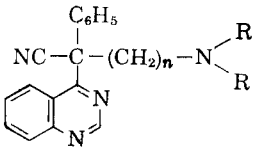
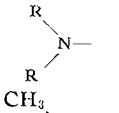
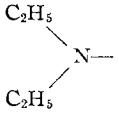
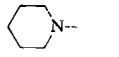
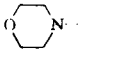
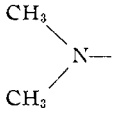
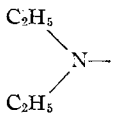
TABLE I.—ω-TERTIARYAMINO-α-(4-QUINAZOLYL)-α-PHENYLALKANENITRILES



No.	n	R	B.p., °C.	mm.	Yield, %	Formula	Analyses[a] Calcd. C	Calcd. H	Found C	Found H
1	2		183–186	0.015	85	$C_{20}H_{20}N_4$	75.91	6.37	75.73	6.84
2	2		195–198	0.025	65	$C_{22}H_{24}N_4$	76.71	7.02	77.04	7.19
3	2		200–202	0.025	60	$C_{23}H_{24}N_4$	77.49	6.78	77.16	6.60
4	2		202–205	0.015	57	$C_{22}H_{23}N_4O$	73.71	6.20	73.50	6.75
5	3		182–186	0.005	74	$C_{21}H_{22}N_4$	76.33	6.71	75.82	6.80
6	3		182–185	0.005	71	$C_{23}H_{26}N_4$	77.05	7.31	77.01	7.62

[a] The analyses were performed in the Research Laboratories of Tanabe Seiyaku Co., Ltd., Toda-cho, Saitama-Ken, Japan and the authors express their gratitude to Dr. K. Abe for this assistance.

dried over anhydrous magnesium sulfate. After evaporation of the solvents and distillation at reduced pressure (b.p. 183–186° at 0.015 mm.) there was obtained 7.0 Gm. (85%) of a red syrup.

Attempted Hydrolysis of α-(4-Quinazolyl)-α-phenyl-γ-diethylaminobutyronitrile.—A solution of 1.0 Gm. of α-(4-quinazolyl)-α-phenyl-γ-diethylaminobutyronitrile in 2 ml. of concentrated sulfuric acid and 2 ml. of water was refluxed for 12 hours. The mixture was poured on ice and made alkaline with sodium hydroxide solution. The 3-diethylamino-1-phenyl-1-(4-quinazolyl)propane which was expected in this hydrolysis did not precipitate. The alkaline solution was treated with ammonium chloride and 0.25 Gm. of colorless crystals was obtained, m.p. 210–212°, which was identified as 4-hydroxyquinazoline by mixed melting point.

REFERENCES

(1) Cutler, R. A., Surrey, A. R., and Cloke, J. B., *J. Am. Chem. Soc.*, **71**, 3375(1949).
(2) Castle, R. N., and Onda, M., *Chem. Pharm. Bull.*, **9**, 1008(1961).
(3) Elderfield, R. C., and Serlin, I., *J. Org. Chem.*, **16**, 1669(1951).
(4) Gabriel, S., and Stelzner, R., *Ber.*, **29**, 1314(1896).

Convenient Routes to Medicinally Important Heterocycles

By CHARLES S. DAVIS

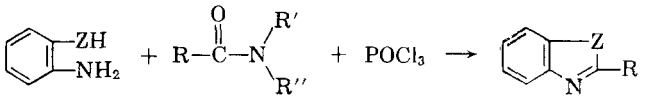
New syntheses of derivatives of benzothiazole, benzoxazole, and benzimidazole are reported.

THE benzothiazole, benzoxazole, and benzimidazole rings have long been prominent in pharmacologically active agents (1). Since it is nearly always a problem to the medicinal chemist to prepare specific structures containing these rings, it is felt that additional methods of synthesis may open avenues to new potential drugs.

The reaction between 2-aminobenzenethiol and the phosphorus oxychloride adduct of dimethylformamide was first reported by Davis, *et al.* (2). It was reported that benzothiazole could be prepared in quite good yields by this method. In 1880,

Received May 11, 1962 from the Research Laboratories of the School of Pharmacy, Purdue University, Lafayette, Ind. Accepted for publication June 11, 1962.

TABLE I.



Z	R	R′	R″	Yield, %	B.p., mm. Hg	Lit.	B.p., mm. Hg
S	CH_3	CH_3	CH_3	82	151 (15)	(4)	151 (15)
S	CH_3	CH_3	H	71	156 (18)	(4)	151 (15)
O	H	CH_3	CH_3	52	185 (747)	(4)	182 (753)
N	H	CH_3	CH_3	50	m.p. 172–173	(5)	m.p. 175
S	—$CH_2CH_2CH_2$—		CH_3	65	144–146 (1.5)[a]		m.p. 104–105[a]

[a] m.p. sulfate. *Anal.*—Calcd. for $C_{11}H_{14}N_2S{\cdot}2H_2SO_4$: C, 32.82; H, 4.57. Found: C, 32.96; H, 4.57.

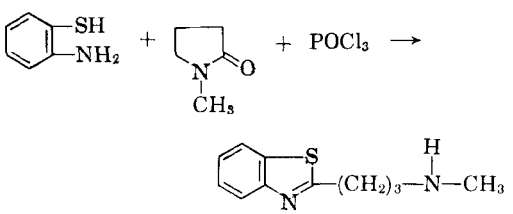
Hofmann (3) reported the preparation of benzothiazole from 2-aminobenzenethiol and formamide. His synthesis required a high temperature and yielded only a small amount of benzothiazole. This note reports convenient syntheses for the derivatives of benzothiazole, benzoxazole, and benzimidazole from the appropriate 2-substituted aniline and a secondary or tertiary amide. A new synthesis for benzimidazole from the acid catalyzed reaction of triethyl orthoformate and *o*-phenylenediamine is also reported.

DISCUSSION

Benzoxazole, benzothiazole, and benzimidazole are formed in good yields when the appropriate substituted aniline is reacted with the phosphorus oxychloride adduct of dimethylformamide. When N-methyl or N,N-dimethylacetamide are reacted with phosphorus oxychloride and 2-aminobenzenethiol, 2-methylbenzothiazole is produced. If acetamide or formamide are allowed to react under the same conditions, no product is formed.

From these experimental results, it is noted that the amide nitrogen must be at least monosubstituted.

To discover the fate of the amide nitrogen in this reaction, it was decided to devise an experiment where the amide nitrogen would remain in the final heterocyclic product. The cyclic amide, N-methylpyrrolidone, was reacted with phosphorus oxychloride and 2-aminobenzenethiol. The product was as expected: 2-(methylaminopropyl)benzothiazole.



EXPERIMENTAL

To a solution of phosphorus oxychloride (0.25 mole) in anhydrous ether (40 ml.) was added dropwise a solution of the appropriate amide (0.25 mole) in anhydrous ether (50 ml.). The addition was carried out at 15°. The amide-phosphorus oxychloride adduct separated as an oily layer or low melting solid and the mixture was allowed to come to room temperature. The adduct was washed with three portions (50 ml.) of anhydrous ether (6).

To the amide-phosphorus oxychloride adduct was added the appropriate *ortho*-substituted aniline (0.125 mole) in anhydrous ether (50 ml.). When the substituted aniline was not sufficiently soluble in ether, the order of addition was reversed. The addition was accomplished with rapid stirring and cooling. After the addition was completed, the ether was evaporated and water (100 ml.) added with cooling. The aqueous solution was extracted with ether and the ethereal solution dried over anhydrous sodium sulfate. The ether was evaporated and the residue distilled; except benzimidazole, which was recrystallized from water. The physical constants of the compounds prepared by this method are listed in Table I.

Benzimidazole *via* the Orthoformate Reaction.—in a 100-ml. round-bottomed flask were placed phenylenediamine (18.4 Gm., 0.17 mole), triethyl orthoformate (37 Gm., 0.25 mole), and 2 drops of concentrated sulfuric acid. The flask was set up for distillation and the ethanol was distilled over a 1-hr. period. After 38 ml. of ethanol was collected, the residue was allowed to cool and solidify. The melting point of the crude material was 162–168°. The solid was recrystallized from water at a melting point of 172–173°; lit. (5) m.p. 175; yield, 17.2 Gm. (88%). This material was identical to that prepared by the phosphorus oxychloride reaction.

REFERENCES

(1) Burger, A., "Medicinal Chemistry," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 262 1071.
(2) Davis, C. S., Knevel, A. M., and Jenkins, G. L., *J. Org. Chem.*, **27**, 1919(1962).
(3) Hofmann, A., *Ber.*, **13**, 1223(1880).
(4) Jenkins, G. L., Knevel, A. M., and Davis, C. S., *J. Org. Chem.*, **26**, 274(1961).
(5) Grundmann, C., and Kreutzberger, A., *J. Am. Chem. Soc.*, **77**, 6559(1955).
(6) Brederech, H., Gomper, R., Klem, K., and Rempfer, H., *Ber.*, **92**, 837(1959).