with cold water, dried and evaporated to dryness *in vacuo*. The residue was crystallized from acetonitrile and two crops were collected, 0.25 g., m.p. 140–141° dec., and 0.1 g., m.p. 136–139° dec.

Anal. Calcd. for $C_{38}H_{48}O_6S$: S, 5.06. Found: S, 4.72.

Using a procedure similar to that described for the preparation of the sulfite, but with phosphorus oxychloride in the place of thionyl chloride, a phosphorus containing substance, m.p. 201–203° dec., was obtained. This was probably the 12-phosphate ester formed by analogy with the esters described previously.

Formation of VIII by the Action of Hydrogen Bromide in Acetic Acid on the Sulfite Ester.—A solution of 200 mg. of sulfite ester in 20 ml. of 0.28 *N* hydrogen bromide in glacial acetic acid was warmed for one minute on the steam-bath, cooled, and 100 ml. of water was added. The resulting precipitate was filtered and crystallized from acetonitrile, giving a crystalline solid, m.p. 165–168°. This substance depressed the melting points of both the sulfite ester and IX. It did not depress the m.p. of VIII, and its infrared spectrum was identical with that of VIII.

BLOOMFIELD, NEW JERSEY RECEIVED NOVEMBER 19, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORY ATTACHED TO TAKEDA PHARMACEUTICAL INDUSTRIES, LTD.]

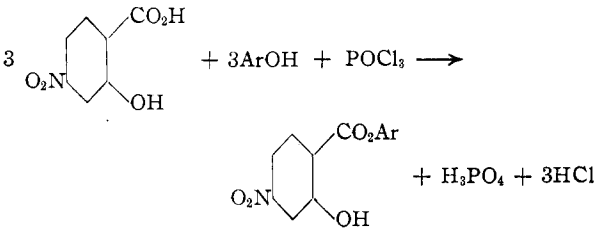
Studies on Antituberculotics. I. Preparation of Aryl *p*-Aminosalicylates

BY SUTTEKITI MARUYAMA AND HISASHI IMAMURA

Several new aryl *p*-aminosalicylates have been prepared for investigation of their use as antituberculotics. Some new derivatives of *p*-aminosalicylic acid have also been prepared. The general methods for their preparation are given.

Freire[1] has recently reported that phenyl *p*-aminosalicylate (I) is about five times as effective as *p*-aminosalicylic acid (PAS) and nearly as effective as streptomycin as an antitubercular agent. However, no description has been made by him of, and no record is present in the literature on, the preparation and the physical and chemical properties of this interesting compound.

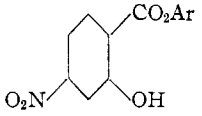
We have prepared I and several other aryl *p*-aminosalicylates as potential antituberculostats. These are listed in Table II. For this purpose, the



a reaction similar to that well-known for the preparation of salol. The use of nitrobenzene (procedure A) was found to be unnecessary for aryl *p*-nitrosalicylates of lower melting points, such as II, III, IV and V. To the nitro-acid esters are common the properties of giving red coloration in dilute alcoholic solution with ferric chloride, of turning red in contact with 1 *N* sodium hydroxide solution, of separating out unchanged from their cold, caustic alkali solution (on carbonation), and of being, unlike free *p*-nitrosalicylic acid, insoluble in 0.1 *N* sodium acetate solution.

TABLE I[d]

ARYL *p*-NITROSALICYLATES



	ArOH	Yield, %	Crystal form; crystallized from	M.p.,[c] °C.	Formula, mol. wt.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I′	Phenol	78[a]	Prisms; methanol	150–151	$C_{13}H_9NO_5$ 259.21	60.23		3.50		5.40	5.51
II′	*p*-Cresol	73[a]	Prisms; methanol	120–122	$C_{14}H_{11}NO_5$ 273.24	61.53	61.26	4.06	4.04	5.13	5.09
III′	*p*-Chloro-*m*-cresol	80[a]	Plates; dil. HAc	120–121	$C_{14}H_{10}NClO_5$ 307.69	54.65	54.61	3.28	3.68	4.55	4.81
IV′	Thymol	76[a]	Prisms; dil. HAc	60–61	$C_{17}H_{17}NO_5$ 315.31	64.75	64.86	5.43	5.75	4.44	4.12
V′	Guaiacol	70[a]	Long prisms; methanol	105–106	$C_{14}H_{11}NO_6$ 289.24	58.13	58.02	3.83	4.85	4.84	4.96
VI′	β-Naphthol	52[b]	Prisms; dil. HAc	188–190	$C_{17}H_{11}NO_5$ 309.27	66.02	66.10	3.59	3.88	4.53	4.55
VII′	*p*-Nitrophenol	[f]	Long prisms; acetic acid[e]	151–152	$C_{13}H_8N_2O_7$ 304.06	51.64	51.47	2.63	2.92	9.15	9.38

[a] Yield of pure product based upon consumed *p*-nitrosalicylic acid. [b] Yield of almost pure product after washing with sodium acetate solution, based upon consumed *p*-nitrosalicylic acid. [c] All melting points are uncorrected values. [d] Analyses were carried out on 3–8-mg. samples (Pregl). [e] Methanol should not be used because of the transesterification which it effects. [f] Not observed.

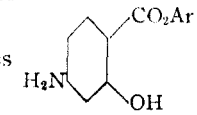
corresponding nitro compounds, listed in Table I, were first prepared by the reaction of *p*-nitrosalicylic acid[2] with the appropriate phenol with (procedure A) or without nitrobenzene (procedure B) as solvent in the presence of phosphorus oxychloride

(1) S. A. Freire, *Compt. rend.*, **231**, 728, 1004 (1950).

(2) (a) W. Borsche, *Ber.*, **42**, 3956 (1909); (b) W. Borsche, *Ann.*, **390**, 3 (1912); (c) J. F. Meghie and C. Morton, *J. Soc. Chem. Ind.*, **68**, 328 (1949).

TABLE II[c]

ARYL *p*-AMINOSALICYLATES



	ArOH	Yield, %	Crystal form; crystallized from	M.p.,[b] °C.	Formula, mol. wt.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
I	Phenol	79[a]	Prisms; dilute methanol	147–148	$C_{12}H_{11}NO_3$ 229.09	68.11	67.83	4.84	4.91		
II	*p*-Cresol	80[a]	Needles; dilute methanol	121–122	$C_{14}H_{13}NO_3$ 243.25	69.12	69.22	5.39	5.59	5.76	5.62
III	*p*-Chloro-*m*-cresol	80[a]	Plates; dilute methanol	133	$C_{14}H_{12}NClO_3$ 277.70	60.55	60.63	4.36	4.38	5.04	5.30
IV	Thymol	86[a]	Prisms and plates; dilute acetic acid	136–137.5	$C_{17}H_{19}NO_3$ 285.33	71.56	71.66	6.71	6.61		
V	Guaiacol	89[a]	Rhombic prisms; dilute methanol	139–140	$C_{14}H_{13}NO_4$ 259.25	64.86	64.75	5.05	5.20	5.40	5.17
					CH_3O	11.99	12.42				
VI	β-Naphthol	83[a]	Prism; dilute methanol	160	$C_{17}H_{13}NO_3$ 279.28	73.11	72.86	4.69	4.41	5.02	4.93

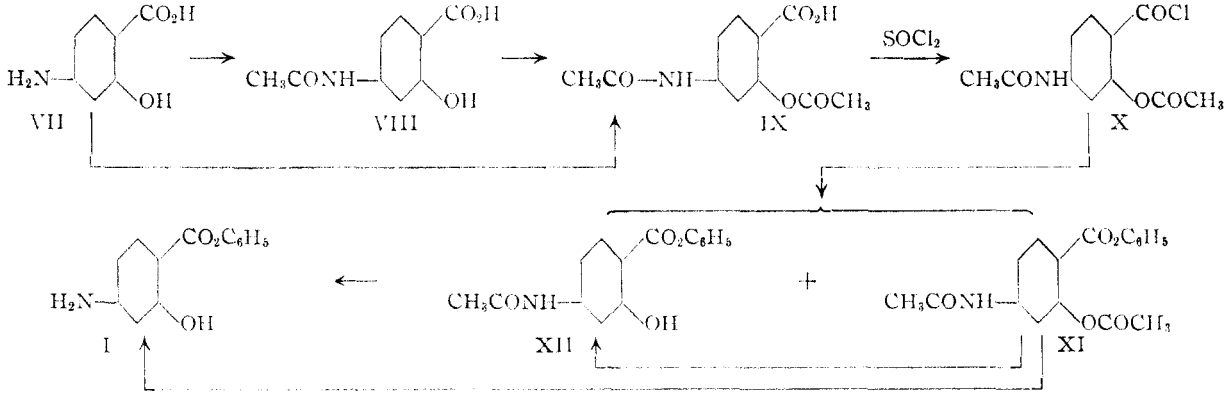
[a] Yield of pure product. [b] All melting points are uncorrected value. [c] Analyses were carried out on 3–8-mg. samples (Pregl).

In this connection, it is interesting to note that the aryl *p*-nitrosalicylates appear to be transformed more or less easily into the alkyl esters by simply longer boiling in an alcoholic solution. A detailed study of this reaction is under way in this Laboratory and will be published later.

Reduction of the aryl *p*-nitrosalicylates (I′–VI′) to the corresponding aryl *p*-aminosalicylates (I–VI) was performed, in excellent yield, by means of stannous chloride in concd. hydrochloric acid–glacial acetic acid medium. An alternative reduction method using zinc dust in the same medium also proved of practical importance. West[3] has described an excellent reduction method of aromatic nitro compounds, including ethyl *p*-nitrobenzoate, to the corresponding amino compounds, in which use is made of iron powder in alcoholic solution in the presence of a trace of concd. hydrochloric acid. The chief advantage of this method is the absence of side reactions such as hydrolysis and chlorination, which sometimes occur with stannous chloride in concd. hydrochloric acid. The method, however, failed to reduce I′ to I. One reason for this is the observed occurrence of the transesterification into the ethyl *p*-nitrosalicylate (m.p. 84–85°); admixture with an authentic sample showed no depression of melting point.

The aryl *p*-aminosalicylates are all insoluble in water, but fairly soluble in common organic solvents with the exception of ligroin and petroleum ether in which they are scarcely soluble in the cold, and separate out unchanged from their cold caustic alkali solution except after too long standing when it is saturated with carbon dioxide. This property was used with advantage in their purification for analytical purpose. The coloration in alcoholic solution with ferric chloride is reddish-violet. Unlike sodium *p*-aminosalicylate, which has bitter taste, they are almost tasteless.

Phenyl *p*-aminosalicylate was also prepared in the following way



In this way, sodium *p*-aminosalicylate (VII) was dissolved, together with an appropriate quantity of sodium carbonate, in water and acetylated in the usual manner with acetic anhydride, so as to yield *p*-acetaminosalicylic acid (VIII), which in turn was converted into O,N-diacetyl-*p*-aminosalicylic acid (IX) by acetylation with acetic anhydride and a trace of sulfuric acid. This was then converted into its acid chloride (X) by treating with thionyl chloride, and the crude product was allowed to react directly with phenol in benzene. In this case, owing to the weakness of the O-acetyl linkage, it underwent partial fission during this reaction, and phenyl N,O-diacetyl-*p*-aminosalicylate (XI) was produced together with phenyl *p*-acetylaminosalicylate (XII). Each could be hydrolyzed to I.

(3) R. W. West, *J. Chem. Soc.*, **127**, 494 (1925).

The final product melted at 148° and when mixed with that prepared above from I', showed no depression of melting point.

In vitro and *in vivo* tests of the aryl *p*-aminosalicylates are in progress in other laboratories and will be reported elsewhere as the work progresses.

Experimental[4]

Preparation of Phenyl *p*-Nitrosalicylate (I'). **Procedure A.**—To a mixture of 50 g. of *p*-nitrosalicylic acid,[2] 30.8 g. of phenol, and 150 ml. of nitrobenzene, heated in an oil-bath at about 110°, was added gradually, with shaking and with the exclusion of moisture from the air, 18.4 g. of phosphorus oxychloride, and heating was continued first at 110° and then at 130–140° for about 2 hr. until the evolution of hydrochloric acid had completely ceased. The desired product separated out for the most part on cooling, and was filtered and washed free from nitrobenzene with benzene. One rapid crystallization of it from 1100 ml. of methanol yielded 39.3 g. (56%) of almost pure phenyl *p*-nitrosalicylate with m.p. 146–148°. Removal of methanol from the mother liquor afforded 11.8 g. of crystalline residue with m.p. 140–200°, which, extracted free from unchanged *p*-nitrosalicylic acid with cold 0.1 *N* sodium acetate solution, yielded 1.1 g. of product with m.p. 144–149°. After distilling off the solvents from the combined first mother liquor and benzene washings, the residue, consisting of almost pure product, was worked up as described above, to yield 5 g. of pure product; m.p. 150–151°. The total yield was 54.4 g. (78.5% of the theoretical amount based upon the consumed *p*-nitrosalicylic acid). VI' also could be prepared in essentially the same way by procedure A.

Phenyl *p*-nitrosalicylate is soluble in not less than about 100 parts of hot methanol, whereas free *p*-nitrosalicylic acid is easily soluble in about 3 parts. Again, it is not soluble in a 0.1 *N* sodium acetate solution, but the free acid is soluble. It has the common properties already mentioned.

Preparation of *p*-Cresyl *p*-Nitrosalicylate (II'). **Procedure B.**—In a 50-ml. round-bottom flask, fitted with a small reflux condenser which in turn was connected, through a calcium chloride tube, to an exit tube, there were mixed 1.83 g. of *p*-nitrosalicylic acid and 1.39 g. of *p*-cresol, and the mixture was heated in an oil-bath at 100°. With shaking, 0.8 g. of phosphorus oxychloride was added in portions. The heating was continued first at 110° for one hour, then at 130–140° for one hour and finally at 140–150° for 30 min. until the gas evolution had ceased. After cooling, the solid which separated out was washed with cold 0.1 *N* sodium acetate solution and water. Recrystallized repeatedly from dilute methanol with decolorizing carbon, this crude product yielded almost colorless prisms melting at 120–122°. The yield was 1.2 g. (73.2%).

p-Cresyl *p*-nitrosalicylate is easily soluble in ether, benzene, chloroform, ethyl acetate or acetone, less soluble in methanol, ethanol or glacial acetic acid, and scarcely soluble in ligroin or water. It has also the other properties common to aryl *p*-nitrosalicylates, already mentioned.

III', IV', IV' and V' also could be prepared in essentially the same way by procedure B.

Preparation of Phenyl *p*-Aminosalicylate (I) (a).—To a solution of 33 g. of crystalline stannous chloride in 36.6 g. of 37% hydrochloric acid and 40 ml. of glacial acetic acid was added in portions, with shaking, 12 g. of powdered phenyl *p*-nitrosalicylate over a period of 10 min., and was boiled for 10 minutes only and immediately cooled. In the meantime the nitroester had gone into solution and a solid appeared instead. Collected and washed successively with small portions (total 50 ml.) of 10% hydrochloric acid and with water, the solid was ground well with excess of aqueous ammonia in a mortar and filtered. The insoluble mass was now extracted two or three times with hot methanol, and the combined and filtered extracts were added with an equal volume of hot water till slightly turbid. On cooling, the desired product separated in the form of long prisms, which, washed with 50% methanol and dried in the air, weighed 8 g. (75%) and melted at 146°. After removal of methanol from the mother liquor, the residue was recrystallized from 50% methanol and gave a further 0.4 g. of product with m.p. 144–146°. The total yield of product with m.p. 144–146° was 8.4 g. (79.5%).

Phenyl *p*-aminosalicylate is easily soluble in methanol, ethanol, acetone, ethyl acetate or benzene, and insoluble in water. When its cold sodium hydroxide solution is saturated with carbon dioxide before too long standing, it separates out unchanged. The color reaction with ferric chloride is reddish-violet. The existence of primary aromatic amino group may be demonstrated by diazotizing, followed by coupling in alkali medium with β-naphthol, yielding a red coloring matter.

Reduction of II', III', IV', V' and VI' to II, III, IV, V and VI, respectively, was performed in the same manner.

(b).—Five grams of powdered phenyl *p*-nitrosalicylate was dissolved in 25 ml. of hot glacial acetic acid and immediately cooled, and 210 ml. of 37% hydrochloric acid was added in one portion, when part of the phenyl ester separated out. To this warm suspension was then added, in portions, with efficient shaking, 6 g. of zinc powder (80% purity) over a period of 10 minutes, the temperature being kept between 50–60°, and the mixture was heated, with vigorous shaking, on a water-bath for only 10 minutes longer and cooled. Enough water was then added to deposit as much of the desired product as possible. When purified as described above, this weighed 3.1 g. (70%), m.p. 147°. Admixture with that prepared under (a) showed no depression of melting point.

As mentioned earlier, West's reduction method[3] failed to reduce the phenyl *p*-nitrosalicylate to phenyl *p*-aminosalicylate, because the trans-esterification occurred to give ethyl *p*-nitrosalicylate, thus:

(c).—0.669 g. of phenyl *p*-nitrosalicylate, 0.258 g. of iron powder and 2.6 ml. of a mixture of 1 ml. of concd. (37%) hydrochloric acid and 99 ml. of 94% ethanol were refluxed together on a water-bath for 4 hours, after which time a dark red solution resulted having the excess of iron deposited. After dilution with 5 ml. of ethanol, just enough of 1 *N* sodium hydroxide in ethanol was added to neutralize the hydrochloric acid used, and heating was applied for awhile. The solid was filtered by the aid of activated carbon and washed with ethanol. The combined filtrates, red in color, were evaporated almost to dryness on a water-bath, in which case a phenol-like odor was detected, and the residue was extracted twice with cold 0.2 *N* sodium hydroxide solution. The combined, clear, red filtrates were saturated with carbon dioxide. The precipitated, light brown solid, when collected and washed with water, and then purified by recrystallization from dilute methanol with activated carbon, produced needle-like crystals with m.p. 84–85°. The product turns red in contact with 1 *N* sodium hydroxide solution, and is easily soluble in cold, more dilute alkali solution to form a light yellow solution, from which it separates out, by examination, unchanged on saturation with carbon dioxide.

Anal. Calcd. for $C_9H_9NO_5$ (211.17): C, 51.19; H, 4.30; N, 6.63. Found: C, 50.87; H, 4.88; N, 6.17.

From these results, it follows that the product is ethyl *p*-nitrosalicylate. In reality, when mixed with a sample of ethyl *p*-aminosalicylate prepared by us directly by the esterification of the free nitro acid with ethanol and sulfuric acid, it showed no depression of melting point.

Preparation of *p*-Acetaminosalicylic Acid (VIII).—*p*-Acetaminosalicylic acid was prepared by acetylating a solution of 10.55 g. of sodium *p*-aminosalicylate and 5.3 g. of anhydrous sodium carbonate in water by means of 7.75 g. of acetic anhydride in the usual manner. The crude product obtained on acidifying the resulting solution with hydrochloric acid was collected and washed with cold water, and weighed 9.3 g. (95.5%) on drying; m.p. 224–225° (decomp.). One recrystallization from hot water did not raise the melting point. Drain,[5] *et al.*, who prepared many derivatives of PAS, reported the m.p. to be 220–222° (dec. on slow heating) and 232° (dec. on rapid heating).

Anal. Calcd. for $C_9H_9NO_4$ (195.17): C, 55.5; H, 4.63; N, 7.16. Found (subs. dried over $CaCl_2$ was analyzed): C, 55.26; H, 4.97; N, 6.96.

p-Acetaminosalicylic acid crystallizes from water in long colorless prisms. It is easily soluble in acetone, methanol or glacial acetic acid, scarcely soluble in benzene, toluene,

(4) All melting points in this paper are uncorrected values. Analyses were all carried out on 3–8-mg. samples (by Pregl method).

(5) D. J. Drain, D. D. Martin, B. W. Mitchell, D. E. Seymour and F. S. Spring, *J. Chem. Soc.*, 1498 (1949).

monochlorobenzene or ethyl acetate, even on heating, and moderately soluble in hot nitrobenzene, insoluble in cold water but soluble in about 150 parts of hot water. Its alcoholic solution gives a reddish-violet coloration with ferric chloride.

Preparation of N,O-Diacetyl-*p*-aminosalicylic Acid (IX).—9.76 g. of the preceding *p*-acetaminosalicylic acid, suspended in 15 g. of acetic anhydride, mixed with 2 drops of concd. sulfuric acid, was heated on a boiling water-bath for about 30 minutes, after which time it had gone into solution to give rise to a dense precipitate. After cooling, the whole was poured into ice-water and allowed to stand overnight. The solid which formed was collected and washed with water. On drying, the product weighed 9.5 g. (80%); m.p. 182–184° (dec.). Careful and rapid recrystallization of one portion from methanol gave a product of fixed melting point of 181–182°.

Anal. Calcd. for $C_{11}H_{11}NO_5$ (237.21): C, 55.25; H, 4.65; N, 5.91. Found: C, 55.07; H, 4.87; N, 6.01.

Properties.—Colorless crystals; m.p. 181–182° (dec.). Drain[6] recorded the m.p. as 189–190.5°. Soluble in hot methanol or ethanol, but less soluble in each in the cold, and very soluble in ethyl acetate even in the cold, but hardly soluble in benzene, toluene, xylene or chloroform. The color reaction with ferric chloride is absolutely negative. It is remarkable inasmuch as the O-acetyl group is very detachable.

N,O-Diacetyl-*p*-aminosalicylic acid could also be prepared in one step from *p*-aminosalicylic acid: (1) By refluxing 53.8 g. of dried and powdered *p*-aminosalicylic acid hydrochloride together with 23.1 g. of freshly fused and powdered sodium acetate and 118 g. of acetic anhydride for 1.5 hours, distilling off most of the excess of acetic anhydride and acetic acid under reduced pressure and pouring the crystalline residue into 610 ml. of ice-water. The precipitated solid was worked up in the usual manner. The product, collected and washed with water, weighed 52 g. on drying and melted at 167–168°. Rapid recrystallization of it from about 160 g. of hot methanol yielded 45 g. (52.2%), m.p. 180.5–181°. (2) 7.65 of powdered, dry *p*-aminosalicylic acid, 20 g. of acetic anhydride and 2 drops of concd. sulfuric acid were heated together on a boiling water-bath for about 1.5 hours, and then poured into 400 ml. of ice-water. The product was isolated and purified as described above.

Preparation of N,O-Diacetyl-*p*-aminosalicyl Chloride (X).—Ten grams of powdered N,O-diacetyl-*p*-aminosalicylic acid, suspended in 40 g. of thionyl chloride, was heated, with occasional shaking, at a temperature below 35°, while avoiding the access of moisture from air, until solution was completed and until the gas evolution had ceased. After heating was continued for 5–10 min. longer, the excess of thionyl chloride was distilled off under reduced pressure, while avoiding temperatures of the bath above 30°. The residual brown mass was kneaded two times with (5:1) petroleum ether–benzene, and then twice with dry petroleum ether (b.p. 50°), each time followed by distilling off the solvent under reduced pressure. The product, light brown in color, melted at about 130° (dec.). For lack of a suitable solvent, no further purification of it was carried out, and analysis was made of it after one day (i) and again after one month (ii) standing in a desiccator over phosphorus pentoxide and by solid potassium hydroxide and also flakes of solid paraffin.

Anal. Calcd. for $C_{11}H_{10}NClO_4$ (255.58): Cl, 13.9. Found: Cl, 11.50 (i), 8.14 (ii).

From these values, the crude product appeared to be of about 83% content of pure N,O-diacetyl-*p*-aminosalicylic chloride, on the unproved assumption that the found Cl content belongs exclusively to this chloride, and to be unstable when stored even in the said condition.

N,O-Diacetyl-*p*-aminosalicyl chloride as obtained is insoluble in petroleum ether, benzine, hardly soluble in benzene, toluene or xylene, also even in chloroform, and easily soluble in acetone.

For characterization, the anilide, m.p. 190–191°, and *p*-acetaminosalicyl anilide, m.p. 252–253°, were prepared simultaneously as follows:

0.2 g. of the crude acid chloride was dissolved by warming in 2 ml. of absolute acetone and immediately cooled, and this solution was dropped into a solution of 0.146 g. of pure aniline in 1 ml. of absolute acetone. After standing at room temperature for 5 minutes, the acetone was removed by evaporation on a water-bath. The oily residue was washed free from unreacted aniline with an excess of dilute (2 *N*) hydrochloric acid and then water. The insoluble solid was extracted several times with ice-cold 1% sodium hydroxide solution. On saturating the combined extracts with carbon dioxide, *p*-acetaminosalicyl anilide separated out. This and the substance which remained undissolved on the alkali extraction were purified by recrystallization from dilute methanol and from methanol, respectively, and *p*-acetaminosalicyl anilide (m.p. 252–253°) and N,O-diacetyl-*p*-aminosalicyl anilide (m.p. 190–191°) were thus obtained.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$ (270.28): C, 66.7; H, 5.19; N, 10.4. Found: C, 66.88; H, 5.49; N, 10.59. (the former substance). Calcd. for $C_{17}H_{16}N_2O_4$ (312.31) (the latter substance): C, 65.37; H, 5.16; N, 8.97. Found: C, 65.60; H, 5.44; N, 8.71.

Preparation of Phenyl N,O-Diacetyl-*p*-aminosalicylate (XI) and Phenyl *p*-Acetaminosalicylate (XII).—The crude N,O-diacetyl-*p*-aminosalicylic chloride as prepared from 4 g. of diacetyl-*p*-aminosalicylic acid as described above, was mixed with 1.6 g. of phenol, diluted with 4 ml. of dry benzene, and was refluxed gently on a water-bath till it had become homogeneous, and evolution of hydrochloric acid had almost ceased. After heating was continued for 10 minutes longer, the solvent and unreacted phenol were removed by distillation under reduced pressure, followed by steam distillation. The residue, collected in the cold, was dissolved in 30 ml. of hot alcohol and allowed to stand. A trace of crystalline precipitate which deposited was filtered off. The alcohol was distilled off from the filtrate, and the brown residue was dissolved in ether and allowed to stand. Some resinous matter which formed was filtered off. The filtrate, dark red in color, was shaken, promptly, first with ice-cold, 5% sodium bicarbonate solution and then with ice-cold, about 0.5 *N* sodium hydroxide solution and finally with water. The now light yellow ether solution, on concentrating, gave a crystalline precipitate, which, collected and washed with a little ether, melted at 141–144°. Recrystallization first from benzene and then from dilute alcohol yielded small, rosette-like aggregates of minute, white needles melting at 147°.

Anal. Calcd. for $C_{17}H_{15}NO_5$ (313.30): C, 65.17; H, 4.83; N, 4.47. Found: C, 65.213; H, 4.77; N, 4.70.

Phenyl N,O-diacetyl-*p*-aminosalicylate is easily soluble in methanol, ethanol, benzene or ethyl acetate, with difficulty soluble in cold ether, but more soluble in hot ether, and insoluble in water. It gives no color reaction with ferric chloride.

Saturation of the above cold 0.5 *N* sodium hydroxide extracts with carbon dioxide gave a crystalline precipitate which was collected and washed with water. When purified by recrystallization first from dilute acetic acid and then from ethyl acetate–petroleum ether, it melted at 178–179° (dec.) and was found to be phenyl *p*-acetaminosalicylate on analysis.

Anal. Calcd. for $C_{15}H_{13}NO_4$ (271.26): C, 66.41; H, 4.8; N, 5.16. Found: C, 65.93; H, 4.71; N, 5.31.

Phenyl *p*-acetaminosalicylate crystallizes from ethyl acetate–petroleum ether in glistening, almost colorless, prismatic crystals, and is easily soluble in methanol, ethanol or ethyl acetate, and hardly soluble in petroleum ether. The color reaction with ferric chloride in alcoholic solution is reddish-violet.

Conversion of Phenyl N,O-Diacetyl-*p*-aminosalicylate (XI) into Phenyl *p*-Acetaminosalicylate (XII) by Partial Hydrolysis.—0.05 g. of the preceding phenyl N,O-diacetyl-*p*-aminosalicylate, dissolved in 1 ml. of warm acetone, was mixed with 0.32 ml. of 1 *N* ammonium hydroxide and allowed to stand, in a small stoppered flask, for 24 hours at room temperature. The addition of 0.16 ml. of 2 *N* hydrochloric acid, followed by enough water, caused the formation of a white precipitate. This was collected and washed with water, and was treated with an excess of cold 0.25 *N* sodium hydroxide solution so as to be freed from a trace of insoluble matter. The clear filtrate was now saturated with carbon dioxide to form a white precipitate. This, after being washed with water, was dissolved in a small amount of ethyl acetate, and while hot was added with petroleum ether until a trace of turbidity appeared. On standing, phenyl *p*-acetaminosalicylate separated out as

prismatic crystals melting at 179–180°. Admixture with that obtained before showed no depression of melting point.

Conversion of phenyl N,O-diacetyl-*p*-aminosalicylate (X) into phenyl *p*-aminosalicylate (I) by partial hydrolysis.

0.03 g. of phenyl N,O-diacetyl-*p*-aminosalicylate, dissolved in 0.3 g. of glacial acetic acid, was mixed with 0.3 ml. of 4 *N* hydrochloric acid and boiled for 5 minutes only and immediately cooled. About 5 ml. of water and then 1.2 ml. of 1 *N* sodium hydroxide were added. The precipitate which formed was collected and washed first with water, then with an excess of cold 2% sodium carbonate solution, and finally with water. To purify the crude product, it was dissolved in ice-cold 0.2 *N* sodium hydroxide solution, and the filtered, clear solution was saturated with carbon dioxide. The precipitated solid, after washing with water, was recrystallized from dilute methanol with decolorizing carbon and formed almost colorless, long prisms melting at 147°. It showed no depression of melting point on mixing with a sample of phenyl *p*-aminosalicylate, prepared from phenyl *p*-nitrosalicylate as described farther above, and in other respects is in accord with the latter.

Anal. Calcd. for $C_{13}H_{11}NO_3$ (229.09): C, 68.11; H, 4.84. Found: C, 67.83; H, 4.91.

We wish to thank heartily Director Dr. Satoru Kuwada for his kind encouragement through this work, and are also indebted to Misses H. Suzuki and Y. Kobayashi, Messrs. M. Kan, H. Kashiwagi and T. Nakata of our Analytical Section.

JUSO, HIGASHIYODOGAWA-KU
OSAKA, JAPAN

RECEIVED OCTOBER 30, 1951

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

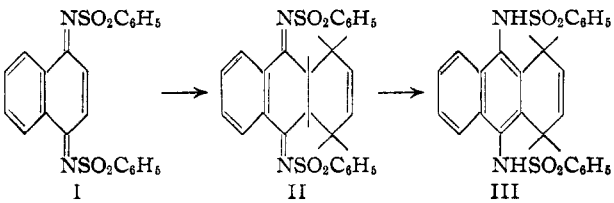
Quinone Imides. IX. Addition of Dienes to 1,4-Naphthoquinonedibenzenesulfonimide

BY ROGER ADAMS AND WILLIAM MOJE

1,4-Naphthoquinonedibenzenesulfonimide adds one molecule of butadiene, isoprene, dimethylbutadiene, chloroprene, cyclopentadiene, anthracene and α-acetoxybutadiene to give the corresponding 1,4,4a,9a-tetrahydro-9,10-anthraquinonedibenzenesulfonimides. The diimides formed from butadiene, isoprene, dimethylbutadiene and chloroprene are rearranged to 1,4-dihydro-9,10-anthracenedibenzenesulfonamides by treatment with mineral acid. The diimides from cyclopentadiene and anthracene dissociate when treated with mineral acid in acetic acid. The diimide from α-acetoxybutadiene when treated with mineral acid is converted to anthracene-9,10-dibenzenesulfonamide. This and 1,4-dihydro-9,10-anthracenedibenzenesulfonamide are oxidized with lead tetraacetate to anthraquinone-9,10-dibenzenesulfonimide which hydrolyzes to anthraquinone by the action of mineral acid. α-Acetoxybutadiene reacts with *p*-quinonedibenzenesulfonimide to give 5-acetoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinonedibenzenesulfonimide which is converted by mineral acid to 1,4-naphthalenedibenzenesulfonamide. This procedure is more convenient than any other previously described for the synthesis of 1,4-naphthalenedibenzenesulfonamide.

p-Quinonedibenzenesulfonimide has been shown to react with dienes[1] but in several instances the products did not correspond to those resulting from the action of dienes on *p*-benzoquinone. In the study of the addition of dienes to 1,4-naphthoquinonedibenzenesulfonimide milder conditions have been employed with excellent results.

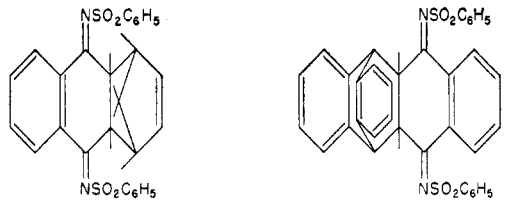
When 1,4-naphthoquinonedibenzenesulfonimide (I) in chloroform was treated with butadiene, isoprene or 2,3-dimethyl-1,3-butadiene, adducts separated. These were readily rearranged by warming with a little mineral acid. The products may be exemplified by the butadiene adduct 1,4,4a,9a-tetrahydro-9,10-anthraquinonedibenzenesulfonimide (II) which rearranged to 1,4-dihydro-9,10-anthracenedibenzenesulfonamide (III). This latter product (III) was also formed when the diimide (I) was heated at 100° with butadiene in benzene, the conditions used previously in the Diels–Alder additions to *p*-quinonedibenzenesulfonimide. Infrared spectra indicate the presence of the carbon–nitrogen double bond in type II and the NH group in type III.



I II III

Chloroprene and 1,4-naphthoquinonedibenzenesulfonimide gave a product (probably of type II) which could not be crystallized but which was converted with hydrobromic acid in acetic acid to a well-defined product of type III.

Cyclopentadiene and anthracene added to 1,4-naphthoquinonedibenzenesulfonimide to give the diimides IV and V, respectively. The adducts



IV V

are unstable and dissociate to the reactants on warming in organic solvents. Attempts to isomerize the adducts IV and V to the corresponding diamides by treatment with mineral acid in acetic acid were unsuccessful.

The diamides of type III derived from butadiene, isoprene, dimethylbutadiene and chloroprene exhibit bright fluorescence when examined under ultraviolet light whereas the corresponding diimides and those from cyclopentadiene and anthracene do not. This fluorescence serves as a satisfactory method for the identification of the primary adducts from 1,4-naphthoquinonedibenzenesulfonimide.

α-Acetoxybutadiene has been added to *p*-benzoquinone and 1,4-naphthoquinone.[2] The adduct

(1) R. Adams and C. R. Walter, THIS JOURNAL, **73**, 1152 (1951).

(2) H. Vollman, F. Schoffer and W. Ostrowski, I. G. Farb. A.-G. (German Patent 739,438); *Chem. Zentr.*, **115**, I, 184 (1944).