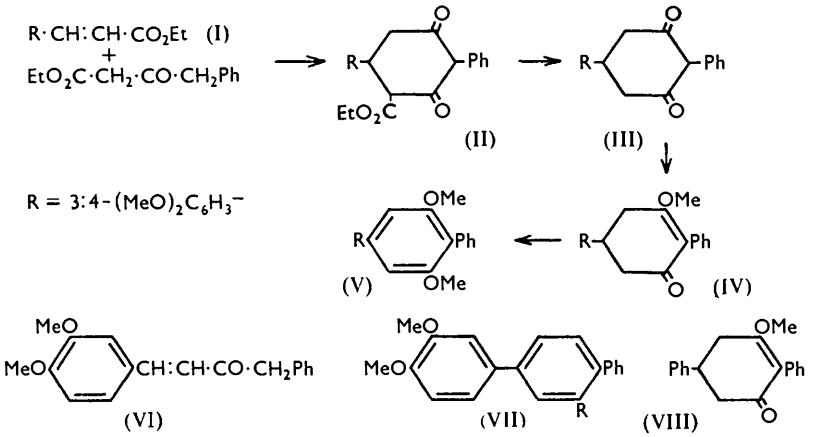
368. cyclo*Hexane*-1 : 3-*diones. Part IV.* The Synthesis of Further Terphenyl Derivatives.*

By G. R. Ames and W. Davey.

3 : 4-Di-, 3 : 4 : 3′-tri-, and 3 : 4 : 3′ : 5′-tetramethoxy-*p*-terphenyl have been prepared from 5-(3 : 4-dimethoxyphenyl)-2-phenyl*cyclo*hexane-1 : 3-dione. 4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione has been converted into 3′ : 5′-dihydroxy- and 3′ : 5′-dimethoxy-*o*-terphenyl. Syntheses of 4′ : 6′-dihydroxy-*m*-terphenyl and of 2′ : 4′- and 4′ : 6′-dimethoxy-*m*-terphenyl are also described.

In Part II of this series [1] it was shown that dehydrogenation of compounds derived from 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione afforded a new and convenient route to a number of *p*-terphenyls substituted in the central ring. This method has now been applied to the synthesis of *p*-terphenyls having methoxyl substituents in two rings, and also to *o*- and *m*-terphenyl derivatives

Polymethoxy-p-*terphenyls.*—The synthesis of terphenyl derivatives from 5-(3 : 4-dimethoxyphenyl)-2-phenyl*cyclo*hexane-1 : 3-dione (III) was examined. The dione was conveniently prepared by Michael addition of ethyl γ-phenylacetoacetate to ethyl 3 : 4-dimethoxycinnamate (I), followed by hydrolysis of the dione-ester (II), and was converted



by diazomethane into the enol ether (IV). Dehydrogenation with sulphur, followed by treatment with dimethyl sulphate, then afforded 3 : 4 : 3′ : 5′-tetramethoxy-*p*-terphenyl (V) in 35% yield.

The alternative route to the dione-ester (II), namely addition of diethyl malonate to the unsaturated ketone (VI), was not examined as the latter could only be prepared in low yield and with difficulty.

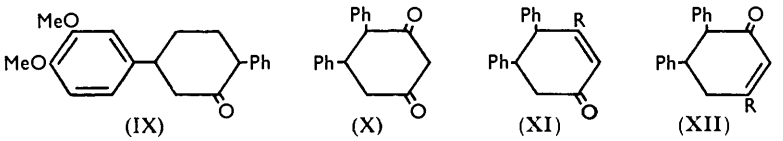
The enol ether (IV) was reduced with lithium aluminium hydride and then dehydrogenated with sulphur, to give 3 : 4-dimethoxy- (VII; R = H) (10%) and 3 : 4-dimethoxy-3′-hydroxy-*p*-terphenyl (VII; R = OH) (17%). The latter product was converted into the triether (VII; R = OMe) by treatment with dimethyl sulphate and alkali. The formation of the diether (VII; R = H) in the above reaction is analogous to that of *p*-terphenyl when the diphenyl enol ether (VIII) was reduced and dehydrogenated in the same way.[1]

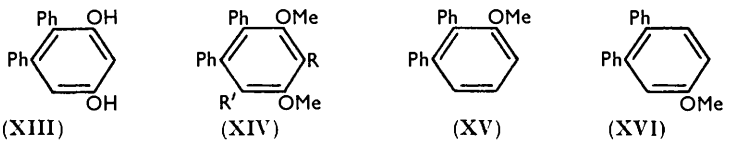
* Part III, *J.*, 1958, 911.

[1] Ames and Davey, *J.*, 1957, 3480.

In an attempt to prepare 3 : 4-dimethoxy-*p*-terphenyl (VII; R = H) by an unambiguous route, the dione (III) was treated with phosphorus trichloride, and the product hydrogenated to the *cyclo*hexanone (IX). However, no crystalline product could be isolated when this ketone was reduced by the Wolff–Kishner method and the product dehydrogenated with selenium.

Attempts to prepare other diaryl*cyclo*hexane-1 : 3-diones by ethoxide-catalysed addition of ethyl γ-phenylacetoacetate to ethyl *m*-nitro-, *m*-benzamido-, or *o*-ethoxycarbonyl-cinnamate were unsuccessful. A convenient modification of the synthesis [2] of *o*-carboxycinnamic acid is described in the Experimental section.

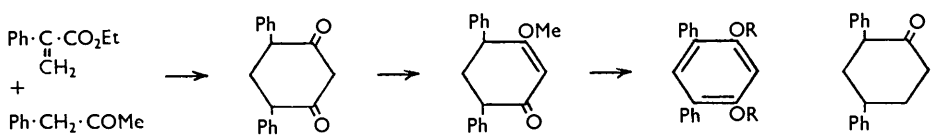




o-*Terphenyl Derivatives*.—4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione [3] (X) with diazomethane gave a mixture of enol ethers, from which one, either (XI; R = OMe) or (XII; R = OMe), was obtained by repeated crystallisation. The mixed ethers were dehydrogenated with sulphur and then demethylated with hydriodic acid, to give 3′ : 5′-dihydroxy-*o*-terphenyl (XIII). Alternatively, treatment of the dehydrogenated material with dimethyl sulphate and alkali yielded the dimethoxy-compound (XIV; R = R′ = H), which, with two mols. of bromine, gave only a monobromo-derivative (XIV; R = Br, R′ = H or *vice-versa*).

Reduction of the purified enol ether by lithium aluminium hydride afforded the corresponding *cyclo*hexenone (XII or XI; R = H). Sulphur dehydrogenation of the latter gave an oil, which on treatment with dimethyl sulphate and alkali yielded 3′- (XV) or 4′-methoxy-*o*-terphenyl (XVI).

Substituted m-*Terphenyls*.—Two *cyclo*hexane-1 : 3-diones, (XVII) and (XXIII), are potential intermediates in the synthesis of *m*-terphenyl derivatives. The former, prepared by Michael addition of phenylacetone to ethyl atropate, was converted into the enol ether (XVIII) and thence into the resorcinol (XIX; R = H) and the diether (XIX; R = Me) by dehydrogenation and either demethylation or further methylation.



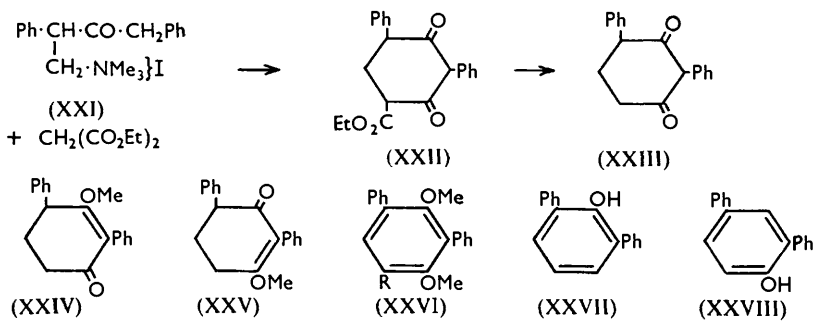
No crystalline product was isolated in attempts to prepare the known [4] 4′-hydroxy-*m*-terphenyl from the enol ether (XVIII) by reduction with lithium aluminium hydride followed by sulphur dehydrogenation, or by selenium dehydrogenation of the ketone (XX),

[2] *Org. Synth.*, 1954, **34**, 8.
[3] Borsche, *Ber.*, 1909, **42**, 4496.
[4] Lüttringhaus and Sääf, *Annalen*, 1945, **557**, 25.

which was prepared from the dione (XVII) by reaction with phosphorus trichloride, followed by catalytic hydrogenation.

Finally, 2 : 4-diphenyl*cyclo*hexane-1 : 3-dione (XXIII) was prepared by Robinson's modification [5] of the Michael reaction, from the methiodide (XXI) of the Mannich base [6] derived from dibenzyl ketone. Treating this compound with diethyl malonate in the presence of two mols. of sodium ethoxide gave an uncrystallisable acidic product, presumably the diketo-ester (XXII), which on hydrolysis with sodium carbonate afforded the dione (XXIII). This did not yield a crystalline enol ether: the product is presumably a mixture of isomers (XXIV) and (XXV). Dehydrogenation of this mixture with sulphur, followed by methylation, yielded 50% of 2′ : 4′-dimethoxy-*m*-terphenyl (XXVI; R = H), characterised as the bromo-derivative (XXVI; R = Br). No crystalline product resulted from demethylation of the dehydrogenation product.

When the mixed enol ethers (XXIV–XXV) were reduced with lithium aluminium hydride and then dehydrogenated with sulphur, the only isolable product was a hydroxyterphenyl, m. p. 101°. The two possible products are 2′- (XXVII) and 4′-hydroxy-*m*-



terphenyl (XXVIII); Lüttringhaus and Sääf [4,7] report that these compounds have m. p. 101° and 89° respectively. Our product is therefore regarded as the 2′-isomer (XXVII), and must be formed from the enol ether (XXIV).

Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε
II	229	17,300	VII; R = OH	277	20,600	XVII	258	18,200
	282	17,200		301	20,200		*290*	6,460
	304	11,200	VII; R = OMe	277	21,800	XVIII	250	19,600
III	228	18,200		301	23,500	XIX; R = H	252	25,000
	272·5	14,800	X	259·5	14,000		*274*	14,300
IV	229	17,900		*290*	6,990		305	9,150
	274·5	14,700	XI or XII;	251·5	18,500	XIX; R = Me	248	26,200
V	281	24,100	R = OMe				270	15,500
	292	23,300	XIII	*226*	23,900		*293—300*	8,720
VI	244	11,200		*252*	15,900	XXVI; R = H	245	25,400
	300	10,900		*285—300*	4,100	XXVI; R = Br	233	32,900
	339·5	19,800	XIV; R = H	*246*	19,200		*285—292*	2,360
VII; R = H	*280*	26,200		*285—293*	4,200	XXVII	238	22,200
	296	28,900	XIV; R = Br, R′ = H or *vice versa*	293	4,780		295	4,820
			XV or XVI	223	27,200			
				226	26,800			

The ultraviolet absorption spectra of most of the compounds described above are given in the Table, for 96% ethanol solutions, determined with a Unicam S.P. 500 Spectrophotometer. Italicised figures denote an inflexion.

[5] " Organic Reactions," Wiley, New York, 1942, Vol. I, p. 321.
[6] Wilson and Kyi, *J.*, 1952, 1321.
[7] Lüttringhaus and Sääf, *Annalen*, 1939, **542**, 241.

Experimental

" Light petroleum " refers to the fraction of b. p. 60—80°.

Ethyl 6-(3 : 4-*Dimethoxyphenyl*)-2 : 4-*dioxo*-3-*phenyl*cyclo*hexanecarboxylate* (II).—To sodium (0·6 g.) in ethanol (50 c.c.) were successively added ethyl γ-phenylacetoacetate (5·2 g.) and ethyl 3 : 4-dimethoxycinnamate (11·8 g.), and the mixture refluxed for 6 hr. and then poured into water. After unchanged starting materials had been removed with ether, acidification yielded the *dione-ester* (1·8 g.), prisms, m. p. 158—159° (from benzene) (Found: C, 69·8; H, 6·4. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1%).

5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexane*-1 : 3-*dione* (III).—The foregoing ester (17·4 g.) was refluxed for 10 hr. with sodium carbonate (decahydrate; 34·8 g.) in water (110 c.c.); the mixture was acidified and then brought to the boil. The *dione* (12·5 g.) was collected and recrystallised from 2-methoxyethanol: it formed needles, m. p. 220° (Found: C, 73·6; H, 6·1. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

5-(3 : 4-*Dimethoxyphenyl*)-3-*methoxy*-2-*phenyl*cyclo*hex*-2-*en*-1-*one* (IV).—Treatment of the above dione with ethereal diazomethane yielded the *enol ether*, prisms, m. p. 189°, from benzene (Found: C, 74·3; H, 6·3. $C_{21}H_{22}O_4$ requires C, 74·5; H, 6·5%).

3 : 4 : 3′ : 5′-*Tetramethoxy*-p-*terphenyl* (V).—The foregoing enol ether (1 g.) was heated at 270° for 2 hr. with sulphur (0·1 g.), and the product refluxed with dimethyl sulphate (2·1 c.c.) and 2N-sodium hydroxide (11 c.c.) for 2 hr., further quantities of the reagents (2·1 c.c. and 11 c.c. respectively) being added after 1 hr. After the excess of dimethyl sulphate had been destroyed, the product was collected and extracted with boiling light petroleum. From the extracts there separated 3 : 4 : 3′ : 5′-*tetramethoxy*-p-*terphenyl* (0·8 g.), plates, m. p. 127·5° (Found: C, 74·9; H, 6·2. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%).

1-(3 : 4-*Dimethoxyphenyl*)-4-*phenylbut*-1-*en*-3-*one* (VI).—Phenylacetone (6·7 g.), veratraldehyde (8·3 g.), and 2N-potassium hydroxide (6·7 c.c.) in water (500 c.c.) were heated at 70—90° for 2 days, more veratraldehyde (2·5 g.) and potassium hydroxide solution (6·7 c.c.) being added after one day. The aqueous layer was decanted and the residual oil taken up in methanol. The *ketone* (2·3 g., 16%) slowly separated (1—3 weeks): it crystallised from methanol as pale yellow plates, m. p. 89—90° (Found: C, 76·2; H, 6·4. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

3 : 4-*Dimethoxy*-p-*terphenyl* (VII; R = H) *and* 3′-*Hydroxy*-3 : 4-*dimethoxy*-p-*terphenyl* (VII; R = OH).—The enol ether (IV) (1·6 g.) in 1 : 2-dimethoxyethane (75 c.c.) was added during 10 min. to lithium aluminium hydride (0·2 g.) in the same solvent (25 c.c.). Working up in the usual way gave an oil which was heated with sulphur (0·16 g.) at 250—260° for 1 hr. Recrystallisation from ethanol afforded 3 : 4-*dimethoxy*-p-*terphenyl* (0·13 g.) as needles, m. p. 157° (Found: C, 82·5; H, 6·1. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·2%). Evaporation of the mother-liquors yielded 3 : 4-*dimethoxy*-3′-*hydroxy*-p-*terphenyl* (0·24 g.), needles, m. p. 173° (from benzene) (Found: C, 78·3; H, 5·7. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

3 : 4 : 3′-*Trimethoxy*-p-*terphenyl* (VII; R = OMe).—The preceding compound (0·12 g.) was refluxed for 2 hr. with dimethyl sulphate (2 c.c.) and 2N-sodium hydroxide (10 c.c.). The excess of dimethyl sulphate was destroyed with alkali and the product was collected. 3 : 4 : 3′-*Trimethoxy*-p-*terphenyl* formed needles, m. p. 103—104°, from light petroleum (Found: C, 78·7; H, 6·4. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%).

5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexanone*.—The dione (III) (7 g.) in chloroform (20 c.c.) was refluxed for 3 hr. with phosphorus trichloride (1·6 c.c.). To the cooled mixture were successively added ice, ethyl acetate, and saturated aqueous sodium hydrogen carbonate. The organic layer was washed with N-sodium hydroxide and with water, dried, and evaporated. The residue, in ethanol (250 c.c.), was shaken under hydrogen with palladous chloride (100 mg.) and triethylamine (10 c.c.). When absorption ceased, the catalyst was removed and the solution concentrated. 5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexanone* (3·4 g.) crystallised from methanol as the *hemihydrate*, needles, m. p. 109° (Found, after drying at 80°/0·1 mm.: C, 74·8; H, 7·1. $C_{20}H_{20}O_3,\frac{1}{2}H_2O$ requires C, 75·2; H, 7·3%). The *oxime*, needles from ethyl acetate, had m. p. 211—212° (Found: C, 73·6; H, 7·0; N, 4·2. $C_{20}H_{23}O_3N$ requires C, 73·8; H, 7·1; N, 4·3%).

Ethyl 3-*benzamidocinnamate*, prepared from the acid [8] by the Fischer–Speier method,

[8] Heller, *Ber.*, 1913, **46**, 3974.

formed needles, m. p. 124°, from ethanol (Found: C, 73·5; H, 5·7; N, 4·6. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%).

2-*Carboxycinnamic Acid*.—To β-naphthol (20 g.) in formic acid (*d* 1·2; 110 c.c.) was added 30% hydrogen peroxide (57 c.c.). After a few minutes an exothermic reaction began; the reaction was moderated by occasional cooling in an ice-bath, the temperature being allowed to rise slowly to 70°. After cooling, the product (15·6 g., 59%), m. p. 205—208°, was collected. Although the yield is somewhat lower, this method appears to be more convenient than the peracetic acid oxidation.[2]

*Synthesis of Diphenyl*cyclo*hexane*-1 : 3-*diones*.—The 4 : 5-isomer was prepared as described by Borsche.[3]

Ethyl atropate. The method described is an improvement on that of Schinz and Hinder.[9] Ethyl oxalate (109·5 g.) and ethyl phenylacetate (162·9 g.) were successively added to sodium ethoxide foam (from 17·4 g. sodium) in benzene (300 c.c.), and the mixture was set aside overnight. The sodium salt which separated was collected, washed with ether, and acidified. To the resulting oxalo-ester in 38% aqueous formaldehyde (90 c.c.) and water (300 c.c.) at 15°, was added, during 30 min., potassium carbonate (81 g.) in water (150 c.c.), and the mixture was stirred for 2 hr. Isolation with ether yielded ethyl atropate (116 g., 88%), b. p. 76—77°/1·2 mm., n_D^{20} 1·5238 (lit., b. p. 124°/16 mm., n_D^{16} 1·52605). Schinz and Hinder obtained a 44% yield.

4 : 6-*Diphenyl*cyclo*hexane*-1 : 3-*dione* (XVII). Phenylacetone (4·3 g.) and ethyl atropate (5·6 g.) were added to a solution of sodium (0·7 g.) in ethanol (20 c.c.), and the mixture was refluxed for 3 hr. An equal volume of water was added and the liquid was decanted and acidified, to give the *dione*, prisms, m. p. 161—163° (Found: C, 81·4; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

2 : 4-*Diphenyl*cyclo*hexane*-1 : 3-*dione* (XXIII). To sodium (10·9 g.) in ethanol (800 c.c.) were added diethyl malonate (37·4 g.) and 2 : 4-diphenyl-3-oxobutyltrimethylammonium iodide [6] (96 g.), and the mixture was refluxed for 7 hr. and then set aside for 3 days. After concentration, water (1 l.) was added and the acidic product, isolated in the usual way, was refluxed for 8 hr. with sodium carbonate decahydrate (48 g.) in water (320 c.c.). The solution was acidified and again brought to the boil. The *dione* (20·4 g.) crystallised from benzene as prisms, m. p. 176—178° (Found: C, 81·5; H, 6·1%). When this experiment was first performed, the product had m. p. 156—157° (Found: C, 81·2; H, 5·9%). This material, which was not isolated from subsequent runs, decomposed to an oil on storage in a glass tube; it was presumably a metastable form of the dione of m. p. 176—178°.

Enol Ethers.—Treatment of the 4 : 5-diphenyl-dione in methanol with excess of ethereal diazomethane yielded an oil, which, on trituration with light petroleum and repeated recrystallisation from benzene–light petroleum, afforded an *enol ether*, plates, m. p. 137° (Found: C, 81·8; H, 6·7. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). The *enol ether* similarly prepared from the 4 : 6-diphenyl-dione crystallised from benzene as prisms, m. p. 172° (Found: C, 81·9; H, 6·4%).

3′ : 5′-*Dihydroxy*-o-*terphenyl* (XIII; R = H).—The crude mixture of enol ethers (from 5·2 g. of the 4 : 5-diphenyl-dione) was heated at 260—270° with sulphur (0·5 g.). The product was refluxed for 6 hr. with hydriodic acid (*d* 1·7; 20 c.c.), then poured into water. Isolation of the acidic fraction furnished 3′ : 5′-*dihydroxy*-o-*terphenyl* (0·5 g.), plates, m. p. 145—146°, from benzene–light petroleum (Found: C, 82·0; H, 5·2. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). 4′ : 6′-*Dihydroxy*-m-*terphenyl* (XIX; R = H), prisms, m. p. 130°, from benzene (Found: C, 82·3; H, 5·0%), was similarly prepared.

3′ : 5′-*Dimethoxy*-o-*terphenyl* (XIII; R = Me).—The mixture of enol ethers (from 10 g. of the 4 : 5-diphenyl-dione) was dehydrogenated as described in the preceding experiment. The product was refluxed for 2 hr. with dimethyl sulphate (20 c.c.) and 2N-sodium hydroxide (100 c.c.), more of these reagents (20 c.c. and 100 c.c. respectively) being added after 1 hr. Isolation with ether gave a fraction, b. p. 180—190°/0·5 mm. (3·4 g.), which, on trituration with light petroleum, yielded the *diether*, plates, m. p. 136—137° (Found: C, 82·6; H, 6·4. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·2%); bromination of this compound in carbon tetrachloride solution afforded a *monobromo-derivative*, prisms, m. p. 196—197° (from benzene–light petroleum) (Found: C, 65·2; H, 4·4; Br, 21·4. $C_{20}H_{17}O_2Br$ requires C, 65·0; H, 4·6; Br, 21·6%).

Similarly prepared were 4′ : 6′- (XIX; R = Me), blades, m. p. 99°, from methanol (Found: C, 83·0; H, 6·6%), and 2′ : 4′-*dimethoxy*-m-*terphenyl* (XXVI; R = H), plates, m. p. 124°, b. p. 161—164°/0·2 mm. from light petroleum (Found: C, 82·4; H, 6·3%). Bromination of the

[9] Schinz and Hinder, *Helv. Chim. Acta*, 1947, **30**, 1349.

latter furnished the *bromo-compound* (XXVI; R = Br), prisms, m. p. 131—132° (from light petroleum) (Found: C, 64·8; H, 4·8%).

4 : 5- or 5 : 6-*Diphenyl*cyclo*hex-2-en-1-one* (XI or XII; R = H).—To lithium aluminium hydride (0·24 g.) in ether (100 c.c.) was added the enol ether of the 4 : 5-diphenyl-dione (1·7 g.; m. p. 133—134°) in benzene (50 c.c.), and the mixture refluxed for 1 hr. Working up in the usual way afforded the *ketone*, prisms, m. p. 90°, from methanol (Found: C, 86·5; H, 6·5. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3′- or 4′-*Methoxy-o-terphenyl* [(XV) or (XVI)].—The foregoing ketone was heated at 260—270° for 2 hr. with sulphur (0·2 g.), and the product treated with dimethyl sulphate and alkali as described above for 3′ : 5′-dimethoxy-*o*-terphenyl. The ether crystallised from methanol as blades, m. p. 110°, b. p. 181—183°/2·5 mm. (Found: C, 87·8; H, 5·9. Calc. for $C_{18}H_{14}O$: C, 87·8; H, 5·7%). Lüttringhaus and Sääf [7] give m. p. 101°.

2 : 4-*Diphenyl*cyclo*hexanone Oxime*.—The 4 : 6-diphenyl-dione (12·3 g.) in chloroform (25 c.c.) was refluxed with phosphorus trichloride (3·4 c.c.) for 3 hr. Ice, ether, and aqueous sodium hydrogen carbonate were then added and the organic layer was separated, washed with aqueous sodium hydroxide, dried, and evaporated. The residue in ethanol (250 c.c.) was shaken under hydrogen with palladous chloride (0·2 g.) and triethylamine (20 c.c.). Evaporation of the filtered solution gave an oil, which was treated with hydroxylamine in the usual way: the *oxime* (28%) formed needles, m. p. 210—211°, from ethyl acetate (Found: C, 81·5; H, 7·3; N, 5·2. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

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