

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinol Imide Acetates. V. The Preparation and Reactions of 4-Methyl- and 4-Phenyl-*p*-quinolbenzenesulfonimide Acetates

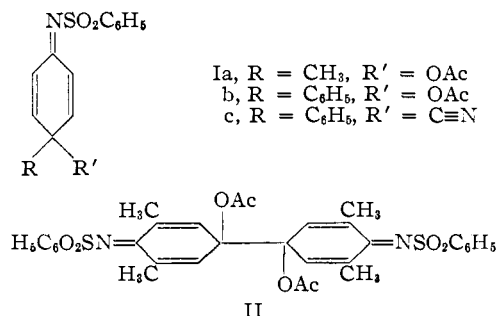
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RECEIVED DECEMBER 14, 1956

Oxidation of *N*-benzenesulfonyl-*p*-toluidine and *N*-benzenesulfonyl-*p*-aminobiphenyl with lead tetraacetate results in the formation of 4-methyl- and 4-phenyl-*p*-quinolbenzenesulfonimide acetate, respectively. These products rearrange rapidly in acidic media to the 3-acetoxy derivatives of the corresponding benzenesulfonamides. The quinol imide acetates react with the sodium derivatives of acetylacetone or diethyl malonate and with sodium cyanide with loss of the acetoxy group and formation of the 3-substituted benzenesulfonamides.

The oxidation of *N*-benzenesulfonyl-*p*-toluidine and *N*-benzenesulfonyl-*p*-aminobiphenyl by lead tetraacetate in acetic acid produces 4-methyl-*p*-quinolbenzenesulfonimide acetate (Ia) and 4-phenyl-*p*-quinolbenzenesulfonimide acetate (Ib), respectively, although Ia is formed in poor yield. No quinol imide acetates could be isolated from the oxidation products of *N*-benzenesulfonyl-*o*-toluidine, *N*-benzenesulfonyl-*o*-aminobiphenyl, *N*-benzenesulfonyl-*p*-*t*-butylaniline or *N*-benzenesulfonyl-*p*-(isopropyl)-aniline.

The oxidation of *N*-benzenesulfonyl-2,6-dimethylaniline by lead tetraacetate in chloroform produces a substance having an elemental analysis and infrared spectrum appropriate to the structure II.



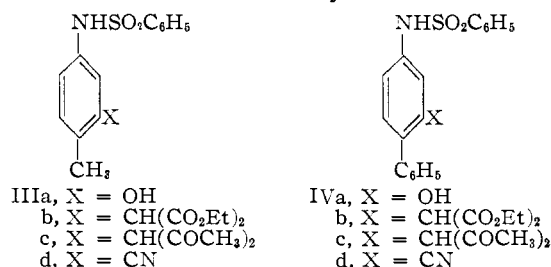
The spectrum shows absorption by CH_3COO and $\text{C}=\text{N}$, while $\text{N}-\text{H}$ is absent. Although the analysis does not preclude the possibility that the substance is 2,6-dimethyl-*o*-quinolbenzenesulfonimide acetate, its lack of color, high melting point and low solubility argue against it. An attempt to determine the molecular weight by the Rast method failed because of reaction of the substance with the camphor.

The reactions of Ia and Ib for the most part resemble those of the *o*-quinol imide acetates.¹ Acidic reagents such as hydrogen chloride presumably cause rearrangement to the acetates of IIIa and IVa rather than addition.

The addition of the sodio derivatives of malonic ester and acetylacetone proceeds readily to form IIIb, IVb, IIIc and IVc. Addition of cyanide to Ia gives a single product, IIId, but to Ib produces both the normal product IVd and a quinonoid cyano compound Ic in which the acetoxy group is merely replaced by a cyano group without any rearrangement.

(1) R. Adams, E. J. Agnello and R. S. Colgrove, *THIS JOURNAL*, **77**, 5617 (1955); R. Adams and K. R. Brower, *ibid.*, **78**, 4770 (1956); R. Adams and J. E. Dunbar, *ibid.*, **78**, 4774 (1956); R. Adams and E. L. DeYoung, *ibid.*, **79**, 417 (1957).

The structures IIIa and IIId were proved by independent syntheses. Compound IIIa was prepared from 5-nitro-*o*-cresol by reduction and ben-



zenesulfonation, and IIId was prepared from 5-nitrotoluamide by reduction and simultaneous benzenesulfonation and dehydration.

Experimental

4-Phenyl-*p*-quinolbenzenesulfonimide Acetate.—A solution of 50 g. of *N*-benzenesulfonyl-*p*-aminobiphenyl in 200 ml. of acetic acid was stirred with 1 mole equiv. of lead tetraacetate (80 g. of the commercial product) until a red homogeneous solution resulted (2 hr.). The solution was poured into water and extracted with ether. The extract was washed with water and 5% aqueous sodium hydroxide, dried, evaporated. The residue crystallized and was recrystallized from ethanol to give 28 g. (50%) of product, m.p. 127–128°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{NO}_4\text{S}$: C, 65.37; H, 4.66. Found: C, 65.45; H, 4.41.

4-Methyl-*p*-quinolbenzenesulfonimide Acetate.—A suspension of 50 g. of *N*-benzenesulfonyl-*p*-toluidine and 1 mole equiv. of lead tetraacetate (102 g. of commercial product) in 200 ml. of acetic acid was heated to 50° and shaken from time to time. A red homogeneous solution resulted after 30 minutes, and it was poured into water and extracted with ether. The ether layer was washed with water, extracted with 5% aqueous sodium hydroxide, dried, evaporated, and crystallized by addition of ethanol to give 6.0 g. (10%) of crude product. After recrystallization from ethanol the substance melted at 114–115°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$: C, 59.00; H, 4.95. Found: C, 59.17; H, 5.09.

***N*-Benzenesulfonyl-3-hydroxy-4-phenylaniline.**—A solution of 1.0 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate in 5 ml. of chloroform was saturated with hydrogen chloride and allowed to stand 4 hours. The reaction mixture was diluted with ether, washed with water, and extracted with 5% aqueous sodium hydroxide. Acidification of the extract gave 1.0 g. (95%) of crude sulfonamide which was purified by recrystallization from benzene, m.p. 157–158°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{S}$: C, 66.43; H, 4.65. Found: C, 66.36; H, 4.56.

***N*-Benzenesulfonyl-3-hydroxy-4-methylaniline. Method A.**—A solution of 0.5 g. of 4-methyl-*p*-quinolbenzenesulfonimide acetate in 5 ml. of dioxane was acidified with one drop of concd. sulfuric acid and heated at 100° for 5 minutes. The solution was poured into water, and extracted with ether, and the sulfonamide was removed from the ether

with 5% aqueous sodium hydroxide. Acidification of the alkaline extract gave 0.4 g. (67%) of product which was recrystallized once from water and twice from benzene, m.p. 132–133°.

Anal. Calcd. for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98. Found: C, 59.89; H, 5.18.

Method B.—A solution of 8 g. of 5-nitro-*o*-cresol² in 30 ml. of ethanol was hydrogenated over platinum oxide catalyst. The product was isolated by evaporation to dryness and benzenesulfonated in pyridine. The reaction mixture was poured into water and the product was recrystallized from boiling water; 8 g. (45%). After further purification by recrystallization from benzene the substance melted at 131–132°, and the melting point of a mixture with the product of method A was not depressed. The infrared spectra of the products were essentially identical.

N-Benzenesulfonyl-3-dicarbethoxymethyl-4-phenylaniline.—To a suspension of diethyl sodiomalonate in 30 ml. of ether, prepared by the interaction of 4 ml. of diethyl malonate and 1.3 g. of sodium, 2.0 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate was added. The reaction mixture boiled and became homogeneous. It was extracted with water and the aqueous layer upon acidification precipitated 1.0 g. (45%) of product. It was recrystallized from ethanol, m.p. 143–144°.

Anal. Calcd. for $C_{25}H_{25}NO_6S$: C, 64.23; H, 5.39. Found: C, 64.56; H, 5.39.

N-Benzenesulfonyl-3-dicarbethoxymethyl-4-methylaniline.—The procedure above was applied to 1.0 g. of 4-methyl-*o*-quinolbenzenesulfonimide acetate, and 0.6 g. (50%) of sulfonamide was obtained. The substance was purified by recrystallization from ethanol, m.p. 105–106°.

Anal. Calcd. for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72. Found: C, 58.95; H, 5.44.

N-Benzenesulfonyl-3-diacetylmethyl-4-phenylaniline.—To a suspension of sodioacetylacetone in 10 ml. of ether, prepared by adding 0.5 g. of sodium methoxide and 1.0 g. of acetylacetone, 1.2 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate was added. After standing overnight the ether was allowed to evaporate, and the residue was washed with water leaving a brown crystalline residue. Recrystallization from ethanol gave 0.6 g. (45%) of the sulfonamide, m.p. 182–183°.

Anal. Calcd. for $C_{23}H_{21}NO_4S$: C, 67.80; H, 5.20. Found: C, 67.99; H, 5.24.

N-Benzenesulfonyl-3-diacetylmethyl-4-methylaniline.—The procedure above was applied to 4-methyl-*p*-quinolbenzenesulfonimide acetate and yielded 0.6 g. (50%) of adduct, m.p. 169–170°.

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.55. Found: C, 62.77; H, 5.57.

N-Benzenesulfonyl-3-cyano-4-phenylaniline.—A mixture of 1.0 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate, 0.5 g. of sodium cyanide and 15 ml. of ethanol was gently warmed and shaken for a few minutes. A fluffy-yellow precipitate formed. After standing one day at room temperature the mixture was filtered, and the precipitate, after

being washed with water and dried, weighed 0.3 g. (30%). The substance was purified by recrystallization from ethanol, m.p. 182–183°.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22; N, 8.38. Found: C, 68.49; H, 4.22; N, 8.34.

The infrared spectrum shows C=N at 1550 cm^{-1} , $-SO_2-$ at 1450 cm^{-1} , C≡N at 2220 cm^{-1} , and no N-H.

The filtrate above was acidified with concd. hydrochloric acid, and 0.7 g. (70%) of tan solid was collected and recrystallized from benzene and from ethanol, m.p. 162–163°. The product presumably is quinol imide acetate with the acetate group replaced by the cyano group.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22. Found: C, 68.54; H, 4.16.

The infrared spectrum shows C≡N at 2220 cm^{-1} and the usual features of benzenesulfonimides.

N-Benzenesulfonyl-3-cyano-4-methylaniline. A.—The procedure above was applied to 1.0 g. of 4-methyl-*p*-quinolbenzenesulfonimide acetate, and no water-insoluble precipitate was formed. Acidification of the solution gave 0.7 g. (75%) of sulfonamide which was recrystallized from ethanol and from benzene, m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.74; H, 4.44. Found: C, 62.16; H, 4.30.

B.—A suspension of 1.8 g. of 5-nitrotoluamide³ in 30 ml. of ethanol was hydrogenated over platinum oxide catalyst, and the product was isolated by evaporation to dryness. The amine was dissolved in 5 ml. of pyridine, and 3 ml. of benzenesulfonyl chloride was added. After heating one hour on the steam-bath, the mixture was poured into water, taken up in ether, and extracted with dilute hydrochloric acid and aqueous sodium hydroxide. The alkaline extract was acidified, and the precipitated sulfonamide was again taken up in ether and dried. When the solution was concentrated to 15 ml., a white precipitate was filtered off (1.0 g.) and the filtrate was evaporated to dryness. The residue, recrystallized from ethanol-water and from benzene-petroleum ether (b.p. 90–100°), weighed 15 mg., m.p. 138–139°.

The melting point of a mixture with the product of method A showed no depression and the infrared spectra are identical.

Oxidation of N-Benzenesulfonyl-2,6-dimethylaniline.—A mixture of 10 g. of N-benzenesulfonyl-2,6-dimethylaniline, 17 g. of lead tetraacetate, and 100 ml. of chloroform was allowed to stand two days at room temperature. The mixture was shaken with water, filtered to remove lead dioxide, washed, concentrated, extended to 100 ml. with ether, and extracted four times with 5% aqueous sodium hydroxide. The amount of material recovered by acidification of the extract was 4.0 g. The ether layer was evaporated to an oil which partially crystallized, and addition of 20 ml. of benzene caused further crystallization. The substance was recrystallized from ethanol to give 3.0 g. (25%) of white crystals, m.p. 176–177°.

Anal. Calcd. for $C_{22}H_{22}O_3N_2S_2$: C, 60.34; H, 5.07. Found: C, 60.11; H, 5.28.

The infrared spectrum shows the usual features of quinol imide acetates.

(3) L. Van Scherpenzeel, *Rec. trav. chim.*, **20**, 171 (1901).

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(2) O. Michel and E. Grandmougin, *Ber.*, **26**, 2351 (1893).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Strong Analgesics. The Preparation of Some Ethyl 1-Aralkyl-4-phenylpiperidine-4-carboxylates¹

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RECEIVED OCTOBER 9, 1956

A series of ethyl 1-aralkyl-4-phenylpiperidine-4-carboxylates has been prepared and evaluated for analgesic potency by the rat thermal stimulus method. The most effective aralkyl groups were those having a three-carbon unsaturated chain.

The study of synthetic analgesics in this Labora-

(1) This paper was presented at the 130th A.C.S. Meeting in Atlantic City, N. J., September, 1956.

tory during the past few years has been concerned with modifying the structure of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.