

179. *Substituted Benzilic Acids and Benzophenones.*

By A. H. FORD-MOORE.

A method for preparing substituted benzilic acids is described. Since these acids can be oxidised smoothly to the corresponding benzophenone, a number of the latter compounds which cannot be prepared by the Friedel-Crafts method are made available. The ethochlorides of the dimethylaminoethyl esters of some of these acids have been prepared, and their mydriatic activity measured against atropine sulphate.

In a recent paper (Ford-Moore and Ing, this vol., p. 55), a number of synthetic mydriatics was described. One of these compounds, benzilyloxyethyldimethylethylammonium chloride (I; $R_1 = R_2 = \text{Ph}$), for which the name "Lachesine" has been suggested, was found to have a mydriatic activity equal to that of atropine sulphate. Certain other compounds in which



substituents were introduced into the benzene nuclei of (I) were also prepared but were not then described. The result of this substitution was to reduce greatly, or even to abolish, the mydriatic activity of the compound.

This paper describes the preparation of the substituted benzilic acids used. These are mainly symmetrically disubstituted acids, but two monosubstituted acids were prepared and are included.

Two methods are available for the preparation of benzilic acids; oxidation of a benzoin with bromate and alkali, and treatment of a benzil with aqueous-alcoholic potash. Since the benzoin of substituted benzaldehydes could not usually be made to solidify, whereas the corresponding benzils were highly crystalline, the second method was adopted. Most of the substituted benzils are, however, so sparingly soluble in aqueous-alcoholic potash that conversion into the benzilic acid either takes place very slowly or not at all. Since these acids decarboxylate somewhat readily to give the benzhydrol, it is not safe to prolong the potash treatment for more than ten minutes.

Rearrangement of the substituted benzils can be brought about very readily by heating for ten minutes or less with a 20% solution of potassium hydroxide in hot *n*-butanol. In certain cases, the potassium salt of the acid separates out and only requires to be filtered off, washed with a little ether, dissolved in water, and acidified. Where the potassium salt is soluble in butanol, it can be extracted with water, a little ether being added to facilitate separation into two layers.

When the aqueous solution of the potassium salt is acidified, there is a strong tendency for the acid to separate in an obstinately gummy condition. Crystallisation can usually be induced by adding a small amount of a suitable solvent (benzene or petrol) and scratching. Seed, if available, will greatly hasten solidification.

The substituted benzilic acids are oxidised smoothly and in good yield by chromic anhydride in acetic acid to the corresponding benzophenone (cf. Jena, *Annalen*, 1870, 155, 83). A number of the latter compounds, which cannot be prepared by the usual Friedel-Crafts method, are therefore made available.

Two monosubstituted benzilic acids, *viz.*, phenyl- α -naphthyl- and phenyl- β -naphthylglycollic acids, were described by Ford-Moore and Ing (*loc. cit.*). The same method as had been used for preparing these acids, *viz.*, *via* the deoxybenzoin, the *isonitroso*-derivative, and the benzil, was adopted for preparing phenyl-*p*-tolylglycollic acid and 4-chlorobenzilic acid. The monosubstituted benzils, obtained in the penultimate step, are much more soluble in aqueous-alcoholic potash than are the disubstituted benzils, and no difficulty was experienced in converting them into the corresponding benzilic acids by means of this reagent.

Mydriatics from Substituted Benzoic Acids.—These compounds were made by the same method as was used for preparing (I), *i.e.*, treatment of β -chloroethyldimethylethylammonium chloride with the potassium salt of the acid in ethanol (Ford-Moore and Ing, *loc. cit.*). The compounds so obtained were useless as mydriatics. Nevertheless, they serve to illustrate the striking decrease in mydriatic activity on introducing substituents into the benzilyloxy-moiety of (I).

EXPERIMENTAL.

2 : 2'-Dimethoxybenzoic Acid.—*o*-Anisil (2 : 2'-dimethoxybenzil) (35 g.) was added to a solution of potassium hydroxide (17 g.) in boiling *n*-butanol (90 c.c.), and the mixture refluxed for 10 minutes. After cooling, the mixture was extracted three times with 100-c.c. portions of water, some ether being added to facilitate separation into two layers. The combined aqueous extracts were extracted once with ether (50 c.c.) to remove any dissolved butanol, freed from ether with a current of air, and acidified to Congo-red with hydrochloric acid. The dimethoxybenzoic acid was precipitated as a sticky mass which, if it did not solidify rapidly, could be made to do so by decanting the water, adding about 20 c.c. of benzene, and scratching. The yield was 33 g., m. p. 160°, after crystallising from methanol (Found : C, 66.4; H, 5.5. $C_{16}H_{16}O_5$ requires C, 66.6; H, 5.6%).

Piperonic (3 : 4 : 3' : 4'-bismethylenedioxybenzoic) acid, m. p. 139° from ethyl acetate (Found : C, 61.0; H, 4.0. $C_{16}H_{14}O_7$ requires C, 60.8; H, 3.8%), 4 : 4'-dimethoxybenzoic acid, m. p. 171° (decomp.), from methanol (Bösler, *Ber.*, 1881, 14, 327, gives 164°) (Found : C, 66.35; H, 5.7. Calc. for $C_{16}H_{16}O_5$: C, 66.6; H, 5.6%), and 3 : 3'-dichlorobenzoic acid, m. p. 110° from benzene-petrol (Klimont, *Diss.*, Heidelberg, 1891, gives 114—115°) (Found : C, 56.4; H, 3.4. Calc. for $C_{14}H_{10}O_3Cl_2$: C, 56.55; H, 3.35%), were prepared similarly. The last compound was rather reluctant to crystallise but could be made to do so by adding petrol (b. p. 40—60°) and scratching.

5 : 5'-Dibromo-2 : 2'-dimethoxybenzoic Acid.—The corresponding benzil (cf. Kuhn, Birkofer, and Möller, *Ber.*, 1943, 76, 903), m. p. 231° (20 g.), was treated with potash-butanol (7 g.; 40 c.c.) as for the dimethoxybenzil. On cooling, the potassium salt of the acid separated. It was filtered off, washed free from butanol with ether, and freed from ether by standing in the air for a short time. It was dissolved in water and acidified with hydrochloric acid; yield, 18 g., m. p. 181°, after crystallising from methanol (Found : C, 42.9; H, 3.25. $C_{16}H_{14}O_5Br_2$ requires C, 43.1; H, 3.15%).

Veratric acid (3 : 3' : 4 : 4'-tetramethoxybenzoic acid) was prepared similarly; it melted at 131° after crystallising from ethyl acetate (Vanzetti, *Atti R. Accad. Lincei*, 1936, 24, II, 468, gives *ca.* 68°) (Found : C, 61.9; H, 5.8. Calc. for $C_{18}H_{20}O_7$: C, 62.05; H, 5.8%).

These acids show a tendency to undergo partial decarboxylation. The benzhydrol so formed is difficult to remove by recrystallisation. Purification is readily effected by dissolution in dilute sodium carbonate solution, filtration (carbon), acidification, and crystallisation from a suitable solvent.

2 : 2'-Dimethoxybenzophenone.—2 : 2'-Dimethoxybenzoic acid (21.5 g.) was dissolved in boiling glacial acetic acid (100 c.c.) and oxidised by gradual addition of powdered chromic anhydride (5.5 g.). The reaction proceeded without the application of heat. When it was complete (10 mins.), the mixture was poured into water. The ketone, which rapidly solidified, was filtered off and washed free from chromium salts successively with water, dilute sodium carbonate, and water; yield 15 g., m. p. 103°, after crystallising from methanol (Graebe and Feer, *Ber.*, 1896, 19, 2610, give 104°; Richter, *J. pr. Chem.*, 1883, 23, 287, gives 98°).

3 : 3' : 4 : 4'-Tetramethoxybenzophenone, m. p. 147° from ethanol (Kostanecki and Tambor, *Ber.*, 1906, 39, 4027, give 145°), 5 : 5'-dibromo-2 : 2'-dimethoxybenzophenone, m. p. 128° (Diels and Rosenmund, *ibid.*, p. 2362, give 123°), and 3 : 3'-dichlorobenzophenone, m. p. 123—124° from methanol (Found : C, 62.3; H, 3.5. $C_{18}H_{16}OCl_2$ requires C, 62.2; H, 3.2%), were prepared similarly from the appropriate benzoic acid.

4-Chlorobenzoic acid and phenyl-*p*-tolylglycollic acid were prepared by the method described in the text. The former melted at 131° (Found : C, 64.1; H, 4.45. $C_{14}H_{11}O_3Cl$ requires C, 64.0; H, 4.2%), and the latter at 132° (Weiss, *Monatsh.*, 1919, 40, 396, gives 131—133°), both having been crystallised from benzene.

Colour with Concentrated Sulphuric Acid.—The benzoic acids described above gave the following colours with concentrated sulphuric acid : 2 : 2'-dimethoxy-, brilliant greenish-blue; 4 : 4'-dimethoxy-, brilliant bluish-green; 3 : 3' : 4 : 4'-tetramethoxy-, brilliant bluish-green; 3 : 4 : 3' : 4'-bis-methylenedioxy-, dark greenish-brown; 5 : 5'-dibromo-2 : 2'-dimethoxy-, brilliant bluish-green; 3 : 3'-dichloro-, violet; 4-chloro-, orange-red; phenyl-*p*-tolylglycollic acid, dark reddish-brown.

Dimethylaminoethyl ester ethochlorides and their mydriatic activity.*

Serial number.	In (I) :		M. p. †	Analysis, %.				R.M.P. ‡
	R ₁ =	R ₂ =		Found :		Reqd. :		
				C.	H.	C.	H.	
E19	3 : 4-CH ₂ O ₂ :C ₆ H ₅		225° (d.)	58.30	5.77	58.46	5.80	0
E18	<i>p</i> -OMe-C ₆ H ₄	<i>p</i> -OMe-C ₆ H ₄	136°	62.54	7.28	62.36	7.08	8
E20	<i>m</i> -Cl-C ₆ H ₄	<i>m</i> -Cl-C ₆ H ₄	218—220° (d.)	55.61	5.50	55.50	5.59	0
E24	<i>p</i> -Me-C ₆ H ₄	Ph	189—190°	67.00	7.44	66.75	7.47	16
E23	<i>p</i> -Cl-C ₆ H ₄	Ph	196—197°	60.33	6.37	60.32	6.33	0

* Cf. Ford-Moore and Ing (*loc. cit.*).

† The solvent used for recrystallisation was ethanol-acetone.

‡ Relative molar potency (atropine sulphate = 100) on mouse eye.

The microanalyses were carried out by Mr. W. Brown and by Messrs. Weiler and Strauss.

The work described in this paper, which is published by permission of the Director General of Scientific Research (Defence), Ministry of Supply, was carried out while the author was a member of Sir Robert Robinson's team in the Dyson Perrins Laboratory, Oxford.

MINISTRY OF SUPPLY,
CHEMICAL DEFENCE EXPERIMENTAL STATION,
PORTON, WILTSHIRE.

[Received, October 23rd, 1946.]
