The hydroxyarsine was obtained by addition of 600 cc. of ammonia water to 25 g. of the chloroarsine, dissolved in 450 cc. of hot alcohol. The oily precipitate, which soon crystallized, was recrystallized from 350 cc. of alcohol; yield 20 g.; m. p. 156–157°.[20]

Anal. Calcd. for $C_{24}H_{16}O_9N_4As_2$ (arsyl oxide): As, 22.92; mol. wt., 654. Calcd. for $C_{12}H_9O_5N_4As$ (hydroxyarsine): As, 22.57; mol. wt., 336. Found: As, 22.62, 22.66; mol. wt., 323 (solvent ethylene bromide).

Summary

Interaction between the following substances has been investigated: (a) phenylarsine with phenylethoxychloroarsine and triphenylchloroarsine, respectively; (b) diphenylarsine with chloroacetyl chloride and chloroacetic acid, respectively; (c) diphenylarsylmagnesium bromide with mercuric chloride, arsenic trichloride, iodine, diphenyliodoarsine, 3,3′-dinitrodiphenyliodoarsine, diphenylbromomethane, triphenylbromomethane, benzophenone chloride, *o*-xylylene bromide and benzophenone, respectively; (d) tetraphenyldiarsyl with chloroacetic acid and mercuric chloride.

(20) Michaelis [*Ann.*, **321**, 145 (1902)], who obtained the compound by a seemingly impossible method, reported the melting point as 149°.

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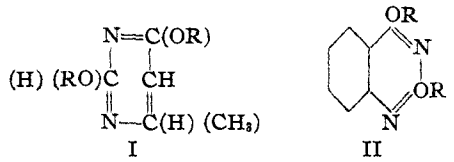
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXLV. Alkamine Ethers of the Pyrimidine and Quinazoline Series[1]

BY JOHN J. DONLEAVY AND MEARL A. KISE

During recent years it has been demonstrated clearly by many investigators that the physiological activity of a great variety of organic compounds can be enhanced greatly by the introduction of basic ether groups. The pharmacological effect of these groups does not appear to be specific in any real sense, since in different types of structures they enhance or produce markedly different physiological behaviors. Thus, *p*-β-diethylaminoethoxyanisole has a strong action upon the heart.[2] Upon the other hand, the hydrochloride of β-naphthyl-β-dimethylaminoethyl ether exerts a local anesthetic action.[3] More recently the alkamine ethers of the heterocyclic nuclei, pyridine, acridine and quinoline, have been found to possess marked physiological activity as antipyretics, etc.[4] In the light of these facts it was of interest to prepare several basic ethers of pyrimidine and quinazoline or benzopyrimidine, in order to note the pharmacological effect of the introduction of the basic ether configurations into these nuclei and to obtain data relative to the toxicity of pyrimidines of this general type.

The various alkamine ethers of pyrimidine and quinazoline listed below were prepared by treating the corresponding chloro compounds with the sodium salts of the requisite dialkylamino alcohols. The pyrimidine and quinazoline ethers are represented by the general types I and II, respectively.



I II

The necessary chloro compounds, prepared from the corresponding oxy compounds, included 2,4-dichloropyrimidine,[5] 6-methyl-2,4-dichloro-pyrimidine,[6] 6-methyl-4-chloropyrimidine[7] and 2,4-dichloroquinazoline.[8]

Experimental

6-Methyl-2,4-dioxypyrimidine.—This pyrimidine was prepared by the following improved modification of the method of Biltz and Heyn.[6]

(1) This, the first of several communications, was constructed in part from the dissertation presented to the faculty of the Graduate School of Yale University by Mearl A. Kise in June, 1933, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Hahl, German Patent, 423,037 (1925); *Frdl.*, **15**, 1642 (1925).

(3) Clemo and Perkin, *J. Chem. Soc.*, **121**, 642 (1922).

(4) Miescher and Urech, U. S. Patent 1,881,236; *C. A.* **27**, 1096 (1933); Callsen and Hahl, German Patent 430,960 (1926); *Frdl.*, **15**, 1644 (1926); Hartmann and Isler, U. S. Patent 1,860,286 (1932); *C. A.* **26**, 3877 (1932); Mietzsch, German Patent 490,418 (1930); *Frdl.*, **16**, II, 2704 (1931).

(5) Davidson and Baudisch, THIS JOURNAL, [2] **48**, 2379 (1926); Johnson and Flint, *ibid.*, [1] **53**, 1079 (1931); Hilbert and Johnson, *ibid.*, [1] **52**, 1155 (1930).

(6) Behrend and Roosen, *Ann.*, **251**, 238 (1889); Biltz and Heyn, *ibid.*, **413**, 109 (1917); Gabriel and Colman, *Ber.*, [2] **32**, 1533 (1899).

(7) Gabriel and Colman, *ibid.*, [3] **32**, 2931 (1899).

(8) Bogert and Scatchard, THIS JOURNAL, [2] **38**, 1612 (1916); Lange, Roush and Asbeck, *ibid.*, **52**, 3696 (1930); Gabriel and Stelzner, *Ber.*, [2] **29**, 1300 (1896); Gabriel and Colman, *ibid.*, [3] **38**, 3559 (1905); Bogert and Scatchard, THIS JOURNAL, **41**, 2061 (1919).

Eighty grams of finely powdered urea was stirred into 173 g. of commercial acetoacetic ester containing 20 cc. of absolute ethanol. The mixture, contained in a large crystallizing dish, was placed in a vacuum over sulfuric acid. The sulfuric acid was changed daily and the mixture stirred frequently until sufficiently dry to pulverize.

The β-uramidocrotonic ester was separated into two portions for convenience and each portion added, with stirring, to a solution of 50 g. of potassium hydroxide in 750 cc. of water at 95°. When solution of the solid was complete, the mixture was cooled to 65° and acidified carefully with concentrated hydrochloric acid. The reaction mixture was allowed to cool in an ice-bath for one hour. The 6-methyluracil was then filtered, washed with small amounts of water, alcohol and ether and dried. The yield was 130 g. or 80% of the theoretical. The product melted at 270–280° with decomposition.

Preparation of Alkamine Ethers.—Twenty-five grams of dry xylene, containing about 15 g. of the necessary amino alcohol, was refluxed with the theoretical quantity of sodium until the sodium dissolved. Twenty-five grams of dry xylene, containing the calculated quantity of the requisite chloro compound, was then added to the alcoholate and the mixture refluxed for several hours to complete the reaction. The sodium chloride was removed by filtration and washed with xylene. The xylene was removed from the solution by distillation on an oil-bath and the residue poured into four volumes of water. If the alkamine ether was insoluble in water it was dissolved by the addition of acetic acid. The solution was filtered and the acidified solution neutralized with sodium carbonate. The oil was extracted with ether and the ether extract dried with sodium sulfate. The ether was removed and the product fractionally distilled under reduced pressure several times. The average yield was 75% of the theoretical. The boiling points, solubilities and analytical data are listed in the table.

		B. p. (uncorr.) °C.	Mm.
I	2,4-Di-β-diethylaminoethoxypyrimidine	190–191	3
II	6-Methyl-2,4-di-β-diethylaminoethoxypyrimidine	198–201	3
III	6-Methyl-2,4-di-β-dibutylaminoethoxypyrimidine	227–230	3
IV	6-Methyl-4-β-diethylaminoethoxypyrimidine	146	5
V	6-Methyl-4-γ-diethylaminopropoxypyrimidine	125–127	4
VI	2,4-Di-β-diethylaminoethoxyquinazoline	209–210	5

	Solubilities					Nitrogen, %	
	Water	Ethanol	Ether	Xylene	Formula	Calcd.	Found
I	sol.	sol.	sol.	sol.	$C_{16}H_{30}O_2N_4$	18.05	18.03
II	sol.	sol.	sol.	sol.	$C_{17}H_{32}O_2N_4$	17.27	17.26
III	insol.	sol.	sol.	sol.	$C_{25}H_{48}O_2N_4$	12.84	12.74
IV	sol.	sol.	sol.	sol.	$C_{11}H_{19}ON_3$	20.09	20.04
V	sol.	sol.	sol.	sol.	$C_{12}H_{21}ON_3$	18.82	18.60
VI	insol.	sol.	sol.	sol.	$C_{20}H_{32}O_2N_4$	15.55	15.48

Pharmacological Data.—A preliminary examination of the pharmacological behavior of the alkamine ethers revealed the following toxicities by intravenous injection of mice.[9]

	M. L. D., mg./kg.
2,4-Di-β-diethylaminoethoxypyrimidine	80
6-Methyl-2,4-β-diethylaminoethoxypyrimidine	175
6-Methyl-4-β-diethylaminoethoxypyrimidine	230
6-Methyl-4-γ-diethylaminopropoxypyrimidine	120

None of the compounds tested pharmacologically possessed local anesthetic action and the irritation was severe in all cases.

Further investigations will be made.

Summary

1. The 2,4-β-diethylaminoethoxy ethers of pyrimidine and 6-methylpyrimidine; the 4-β-diethylaminoethoxy and 4-γ-diethylaminopropoxy ethers of 6-methylpyrimidine; and the 2,4-di-β-diethylaminoethoxy ether of quinazoline have been prepared.

2. The toxicities of the various alkamine ethers were determined.

3. The compounds were tested for local anesthetic action.

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(9) The authors are indebted to the Lilly Research Laboratories of Eli Lilly and Company for the pharmacological testing of the compounds listed in this paper.