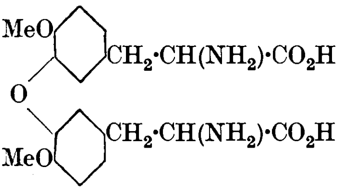
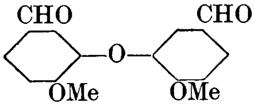
CCCCXXXIX.—*Preliminary Synthetical Experiments in the Morphine Group. Part II. Some Derivatives of Diphenyl Ether.*

By ROBERT ROBINSON and SHIGEHIKO SUGASAWA.

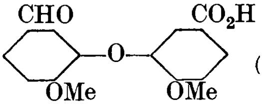
FOR reasons explained in Part I we are very interested in the properties of the amino-acid (I) and although our work is not yet completed some progress can be reported.

(I.)





(II.)



(III.)

The preparation of 2 : 2′-dimethoxydiphenyl ether (Ullmann and Stein, *Ber.*, 1906, **39**, 624) from *o*-bromoanisole and guaiacol in the presence of potassium carbonate has been improved by the addition of pyridine, and the Gattermann aldehyde-synthesis applied to the ether gives a poor yield of 2 : 2′-*dimethoxy*-5 : 5′-*diformyldiphenyl ether* (II).

The constitution of the dialdehyde follows from its synthesis from *iso*vanillin and 2-bromoanisaldehyde, but, although it condenses normally with hippuric acid to a bis(arylidene)bisphenyloxazolone, a better method of preparation must be our next objective in order to render feasible the continuation of the research.

The route through 5 : 5′-dinitro-2 : 2′-dimethoxydiphenyl ether failed at the stage of replacement of the amino-groups of the related amine by cyano-groups, but the synthesis of 2 : 2′-dimethoxy-5-formyl-5′-carboxydiphenyl ether (III) gave moderately satisfactory results. The work is being continued.

EXPERIMENTAL.

2 : 2′-*Dimethoxy*-5 : 5′-*diformyldiphenyl Ether* (II).—2 : 2′-Dimethoxydiphenyl ether was prepared by the method of Ullmann and Stein (*loc. cit.*) and the following improved modification furnishes the same substance.

A mixture of guaiacol (9·3 g.), *o*-bromoanisole (9·3 g.), copper bronze (0·5 g.), anhydrous potassium carbonate (7 g.), and pyridine

(1 g.) was heated (oil-bath) for an hour at 180°. Dilute hydrochloric acid was added after cooling and unchanged substances were removed in a current of steam. The product was isolated from the residue by means of ether and was crystallised from light petroleum with the addition of a little benzene (yield, 6—7 g.; m. p. 77—78°).

In applying the Gattermann synthesis to this ether, zinc chloride was found to be inadequate as a condensing agent.

Finely powdered aluminium chloride (7·0 g.) was gradually added to a solution of dimethoxydiphenyl ether (4·2 g.) in benzene (30 g.) and, after cooling, anhydrous hydrogen cyanide (2·7 g.) was introduced in one portion. The mixture was stirred and cooled in melting ice; dry hydrogen chloride was led into the mixture during an hour, the temperature was then raised to, and maintained at, 45—50°, and the passage of the gas continued for 1 hour. After cooling, the benzene layer was decanted and the residue washed with ether; the brown mass was decomposed with ice-water and hydrochloric acid and the process was completed on the steam-bath. The aqueous solution was fully extracted with ether and in this way a small amount of a pale yellow substance was isolated; this crystallised from benzene–light petroleum in clusters of needles, m. p. 136° (yield, 0·3 g.).

This is the *dialdehyde*, as was proved by the following alternative synthesis.

A mixture of *iso*vanillin (3 g.), bromoanisaldehyde (4·3 g.), copper-bronze (0·2 g.), potassium carbonate (2·8 g.), and pyridine (0·5 c.c.) was heated (oil-bath) at 190° for 1 hour. The aldehydes contained in the product were extracted with sodium bisulphite solution, liberated by sodium hydroxide, and isolated by means of ether. The solid, freed from bromoanisaldehyde by trituration with benzene, crystallised from benzene–light petroleum in pale yellow needles, m. p. 136—137° (Found: C, 67·1; H, 5·1. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The melting point of a mixture of the specimens made by the two methods was 135—136°.

The *dioxime* crystallises from alcohol in colourless needles, m. p. 192° (Found: C, 60·4; H, 5·3; N, 8·9. $C_{16}H_{16}O_5N_2$ requires C, 60·6; H, 5·1; N, 8·9%). This derivative was also prepared from both specimens and the melting point of a mixture was not depressed.

Dianhydro-(2 : 2′-dimethoxy-5 : 5′-diformyldiphenyl ether) bis-2-phenyloxazolone.—The dialdehyde (0·4 g.) along with hippuric acid (0·5 g.), fused sodium acetate (0·2 g.), and acetic anhydride (5 c.c.), was heated for 1 hour on the steam-bath. The yellow crystalline product was successively washed with alcohol, hot water, alcohol and ether and crystallised from acetic acid. The compact yellow crystals had m. p. 223—225° (Found : N, 5·1. $C_{34}H_{24}O_7N_2$ requires N, 4·9%). The substance has the properties of the type.

5 : 5′-*Dinitro*-2 : 2′-*dimethoxydiphenyl Ether.*—Nitric acid (50 g., *d* 1·42), mixed with acetic acid (50 g.), was gradually added to a solution of 2 : 2′-dimethoxydiphenyl ether (15 g.) in acetic acid (25 c.c.) with cooling in running water. On standing, the solution became filled with a yellow substance, which was isolated and found to melt over a range (115—165°); it was therefore by no means homogeneous. The more soluble constituents could be removed by repeated extraction with small volumes of hot methyl alcohol, and the residue then melted at 170°. It crystallised from acetic acid in yellow prisms, m. p. 174° (Found: C, 52·2; H, 3·7; N, 9·1. $C_{14}H_{12}O_7N_2$ requires C, 52·5; H, 3·7; N, 8·9%).

The related diamine (m. p. 163°, not quite pure) had the properties of a *p*-aminoanisole of this series and developed a blue colour with ferric chloride in dilute hydrochloric acid solution (compare Luff, Perkin, and Robinson, J., 1910, **97**, 1131). For this reason, and also on account of the experiments of Lea and Robinson (J., 1926, 411) on the relative directive powers of alkyloxy- and aryloxy-groups, the constitution given in the title is proposed.

The Sandmeyer method for the introduction of the cyano-group has not yet given satisfactory results in this case.

2 : 2′-*Dimethoxy*-5-*formyl*-5′-*carboxydiphenyl Ether* (III).—*iso*-Vanillic acid was prepared by the partial hydrolysis of veratric acid by means of hydrogen bromide (compare Lovecy, Robinson, and Sugasawa, J., 1930, 817).

The potassium salt of ethyl *iso*vanillate was obtained by mixing ethyl *iso*vanillate with the theoretical amount of potassium ethoxide in alcoholic solution. Dry ether was added to complete the separation of the salt, which was collected and dried in a vacuum. A mixture of the potassium salt of ethyl *iso*vanillate (5 g.), 2-bromoanisaldehyde (5 g.), copper bronze (0·2 g.), and dry copper acetate (0·2 g.) was heated (oil-bath at 170—180°) for 4 hours. The dark brown resinous mass was extracted thoroughly with ether, the solvent removed, and the residue hydrolysed by means of alcoholic potassium hydroxide.

After removal of the alcohol, water was added and the solution repeatedly extracted with ether; the aqueous layer was then acidified and the precipitate was collected and treated with hot aqueous sodium bisulphite, which dissolved almost the whole of it. The cooled solution was clarified by filtration through a moistened paper, and acidified with hydrochloric acid, and the voluminous precipitate collected and crystallised, first from alcohol and then from benzene–alcohol; it formed colourless grains, m. p. 212° after sintering at

208—209° (Found : C, 63·7; H, 4·8. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). It is curious that this preparation gave inferior results when the potassium salt of methyl *iso*vanillate was employed.

UNIVERSITY COLLEGE, LONDON.
THE UNIVERSITY OF OXFORD.

[*Received, November* 12*th*, 1931.]