[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

2-Alkyl(aryl)- and 2,7-Dimethyl-4-substituted Aminopyrrolo[2,3-*d*]pyrimidines

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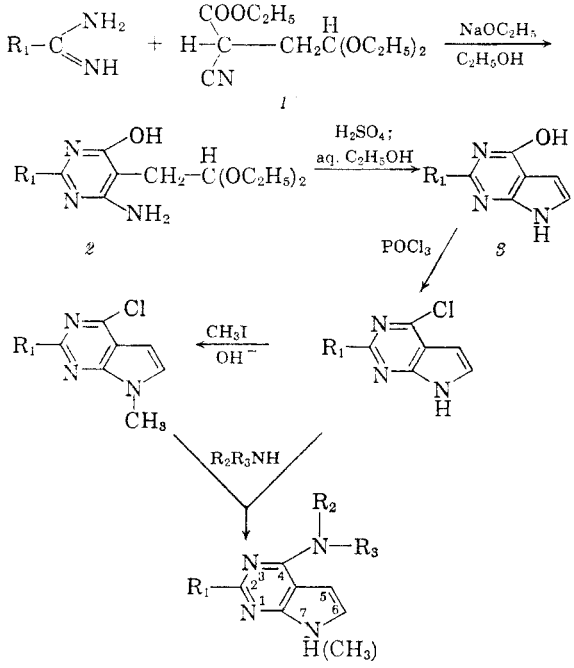
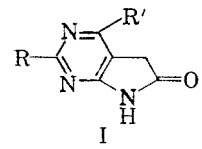
Amidines condense with ethyl a-cyano-γ,γ-diethoxybutyrate yielding pyrimidine derivatives which are further cyclized to 4-hydroxypyrrolo[2,3-d]pyrimidines. The various 4-chloropyrrolopyrimidines resulting from treatment of the hydroxy compounds with phosphoryl chloride react readily with amines yielding 4-substituted amino derivatives having pharmacological activity.

The pyrrolo[2,3-*d*]pyrimidine bicycle bears structural analogy both to purine and indole and as such might be expected to have pharmacological interest and perhaps clinical value. Therefore we have prepared a variety of 2-alkyl- and 2,7-dimethyl-4-substituted amino derivatives, for pharmacological testing, through the synthetic route shown below:



The ethyl α-cyano-γ,γ-diethoxybutyrate (1) and 4-chloropyrrolo[2,3-*d*]pyrimidine used as intermediates in this investigation were first reported by West, Ledig, and Hitchings.[1] Previous to their publication, the only pyrrolo[2,3-*d*]pyrimidines reported were three derivatives of 5,6-dihydro-6-oxopyrrolo[2,3-*d*]pyrimidine (I) (where R = R′ = OH[2]; R = CH_3, R′ = OH[3]; and R = CH_3, R′ = H[4]) prepared by cyclization of 4-aminopyrimidylacetic acid derivatives.



I

The amidines employed were prepared by the method of Pinner[5] and included acetamidine, propamidine, *n*-butyramidine, and benzamidine. These amidines reacted with ethyl α-cyano-γ,γ-diethoxybutyrate under alkaline conditions to yield 2-alkyl(aryl)-4-hydroxy-6-amino-5-(β,β-diethoxy)ethyl pyrimidines (2) in good yields (Table I). These 5-"acetalyl" pyrimidines cyclized readily under acidic conditions (presumably through the aldehyde) yielding those 4-hydroxypyrrol[2,3-*d*]pyrimidines (3) indicated in Table II. Under conventional phosphorus oxychloride treatment, the 4-hydroxy compounds yielded the 4-chloro intermediates also presented in Table II.

Two of the chloro compounds (R_1 = H and CH_3) yielded 7-methyl derivatives when treated with methyl iodide under mildly alkaline conditions. However the 4-hydroxy compounds upon alkaline methylation (one equivalence of methyl iodide) yielded the *3-methyl* compounds which may be further methylated at the 7- position. The relative ease with which *N*-7 methylation occurs in the 4-chloropyrrolopyrimidines is in contrast to the more strongly basic conditions required for *N*-methylation of pyrroles.[6] The 4-chloropyrrolopyrimidines are rather soluble in 10% sodium hydroxide and may be precipitated quantitatively by acetic acid neutralization. The considerably lower melting points of the 7-methyl relative to the 7-hydro compounds also suggest that the pyrrole-imino group in this bicycle is rather acidic. This may be a reflection of strong hydrogen-bonding between a rather strongly acid imino group and the pyrimidine nitrogens. It appears therefore that the pyrimidine ring fusion with pyrrole (at least this [2,3-*d*] fusion) enhances the acidity of the pyrrole moiety. This acidity may be accounted for by resonance considerations. The anion formed should be stabilized by delocalization of the negative charge over the pyrimidine carbons as well as the β-pyrrole carbon

(1) R. A. West, K. Ledig, and G. H. Hitchings, Wellcome Foundation Ltd., British Patent 812,366, April 22, 1959; *Chem. Abstr.*, **54**, 592i, 1960.

(2) T. B. Johnson and E. F. Kohmann, *Am. Chem. J.*, 49, 186 (1913).

(3) Z. Földi, G. v. Fodor, I. Demién, H. Szekeres, and I. Halmos, *Ber.*, **75**, 755 (1942).

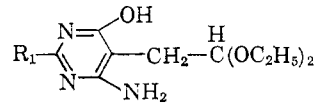
(4) P. Nesbitt and P. Sykes, *J. Chem. Soc.*, 3057 (1954).

(5) A. Pinner, *Ber.*, **16**, 1654 (1883); **17**, 178 (1884).

(6) K. Hess and F. Wissing, *Ber.*, **47**, 1422 (1914).

TABLE I

4-HYDROXY-6-AMINO-5-(β,β-DIETHOXY)ETHYLPYRIMIDINES

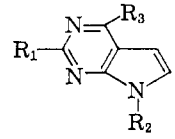


R_1	Yield, %	M.P.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	89	249–250	$C_{11}H_{19}N_3O_3$	54.7	54.4	7.8	7.5	17.4	17.5
C_2H_5	93	233–235	$C_{12}H_{21}N_3O_3$	56.5	56.6	8.2	7.8	16.5	16.6
n-C_3H_7	77	207–209	$C_{13}H_{23}N_3O_3$	58.1	58.1	8.6	8.6	15.6	15.7
C_6H_5	71	174–176	$C_{16}H_{21}N_3O_3$	63.4	63.7	7.0	7.3	13.9	13.9

[a] From heptane or benzene-heptane.

TABLE II

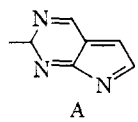
4-HYDROXY AND 4-CHLOROPYRROLO[2,3-*d*]PYRIMIDINES



R_1	R_2	R_3	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	H	OH	76	[a]	$C_7H_7N_3O$	56.2	55.9	4.5	4.7	28.2	28.1
C_2H_5	H	OH	85	[a]	$C_8H_9N_3O$	58.9	59.0	5.5	5.4	25.7	25.4
n-C_3H_7	H	OH	85	[a]	$C_9H_{11}N_3O$	61.0	60.8	6.3	5.8	23.4	23.4
C_6H_5	H	OH	93	[a]	$C_{12}H_9N_3O$	68.2	68.3	4.2	4.1	19.8	19.6
H	CH_3	Cl[b,c]	75	130	$C_7H_6N_3Cl$	—	—	—	—	25.1	25.2
CH_3	H	Cl[c]	83	205–207	$C_7H_6N_3Cl$	50.0	49.9	3.6	3.6	25.1	24.9
CH_3	CH_3	Cl[c]	70	121–122	$C_8H_8N_3Cl$	52.9	52.8	4.4	4.2	23.1	23.1
C_2H_5	H	Cl[c]	72	125–127	$C_8H_8N_3Cl$	52.9	52.8	4.4	4.1	23.1	23.3
n-C_3H_7	H	Cl[c]	82	129–130	$C_9H_{10}N_3Cl$	54.3	54.3	4.8	5.1	21.5	21.5
C_6H_5	H	Cl[c]	80	225–226	$C_{12}H_8N_3Cl$	62.6	62.4	3.5	3.6	18.2	17.9

[a] No melting or dec. (to 320°). [b] Chlorine calculated for $C_7N_6N_3Cl$: 21.2. Found: 21.3. [c] Recrystallized from heptane or benzene-heptane.

and the pyrrole nitrogen as indicated in one such contribution below (A):



A

The 4-chloro compounds were treated with a variety of amines as well as ammonia giving 4-amino or substituted amino derivatives in excellent yields. The ammonia displacement reactions were carried out at elevated temperatures in bombs using considerable excesses of concentrated ammonium hydroxide. Two sets of conditions were employed in the reaction with amines depending on the presumed nucleophilicity of the particular amine. Thus monoalkyl-, dialkyl, aralkyl-, and alkyl-heterocyclic amines gave good yields of the corresponding derivatives when refluxed for a short time in water using potassium carbonate as the proton acceptor (method A). The 7-methylchloro compounds react readily with amines under the same conditions. Weaker nucleophiles, as aniline and substituted anilines, failed to react under the conditions of method A but gave excellent yields of the desired derivatives using 3 equivalents of the arylamine in dimethylformamide at 145° (method B).

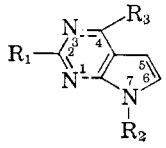
All amines reacted by method A or B regardless of the nature of the substituent at the 2- position. It is possible that the 2-phenyl substituent may particularly affect the displaceability of the 4-chlorine. This will be further investigated; however, under the conditions herein employed no difference was noted.

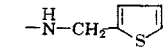
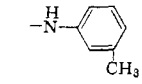
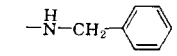
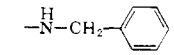
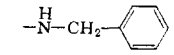
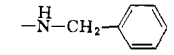
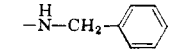
The 4-substituted amino derivatives form water-soluble, nonhygroscopic monohydrochlorides (despite a considerable excess of hydrogen chloride used). One of these salts is included in Table III which presents specific examples of the types of amine derivatives prepared in this investigation.

The 5-"acetalyl" and the various substituted pyrrolopyrimidines have characteristic ultraviolet spectra. Examples of spectral characteristics based on general types of derivatives are indicated in Table IV.

TABLE III

4-SUBSTITUTED AMINOPYRROLO[2,3-*d*]PYRIMIDINES



R_1	R_2	R_3	M.P.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	CH_3	$-NH-C_2H_5$	157–158	88	61.2	61.1	6.8	6.9	—	—
CH_3	H	$-NH-C_2H_5$	189–190[a]	89	61.2	61.2	6.8	6.5	31.8	31.8
CH_3	H	$-N(CH_3)-C_3H_7$	124–125[a]	93	64.7	64.5	7.9	7.6	27.4	27.5
CH_3	H		214–215[b]	91	59.0	59.2	4.9	5.1	22.9	23.1
CH_3	H		248[a]	98[c]	70.5	70.2	5.9	5.9	23.5	23.6
CH_3	CH_3		147–148[b]	90	71.6	71.6	6.3	6.1	22.2	21.9
CH_3	H		223–224[b,d]	93[d]	61.1	61.2	5.4	5.2	20.3	20.0
C_2H_5	H		183[b]	90	71.6	71.3	6.3	6.7	—	—
n-C_3H_7	H		170–171[b]	92	72.2	72.2	6.8	6.9	—	—
C_6H_5	H		162–164[b]	92	76.0	75.8	5.4	5.4	—	—

[a] Recrystallized from benzene. [b] Recrystallized from benzene-heptane. [c] Prepared by method B. [d] Isolated as, and analyzed for, the monohydrochloride of the base ($C_{14}H_{14}N_4 \cdot HCl$). Recrystallized from methanol ether.

TABLE IV

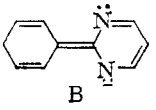
ULTRAVIOLET SPECTRAL DATA ON PYRROLO[2,3-*d*]PYRIMIDINES AND PRECURSORS

4-Hydroxy-6-amino-5-(β,β-diethoxy)ethyl-pyrimidines	*p*H 1.0 λ_{max} (mμ)	*p*H 1.0 ε(10^3)	*p*H 11.0 λ_{max} (mμ)	*p*H 11.0 ε(10^3)
2-Methyl	263	10.70	263	8.82
2-Phenyl	307	13.50	282	7.82
Pyrrolo[2,3-*d*]pyrimidines				
2-Methyl-4-chloro	277	4.3	285	4.18
2-Phenyl-4-chloro	253	32.9	253	13.4
	302	32.9	302	13.4
2-Methyl-4-hydroxy	265	9.75	265	10.85
2-Phenyl-4-hydroxy	307	12.55	305	11.90
2-Methyl-4-*n*-propylamino	277	14.10	277	15.20
2,7-Dimethyl-4-*n*-propyl-amino	277	13.50	277	13.80
2-Methyl-4-methyl-*n*-propylamino	288	13.50	285	16.40
2-Methyl-4-anilino	293	13.20	298	18.60
2-Methyl-4-benzylamino	282	14.70	278	16.80
2-Phenyl-4-ethylamino	235	26.05	244	11.40
	287	14.00	313	11.40

Several features of these compiled spectral data are noteworthy. The nature of the 2-alkyl, or the presence of a 7-methyl group, has little effect on the spectra. However, a 2-phenyl group exerts a pronounced bathochromic and hyperchromic effect over a 2-alkyl group. This may indicate an extension of conjugation ($\pi - \pi$ effect), therefore resonance interaction between the benzene and pyrimidine rings.[7] If this be true, then these rings are coplanar, or nearly so. Spectral characteristics of the mono-alkylamino versus the dialkylamino derivatives indicates a greater auxochromic effect of the latter. The effect, on the spectrum, of a 4-anilino substituent is particularly striking. Since a defined shift occurs in going from acid to alkaline solution and since a pronounced hyperchromic effect is noted under alkaline conditions, considerable acidity of the anilino moiety may be indicated.

Some of these substituted amino compounds have pronounced pharmacological effects in test animals including anticonvulsant, muscle-relaxant, hypotensive, and "tranquilizer" activities. Details of

(7) This interaction is possible through such charge-separated structures as the example given (B).



B

this pharmacology will be presented soon in an appropriate journal.

The experimental details given below serve to exemplify the general methods employed throughout the reaction scheme.

EXPERIMENTAL[8]

2-Methyl-4-hydroxy-5-(β,β-diethoxy)ethylpyrimidine. Acetamidine hydrochloride (0.05 mole; 4.7 g.) was added to a 75-ml. solution of 0.1 mole sodium ethoxide. After 0.5 hr. of stirring at room temperature, the resultant sodium chloride was removed by filtration. The filtrate was added to ethyl α-cyano-γ,γ-diethoxybutyrate (0.05 mole; 11.5 g.) and the reaction solution was refluxed for 5 hr. Three fourths of the solvent was driven off in a dish over steam and the remaining slurry was dissolved in 80 ml. of ice water. The desired pyrimidine was precipitated at *p*H 7.0 in a pure state by the addition of acetic acid. After chilling overnight, filtering, and vacuum desiccating (Drierite), 10.8 g. of the white product was obtained representing an 89% yield. The pyrimidine decomposed at 253–260° to a dark oil.

2-Methyl-4-hydroxypyrrolo[2,3-d]pyrimidine. The above pyrimidine (4.5 g.; 0.187 mole) was added to a solution of 2 ml. of concd. sulfuric acid in 110 ml. of 95% ethanol and refluxed for 2 hr. Upon addition of an equal volume of water and by chilling overnight, 2.1 g. of the white amorphous product was obtained. The pyrrolopyrimidine neither melted nor decomposed (below 300°) and was sufficiently pure for analysis.

2-Methyl-4-chloropyrrolo[2,3-d]pyrimidine. A suspension of 25 g. (0.168 mole) of the above hydroxypyrrolopyrimidine in 175 ml. of phosphorus oxychloride was refluxed for 45 min. after solution was attained. The excess phosphorus oxychloride was removed under reduced pressure using a 55–60° water bath. The residual viscous oil was dropped slowly into 1 l. of ice water mixture with vigorous stirring. The resultant chloro compound was extracted from the suspension using three 275-ml. portions of ether. The combined ethereal extracts were dried over anhydrous sodium sulfate. When taken to dryness, 23.2 g. (83% yield) of slightly yellow product remained which was sufficiently pure to be used as an intermediate.

2,7-Dimethyl-4-chloropyrrolo[2,3-d]pyrimidine. Five grams (0.03 mole) of 2-methyl-4-chloropyrrolopyrimidine was added to 1.9 g. of sodium methoxide (0.035 mole) in 50 ml. of absolute ethanol at 5–10°. To this was added 0.0388 mole (2.4 ml.) of methyl iodide and the reaction was allowed to proceed in a sealed flask for 2 days with occasional shaking, in a 40–45° bath. The solvent was allowed to evaporate in a dish at room temperature. The remaining solid was triturated with 30 ml. of cold water, filtered off and vacuum-desiccated, yielding 4.0 g. (70% yield) of the desired product. This chloro compound may be used in this state as an intermediate (crude m.p. 119–120°).

Reactions of amines with 4-chloropyrrolopyrimidines. Method A. 2-Phenyl-4-benzylaminopyrrolo[2,3-d]pyrimidine. One gram of 2-phenyl-4-chloropyrrolo[2,3-*d*]pyrimidine (0.0043 mole) was added to 35 ml. of water containing 0.9 g. (0.0065 mole) of potassium carbonate and 1.0 g. (0.0093 mole) of benzylamine. The mixture was refluxed rapidly for 3 hr. After cooling overnight, 1.2 g. of the crude 2-phenyl-4-benzylamino derivative was obtained (92% yield). The product recrystallized from benzene-heptane melted at 162–164°.

Method B. 2-Methyl-4-(2'-methoxy)anilinopyrrolo[2,3-d]pyrimidine. Into 17 ml. of dimethylformamide was added 2.06 g. (0.123 mole) of 2-methyl-4-chloropyrrolopyrimidine and 6.04 g. (0.049 mole) of *o*-anisidine. The reaction mixture was refluxed for 1.5 hr. An equal volume of water was added and the mixture was chilled overnight. After filtration and vacuum dessication, 3.1 g. (99% yield) of tan product was obtained. Upon recrystallization from benzene-heptane, the colorless product melted at 255–256° with evidence of decomposition.

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.1; H, 5.5. Found: C, 66.3; H, 5.7.

Reaction with ammonia. 2-Methyl-4-aminopyrrolo[2,3-d]pyrimidine. Two grams (0.0123 mole) of 2-methyl-4-chloropyrrolopyrimidine was suspended in 40 ml. of concd. aqueous ammonia and heated in a bomb at 145° for 4.5 hr. After driving off the excess ammonia on the steam bath the pure 4-amino compound was filtered off yielding 1.3 g. of product which decomposed at 305–307°.

Anal. Calcd. for $C_7H_8N_4$: N, 37.8. Found: N, 37.6.

Acknowledgment. We wish to thank Dr. Samuel Blackman and Mr. Charles Marr for their microanalytical contribution.

TUCKAHOE, N. Y.

(8) All melting points uncorrected on a Köfler hot plate.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Indenoquinolines. I. Derivatives of 11*H*-Indeno[1,2-*b*]quinoline

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11*H*-Indeno[1,2-*b*]quinolin-11-one (III) adds organometallic reagents in a 1,2-fashion to produce tertiary carbinols. Hydrogenation of III by the Meerwein-Ponndorf method produced only the secondary alcohol while catalytic hydrogenation gave some hydrogen addition to the heterocyclic ring. 11*H*-Indeno[1,2-*b*]quinoline (II) reacted with *N*-bromosuccinimide to produce the 11-bromo derivative which was in turn converted to 11-substituted amino derivatives. The *N*-oxide of II was prepared, which was converted with phosphorus oxychloride to the 10-chloro derivative. These compounds have been synthesized for biological study by others.

As a logical extension of current investigations of some new chemistry of polycyclic nitrogen heterocyclic compounds, we have now extended our studies to include derivatives of the 11*H*-indeno-[1,2-*b*]quinolines (C) which are related structurally to the benz[*c*]acridines (A)[2] and benz[*b*]acridines

(1) U. S. Public Health fellow, 1958–1960, National Institute of Allergy and Infectious Diseases.

(2)(a) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, 23, 789 (1958); (b) N. H. Cromwell and V. L. Bell, *J. Org. Chem.*, 24, 1077 (1959).