Experimental Section[12]

1-Methyl-α,α-diphenyl-1,2,3,6-tetrahydro-4-pyridinemethanol (2).—A mixture of 100 g (0.38 mole) of diphenyl-4-pyridinemethanol, 100 ml of dioxane, and 50.5 g (0.40 mole) of Me_2SO_4 was heated on a steam bath for about 30 min, the solvent was removed under vacuum, and the resulting residue was dissolved in *i*-PrOH. The pyridinium salt 1 was precipitated by addition of 1.5 vol of petroleum ether (bp 75–90°); 136 g, mp 169–171°. It was dissolved in a mixture of 1 l. of H_2O, 2 l. of MeOH, and 50 ml of 50% aqueous NaOH. The reaction flask was cooled in an ice bath and a solution of 77 g of $NaBH_4$ in 400 ml of H_2O was added dropwise. Cooling was continued for 2 hr after which time the mixture was heated on a steam bath to allow evaporation of methanol. The product crystallized from the reaction mixture on cooling, was collected, washed (H_2O), and recrystallized from EtOAc to give 95.5 g (85% yield) of **2**: mp 179–180.5° (lit.[4b] mp 179.0–179.8°); λ_{max} (MeOH) 248 mμ (ε 282), 253 (368), 259 (446), 265 (343).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.67; H, 7.55; N, 4.89.

3-Hydroxy-1-methyl-4-(diphenylmethylene)piperidine (5a) and Acetate (5b).—A mixture of 25.0 g of carbinol **2** and 500 ml of 1 *N* HCl was stirred for 24 hr. The resulting clear red solution was neutralized with concentrated NH_4OH and the product was extracted into ether. The extract was washed (H_2O) and dried (Na_2SO_4) and the product, obtained after evaporation of solvent, was recrystallized once from ether to give 23.5 g (94% yield) of **5a**: mp 109–110°; λ_{max} (MeOH) 225.5 mμ (ε 13,600), broad shoulder at higher wavelength.

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.84; H, 7.61; N, 4.97.

A hydrochloride salt was prepared, mp 230°, that also analyzed correctly for C, H, and N. The acetate **5b** was prepared by heating **5a** in excess Ac_2O–pyridine (10:1) for 1 hr on a steam bath. The product, obtained after conventional work-up, was converted to the acid maleate salt and recrystallized from *i*-PrOH, mp 171–172°.

Anal. Calcd for $C_{21}H_{23}NO_2 \cdot C_4H_4O_4$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.74; H, 6.24; N, 3.19.

(12) We are indebted to Dr. H. J. Keily, M. J. Gordon, and associates for microanalyses and spectral data.

Dihydropyrrolo[3,4-*c*]pyrazoles

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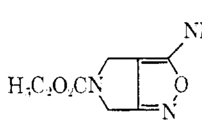
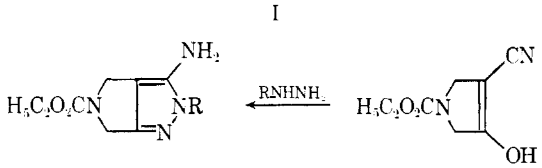
In view of the hypotensive activity observed for a number of dihydropyrrolo[3,4-*c*]isoxazoles (I) in experimental animals,[1] we undertook the syntheses of the isosteric dihydropyrrolo[3,4-*c*]pyrazoles (II).



I



II III

(1) S. M. Gadekar, S. Nibi, B. D. Johnson, E. Cohen, and J. R. Cummings, *J. Med. Chem.*, **11**, 453 (1968).

The 3-aminopyrrolopyrazole derivatives, listed in Table I, were prepared by condensing a cyano ketone (III) with a salt of the appropriate hydrazine.[2] The 5-acetyl compound **17** was obtained by a similar condensation of 1-acetyl-4-cyano-3-oxopyrrolidine[3] with phenylhydrazine hydrochloride. In view of the increased hypotensive activity seen in the isoxazole series for the N-acetyl derivative, several acylated derivatives of II (Table II) were prepared. Compound **3** when acetylated with either acetic anhydride alone or acetyl chloride and pyridine gave the acetyl derivative **19**. If pyridine was used along with the anhydride the product was a diacetyl derivative **27**. Compounds **20** and **23** were obtained by the usual benzoylation procedure.

Unlike the 3-aminopyrrolo[3,4-*c*]isoxazoles,[1] none of the compounds listed in the two tables showed significant hypotensive activity.

Experimental Section[4]

Methyl N-(2-Cyanoethyl)-2-methylalaninate (IV).—The base prepared from 40 g (0.26 mole) of methyl 2-methylalaninate hydrochloride by the addition of 16 g (0.29 mole) of KOH in 25 ml of H_2O was treated gradually at 0° with 19.4 g (0.36 mole) of acrylonitrile. The mixture was then heated at 70–80° for 1 hr. An oil formed, which was extracted with Et_2O, and the Et_2O layer was distilled. The nitrile ester weighed 26 g (42%), bp 95–96° (1 mm), $n^{25}D$ 1.4470. *Anal.* ($C_8H_{15}N_2O_2$) C, H, N.

Methyl N-Carbethoxy-N-(2-cyanoethyl)-2-methylalaninate (V).—An ice-cold mixture containing 8.22 g (0.045 mole) of the preceding cyano ester, 3.8 g (0.045 mole) of $NaHCO_3$, and 15 ml of H_2O was treated with 4.5 g (0.045 mole) of ethyl chlorocarbonate. The mixture was stirred for 2 hr and the acylated ester was extracted and distilled. The ester weighed 7.8 g (73%), bp 128–130° (0.5 mm). *Anal.* ($C_{11}H_{18}N_2O_4$) C, H; N: calcd, 11.6; found, 12.1.

N-Carbethoxy-2,2-dimethyl-4-cyano-3-pyrrolidone (VI).—A mixture of 9.9 g (0.045 mole) of the above cyano ester, 2.2 g (0.045 mole) of NaOMe, and C_6H_6 (50 ml) was refluxed for 3 hr. The resultant sodium salt was filtered off and dissolved in H_2O and the pyrrolidone was liberated by acidifying with 50 ml of 1 *N* HCl. The crystalline product, 6.5 g (82%), was recrystallized from EtOH; mp 127–129°. *Anal.* ($C_{10}H_{14}N_2O_3$) C, H, N.

Ethyl 3-Amino-2-ethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5-(4H)-carboxylate (2).—A solution containing 2.0 g (0.01 mole) of 1-carbethoxy-4-cyano-3-pyrrolidone monohydrate,[1] 1.33 g (0.01 mole) of ethyl hydrazine dihydrochloride, and 20 ml of EtOH was refluxed for 3 hr. The gum, which was obtained on evaporation of the mixture, was dissolved in a minimum amount of H_2O and rendered basic with 10 *N* NaOH, and the crude pyrazole which precipitated was collected and dried *in vacuo*.

Ethyl 3-Amino-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5-(4H)-carboxylate (3).—A mixture containing 8.0 g (0.04 mole) of 1-carbethoxy-4-cyano-3-pyrrolidone monohydrate,[1] 5.8 g (0.04 mole) of phenyl hydrazine hydrochloride, and 100 ml of EtOH was refluxed for 5 hr. The solvent was removed under diminished pressure and the residual gum was dissolved in 100 ml of 5 *N* HCl and decolorized with charcoal. Basifying the filtrate with 60 ml of 10 *N* NaOH, with caution, gave a solid which was recrystallized from 95% EtOH.

The other compounds listed in Table I were prepared similarly.

Ethyl 3-Acetamido-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4H)-carboxylate (21).—A mixture prepared by a gradual addition of 2.72 g (0.01 mole) of ethyl 3-amino-2-phenyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4H)-carboxylate (**3**) to 40 ml of Ac_2O was heated on a steam bath for 0.5 hr. The solution on evaporation gave a solid which was recrystallized twice from C_6H_6.

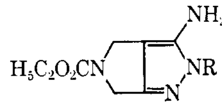
(2) (a) E. L. Anderson, J. E. Casey, L. C. Greene, J. Lafferty, and H. E. Reiff, *ibid.*, **7**, 259 (1964); (b) F. Hoffman-LaRoche and Co., A.G., British Patent 788,140 (1957).

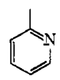
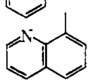
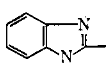
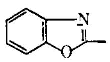
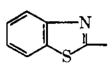
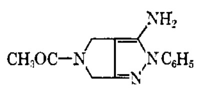
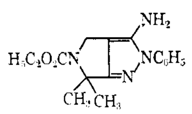
(3) T. Sheradsky and P. Southwick, *J. Org. Chem.*, **30**, 194 (1965).

(4) All melting points were determined in a capillary tube in a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE I

3-AMINO-2,6-DIHYDROPYRROLO[3,4-c]PYRAZOLES

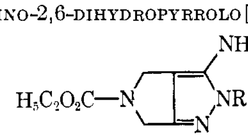


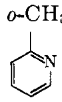
No.	R or structure	Mp, °C	Yield, %	Crystn solvent	Formula	Analyses
1	CH_3	119–125	8	Aq MeOH	$C_9H_{14}N_4O_2 \cdot 2H_2O$[a]	C, H, N
2	C_2H_5	156–157	45	C_6H_6	$C_{10}H_{16}N_4O_2$	C, H, N
3	C_6H_5	195–199	68	MeOH	$C_{14}H_{16}N_4O_2$	C, H, N
4	o-$OCH_3C_6H_4$	159–162	24	Aq EtOH	$C_{15}H_{18}N_4O_3$	C, H, N
5	m-ClC_6H_4	177–179	36	DMF	$C_{14}H_{15}ClN_4O_2$	C, H; N[d]
6	p-$CH_3C_6H_4$	176–179	94	EtOH	$C_{15}H_{18}N_4O_2$	C, H, N
7	p-FC_6H_4	163–166	29	Aq EtOH	$C_{14}H_{15}FN_4O_2$	C, H, N
8	o-CH_3-m-ClC_6H_3	184–192	46	Aq EtOH	$C_{15}H_{17}ClN_4O_2$	C, H, N
9	m,p-$Cl_2C_6H_3$	220–221	73	EtOH	$C_{14}H_{14}Cl_2N_4O_2$	C, H, N
10	$C_6H_5CH_2$	142–144	33	EtOH	$C_{15}H_{18}N_4O_2 \cdot 0.25H_2O$[b]	C, H, N
11	$C_6H_5(CH_2)_2$	187–195	34	MeOH–EtOH	$C_{16}H_{20}N_4O_2$	C, H, N
12		217–221	55	95% EtOH	$C_{13}H_{15}N_5O_2$	C, H, N
13		243–247	17	MeOH	$C_{17}H_{17}N_5O_2 \cdot 1.25H_2O$[c]	C, H, N
14		298 dec	25	DMF	$C_{15}H_{16}N_6O_2$	C, H, N
15		272–273	33	EtOH	$C_{15}H_{15}N_5O_3$	C, H, N
16		282–284	88	DMF	$C_{15}H_{15}N_5O_2S$	C, H, N
17		240–242	33	95% EtOH	$C_{13}H_{14}N_4O$	H, N; C[e]
18		166–169	26	Aq EtOH	$C_{16}H_{20}N_4O_2$	C, H, N

[a] *Anal.* $2H_2O$: calcd, 14.6; found, 13.0. [b] *Anal.* $0.25H_2O$: calcd, 1.55; found, 1.7. [c] *Anal.* $1.25H_2O$: calcd, 6.51; found, 7.29. [d] N: calcd, 18.3; found, 17.8. [e] C: calcd, 64.6; found, 64.1.

TABLE II

3-ACYLAMINO-2,6-DIHYDROPYRROLO[3,4-c]PYRAZOLES



No.	R	R_1	Mp, °C	Yield, %	Formula	Analyses
19	C_2H_5	CH_3	198–202	62	$C_{12}H_{18}N_4O_3$	C, H, N
20	C_2H_5	3,4,5-$(CH_3O)_3C_6H_2$	212–215	44	$C_{20}H_{26}N_4O_6$	C, H, N
21	C_6H_5	CH_3	178–183	48	$C_{16}H_{18}N_4O_3 \cdot 0.5H_2O$[a]	C, H, N
22	C_6H_5	CF_3	195–199	44	$C_{16}H_{15}FN_4O_3$	C, H, N
23	C_6H_5	3,4,5-$(CH_3O)_3C_6H_2$	216–217	42	$C_{24}H_{26}N_4O_6$	C, H, N
24	m-ClC_6H_4	CH_3	207–211	54	$C_{16}H_{17}ClN_4O_3$	C, H, N
25	o-CH_3-m-ClC_6H_3	CH_3	180–184	48	$C_{17}H_{19}ClN_4O_3$	C, H, N
26		CH_3	229–233	57	$C_{15}H_{17}N_5O_3$	C, H, N

[a] $0.5H_2O$: calcd, 2.78; found, 3.09.

The acetyl derivative was also obtained by acetylation of **3** with AcCl and pyridine in CH_2Cl_2.

Compounds **19**, **22**, and **24–26** in Table II were prepared similarly.

Ethyl 3-(Diacetylamido)-2-phenyl-2,6-dihydropyrrolo[3,4-c]-pyrazole-5(4H)-carboxylate (27).—A mixture containing 1.8 g of **3**, 25 ml of Ac_2O, and 1 ml of pyridine was heated (90°) for 1.5 hr. The excess anhydride was evaporated and the oil was triturated with cold H_2O whereupon the diacetyl derivative precipitated. It was recrystallized from 95% EtOH to give 1.5 g (73%) of a product, mp 143–145°. Tlc on silica gel using 5% MeOH in CH_2Cl_2 showed that the product was homogeneous. The ir spectrum in $CHCl_3$ showed no evidence of NH absorption in the 3000–3500-cm^{-1} region. In the nmr a single peak for six protons for the two acetyl groups was observed at τ 7.8. There was relatively no shift in the uv absorption for the diacetyl derivative [249 mμ (ϵ 12,800)] as compared to the unsubstituted amino derivative **3** [246 mμ (ϵ 13,850)]. *Anal.* ($C_{18}H_{20}N_4O_2$) C, H, N.

Ethyl 3-(3,4,5-Trimethoxybenzamido)-2-phenyl-2,6-dihydro-pyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (23).—A solution of 1.15 g (0.005 mole) of 3,4,5-trimethoxybenzoyl chloride in 5 ml of CH_2Cl_2 was added to another solution of 1.36 g (0.005 mole) of

3, 0.4 ml of pyridine, and 20 ml of CH_2Cl_2. The mixture was stirred for 2.5 hr and evaporated to a solid, which was recrystallized from EtOH to give the desired product.

Compound **20** in Table II was prepared similarly.

Acknowledgment.—The microanalyses were performed by Mr. L. M. Brancone and his associates. The spectral data were obtained from Mr. W. Fulmor and his associates.

Pteridines. XI.[1,2] Pteridines Related to the Diuretic, 2,4-Diamino-6,7-dimethylpteridine

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Significant diuretic activity of a pteridine was first observed in our laboratory with 2,4-diamino-6,7-dimethylpteridine. In this note we will describe some work carried out in order to explore the structure–activity relationships of compounds related to this lead.

The Isay reaction,[3] which is the condensation of a 4,5-diaminopyrimidine with a 1,2-dicarbonyl compound to form a pteridine, was used to prepare the compounds in Table I. When unsymmetrical dicarbonyl compounds are used it is often possible to direct the course of the synthesis by altering the pH of the reaction medium. The 5-amino group usually is the more reactive of the amino groups and it will react with the most reactive carbonyl group. However, at low pH it also protonates first, and thus allows the less basic 4-amino group to react with the most reactive carbonyl group.[4] Reaction of 4,5,6-triamino-2-phenylpyrimidine and pyruvaldehyde in an acetic acid–potassium acetate buffer gave 4-amino-7-methyl-2-phenylpteridine.[5] Attempts to obtain the 6-methyl isomer by the use of mineral acid failed to alter the course of the reaction. However, the 6-methyl isomer was obtained by allowing pyruvaldehyde to react with 2 moles of hydrazine before addition of the pyrimidine.[6]

In order to extend the Isay reaction to the preparation of a 6,7,8-trialkylpteridine, 2,5-diamino-4,6-bismethylaminopyrimidine was treated with 2,3-butanedione. This gave 2-amino-4-methylamino-6,7,8-trimethylpteridinium chloride (I), the cation of which can be represented by several resonance forms.

(1) Previous paper in this series: H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *J. Med. Chem.*, **11**, 568 (1968).

(2) A portion of this work was reported at the 3rd International Pteridine Symposium, Stuttgart, Germany, 1962. See J. Weinstock and V. D. Wiebelhaus in "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press, Oxford, 1964, p 37.

(3) See A. Albert, *Quart. Rev.* (London), **6**, 197 (1952), and W. Pfleiderer, *Angew. Chem. Intern. Ed. Engl.*, **3**, 114 (1964), for brief reviews of this reaction.

(4) (a) G. B. Elion, G. H. Hitchings, and P. B. Russell, *J. Am. Chem. Soc.*, **72**, 78 (1950); (b) W. Pfleiderer and R. Lohrmann, *Ber.*, **94**, 2708 (1961).

(5) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, **28**, 1197 (1963).

(6) H. S. Forrest and J. Walker, *J. Chem. Soc.*, 2077 (1949).

TABLE I

PTERIDINES PREPARED BY THE ISAY REACTION

Pteridine	Dicarbonyl reactant	Reaction conditions: Solvent	Reaction conditions: Time, hr	Temp, °C	Yield, %	Recrystn solvent	Mp, °C	R_f (system)	Formula[e]
4-Amino-2-phenyl	Glyoxal bisulfite	H_2O	1	100	45	EtOH	239	0.89 (4)	$C_{12}H_9N_5$
4-Amino-6,7-dimethyl-2-phenyl	Biacetyl	H_2O, pH 5.5	0.5	80	52	DMF–H_2O	308–310	0.71 (5)	$C_{14}H_{13}N_5$
4-Amino-2,6,7-triphenyl	Benzil	EtOH	2	80	70	DMF–H_2O	250–251		$C_{24}H_{17}N_5$
4-Amino-2,6,7-trimethyl	Biacetyl	H_2O, pH 5	1	60	52	H_2O	249–250	0.83 (6)	$C_9H_{11}N_5$[g]
4-Amino-2-phenylcyclopenta[g]	1,2-Cyclopentanedione	EtOH	1	80		c	295 dec	0.82 (3)	$C_{15}H_{13}N_5$
4-Amino-2-anilino-6,7-dimethyl	Biacetyl	EtOH–H_2O, pH 5.5	0.75	25	54	MeOH	258–258.5	0.89 (4)	$C_{14}H_{14}N_6$
2-Amino-4,6,7-trimethyl	Biacetyl	H_2O, pH 5.5	0.33	100	56	EtOH	>300	a	$C_9H_{11}N_5$
2-Amino-4-carbamyl-6,7-dimethyl	Biacetyl	EtOH–H_2O, pH 5.5	3	25		c	>330		$C_9H_{10}N_6O$[f]
2,4-Diamino-6(7)-ethyl-7(6)-methyl[d]	2,3-Pentanedione	EtOH–H_2O	0.2 1	100 25	67	Dil HCl	>300	0.63 (1)	$C_9H_{12}N_6 \cdot HCl \cdot 0.5H_2O$
2,4-Diamino-cyclopenta[g][b]	1,2-Cyclopentanedione	EtOH–H_2O	0.7	100	35	H_2O, pH 2.5	>250		$C_9H_{10}N_6 \cdot HCl \cdot H_2O$
4-Amino-7-hydroxy-6-methyl-2-phenyl	Methyl pyruvate	EtOH	1	100	47	DMF–H_2O	282–284	0.64 (2)	$C_{13}H_{11}N_5O$

[a] $\lambda_{max}^{1\ N\ NaOH}$ 364 mμ (log ε 3.87), 260 (sh) (3.87); $\lambda_{max}^{4.5\%\ HCOOH}$ 352 mμ (log ε 4.08), 364 (sh) (4.00). [b] Hydrochloride hydrate. [c] Dissolve in dilute HCl, precipitate with NH_4OH. [d] Hydrochloride hemihydrate. [e] All compounds were analyzed for C, H, N except as noted. [f] C, H, analysis only. [g] N: calcd, 37.02; found, 37.69.