CVI.—*A Synthesis of Unsymmetrical Diphenyl Derivatives.*

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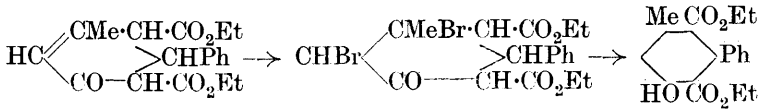
THE systematic extension of the researches on the chemistry of diphenyl, with which one of us has been concerned, would clearly be facilitated by a method which would render unsymmetrical derivatives as accessible as symmetrical derivatives have been since Ullmann worked out his copper powder method (*Annalen*, 1904, **332**, 38). Although this method has recently been applied with success to the preparation of 2 : 4-dinitro- and 2 : 4 : 6-trinitro-diphenyl, 2 : 4-dinitrodiphenyl-6-carboxylic acid and its 2′-methyl derivative (Gull and Turner, J., 1929, 491; Lesslie and Turner, J., 1930, 1758), limitations to its general use for the synthesis of unsymmetrical derivatives are to be expected, and these were encountered by Späth and Gibian in their recent synthesis of 2 : 4 : 3′ : 4′-tetramethoxydiphenyl (*Monatsh.* 1930, **55**, 342; compare Mayer and Freitag, *Ber.*, 1921, **54**, 356).

An alternatively possible mode of approach would consist in the oxidation of the numerous derivatives of 5-phenyl*cyclo*hexene-1-one, prepared by Knoevenagel and his collaborators (*Annalen*, 1898, **303**, 223). Since, however, these workers had previously recorded the oxidation by bromine of the corresponding methyl*cyclo*hexenones to derivatives of *m*-cresol (*Annalen*, 1894, **281**, 25), it can hardly be doubted that they also attempted to apply their method to the phenyl derivatives, but without success. A similar failure has latterly been recorded by Petrow (*Ber.*, 1929, **62**, 642) in the case of 3 : 5-diphenyl-Δ^2-*cyclo*hexen-1-one.

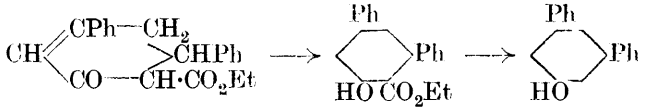
We have, however, found that the carbethoxy-derivatives, from which these *cyclo*hexenones were obtained, are susceptible of oxidation. For instance, ethyl 5-phenyl-3-methyl-Δ^2-*cyclo*hexen-1-one-4 : 6-dicarboxylate (I) yields a *dibromide* (II), which has such a tendency to suffer loss of hydrogen bromide that even after repeated crystallisation from mixed solvents at the ordinary temperature we were unable to obtain a specimen containing quite as

much bromine as the formula demands. It is, therefore, not surprising that the dibromide is smoothly convertible by treatment



(I.) (II.) (III.)

with quinoline into *ethyl 3-hydroxy-5-methyldiphenyl-2 : 6-dicarboxylate* (III), which has been further characterised by its *methyl* ether and hydrolysis of the latter to the corresponding *dicarboxylic acid*, and to its *monoethyl* ester.



(IV.) (V.)

The diphenyl*cyclo*hexenone studied by Petrow was obtained by Knoevenagel from the ester of its 6-carboxylic acid, and we find that in the case of the latter compound the tendency of the dibromide to pass into the aromatic condition is so pronounced that it is convenient to carry out the formation of the dibromide at a low temperature in glacial acetic acid solution, and then, by raising the temperature, to proceed at once to the formation of *ethyl* 4 : 6-*diphenylsalicylate* (IV). The free *acid* is formed in certain amount under these conditions, and it has also been obtained in the usual manner by hydrolysis. It furnishes the usual blue salicylic acid coloration with ferric chloride, and 3 : 5-*diphenylphenol* (V) has been obtained from it in satisfactory yield by distillation with lime. This compound resembles *m*-5-xylenol in that it gives no coloration with ferric chloride.

The alkaloid salts of 3-methoxy-5-methyldiphenyl-2:6-dicarboxylic acid are in general not easy to obtain in the crystalline condition, but we isolated a well-defined *acid quinine* salt and also a *codeine* salt, which is, however, less easy to manipulate. Neither of these afforded any evidence that the acid could exist in enantiomorphous forms, and this evidence, so far as it goes, confirms the conclusion reached by Turner and Lesslie (*loc. cit.*). The alkaloid salts derived from the ethyl hydrogen ester were also not amenable to crystallisation. Further evidence in this connexion will, however, become available by extensions of the synthesis which will be described later.

This is, however, by no means the only interest attaching to these experiments, for it is evident from the results now communicated that illuminating gradations in the readiness of transition to the aromatic condition may be expected. It is clear that the α-ketonic

ester group is an essential factor in this, and that its influence is due to its providing a centre of unsaturation in the ring structure itself, for both of the dibromides from which the aromatic compounds are prepared impart a strong reddish-purple colour to ferric chloride solution.

EXPERIMENTAL.

Dibromide of Ethyl 5-*Phenyl*-3-*methyl*-Δ^2-cyclo*hexen*-1-*one*-4 : 6-*dicarboxylate*.—A solution of bromine (9·7 g.) in carbon disulphide (20 c.c.) was added to a solution of the unsaturated ester (20 g.) in carbon disulphide (25 c.c.) previously cooled in ice. Decolorisation was immediate, all crystalline material passed into solution, and some evolution of hydrogen bromide always occurred. The solvent was removed by aspirating a current of air through the solution, and warming it on the water-bath. When stirred with alcohol, the residue at once formed prismatic crystals (17 g.), m. p. about 93°. It was sufficiently pure for the subsequent treatment with quinoline, and imparted to ferric chloride solution a strong reddish-purple colour quite distinct from that produced by the phenol devolved from it. For analysis, it was purified by addition of alcohol to its solution in acetone prepared at the ordinary temperature. However, even when heat was avoided throughout the above preparation, and the product was crystallised three times until it melted constantly at 93—94°, the content of bromine could not be raised above 30·6% ($C_{19}H_{22}O_5Br_2$ requires Br, 32·65), and hydrogen bromide was evolved when the product was kept in a stoppered bottle. The formation of the *dibromide* occurred much less slowly in glacial acetic acid.

Ethyl 3-*Hydroxy*-5-*methyldiphenyl*-2 : 6-*dicarboxylate*.—A mixture of the above dibromide (20 g.) with freshly distilled quinoline (20 c.c.) was heated in an oil-bath. Reaction set in when the temperature of the mixture was about 90°, this rose rapidly to about 110°, and was only overtaken by that of the surrounding medium after further heating. Evolution of gas commenced at 143°, and was the signal to discontinue the operation and isolate the product. This was achieved by treatment with dilute sulphuric acid at 90°, followed by extraction of the cooled mixture with ether. The washed ethereal extract was treated with dilute sodium hydroxide solution, and the latter acidified. The *ester* (15 g.) at once crystallised and, after purification by crystallisation from alcohol, was obtained in stout prisms, m. p. 94° (Found : C, 69·3; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). It imparted a dull wine-red colour to ferric chloride solution, but this gradually faded to light brown.

An attempt to combine the above two operations by the use of

quinoline perhydrobromide (Rosenmund and Kuhnhenn, *Ber.*, 1923, **56**, 1264) met with no success.

The *methyl* ether, prepared in the usual manner by the aid of methyl sulphate, separated from alcohol or ligroin in leaflets, m. p. 98° (Found : C, 69·9; H, 6·4. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%). It underwent hydrolysis in two stages.

The corresponding *dicarboxylic acid* was obtained when this methyl ether (4 g.) was boiled with a solution (30 c.c.) of potassium hydroxide (6 g.) in methyl alcohol for 18 hours. It crystallised from hot water, containing alcohol (5%), in small leaflets, m. p. 297° (decomp.) (Found : C, 67·2; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The *acid quinine* salt was prepared by mixing equivalent quantities of the acid and the base in methyl-alcoholic solution. It crystallised from alcohol in fine needles, m. p. 186° (decomp.) (Found : N, 4·6. $C_{36}H_{38}O_7N_2$ requires N, 4·6%). For a 0·15% solution in chloroform, $[\alpha]_D^{20·5°} = -43°$, and a solution of the ammonium salt of the regenerated acid was quite inactive towards polarised light. The *acid codeine* salt (minute leaflets), similarly prepared, melted somewhat indefinitely at 161—165° (Found : N, 2·45. $C_{34}H_{35}O_8N$ requires N, 2·4%). For a 0·6% solution in water, $[\alpha]_D^{16°} = -99·1°$, and the solution of the ammonium salt prepared from it was quite inactive. An *ethyl hydrogen* ester could be isolated when the above process of hydrolysis was interrupted after 4 hours. The mixture of acid products was extracted with hot benzene, in which the dicarboxylic acid is very sparingly soluble. The acid ester crystallised from the solution, and after further purification by crystallisation from dilute formic acid, prisms, m. p. 153°, were obtained (Found : C, 68·6; H, 5·5. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). We were unable to discover an alkaloid salt of the acid ester amenable to crystallisation.

Ethyl 4 : 6-*Diphenylsalicylate.*—When an ice-cold suspension of ethyl 3 : 5-diphenyl-Δ^2-*cyclo*hexen-1-one-6-carboxylate (5·8 g.) in carbon disulphide (20 c.c.) was treated with a solution of bromine (2·9 g.) in carbon disulphide (10 c.c.), hydrogen bromide was at once evolved, and further quantities of the gas were generated when an ethereal solution of the crude product was washed with dilute sodium carbonate solution, dried, and evaporated on the steam-bath. In subsequent operations, therefore, a solution of the ester (60 g.) in glacial acetic acid (100 c.c.), cooled in ice, was carefully treated with a solution of bromine (30 g.) in glacial acetic acid (30 c.c.). After 10 minutes the evolution of hydrogen bromide had slackened sufficiently to allow water to suck back from a wash-bottle connected to the apparatus. The mixture was then gently boiled until similar evidence was obtained that the further evolution was

complete. The mixture was then poured into twice its volume of water, and the precipitate dissolved in hot ligroin. A quantity of diphenylsalicylic acid having been removed by washing the solution with dilute sodium carbonate solution, the *ester* was obtained in magnificent prisms, m. p. 89° (Found : C, 79·15; H, 5·8. $C_{21}H_{18}O_3$ requires C, 79·2; H, 5·7%). The material imparted a dark reddish-purple colour to ferric chloride solution, but this gradually lightened to a brown colour.

The *methyl* ether separated from ligroin in prisms, m. p. 115° (Found : C, 79·4; H, 6·2. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%).

4 : 6-*Diphenylsalicylic acid* was obtained in the manner already indicated, or by boiling a solution of the ester (10·5 g.) and of potassium hydroxide (20 g.) in methyl alcohol (50 c.c.) for 12 hours. It crystallised from alcohol in soft masses of needles, m. p. 204° (decomp.) (Found : C, 78·5; H, 5·0; equiv., 289. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%; *M*, 290).

4 : 6-*Diphenyl*-o-*anisic acid*, similarly prepared from its methyl ester, crystallised from alcohol in triangular plates, m. p. 218° (Found : C, 78·7; H, 5·4. $C_{20}H_{16}O_3$ requires C, 78·9; H, 5·3%).

3 : 5-*Diphenylphenol* was produced when an intimate mixture of diphenylsalicylic acid (1 g.) with lime (5 g.) was distilled. It separated from ligroin in masses of minute prisms, m. p. 95° (Found : C, 87·6; H, 5·8. $C_{18}H_{14}O$ requires C, 87·8; H, 5·7%). The phenol was not soluble in sodium carbonate solution. Its *benzoyl* derivative crystallised from dilute alcohol in a felted mass of soft needles, m. p. 124° (Found : C, 85·9; H, 5·4. $C_{25}H_{18}O_2$ requires C, 85·7; H, 5·1%).

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