Soxhlet apparatus, and then extracted exhaustively with chloroform. During the extraction, quantities of permanganate-colored, glittering crystals separated from the brownish-violet solution. Further amounts were obtained by concentration of the solution. Total yield of crystals was 11.4% of the dry weight of the mushroom. The crystals were very sparingly soluble in cold ether, chloroform, xylene, and pyridine, but soluble in alkali. They were iridescent in polarized light and possessed a slight mushroom odor.

Identification.—A sample which crystallized from pyridine as orange needles, turning brown on drying, was sublimed *in vacuo* and then recrystallized from chloroform to give shiny purple plates, m.p. 310.5–312°[2] (sealed capillary), $\lambda_{max.}^{EtOH}$ 205, 256, 262, infl. 330 and 465 mμ (ε, 48,000, 43,000, 43,000, 11,600, and 400, respectively), $\lambda_{max.}^{EtOH-NaOH}$ 530 mμ, (ε 200). Literature: m.p. 303–305° (1), $\lambda_{max.}^{dioxane}$ 261, 332 (4.45 and 3.86) (2), $\lambda_{max.}^{pyridine-H_2O}$ 530 mμ (3). The infrared spectrum of this compound was identical with that of an authentic sample of polyporic acid.

Anal.—Calcd. for $C_{18}H_{12}O_4$: C, 73.95; H, 4.14. Found: C, 74.02; H, 4.37.

The diacetate derivative of polyporic acid was prepared using acetic anhydride and pyridine and showed m.p. 212–214° after recrystallization from methylene chloride-ether, $\lambda_{max.}^{EtOH}$ 236, 240 mμ (ε 1,100, 2,350). Literature: m.p. 215° (4); $\lambda_{max.}^{dioxane}$ 240 and 336 mμ (4.33 and 3.78).

The dimethyl ether of polyporic acid was prepared by adding an excess of diazomethane in ether to a suspension of the acid in methylene chloride. The solvents were removed immediately and the residue recrystallized from benzene-petroleum ether to give an orange solid, m.p. 192–194° [reported (5) m.p. 192°].

[2] All melting points are uncorrected.

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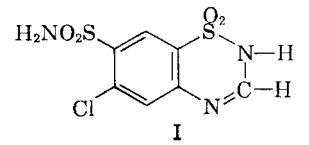
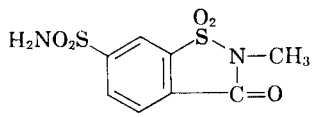
Saccharin Derivatives VI. Synthesis and Diuretic Activity of 2-Methyl-6-sulfamoylsaccharin

By GLENN H. HAMOR

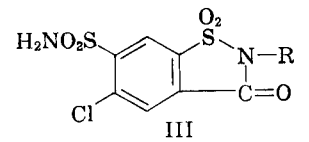
THE APPEARANCE in the literature in 1957 of a report describing the diuretic activity of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (I) (1) led to the preparation of a series of structurally related saccharins. This paper relates the synthesis and result of pharmacological testing of 2-methyl-6-sulfamoylsaccharin (II). Novello, in a recent paper (2), describes the preparation of certain 5-chloro-6-sulfamoylsaccharins (III).



I



II



III

The 2-methyl-6-sulfamoylsaccharin was synthesized by chlorosulfonation of toluene, followed by treatment with 28% ammonia, which gave toluene-2,4-disulfonamide. Oxidation of this compound, succeeded by a Williamson reaction of the resulting 6-sulfamoylsaccharin with methyl iodide, gave the desired 2-methyl-6-sulfamoylsaccharin.

Pharmacological screening in rats has indicated that 2-methyl-6-sulfamoylsaccharin possesses marked diuretic activity (Table I). Testing in the dog for effect on renal clearance of electrolytes and water shows primarily an increase in urine volume accompanied by a slight increase in the excretion of sodium and an increased excretion of potassium.[1]

TABLE I.—DIURETIC EFFECT IN RATS[a]

Dose, mg./Kg. p.o.	Excreted, %	Effect Excreted, %[b]
Control	60[c]	...
5	84	24
15	111	51
30	154	94
60	171	111

[a] Eight rats per group; each group hydrated with 25 ml./Kg. of 0.9% sodium chloride p.o.; length of test was 5 hours. [b] Test minus control. [c] Experience has fixed the control per cent excretion value at 60% for rats. An effect of 22% or greater (82% or more excreted) shows a significant diuretic response.

EXPERIMENTAL[2]

6-Sulfamoylsaccharin.—This compound was prepared by alkaline potassium permanganate oxidation of toluene-2,4-disulfonamide by the method used by Noyes (3) to synthesize 6-nitrosaccharin. The toluene-2,4-disulfonamide was synthesized according to Wynne and Bruce, m.p. 173–174.5° [reported

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[1] The author is indebted to Drs. Alfred Maass and Virgil Wiebelhaus, Smith Kline and French Laboratories, Philadelphia, Pa., for pharmacological testing.
[2] Melting points are uncorrected and were determined by the open capillary tube method.

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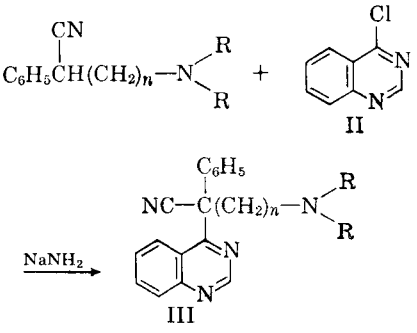
Quinazolines I. ω-Tertiaryamino-α-(4-quinazolyl)-α-phenylalkanenitriles

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.