Anal. Calcd. for $(C_{22}H_{24}N_2O_3)_2 \cdot H_2SO_4$: C, 63.9; H, 6.09. Found: C, 63.5; H, 6.26.

β-Colubrine, recovered from the purified sulfate, was crystallized from ethyl acetate, from which it separated slowly as large, rhombic tablets, m.p. 219.5–220.5°, $[\alpha]^{20}D$ −104° (*c*, 1.1) (reported −108°, 80% alcohol[8]).

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.6; H, 6.65. Found: C, 72.3; H, 6.86.

β-Colubridine.—β-Colubrine (1.0 g.) was reduced with lithium aluminum hydride, according to the procedure for dehydrobrucidine, to β-colubridine (80% yield of crude product). Purified from methanol, it consisted of faintly yellow aciculae containing methanol of crystallization. It sublimed about 135° (1 mm.); m.p. 170–171.5°, $[\alpha]^{21}D$ −41° (*c*, 0.9).

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 7.48; CH_3O, 8.96. Found: C, 75.3; H, 7.69; CH_3O, 8.92.

β-Colubridine methiodide was prepared in and purified from methanol using stoichiometric amounts of base and methyl iodide: slender, faintly yellow prisms, m.p. 309° *in vacuo*.

Anal. Calcd. for $C_{23}H_{29}IN_2O_2$: C, 56.10; H, 5.94; I, 25.8. Found: C, 56.24; H, 6.19; I, 25.6.

Diketonucidine (a) from α-Colubridine.[16]—α-Colubridine (0.59 g.) was dissolved in water (8.7 ml.) and sulfuric acid (0.70 ml., sp. gr. 1.84), and the cold mixture treated with two-thirds of a solution of chromium trioxide (0.77 g.) in water (3.1 ml.). The dark reddish-purple salt which separated became yellowish and gradually dissolved as the mixture was warmed. After heating 35 minutes at 65–70° with occasional stirring the remainder of the aqueous chromium trioxide was added slowly, and heating maintained an additional 30 minutes. The hot mixture was made strongly ammoniacal and filtered from precipitated chromium hydroxide. The residue was leached once with hot water. The red filtrates were extracted with chloroform (4 × 50 ml.). The reddish-brown residue recovered from the extracts was converted to the perchlorate salt and decolorized with charcoal. Recovered from the perchlorate, the base was crystallized once from alcohol: 50 mg. of stout tan prisms, m.p. 268–271°; mixed m.p. with authentic diketonucidine, 267.5–270°.

(b) From β-Colubridine.—In similar manner β-colubridine (0.34 g.) was converted to diketonucidine: 30 mg., m.p. 263–266°; methiodide, m.p. 315° *in vacuo;* $[\alpha]^{20}D$ +82° (*c*, 0.7).

Color Reactions of α- and β-Colubridine.[9]—When ferric chloride was added to α-colubridine in 0.1 *N* hydrochloric acid, a crimson coloration was produced which changed immediately to orange and then to yellow. Under the same conditions β-colubridine gave an orange-red color. When a trace of potassium dichromate was added to a solution of α-colubridine in dilute sulfuric acid, the solution acquired a purplish-red color which slowly underwent a transition to green. β-Colubridine gave a red color soon changing to yellowish-brown under these conditions.

(16) *Cf.* H. Leuchs and H. S. Overberg, *Ber.*, **64**, 1009 (1931).

BETHESDA 14, MD. RECEIVED NOVEMBER 24, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Arylaminoheterocycles. VI. Trisubstituted Pyrimidines

BY MARIE-JO LANGERMAN AND C. K. BANKS[1]

The preparation and properties of a number of 2,4,6-trisubstituted pyrimidines are reported.

As an extension of a previous investigation concerning 2-amino-4-arylaminopyrimidines[2] it was considered of interest to prepare some trisubstituted pyrimidines which would be isosteric with several groups of symetrical triazines of pharmaceutical interest.[3,4,5] For this purpose 2,4,6-trichloropyrimidine was chosen as the starting material. Barbituric acid has been converted to the trichloropyrimidine[6] using phosphorus oxychloride in sealed tubes. The use of dimethylaniline in catalytic amounts obviated the necessity of pressure and gave excellent yields of the desired compound.[7] Since the reaction of ammonia and other amines with 2,4,6-trichloropyrimidine does not lead to unique compounds, it was convenient to convert certain aminohydroxypyrimidines of known structure to the corresponding aminochloropyrimidines by the same method. Both 2-amino-4,6-dihydroxypyrimidine and 2,4-diamino-6-hydroxypyrimidine chlorinated without difficulty but 4-amino-2,6-dihydroxypyrimidine failed to yield a dichloro compound under similar conditions. 4-Amino-2,6-dichloropyrimidine was obtained by separating it from 2-amino-4,6-dichloropyrimidine in the mixture obtained by amination of 2,4,6-trichloropyrimidine with ammonia.[8]

Dimethylamine, diethylamine and morpholine reacted with the aminodichloropyrimidines to yield chlorodiaminopyrimidines. 2-Amino-4-diethylamino-6-chloropyrimidine has been prepared previously by the reaction of diethylamine and 2-amino-4,6-dichloropyrimidine under pressure at 120–130° or at reflux temperature with copper–bronze as a catalyst.[9] It was found that dimethylamine and morpholine required no catalyst for the reaction. Arylamines reacted with the third halogen in slightly acid suspension under conditions established previously for this type of reaction.[2] While alkylamines normally do not replace the third halogen below 200°,[8,9] morpholine behaved similarly to the arylamines. This behavior of morpholine has been noted previously in reactions with 2-amino-4-chloropyrimidine and 2,4-diamino-6-chlorotriazine.[2,5]

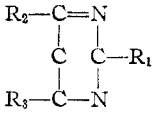
Several alkoxydiaminopyrimidines were prepared for antihistaminic studies but, unlike the isosteric triazines,[4] they were inactive.

Comparison of the reactivities of the halogens of 2,4,6-trichloropyrimidine with the halogens of cyanuric chloride (2,4,6-trichloro-*s*-triazine) indicates that in general the halogens of the triazine are more reactive than those of the pyrimidine.

(1) Metal and Thermit Corporation, Rahway, N. J.
(2) Banks, THIS JOURNAL, **66**, 1131 (1944).
(3) Controulis and Banks, *ibid.*, **67**, 1946 (1945).
(4) Pearlman, Mitulski and Banks, *ibid.*, **71**, 3248 (1949).
(5) Walker, L'Italien, Pearlman and Banks, *J. Amer. Phar. Assn.*, **39**, 393 (1950).
(6) Gabriel, *Ber.*, **33**, 3666 (1900).
(7) Baddeley and Topham, *J. Chem. Soc.*, 678 (1944).
(8) Büttner, *Ber.*, **36**, 2228 (1903).
(9) Braker, Pribyl, Sheehan, Spitzmiller and Lott, THIS JOURNAL, **69**, 3077 (1947).

TABLE I

2,4,6-TRISUBSTITUTED PYRIMIDINES



R_1	R_2	R_3	Method of prepn.	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
NH_2	$N(CH_3)_2$	Cl	II	162–165	89	41.75	41.86	5.25	5.29
NH_2	NC_4H_8O[a]	Cl	II	212–213	67	44.74	44.79	5.15	4.96
NH_2	NH_2	NHC_6H_5	III	174–175	30	59.69	59.27	5.51	5.32
NH_2	$N(CH_3)_2$	$NHC_6H_4Cl(p)$	III	169–171	40	54.63	54.83	5.34	5.38
NH_2	$N(CH_3)_2$	OC_2H_5	IV	145–147	45	52.79	52.82	7.74	7.53
NH_2	$N(CH_3)_2$	OC_4H_9	IV	90–92	50	57.61	57.54	8.62	8.67
NH_2	NC_4H_8O[a]	OC_2H_5	IV	115–116	44	53.55	53.36	7.19	6.99
$N(CH_3)_2$	$N(CH_3)_2$	Cl	II	45–46	80	47.87	47.92	6.52	6.30
$N(CH_3)_2$	$N(CH_3)_2$	$NHC_6H_4Cl(p)$	III	206–208	25	57.58	57.45	6.23	5.92
$N(CH_3)_2$	$N(CH_3)_2$	$NHC_6H_4CH_3(p)$	III	163–164[b]	36	66.40	66.44	7.81	7.88
$N(CH_3)_2$	NHC_6H_5	NHC_6H_5	III	168–170	8	70.49	70.70	6.32	6.12
$N(CH_3)_2$	$NHC_6H_4CH_3(p)$	$NHC_6H_4CH_3(p)$	III	165–167[b]	12	72.04	71.79	6.95	6.67
$N(CH_3)_2$	NH_2	Cl	II	142–143	50	41.75	41.75	5.25	5.17
NC_4H_8O[a]	NH_2	NC_4H_8O[a]	II	152–154	46	54.32	54.32	7.22	6.88

[a] Morpholino. [b] Mixed m. p. of the two compounds 147°.

Ammonia replaces one chlorine atom of cyanuric chloride below 0°[6] and two chlorine atoms at room temperature,[10] only one chlorine atom is removed from 2,4,6-trichloropyrimidine from room temperature to the reflux temperature of concd. ammonia solution.[8] Similarly, alkylamines react with 2-amino-4,6-dichloro-*s*-triazine at room temperature or slightly higher to replace a chlorine atom[10] while reflux temperatures are necessary to replace a chlorine atom in 2-amino-4,6-dichloropyrimidine. Elevated temperatures were usually necessary to replace the last chlorine in both compounds but it is significant that dimethylamine would convert cyanuric chloride to tris-dimethylaminotriazine at 40°[10] whereas the reflux temperature of a benzene solution of dimethylamine caused the substitution of only two chlorine atoms of 2,4,6-trichloropyrimidine. The general order of reactivity can be expressed 1st triazine > 1st pyrimidine ≳ 2nd triazine > 3rd triazine > 2nd pyrimidine > 3rd pyrimidine. It is apparent that the —N= group of the *s*-triazine ring which replaces the —CH= at the 5-position in pyrimidines confers enhanced reactivity on the triazine ring.

Experimental

I. Chlorination of Hydroxypyrimidines.—2,4-Diamino-6-hydroxypyrimidine (0.2 mole) was refluxed with 150 ml. of phosphorus oxychloride and 1 ml. of dimethylaniline for eight hours. The pyrimidine dissolved slowly. The excess phosphorus oxychloride was removed under reduced pressure, leaving a viscous oil which was added to 200 ml. of ice and water. After the decomposition of the residual oxychloride had occurred, the solution was neutralized with 10 *N* sodium hydroxide with external cooling. The precipitate was filtered off and dried *in vacuo* at 50°. The melting point of the crude material was 198–200°.[11] The yield was poor. Barbituric acid was converted to 2,4,6-trichloropyrimidine and 2-amino-4,6-dihydroxypyrimidine to 2-amino-4,6-dichloropyrimidine in better than 80% yield by the same procedure.

II. Reaction of Amines with Dichloropyrimidines.—2-Amino-4,6-dichloropyrimidine (0.1 mole) was refluxed with more than two equivalents of dimethylamine in benzene for 54 hours. The solvent was removed and the residue recrystallized from an alcohol–water mixture. In some instances carbon tetrachloride was a convenient solvent. Copper–bronze catalyst was used with diethylamine.[8] Only one chlorine atom was replaced except in the reaction of 4-amino-2,6-dichloropyrimidine and morpholine, in which both chlorine atoms were replaced.

III. Reaction of Arylamines with Diaminochloropyrimidines.—One equivalent of the diaminochloropyrimidine was refluxed with 2.5 equivalents of the arylamine in 200 ml. of water, adjusting the solution with hydrochloric acid to *p*H 5–6. The pyrimidines dissolved slowly and the reaction required up to 96 hours. If starting materials separated on cooling, they were removed and the filtrate neutralized with ammonium hydroxide or sodium carbonate. The excess arylamine was extracted with chloroform or removed by steam distillation and the products recrystallized from water or dilute ethanol.

2,4-Bis-dimethylamino-6-chloropyrimidine gave an additional unexpected product with aniline and *p*-toluidine. With aniline, 12% of 2(or 4)-dimethylamino-4(or 2),6-dianilinopyrimidine was isolated while *p*-toluidine gave 8% of a corresponding dimethylaminoditoluidinopyrimidine. While such compounds could be produced by any 2-dimethylamino-4,6-dichloropyrimidine present as an impurity, the analytical values for the starting material would indicate that the impurity should not be of the order of 10%. The only other alternative would be that the arylamine displaced a dimethylamino group.

IV. Pyrimidine Ethers.—Metallic sodium (1 equivalent) was dissolved in an excess of the desired alcohol (anhyd.) and 1 equivalent of the chlorodiaminopyrimidine added. The solution was refluxed for 20 to 54 hours. If possible, sodium chloride was removed and the filtrate taken to dryness *in vacuo*. The residue was recrystallized from water or dilute alcohol.

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(10) Pearlman and Banks, THIS JOURNAL, **70**, 3726 (1948).

(11) Büttner, ref. 8, prepared this compound by the diamination of 2,4,6-trichloropyrimidine, m.p. 198°. Braker, *et al.*, ref. 9, report m.p. 200°.