m.p. 190–191°) (4)]. Recrystallization of the 6-sulfamoylsaccharin from acetone gave yields of approximately 40% of white crystalline solid, m.p. 276–278° (decompn.). Herzog has reported the synthesis of 6-sulfamoylsaccharin, but gives no m.p. (5).

Anal.[3]—Calcd. for $C_7H_6N_2O_5S_2$: C, 32.08; H, 2.31. Found: C, 32.02; H, 2.42.

2-Methyl-6-sulfamoylsaccharin.[4]—In a 250-ml. round-bottom flask fitted with a reflux condenser, heating mantle, and magnetic stirrer were placed 1.0 Gm. (0.01 mole) of sodium carbonate, 10 ml. of water, and 5.0 Gm. (0.02 mole) of 6-sulfamoylsaccharin. To this was added 4.26 Gm. (0.03 mole) of methyl iodide in 50 ml. of diethylene glycol monobutyl ether. The solution was refluxed for 3 hours and then poured into approximately 400 ml. ice water. The mixture was let stand overnight in the refrigerator, then filtered to give 3.6 Gm. (68%) of yellow-tan powder, m.p. 230–232°. Recrystallization from ethanol gave a white solid, m.p. 241–242°.

Anal.—Calcd. for $C_8H_8N_2O_5S_2$: C, 34.79; H, 2.9. Found: C, 35.44; H, 3.17.

[3] Analyses were performed by Elek Micro Analytical Laboratories, Los Angeles, Calif.

[4] *Chemical Abstracts* nomenclature: 2-methyl-6-sulfamoyl-1,2-benzisothiazolin-3-one-1,1-dioxide.

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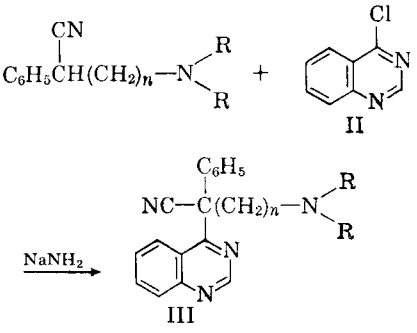
Quinazolines I. ω-Tertiaryamino-α-(4-quinazolyl)-α-phenylalkanenitriles

By RAYMOND N. CASTLE and MASAYUKI ONDA†

Six new ω-tertiaryamino-α-(4-quinazolyl)-α-phenylalkanenitriles have been prepared for pharmacological screening and have been tested for anti-inflammatory activity. Attempts to hydrolyze and decarboxylate these nitriles into the corresponding ω-tertiaryamino-α-(4-quinazolyl)-α-phenylalkanes in acid solution gave none of the desired products. Instead, the only compound isolated was 4-hydroxyquinazoline.

THE PURPOSE of the present work was the synthesis of several ω-tertiaryamino-α-(4-quinazolyl)-α-phenylalkanenitriles for pharmacological screening.

These nitriles were prepared by the methods of Cutler, Surrey, and Cloke (1) with some modification shown in the diagram below. The α-phenyl-ω-tertiaryaminoalkanenitriles used in this work that have not been previously reported in the literature are described in another publication by the present authors (2).



Attempts to convert III to the ω-tertiaryamino-α-(4-quinazolyl)-α-phenylalkanes by heating with 60 per cent sulfuric acid solution resulted only in the isolation of 4-hydroxyquinazoline in each instance attempted. This is in accord with the report of Elderfield and co-workers (3) involving treatment of similar quinazolines with mineral acids.

All six compounds of type III were tested[1] for anti-inflammatory activity in rats. The decrease in intrapleural fluid volume was measured. Compounds 1, 3, 5, and 6 were classed as being active at dose levels of 20 mg./Kg.

EXPERIMENTAL[2]

4-Chloroquinazoline.—The method of Gabriel and Stelzner (4) was modified as follows: a mixture of 3.0 Gm. of 4-hydroxyquinazoline, 6.0 Gm. of phosphorus pentachloride, and 12 ml. of phosphorus oxychloride was heated at 120–130° for 50 minutes. The resulting clear solution was evaporated to dryness *in vacuo* at 80°. Chloroform was added to dissolve most of the solid and the mixture poured on a mixture of crushed ice and concentrated ammonia. The product dissolved in the chloroform layer and this solution was washed with dilute sodium carbonate solution, then with water and dried over anhydrous magnesium sulfate. After evaporation *in vacuo* there was obtained 3.2 Gm. (95%) of a white solid, m.p. 95–97° (literature m.p. 96°) (4).

Preparation of α-(4-Quinazolyl)-α-phenyl-γ-dimethylaminobutyronitrile.—To a solution of 5.4 Gm. of α-phenyl-γ-dimethylaminobutyronitrile in 54 ml. of dry toluene was added 1.3 Gm. of sodium amide and the mixture was refluxed with stirring for 1.5 hours. After cooling, 4.3 Gm. of 4-chloroquinazoline was added and the mixture refluxed and stirred for 3 hours. The mixture was diluted with ether, washed with water and the ether layer

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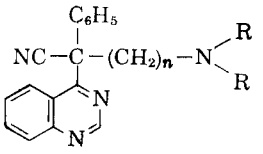
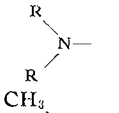
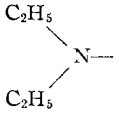
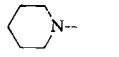
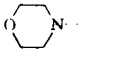
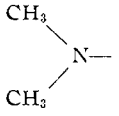
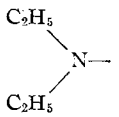
[1] The biological screening was performed in the Smith Kline & French Laboratories and gratitude is expressed for these data.

[2] All melting points are uncorrected.

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.

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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,

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