of the thioamide (X). 3-Amino-6-chloropyrazinecarbonitrile (IVd), with hydrazine, readily formed the amidrazone (IX).

Structure–Activity Relationships.—The N-amidinopyrazinecarboxamidines and 2,4-diaminopteridines recorded in Table I were assayed[13] for their deoxycorticosterone acetate (DOCA) inhibitory activity using the adrenalectomized rat according to the method already described.[1,9] The compounds were administered subcutaneously; the activity scores presented in Table I are in accordance with the scoring method used previously.[1,9]

The four N-amidinopyrazinecarboxamidines (VIIa–d) prepared in this study are considerably less active than the corresponding N-amidinopyrazinecarboxamides reported earlier.[1,9,10] However, the most potent member is VIIb which bears 5 and 6 substituents of the same type as the most active members of the N-amidinopyrazinecarboxamide series.

The 2,4-diaminopteridines (VIII) were generally more active than the N-amidinopyrazinecarboxamidines (VII) from which they were derived but they were less potent than the corresponding N-amidinopyrazinecarboxamides. Weak activity was observed with 6-methyl-2,4-diaminopteridine (VIIIa) and the 6-halo analogs (VIIIc and d). A marked increase in potency was noted with the introduction of a 7-amino (or sub-

(9) E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. B. Bicking, S. F. Kwong, and J. H. Jones, *J. Med. Chem.*, **10**, 66 (1967), paper II of this series.

(10) J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, Jr., *ibid.*, **10**, 598 (1967), paper III of this series.

(11) J. H. Jones, J. B. Bicking, and E. J. Cragoe, Jr., *ibid.*, **10**, 899 (1967), paper IV of this series.

(12) C. S. Marvel, P. deRodzitske, and J. J. Brader, *J. Am. Chem. Soc.*, **77**, 5997 (1955).

(13) Drs. M. S. Glitzer, S. L. Steelman, and their associates supplied these biological data.

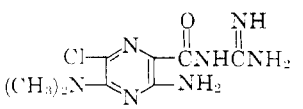
TABLE I

No.	Rat DOCA inhib score[a]	Normal rat score[b]
VIIa	±	+1
VIIb	+1	+2
VIIc	±	0
VIId	0	±
VIIIa	±	+2
VIIIb	0	+2
VIIIc	±	+2
VIIId	±	+1
VIIIe	+3	+3
VIIIf	+1	+3
VIIIg	+2	+3
VIIIh	+1	+2
VIIIi	+2	+2
VIIIj	+1	+2
VIIIk	0	+3
Spironolactone	+1	...
Triamterene	+2	+2

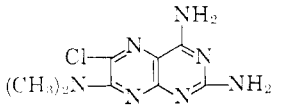
[a] For the scoring system see previous papers.[1,9] Compounds which scored 0 were tested only at a maximum dose of 800 μg/rat; thus, the possibility exists that activity would be observed at higher doses. [b] The scoring system has been described previously.[11]

stituted amino) group into the 2,4-diamino-6-chloropteridine molecule. Maximal activity was noted with the 7-amino (VIIIe) member, while the 7-dimethylamino (VIIIi) and 7-isopropylamino (VIIIg) were somewhat less potent and the 7-ethylamino, 7-allylamino, and 7-diethylamino (VIIIf, h, and j) still less active. The introduction of an isopropoxy group into the 7 position of VIIIc (VIIIk) caused a decrease in DOCA-inhibitory properties.

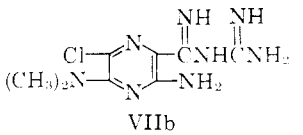
Direct comparison of the three series, N-amidinopyrazinecarboxamides, N-amidinopyrazinecarboxamidines, and 2,4-diaminopteridines can be made from the data regarding XII, VIIb, and VIIIi which have DOCA inhibition scores of +4, +2, and +1.



XII



VIIIi



VIIb

Each of the compounds recorded in Table I was tested intraperitoneally in normal rats;[14] it will be noted that the activity of individual members of each series generally paralleled those observed in the adrenalectomized rat. A few selected compounds were tested intravenously in dogs[14] and found to be active, although the diuresis and saluresis are not as pronounced in this species as in rats.

Experimental Section[15]

Details of the synthesis of the new compounds are presented. Where several compounds of one type have been prepared by a particular method, only one example is given. Pertinent data regarding each compound is recorded in Tables II and III.

TABLE II

No.	Synthetic method[a]	% yield	Recrystn solvent	Mp, °C	Formula
	3-Aminopyrazinecarboxamides				
IIa	*b*				
IIb	1[c]				
IIc	1[d]				
IId	1	88	H_2O	231–232	$C_5H_5ClN_4O$
IIe	1	60	C_6H_6	215–216	$C_5H_5BrN_4O$
	3-N-Formamidinopyrazinecarbonitriles				
IIIa	2	48	*f*	117–119	$C_6H_3Cl_2N_5$
IIIb	2	*e*			
IIIc	2	73	*g*	118–120	$C_7H_5N_5$
IIId	2	69	*g*	114–116	$C_6H_4ClN_5$
IIIe	2	*e*			
	3-Aminopyrazinecarbonitriles				
IVa	3A	95	C_6H_6	213–215	$C_5H_3Cl_2N_3$
IVb	3A	14	H_2O	171–172	$C_5H_4N_4$
IVc	3A	67	C_6H_6	172–173	$C_5H_4N_4$
IVd	3A	95	*g*	151–153	$C_5H_4ClN_3$
IVe	3A	53	EtOH	181–183	$C_5H_3BrN_4$
IVf	3B	50	H_2O	295	$C_5H_3ClN_4$
IVg	3B	61	H_2O–*i*-PrOH	107–109	$C_7H_8ClN_3$
IVh	3B	72	*f*	126–128	$C_8H_{10}ClN_3$
IVi	3B	70	BuCl	103–105	$C_8H_8ClN_3$
IVj	3B	79	H_2O–*i*-PrOH	118–120	$C_7H_8ClN_3$
IVk	3B	69	*f*	114–116	$C_8H_{10}ClN_3$
IVl	*h*				

[a] See the Experimental Section for the number that corresponds to each synthetic method. [b] Reference 9. [c] Reported by O. Vogel and E. C. Taylor, *J. Am. Chem. Soc.*, **81**, 2472 (1959). [d] See ref 10. [e] This compound was not isolated and characterized before use in the next step. [f] Methylcyclohexane. [g] Cyclohexane. [h] See ref 6. [i] All analyses (C, H, N) were within acceptable limits except IVh (C: calcd, 45.5; found, 44.8).

TABLE III

No.	Synthetic method[a]	% yield	Recrystn solvent	Mp, °C	Formula[c]
	N-Amidino-3-aminopyrazinecarboxamidines				
VIIa	4A	33	*b*	310 dec	$C_6H_5N_7$
VIIb	4C	84	*b*	115 dec	$C_8H_{13}ClN_8$
VIIc	4B	39	*b*	149–150 dec	$C_8H_{10}ClN_7$
VIId	4C	45	C_6H_6	>290	$C_8H_9Cl_2N_7$
	2,4-Diaminopteridines				
VIIIa[d]	5	39	*b*	>330	$C_7H_5N_6$
VIIIb	5	85	*b*	>300	$C_9H_{10}N_6$
VIIIc	5	75	*b*	295 dec	$C_8H_5ClN_6$
VIIId	5	50	*b*	>300	$C_8H_5BrN_6$
VIIIe	5	92[e]	*b*	>310	$C_8H_6ClN_7$
VIIIf	5	86[e]	EtOH	256–259	$C_9H_{10}ClN_7$
VIIIg	5	79[e]	EtOH	233–235	$C_9H_{12}ClN_7$
VIIIh	5	83[e]	EtOH	245–247	$C_9H_{10}ClN_7$
VIIIi	5	66[e]	*b*	263 dec	$C_8H_{10}ClN_7$
VIIIj	5	84[e]	EtOH	268–271	$C_{10}H_{14}ClN_7$
VIIIk	5	52[e]	C_6H_6	238–240	$C_9H_{12}ClN_6O$

[a] See the Experimental Section for the number that corresponds to each synthetic method. [b] Dissolved in dilute aqueous HCl and precipitated with dilute aqueous NaOH. [c] Seeger, *et al.*,[3] who describe the synthesis of VIIIa by another method, do not report the melting point of their material. [d] The reaction was carried out using *i*-PrOH as a solvent. [e] All analyses (C, H, N) were within acceptable limits.

1. 3-Aminopyrazinecarboxamides (II). 3-Amino-6-bromopyrazinecarboxamide (IIe).—A suspension of Ie[16] (2.0 g, 0.01 mole) in concentrated NH_4OH (100 ml) was stirred at room temperature for 20 hr. The solid product was separated by filtration, washed with H_2O, dried, and recrystallized.

2. N,N-Dimethyl-N′-(3-cyano-2-pyrazinyl)formamidines (III). N,N-Dimethyl-N′-(3-cyano-6-chloro-2-pyrazinyl)formamidine (IIId).—A suspension of IId (17.2 g, 0.1 mole) in DMF (170 ml) was stirred and treated with $POCl_3$ (17 ml). The temperature

(14) Dr. J. E. Baer and his associates conducted these studies using procedures which have been described previously.[11]

(15) Mr. K. B. Streeter, Mr. Y. C. Lee, and their staff have provided the analytical data. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values. The melting points are corrected (open capillaries).

(16) R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **71**, 2798 (1949).

spontaneously rose to about 80°; this temperature was maintained for 10 min by application of heat. The resulting solution was poured onto crushed ice (1 kg) and neutralized with NH_4OH. The product was separated by filtration, dried, and recrystallized; the yield was 14.2 g.

3. 3-Aminopyrazinecarbonitriles (IV). Method A. 3-Amino-6-chloropyrazinecarbonitrile (IVd).—A solution of IIId (4.0 g, 0.02 mole) in 2.5% HCl (100 ml) was stirred and heated on a steam bath for 10 min. The product began separating during the heating; after cooling, the mixture was filtered, dried, and recrystallized.

Method B. 3-Amino-5-dimethylamino-6-chloropyrazinecarbonitrile (IVj).—A solution of IVa (10.0 g, 0.05 mole) in DMSO (50 ml) was stirred and treated with 25% aqueous Me_2NH (20 ml). The mixture was heated at 65° for 15 min and poured into H_2O (150 ml). The precipitate which separated was removed by filtration, washed with H_2O, dried, and recrystallized.

For the synthesis of related compounds, the pure liquid or gaseous amines were used.

4. N-Amidinopyrazinecarboxamidines (VII). Method A. N-Amidino-3-aminopyrazinecarboxamidine (VIIa).—3-Aminopyrazinecarbonitrile[6] (2.2 g, 0.018 mole) was added to HCl (10 g) in EtOH (100 ml), and the mixture was allowed to stand overnight. The imino ether hydrochloride (V) which separated was removed by filtration and dried, mp 205° dec; it was used in the following reaction without purification or characterization.

A solution of guanidine in MeOH was prepared by dissolving Na (0.92 g, 0.04 g-atom) in MeOH (50 ml), adding guanidine hydrochloride (4.0 g, 0.04 mole), and stirring for 15 min. Compound V was added, and within a few minutes a solid began to separate. After 2 hr, the solid was collected on a filter, suspended in H_2O, and dissolved by adding dilute HCl. Precipitation of the product with dilute NaOH gave VIIa.

Method B. N-(2-Imidazolin-2-yl)-2-amino-6-chloropyrazinecarboxamidine (VIIc). Step 1. Methyl 3-amino-6-chloropyrazinethiocarboximidate (VI).—CH_3SH (2.5 g, 0.053 mole) was admitted below the surface of EtOH (100 ml) containing 5% NaOH (2 drops). The solution was stirred, IVd (5.0 g, 0.032 mole) was added, and the mixture was heated to effect solution. After stirring at room temperature for 15 min, H_2O (100 ml) was added. The precipitated VI was isolated (6.2 g, 95%) and twice recrystallized from EtOH to give pure VI, mp 192–194° dec. *Anal.* ($C_6H_7ClN_4S$) C, H, N.

Step 2. VIIc.—Na (0.46 g, 0.02 g-atom) was dissolved in MeOH (50 ml); 2-amino-2-imidazoline·HCl (2.44 g, 0.02 mole) was added, and the solution refluxed for 15 min. The NaCl was removed by filtration, the filtrate was treated with VI (2.0 g, 0.01 mole), and the mixture was refluxed for 30 min. After cooling, the product that separated was removed by filtration, washed with water, dried, and purified by reprecipitation.

Method C. N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamidine (VIIb).—Na (460 mg, 0.02 g-atom) was dissolved in *i*-PrOH (50 ml), guanidine·HCl (1.91 g, 0.02 mole) was added, and the mixture was refluxed for 30 min. After cooling, IVj (3.95 g, 0.02 mole) was added, and the solution was evaporated *in vacuo* to a volume of 10 ml. After standing at 25° for 2 hr, H_2O (100 ml) was added; the precipitate that formed was removed by filtration and purified by reprecipitation.

5. 2,4-Diaminopteridines (VIII). 2,4-Diamino-6-chloropteridine (VIIIc).—Na (920 mg, 0.04 g-atom) was dissolved in MeOH (50 ml), guanidine·HCl (4.0 g, 0.043 mole) was added, and the mixture was refluxed for 30 min. After filtration, the filtrate was cooled and treated with IVd (2.0 g, 0.013 mole); the mixture was refluxed for 30 min. Upon chilling, VIIIc (1.9 g, 75%) separated. The product was removed by filtration and purified by reprecipitation.

6. Other Syntheses. 3-Amino-6-chloropyrazinethiocarboxamide (X).—A suspension of VI (2.0 g, 0.01 mole) in pyridine (20 ml) was stirred, and a steam of H_2S gas was admitted below the surface of the solvent for 2 hr. The solvent was evaporated *in vacuo* and the residual yellow solid was recrystallized from C_6H_6; yield 1.8 g (98%), mp 193–195°. *Anal.* ($C_5H_5ClN_4S$) C, H, N.

3-Amino-6-chloropyrazinecarboximidic Acid Hydrazone (IX).—To a solution of NH_2NH_2 (1.34 g, 0.042 mole) in EtOH (65 ml) was added IVd (6.5 g, 0.042 mole), and the solution was refluxed for 1.5 hr. After cooling, the precipitate was separated by filtration; yield 5.4 g (69%), mp 168–170°. Recrystallization from EtOH gave material melting at 169–171°. *Anal.* ($C_5H_7ClN_6$) C, H, N.

Antidepressants. Tetrabenazine-Antagonizing Activity in a Series of 5H-Dibenzo[*a,d*]cycloheptene-5-propylamines

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Received November 6, 1967

A series of 5H-dibenzo[*a,d*]cycloheptene-5-propylamine derivatives has been synthesized and studied for tetrabenazine-antagonizing activity. In both the nortriptyline (Ia) and protriptyline (II) series, activity was maximal in compounds with a 10,11 double bond. Nuclear substituents reduced potency in both series. A striking difference in activity between geometric isomers was observed in the two pairs studied. In one pair, demethylation of the tertiary amine that is the more active in blocking conditioned avoidance gives rise to the more potent tetrabenazine antagonist. The primary amine congeners of nortriptyline and protriptyline have reduced activity, relative to the parent compounds.

Demethylation to desipramine is one of the transformations occurring in the metabolism of imipramine.[2,3] Studies in these laboratories[4,5] demonstrated that N-demethylation is involved in the metabolism of amitriptyline.

Sulser, Watts, and Brodie[6] found desipramine to be a potent antagonist of the central effects of reserpine and 2-ethyl-1,3,4,6,7,11b-hexahydro-3-isobutyl-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-ol. Nortriptyline (Ia) was found to retain the antibenzoquinolizine action of amitriptyline (Ib).[6,7]

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