326. *Preparation of 4,4′-Diamino-2,2′-dihydroxybenzophenone, a Possibly Tuberculostatic Compound.*

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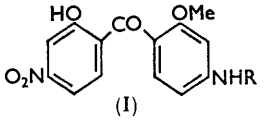
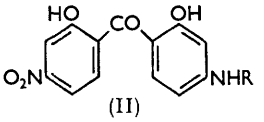
Friedel–Crafts acylation of *N*-acetyl-*m*-anisidine with 4-nitrosalicyloyl chloride yields a mixture of benzophenone derivatives, their yield and nature varying with source of catalyst. 4-Acetamido-2′-hydroxy-2-methoxy-4-nitrobenzophenone and the 2,2′-dihydroxy-analogue are always obtained, sometimes accompanied by 2-acetamido-2′-hydroxy-4-methoxy-4′-nitrobenzophenone. The last ketone appears not to undergo demethylation during the acylation. All three products have been hydrolysed and reduced, to yield two isomeric diaminodihydroxybenzophenones which are to be tested for tuberculostatic activity.

An examination of the tuberculostatic activity and the pharmacological properties of the drugs which combine the active groupings of both *p*-aminosalicylic acid and 4,4-diaminodiphenyl sulphone led Linnell and Stenlake [1] and others [2] to synthesise 4,4′-diamino-2,2′-dihydroxydiphenyl sulphone on the assumption that compounds of this type might exhibit tuberculostatic properties at least of the same order as those compounds on which they were structually based. The activity of the diaminodihydroxy-compound was of the same order as that of 4,4′-diaminodiphenyl sulphone but the toxicity was much lower. It was thought that 4,4′-diamino-2,2′-dihydroxybenzophenone might be a potential inhibiter of *Mycobacterium tuberculosis* as it contained *p*-aminosalicyloyl fragments; it was therefore synthesised.

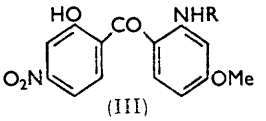
Julia [2] obtained 4,4′-diamino-2,2′-dimethoxydiphenyl sulphone by treating *N*-acetyl-*m*-anisidine and thionyl chloride with excess of anhydrous aluminium chloride in carbon disulphide. Attempts to synthesise the corresponding benzophenone by using carbonyl chloride under various conditions met with failure, the starting material being recovered



(I)



(II)



(III)

in about 90% yield. Julia and Baillarge [3] claimed that the Friedel–Crafts acylation of *N*-acetyl-*m*-anisidine took place in the position *para* to the acetamido-group, the methoxy-group undergoing demethylation during the process. By using *p*-nitrobenzoyl chloride they obtained 4-acetamido-2-hydroxy-4′-nitrobenzophenone. Acylation with 4-nitrosalicyloyl chloride should therefore yield 4-acetamido-2,2′-dihydroxy-4′-nitrobenzophenone.

p-Nitrosalicylic acid was prepared [4,5] from phenylacetic acid, and the corresponding acid chloride obtained by use of thionyl chloride in benzene without previous protection of the phenolic hydroxyl group.

Attempts to synthesise the benzophenones by Fries rearrangement of *m*-acetamidophenyl 4-nitrosalicylate (prepared by the action of 4-nitrosalicyloyl chloride on *m*-acetamidophenol) were unsuccessful.

Friedel–Crafts reaction of acetyl-*m*-anisidine and 4-nitrosalicyloyl chloride with excess of

[1] Linnell and Stenlake, *J. Pharm. Pharmacol.*, 1950, **2**, 736.
[2] Amstutz, *J. Amer. Chem. Soc.*, 1950, **72**, 3420; Julia, *Bull. Soc. chim. France*, 1951, 37.
[3] Julia and Baillarge, *Bull. Soc. chim. France*, 1952, 639.
[4] Borsche, *Ann. Chim.*, 1912, **390**, 1.
[5] McGhie, Moreton, Reynolds, and Spence, *J. Soc. Chem. Ind.*, 1949, **68**, 328.

granulated anhydrous aluminium chloride gave a 90% yield of a mixture of 4-acetamido-2'-hydroxy-2-methoxy-4'-nitrobenzophenone (I; R = Ac), 4-acetamido-2,2'-dihydroxy-4'-nitrobenzophenone (II; R = Ac) and 2-acetamido-2'-hydroxy-4-methoxy-4'-nitrobenzophenone (III; R = Ac), the ratio of (III) to (I) + (II) being 1 : 3. Only compounds (I) and (II) were obtained when powdered aluminium chloride was used. All three compounds were deacetylated by refluxing hydrochloric acid to the corresponding aminonitrobenzophenones. Compound (II) was also obtained by the action of hydrobromic acid on (I).

Compound (I; R = H) was converted into the corresponding diaminodihydroxybenzophenone by constant-boiling hydriodic acid, and the same treatment of compound (III; R = H) gave 2,4'-diamino-2',4-dihydroxybenzophenone and 2-amino-8-hydroxyxanthone in almost equal yields.

Attempts to confirm the structure of 4,4'-diamino-2,2'-dihydroxybenzophenone by its conversion into 2,8-diaminoxanthone [6] failed but on diazotisation followed by treatment with hypophosphorous acid it gave a trihydroxybenzophenone which was neither 2,4,4'- [7] nor 2,2',6-trihydroxybenzophenone (mixed m. p.). Hence it must be the unknown 2,2',4-trihydroxybenzophenone. Deamination of 4,4'-diamino-2,2'-dihydroxybenzophenone gave 2,2'-dihydroxybenzophenone [8] whilst 2,4'-diamino-2',4-dihydroxybenzophenone gave 2,4'-dihydroxybenzophenone, thus confirming the structure of the two diaminodihydroxybenzophenones.

Friedel–Crafts acylation of *N*-acetyl-*m*-anisidine could have taken place in position 2, 4, or 6, the latter being the most likely. Establishment of the structure of the two diaminodihydroxybenzophenones and the fact that 4-amino-2'-hydroxy-2-methoxy-4'-nitrobenzophenone gave an azo-dye and formed a picrate prove that acylation took place mainly at position 6. Had condensation taken place at position 2, the amino-group would have been in the *ortho*-position to the carbonyl group and like compound (III; R = H) would probably not have yielded an azo-dye or formed a picrate because of steric hindrance. The melting point of (I; R = Ac) is higher than that of the isomer (III; R = Ac) but in the corresponding deacetylated compounds the reverse is the case, probably owing to internal salt formation in (III; R = H). The absence of xanthone from products of reaction of the compound (I; R = H) with hydriodic acid unlike the compound (III; R = H) is further evidence in favour of acylation's occurring in position 6.

Experimental

4-Nitrosalicyloyl Chloride.—A mixture of 4-nitrosalicylic acid (25 g.), dry benzene (125 c.c.), and thionyl chloride (60 c.c.) was refluxed for 2½ hr.; the solvent was then removed under reduced pressure and the residue dried under vacuum. 4-Nitrosalicyloyl chloride (27 g.) formed white needles, m. p. 57—60°, from light petroleum (b. p. 60—80°).

m-*Acetamidophenyl 4-Nitrosalicylate.*—To 4-nitrosalicyloyl chloride (from 7·5 g. of the acid) in benzene (30 c.c.) was added *m*-acetamidophenol [9] (7·5 g.) followed by two drops of pyridine; the mixture was refluxed for 2½ hr. The mixture was then cooled and the solvent decanted from the crude ester, which was crystallised from methyl alcohol (charcoal), forming needles of m-*acetamidophenyl 4-nitrosalicylate* (71·0 g., 53%), m. p. 165—166° (Found: C, 57·0; H, 3·6; N, 8·9. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8; N, 8·9%).

4-*Acetamido*-2'-*hydroxy*-2-*methoxy*-4'-*nitrobenzophenone* (I; R = Ac).—4-Nitrosalicyloyl chloride (from 10 g. of the acid) and *N*-acetyl-*m*-anisidine were dissolved in freshly distilled ethylene dichloride (100 c.c.), and to the clear solution powdered anhydrous aluminium chloride (20 g.; May and Baker Ltd.) was added in small portions. The mixture was then refluxed for 3 hr., cooled, and poured into ice and water containing a little hydrochloric acid. After

[6] Julia, *Bull. Soc. chim. France*, 1952, 546; Goldberg and Walker, *J.*, 1953, 1348.
[7] Komoswoski, *Ber.*, 1894, **27**, 1999.
[8] Freer, *Ber.*, 1886, **19**, 2609.
[9] Reverdin and De Luc, *Ber.*, 1914, **47**, 1537.

several hours a yellow precipitate separated. The solvent layer was extracted with 5% sodium hydroxide solution and acidified with dilute hydrochloric acid; more yellow precipitate was thus obtained. The two fractions were combined and treated with sodium hydrogen carbonate solution, and the residue was separated and washed with water to give a mixture (11 g.) of 4-acetamido-2′-hydroxy-2-methoxy-4′-nitrobenzophenone (I; R = Ac) and 4-acetamido-2,2′-dihydroxy-4′-nitrobenzophenone (II; R = Ac). This was dissolved in boiling alcohol (250 c.c.), treated with charcoal and filtered, and the filtrate concentrated to 100 c.c.; bright yellow crystals of *4-acetamido-2′-hydroxy-2-methoxy-4′-nitrobenzophenone* (4·5 g.), m. p. 273—275°, first separated (Found: C, 58·0; H, 4·2; N, 8·6; MeO, 9·1. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·2; N, 8·5; MeO, 9·3%).

4-Acetamido-2,2′-dihydroxy-4′-nitrobenzophenone (II; R = Ac).—The mother liquor from the previous experiment was concentrated under reduced pressure to 20 c.c. and diluted with water; *4-acetamido-2,2′-dihydroxy-4′-nitrobenzophenone* (4·25 g.) then separated, and two crystallisations from methyl alcohol gave yellowish needles, m. p. 241—243° (Found: C, 56·9; H, 3·9; N, 8·7. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8; N, 8·9%).

4-Amino-2′-hydroxy-2-methoxy-4′-nitrobenzophenone (I; R = H).—The acetamido-compound (5 g.) was refluxed with 20% hydrochloric acid (85 c.c.) for 3 hr., and the solution cooled, diluted, and made alkaline with sodium hydrogen carbonate; a red precipitate of *4-amino-2′-hydroxy-2-methoxy-4′-nitrobenzophenone* (3·4 g.) separated, and formed red needles, m. p. 176—178° (from methyl alcohol) (Found: C, 58·2; H, 4·2; N, 10·0. $C_{14}H_{12}O_5N_2$ requires C, 58·3; H, 4·2; N, 9·7%).

4-Amino-2,2′-dihydroxy-4′-nitrobenzophenone (II; R = H).—*Method A.* The above hydrolysis was repeated with 4-acetamido-2,2′-dihydroxy-4′-nitrobenzophenone (3 g.), and the precipitate was recrystallised from 70% alcohol, giving brownish-yellow needles of *4-amino-2,2′-dihydroxy-4′-nitrobenzophenone*, m. p. 224—226° (Found: C, 56·8; H, 3·6; N, 10·1. $C_{13}H_{10}O_5N_2$ requires C, 57·0; H, 3·6; N, 10·2%).

Method B. The compound (I; R = H) (1 g.) was refluxed with a mixture of acetic acid (2 c.c.) and 50% w/w hydrobromic acid (15 c.c.) for 6 hr. and then worked up as described above; 4-amino-2,2′-dihydroxy-4′-nitrobenzophenone (0·75 g.) crystallised from 70% ethyl alcohol, and had m. p. 221—223° alone and in admixture with the sample from method A (Found: C, 56·4; H, 3·4; N, 10·3%).

4,4′-Diamino-2,2′-dihydroxybenzophenone.—4-Amino-2′-hydroxy-2-methoxy-4′-nitrobenzophenone (I; R = H) (5·8 g.) was refluxed with freshly distilled constant-boiling hydriodic acid (75 c.c.) at 140° for 7 hr. The mixture was cooled, diluted, decolorised with sulphur dioxide, and neutralised with sodium carbonate, whereupon *4,4′-diamino-2,2′-dihydroxybenzophenone* (4 g.) was precipitated. Crystallisation from ethyl alcohol gave brown prisms, m. p. 247—248° (Found: C, 64·3; H, 4·9; N, 11·2. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9; N, 11·5%).

4,4′-Diamino-2,2′-dihydroxybenzophenone Dihydrochloride.—The above base (3 g.) was refluxed with a mixture of ethyl alcohol (30 c.c.), hydrochloric acid (5 c.c.), and water (3 c.c.) until a clear solution was obtained, animal charcoal was then added and the solution filtered. Dry hydrogen chloride was then passed into the cold filtrate until it just became cloudy. The *dihydrochloride* (2·9 g.) slowly separated as small dull yellow prisms, m. p. 208° (decomp.) (Found: Cl, 22·4%; *M*, 321. $C_{13}H_{14}O_3N_2Cl_2$ requires Cl, 22·4%; *M*, 317).

2-Acetamido-2′-hydroxy-4-methoxy-4′-nitrobenzophenone (III; R = Ac).—The Friedel–Crafts reaction was repeated but the catalyst used was granulated and made by a different firm (B.D.H. Ltd.). There was isolated a mixture (14·2 g.) of 2-acetamido-2′-hydroxy-4-methoxy-4′-nitrobenzophenone (III; R = Ac), 4-acetamido-2′-hydroxy-2-methoxy-4′-nitrobenzophenone (I; R = Ac), and 4-acetamido-2,2′-dihydroxy-4′-nitrobenzophenone (II; R = Ac). This mixture was refluxed with ethyl alcohol (300 c.c.), treated with charcoal, filtered, and concentrated under reduced pressure to 200 c.c. On cooling very fine white needles (3·5 g.), m. p. 213—215°, of *2-acetamido-2′-hydroxy-4-methoxy-4′-nitrobenzophenone* crystallised (Found: C, 58·5; H, 4·1; N, 8·3. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·2; N, 8·5%).

After the separation of the 2-acetamido-compound the mother liquor was evaporated to leave a residue (10 g.) which was hydrolysed and then treated with hydriodic acid to give 4,4′-diamino-2,2′-dihydroxybenzophenone (6·6 g.).

2-Amino-2′-hydroxy-4-methoxy-4′-nitrobenzophenone (III; R = H).—The compound (III; R = Ac) (2 g.) was refluxed with 20% hydrochloric acid for 3 hr. From the mixture 2-amino-2′-hydroxy-4-methoxy-4′-nitrobenzophenone (1·6 g.) was isolated. Recrystallisation from alcohol

gave bright yellow prisms, m. p. 224—226°, of the *benzophenone* (Found: C, 58·5; H, 4·0; N, 9·3; MeO, 10·8. $C_{14}H_{12}O_5N_2$ requires C, 58·3; H, 4·2; N, 9·7; MeO, 10·8%). The compound does not give an azo-dye or form a picrate.

2,4′-*Diamino*-2′,4-*dihydroxybenzophenone*.—The compound (III; R = H) (3 g.) was treated with hydriodic acid in the same way as was compound (I; R = H). The precipitate obtained after neutralisation with sodium carbonate was refluxed with dilute hydrochloric acid (50 c.c.) for 3 hr. and cooled, a red solid then separated (see next experiment). The filtrate was neutralised with sodium hydrogen carbonate and the precipitate (1·6 g.) crystallised from aqueous alcohol, giving yellow needles, m. p. 190—191°, of 2,4′-*diamino*-2′,4-*dihydroxybenzophenone* (Found: C, 64·0; H, 5·0; N, 11·0. $C_{13}H_{12}O_3N_2$ requires C, 64·0; H, 4·9; N, 11·5%).

2-*Amino*-8-*hydroxyxanthone Hydrochloride*.—An ethanolic solution of the red solid (1·2 g.) from the previous experiment was passed through charcoal, and the alcohol then removed. Crystallisation from 50% alcohol with a little dilute hydrochloric acid gave brown needles of 2-*amino*-8-*hydroxyxanthone hydrochloride*, m. p. >400° (Found: C, 59·2; H, 4·1; N, 4·1. $C_{13}H_{10}O_3NCl$ requires C, 59·2; H, 3·8; N, 5·3%). The compound is hygroscopic.

2,4′-*Diamino*-2′,4-*dihydroxybenzophenone Dihydrochloride*.—2,4′-Diamino-2′,4-dihydroxybenzophenone (3 g.) was refluxed with dilute hydrochloric acid until a clear solution was obtained; this was treated with charcoal, and the filtrate concentrated to $\frac{1}{3}$ of its volume under reduced pressure. 2,4′-*Diamino*-2′,4-*dihydroxybenzophenone dihydrochloride* (2·8 g.) was obtained as minute dull-yellow prisms, m. p. 218° (decomp.) (Found: C, 49·4; H, 4·3; N, 8·7. $C_{13}H_{14}O_3N_2Cl_2$ requires C, 49·2; H, 4·4; N, 8·8%).

Deamination of 4,4′-*Diamino*-2,2′-*dihydroxybenzophenone*.—The 4,4′-diamino-compound (500 mg.), in dilute hydrochloric acid, was diazotised, and then 50% hypophosphorous acid (10 c.c.) was added and stirring continued for 1 hr. The mixture was left for 24 hr., then extracted with chloroform, and the extract dried (Na_2SO_4) and passed through charcoal. Solvent was removed under reduced pressure, the residue (300 mg.) was refluxed with light petroleum (b. p. 60—80°), and the extract filtered and cooled in solid carbon dioxide–acetone to give 2,2′,4-*trihydroxybenzophenone* (125 mg.), needles (from light petroleum), m. p. 132—133° (Found: C, 67·6; H, 4·4. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%). The m. p. was depressed in admixture with 2,2′,6-trihydroxybenzophenone,[10] m. p. 133—134°.

From the mother-liquor yellow crystals were isolated (150 mg.) having m. p. 54—56°; this was probably the 2,2′-dihydroxybenzophenone.

Deamination of 2,4′-*Diamino*-2′,4-*dihydroxybenzophenone*.—The 2,4′-diamino-compound (200 mg.) was similarly deaminated; the mixture after removal of chloroform yielded 2,4′-dihydroxybenzophenone (100 mg.), as plates (from water), m. p. and mixed m. p. 143—145° (Found: C, 71·6; H, 4·5. Calc. for $C_{13}H_{10}O_3$: C, 71·9; H, 4·7%).

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[10] Michael, *Amer. Chem. J.*, 1883, **5**, 89.