3-*p*-Toluenesulfonyl-4-quinazolinone and Some of Its Reactions

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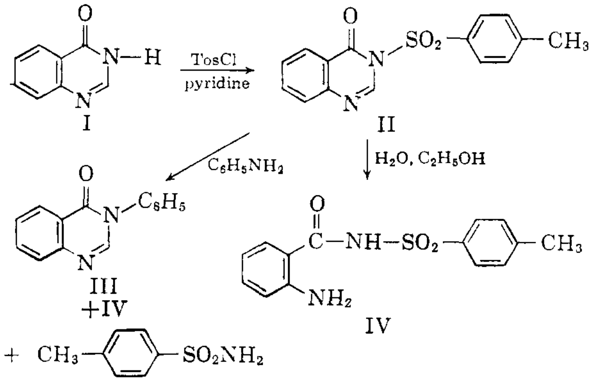
The reaction of 4-quinazolinone (I) with *p*-toluenesulfonyl chloride in cold anhydrous pyridine produced not 4-(*p*-toluenesulfonoxy)quinazoline, as had been hoped from analogy with formally similar reactions,[3,4] but rather a compound identified as 3-*p*-toluenesulfonyl-4-quinazolinone (II). The yield was excellent.

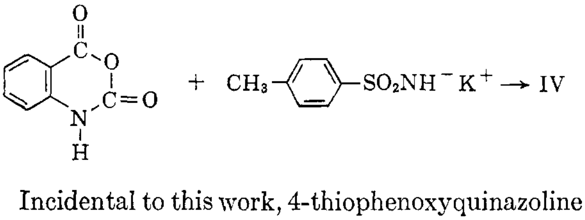
Evidence for the structure assigned includes analyses for C, H, and N, strong infrared absorption at 5.87 μ, characteristic of a carbonyl group [2-(*p*-toluenesulfonoxy)lepidine[4] possesses no such absorption], and the fact that reaction with aniline in benzene at room temperature produced 3-phenyl-4-quinazolinone (III) and *p*-toluenesulfonamide. Isolation of *p*-toluenesulfonamide shows the tosyl group to be bound to nitrogen. The possibility that 4-(*p*-toluenesulfonoxy)quinazoline were the structure, and that it were cleaved by S—O scission[4] with formation of *p*-toluenesulfonanilide and I, is further eliminated by the facts that no *p*-toluenesulfonanilide was formed and that I reacts with aniline to form III only in poor yield and under much more severe conditions.[5]

An effort at independent synthesis of II through condensation of ethyl anthranilate, *p*-toluenesulfonamide, and ethyl orthoformate was unsuccessful.

A by-product (12% yield) from the reaction of II with aniline was a new compound, IV. Alternatively, IV was produced in 98% yield by heating II at reflux in 90% ethanol for ten hours. It was also obtained (28% yield) by allowing II to stand with 2% sodium hydroxide in 55% dioxane–45% water for twenty-four hours at room temperature; 10% of *p*-toluenesulfonamide was also isolated.



IV was quickly soluble in aqueous alkali, difficulty soluble in aqueous mineral acid, and on treatment with nitrous acid and then alkaline β-naphthol gave the color phenomenon typical of azo dye formation. These observations, together with analytical data, suggested the structure N-(*o*-aminobenzoyl)-*p*-toluenesulfonamide (IV). This structure was confirmed by independent synthesis through condensation of isatoic anhydride with the potassium salt of *p*-toluenesulfonamide.[6]



Incidental to this work, 4-thiophenoxyquinazoline was prepared from 4-chloroquinazoline and sodium thiophenoxide.

Experimental

3-*p*-Toluenesulfonyl-4-quinazolinone (II).—4-Quinazolinone (I) (3.0 g., 0.0206 mole) and 4.8 g. (0.025 mole) of *p*-toluenesulfonyl chloride were added to 25 cc. of chilled pyridine, freshly distilled from sodium. The mixture was maintained at 0–10° with frequent shaking until solution was complete. It was then placed in a "deep freeze" cabinet at about −20° and left there 12 hr. The white solid that separated was collected, washed with ligroin, and dissolved in hot benzene. The solution was treated with carbon, filtered, and diluted with ligroin. On cooling, a white solid separated. The m.p. was 185–188°; the weight was recorded as 6.2 g. (quantitative).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.33. Found[7]: C, 60.27; H, 4.26; N, 9.23 (micro-Kjeldahl), 9.24 (Dumas).

Reaction of II with Aniline.—A solution of 1.00 g. of II in 2 cc. of benzene and 2 cc. of aniline was allowed to stand 10 hr. at room temperature. It was then poured into 20 cc. of benzene and the resulting solution was extracted three times with 25 cc. of 5% sodium hydroxide in water.

Steam was passed through the benzene layer to remove excess aniline (and benzene). The aqueous solution in the distillation pot was extracted with three 20-cc. portions of benzene, and the combined benzene layers were heated with carbon, filtered, and diluted with ligroin. On cooling, a white solid (0.58 g.; 78%) separated. Its m.p. was 133–136°; 3-phenyl-4-quinazolinone (III) is reported[5] to have m.p. 136–137°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found[7]: C, 75.75; H, 4.44; N, 12.89 (micro Kjeldahl), 12.50 (Dumas).

The aqueous layer from the extraction was neutralized, cooled and thrice extracted with 30-cc. portions of benzene, and the benzene extracts in turn were extracted with three 25-cc. portions of 5% hydrochloric acid in water. The benzene layer was evaporated to about 20 cc. and diluted with ligroin. The solid which separated on cooling weighed 0.19 g. (34%), and had m.p. 125–130°. The mixture

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[1] Brown University, Providence 12, R. I.

[2] R. J. Reynolds Fellow, 1956–1957. This manuscript is based on the Ph.D. thesis of J. Y. Bassett, Jr., October, 1957.

(3) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1927 (1944).

(4) J. F. Bunnett and J. Y. Bassett, Jr., *J. Org. Chem.*, **27**, 1887 (1962).

(5) N. J. Leonard and W. V. Ruyle, *ibid.*, **13**, 903 (1948).

(6) *Cf.* R. P. Staiger and E. B. Miller, *ibid.*, **24**, 1214 (1959).

(7) Analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Illinois.

melting point with an authentic sample of *p*-toluenesulfonamide was 131–134°. The literature melting point for this compound is 137.4°.[8]

The above acidic aqueous layer was neutralized, cooled, and extracted with benzene. Evaporation of the benzene solution yielded 0.11 g. (12%) of IV, m.p. 180–183°. The mixture melting point with an authentic sample (see below) was not depressed.

Identification of the product of m.p. 133–136° as III was substantiated by its behavior with hydrazine under conditions described by Leonard, Ruyle, and Bannister.[9] A product of m.p. 208–210° was obtained in 85% yield. These authors report m.p. 209–210° for 3-amino-4-quinazolinone prepared in this fashion.

Hydrolysis of II.—A solution of 3.10 g. of II in 200 cc. of 90% ethanol: 10% water was heated 10 hr. at reflux. Hot water was slowly added to the hot solution until a faint turbidity appeared. Cooling with ice caused white leaflets to separate, and a small second crop was gained by extracting the mother liquor with ether. The total yield of IV was 2.96 g. (98%), and the m.p. 182–185°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.86; N, 9.65; neut. equiv., 290. Found[7]: C, 57.91; H, 4.68; N, 9.64 (micro Kjeldahl); neut. equiv. 291, 292 (potentiometric titration *vs.* NaOH solution).

To a solution of 3.0 g. of II in 50 cc. of dioxane, 40 cc. of 5% aqueous sodium hydroxide was added. The mixture was kept 24 hr. at room temperature, poured into 50 cc. of water, and extracted with three 40-cc. portions of benzene There was no residue on evaporation of the benzene. Neutralization and cooling of the aqueous layer caused 0.80 g. (28%) of IV, m.p. 179–183° to separate. The aqueous mother liquor was acidified and 0.28 g. (16%) of *p*-toluenesulfonamide, m.p. 128–132°, was thereby obtained.

Preparation of IV from Isatoic Anhydride.—*p*-Toluenesulfonamide (20.5 g., 0.12 mole) was allowed to react with 5.0 g. (0.09 mole) of potassium hydroxide in 10 cc. of water. The resulting salt was dried, though not purified. All of it was combined with 4.9 g. (0.03 mole) of isatoic anhydride (generously furnished by the Maumee Chemical Co.) and 50 cc. of dimethylformamide. The potassium salt dissolved as the mixture was slowly heated to 160°, at which temperature it was held for 7 hr. It was cooled and poured into 250 cc. of cold water. The resulting solution was cloudy, and a solid separated on acidification. Water (400 cc.) was added, and the mixture was heated to boiling and filtered hot. The white solid collected on the filter was extracted by 300 cc. of boiling water and dried. The IV so obtained, m.p 180–183°, weighed 3.7 g. (44%). The mixture melting point with IV from hydrolysis of II was 183–185°, and the infrared spectra were identical.

4-Thiophenoxyquinazoline.—Solutions of 1.7 g. of 4-chloroquinazoline[10] in 30 cc. of dioxane and of 5.2 g. of thiophenol in 25 cc. of 5% aqueous sodium hydroxide were combined and allowed to stand 2 hr. at room temperature. The product was isolated by standard procedures and finally crystallized from aqueous ethanol. 4-Thiophenoxyquinazoline (1.07 g.; 45%) was obtained as white crystals of m.p. 115–116°.

Anal. Calcd. for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23. Found[7]: C, 70.86; H, 4.78.

Acknowledgment.—This research was supported in part by the U.S. Army Research Office (Durham). We thank Professors Robert L. McKee and Roger P. Staiger for helpful discussions.

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[8] P. V. McKie, *J. Chem. Soc.*, **113**, 799 (1918).

[9] N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *J. Org. Chem.*, **13**, 617 (1948).

[10] A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **67**, 2112 (1945).

The Determination of the Styryl[1] Geometry of the 6-Styryl-4-methoxy-2-pyrones by Proton Magnetic Resonance Spectroscopy

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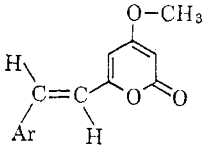
The proton magnetic resonance spectra of a 6-styryl-4-methoxy-2-pyrone derived from a pyrone isolated from a fungus[2] and of the 6-styryl-4-methoxy-2-pyrones and the 5,6-dihydro-6-styryl-4-methoxy-2-pyrones realized from the higher plants[3] confirm a *trans* geometry for the styryl groups in these compounds.

Actually, the syntheses of the 6-styryl-4-methoxy-2-pyrones indicate that the styryl system is *trans* substituted. Yangonin[4] (I) and tri-O-methylhispidin[2] (II) have been synthesized by the base-catalyzed condensation of 6-methyl-4-methoxy-2-pyrone (III) with the appropriate aldehyde; a method which has produced *trans* styryl groups in similar cases.[5,6] The syntheses 5,6-dehydrokawain[7] (IV), kawain[8,9] (V), and methysticin[10] (VI) proceeded from *trans* cinnamyl compounds



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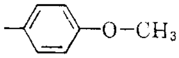

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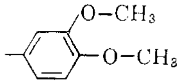

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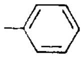

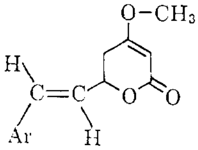

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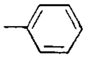

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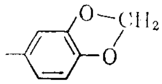
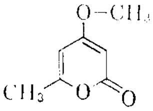
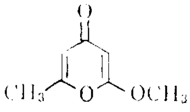




III



VII

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[1] The term styryl is used herein, as in the previous literature, to denote an Ar—CH=CH— group.

[2] R. L. Edwards, D. G. Lewis, and D. V. Wilson, *J. Chem. Soc.*, 4995 (1961); J. D. Bu'lock and H. G. Smith, *Experientia*, **17**, 553 (1961).

[3] See R. Hänsel, P. Bähr, and J. Elich, *Arch. Pharm.*, **294**, 739 (1961), footnotes 4 and 5 for leading references to the chemistry and pharmacology of these compounds. A reasonable biosynthesis for these compounds has recently been proposed by A. J. Birch, "XVIIth International Congress of Pure and Applied Chemistry," Butterworths, London, 1960, p. 73.

[4] J. D. Bu'lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960).

[5] D. S. Noyce, G. L. Woo, and M. J. Jorgenson, *J. Am. Chem. Soc.*, **83**, 1160 (1961).

[6] W. B. Black and R. B. Lutz, *ibid.*, **77**, 5134 (1955).