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

Arylaminoheterocycles. II. Arylaminopyrimidines

BY C. KENNETH BANKS

Relatively few di-(arylamino)-pyrimidines and amino-arylaminopyrimidines are recorded in the literature.[1,2,3,4,5] These compounds were prepared by refluxing a halo- or ethylmercapto-pyrimidine in the liquid amine and were limited to those containing simple aryl groups such as phenyl and tolyl. In the preceding paper of this series,[6] the condensation of 2-amino-4-chloropyrimidine and aniline was studied to determine the rate of reaction under varying conditions of alkalinity and acidity. The compound formed, 2-amino-4-anilinopyrimidine, was isolated and studied pharmacologically. It caused a presser response in anesthetized dogs equal to that of benzedrine but of shorter duration. It also appeared to have analgetic activity.[7] Since the structure of this compound differs widely from other compounds having similar pharmacological activity, a number of compounds having substituents in the benzene ring were prepared.

All of the arylamines and halo-aminopyrimidines used are commercially available or adequately described in the literature. The condensation of amine and heterocycle was carried out under the optimum reaction conditions previously described.[6] The yields were nearly theoretical. Morpholine was also condensed with 2-amino-4-chloropyrimidine, using the same procedure, in yields of 66–75%. The compounds so formed are now being studied for pharmacological activity.

Experimental

2-Amino-4-anilinopyrimidine.—One-tenth mole of aniline, 0.1 mole of 2-amino-4-chloropyrimidine and 1 ml. of hydrochloric acid in 100 ml. of water were refluxed for thirty minutes. A clear solution was formed, which was charcoaled (Darco) and filtered while hot. A test for unreacted amine indicated that over 99% reaction had occurred. The filtrate was cooled, made strongly alkaline with 10 *N* sodium hydroxide and the precipitated product filtered off and recrystallized from alcohol–water. The over-all yield was 92%. The monoacetate salt was formed by dissolving the base in hot dilute acetic acid and cooling. The diacetate was prepared by solution of the base in glacial acetic acid and precipitating with anhydrous ether. These compounds were dried *in vacuo* (1 mm.) for twenty-four hours at room temperature. The diacetate loses one mole of acetic acid when heated *in vacuo*. The hydrochloride was formed by solution of the base in alcoholic hydrochloric acid, addition of five volumes of butyl acetate and crystallization started by scratching. The crystals were filtered off and dried twenty-four hours at 100° *in vacuo*. Similar procedures were followed in preparing compounds 3, 15, 16, 17, 18 and 19 of the table. The remainder were prepared by carrying out the condensation in the same manner but after charcoaling and filtering, an equal volume of concentrated hydrochloric acid was added and the solution chilled in an ice-bath. The product was filtered off and recrystallized from dilute hydrochloric acid. To obtain the free bases of these hydrochlorides, aqueous solutions of the salts were made alkaline with sodium hydroxide, the precipitates removed and purified from aqueous alcohol or aqueous acetone. The sodium salt, No. 6, was precipitated from an aqueous solution with alcohol.

TABLE OF COMPOUNDS

	Pyrimidine[a]	M. p., °C., cor.	N Analyses,[b] % Calcd.	Found
1	2-Amino-4-anilino-	155–156	30.09	29.98
	diacetate	170	18.30	18.05
	monoacetate	176–178	22.75	22.61
	hydrochloride[c]	184–185	25.15	24.99
2	4-Amino-2-anilino-, hydrochloride	149–150	25.15	25.05
3	2-Amino-4-anilino-6-methyl-	170–172	28.00	28.20
4	2,4-Dianilino- hydrochloride	136–138	21.36	21.22
		194–195	18.09	17.94
5	2-Amino-4-(4′-carboxyanilino)- diethylaminoethanol ester·3HCl	295–297 d.	24.34	24.47
		>250	15.98	16.03
6	2-Amino-4-(2′-carboxyanilino)-, sodium salt	>250	22.19	22.35
7	2-Amino-4-(2′-hydroxyanilino)-, dihydrochloride	indef. >200	20.15	20.09
8	2-Amino-4-(3′-hydroxyanilino)-, hydrochloride	178–180	23.42	23.33
9	2-Amino-4-(4′-hydroxyanilino)- hydrochloride	245–247 d.	27.75	27.83
		275–277	23.42	23.40
10	2-Amino-4-(2′,6′-dihydroxyanilino)-, dihydrochloride	123–124	19.24	18.96
11	2-Amino-4-(4′-methoxyanilino)-, hydrochloride	276–278	22.26	22.12
12	2-Amino-4-(3′,4′-dimethoxyanilino)-, hydrochloride	270	19.85	19.62
13	2-Amino-4-(4′-acetaminoanilino)-, dihydrochloride	299–300	22.15	22.13
14	2-Amino-4-(4′-acetylanilino)-, hydrochloride	275–276	21.17	21.15
15	2-Amino-4-(2′,6′-dimethylanilino)-	186–187	26.15	25.85
16	2-Amino-4-(4′-phenylanilino)-	193–195	21.36	21.39
17	2-Amino-4-(2′-phenylanilino)-	130–132	21.36	21.55
18	2-Amino-4-(α-naphthylamino)-	133–134	23.72	23.63
19	2-Amino-4-morpholino-	157–161	31.14	31.22

[a] All the compounds described are white. [b] Micro-Dumas analyses by Margaret McCarthy Ledyard. [c] Calcd.: Cl, 15.91. Found: (by electrometric titration), Cl, 15.89. All the hydrochlorides of the series were identified by titration.

Summary

A number of primary aromatic amines have been treated with halopyrimidines in an aqueous suspension in the presence of acid to give arylaminopyrimidines.

DETROIT, MICHIGAN RECEIVED APRIL 13, 1944

(1) Wheeler and Bristol, *Am. Chem. J.*, **33**, 459 (1905).
(2) Johnson and Storey, *ibid.*, **40**, 141 (1908).
(3) Schlenker, *Ber.*, **34**, 2826 (1901).
(4) Gabriel and Coleman, *ibid.*, **32**, 2929 (1899).
(5) Byk, *ibid.*, **36**, 1920 (1903).
(6) Banks, THIS JOURNAL, **65**, 1127 (1944).
(7) Pharmacological work under the supervision of Drs. C. C. Pfeiffer and E. R. Loew of our laboratories.