414. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part I. The Cyclisation of Tertiary Aromatic Acid Chlorides.*

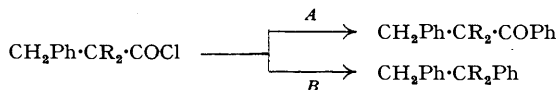By Eugene Rothstein and Rowland W. Saville.

When tertiary acid halides are used in the Friedel–Crafts reaction, they afford, in general, hydrocarbons with the simultaneous liberation of carbon monoxide (Rothstein and Saboor, *J.*, 1943, 425). On the other hand, aryl-$\alpha\alpha$-dialkyl-propionic and -butyric acid derivatives yield the cyclic ketones normally expected. Experiments indicate that this is probably the result of the juxtaposition of the acyl group with a reactive point on the aromatic nucleus and not the influence of the phenyl group through the carbon chain. If the length of this chain is decreased, or if the nucleus is deactivated by the usual *meta*-directing groups, tertiary acid halides alkylate the aromatic compound, losing carbon monoxide, whilst primary acid derivatives are recovered unchanged. It is concluded that of the three possible reactions, *i.e.*, cyclisation, acylation, or alkylation, the preferred course for aryl tertiary acids is the first.

This group of papers embodies the results of a preliminary enquiry into the stability of the group CRR′R″·CO– and is based on the observation made by Rothstein and Saboor (*J.*, 1943, 425), that tertiary aliphatic acid derivatives eliminate carbon monoxide when mixed with aluminium chloride. That paper dealt more specifically with the acid anhydrides, but it was evident that the halides would, in general, behave in the same way and that with suitable changes the mechanisms there put forward would be equally applicable. It may be stated parenthetically that it is not intended necessarily to limit the investigations either to the Friedel–Crafts reaction or to acid chlorides; nevertheless as is elaborated more fully in Part V, the reaction whereby an acid chloride affords either a ketone or a hydrocarbon accompanied by the loss of carbon monoxide forms a convenient criterion for assessing the stability of the acyl group since it can be followed quantitatively as well as qualitatively. Before commencing a detailed study it became necessary to review the different aspects of the field owing to the great number of largely disconnected phenomena involved. One of them is the subject of this communication, whilst its complement is dealt with in Part II. Parts III and IV describe certain kinetic measurements. The correlation of these results with those of other investigators as well as some of the theoretical implications are deferred to Part V; for this reason any discussion in the first four papers is limited to the particular problem.

In their paper, Rothstein and Saboor had noted the inability of a *tertiary aliphatic* acid anhydride to yield a ketone with benzene; at that time no extension to the aromatic series had been made, though there was a reference to the cyclisation of β-phenyltetramethylpropionic acid (I) by sulphuric acid :
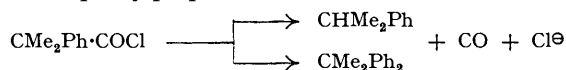

$$CMe_2Ph·CMe_2·CO_2H \longrightarrow$$

(I.)   CO   (II.)
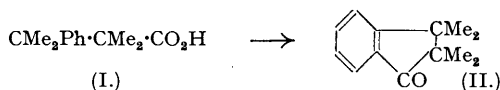
and in fact good yields of the corresponding hydrindones are obtained when the β-phenyl-$\alpha\alpha$-dialkylpropionyl chlorides are treated with aluminium chloride (Haller and Bauer, *Ann. Chim.*, 1921, [ix], **16**, 340) and similarly for the derivatives of γ-phenyl- and γ-naphthyl-$\alpha\alpha$-dialkylbutyric acids (Sen Gupta, *J. pr. Chem.*, 1938, **151**, 82; 1939, **152**, 9; *J. Indian Chem. Soc.*, 1934, **11**, 389). When benzene is substituted for ligroin as solvent, the experiments of Haller and Bauer have been repeated with substantially the same results; little carbon monoxide was liberated and products corresponding to neither of the reactions *A* nor *B* were isolated :

$$CH_2Ph·CR_2·COCl \longrightarrow \begin{array}{l} \xrightarrow{A} CH_2Ph·CR_2·COPh \\ \xrightarrow{B} CH_2Ph·CR_2Ph \end{array}$$

Hence it is to be inferred that the rate of cyclisation is very much greater than in either of these reactions. The experimental evidence of the present paper indicates that one of the principal factors leading to these " anomalous " results is the well-known ease with which five- and six-membered rings are formed, and perhaps the scarcely less important activation of the benzene ring by the aliphatic side-chain. If ring-formation is precluded by shortening the side-chain, then neither the cyclic nor the open-chain ketone is obtained. As a result aluminium

chloride reacts with a benzene solution of α-phenyl*iso*butyryl chloride to give a mixture of *iso*propylbenzene and 2 : 2-diphenylpropane :

$$CMe_2Ph \cdot COCl \longrightarrow \begin{array}{l} \longrightarrow CHMe_2Ph \\ \longrightarrow CMe_2Ph_2 \end{array} + CO + Cl^{\ominus}$$

Similarly, αα-diphenylpropionyl chloride affords 1 : 1-diphenylethane and a hydrocarbon, m.p. 143°, isomeric with triphenylethane. The yields of carbon monoxide in the two experiments were 85% and 86%, respectively. Triphenylacetyl chloride furnished rather less carbon monoxide, the crystalline product yielding triphenylmethane when reduced.

The broad inference is clearly that the retention of the carbonyl group when cyclisation occurs is not due to the influence of the phenyl groups, since an increase in their number does not lead to the formation of a ketone. On the contrary, it is shown in Part V that they have an opposite effect. We also show later that the production of a ketone is not inevitable, even when carbon monoxide is not evolved. Furthermore, so far as cyclisation is concerned, activation of the ring is not a primary factor, otherwise the interaction of two or more molecules should have resulted in a ketone.
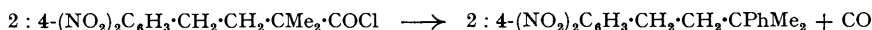
$$2CMe_2Ph \cdot COCl \longrightarrow CMe_2Ph \cdot CO \cdot C_6H_4 \cdot CMe_2 \cdot CO \cdot \ldots$$

To test the remaining possibility, namely that a phenyl group in a β- or a γ-position might stabilise the acyl group, p-*nitrophenylpivaloyl* and γ-2 : 4-*dinitrophenyl-αα-dimethylbutyryl chloride*, p-$NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CMe_2 \cdot COCl$ and $2 : 4\text{-}(NO_2)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot CMe_2 \cdot COCl$, respectively, were prepared. It was considered that a nitro-group, whilst deactivating the nucleus, would at the same time favour the retention of the carbonyl group (although the $-I$ effect, relayed through the carbon chain, would be largely damped down). Hoyer (*J. pr. Chem.*, 1934, **139**, 94) succeeded in cyclising β-*o*-nitrophenylpropionyl chloride in carbon disulphide, but the *p*-nitro-derivative was recovered unchanged (Ingold and Piggott, *J.*, 1923, 1469). When we repeated their experiment in benzene solution, neither ω-*p*-nitrobenzylacetophenone nor 4-nitrodibenzyl resulted, and unlike the above authors we were unable to isolate any *p*-nitrophenylpropaldehyde. Repetition in carbon disulphide solution yielded a sulphur-containing substance, the melting point of which was considerably higher than that recorded by Ingold and Piggott for 6-nitro-1-indan-1-one prepared by a different method.

As expected, *p*-nitrophenylpivaloyl chloride eliminated carbon monoxide forming 2-*phenyl*-1-p-*nitrophenyl*iso*butane*

$$p\text{-}NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CMe_2 \cdot COCl \longrightarrow p\text{-}NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CPhMe_2 + CO$$
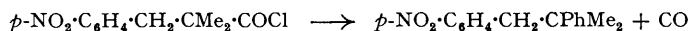
and similarly, the dinitro-acid chloride afforded 2-*phenyl*-4-2′ : 4′-*dinitrophenyl*-2-*methylbutane* :

$$2 : 4\text{-}(NO_2)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot CMe_2 \cdot COCl \longrightarrow 2 : 4\text{-}(NO_2)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot CPhMe_2 + CO$$

We therefore conclude that of the three possibilities, namely cyclisation, ketone formation, or decomposition, in the absence of any specific factor that may hinder one of them, the preferred course in the case of arylated *tertiary* acids is the first. The second occurs only in specially favourable conditions, and forms the subject of Part II of this series. It may be noticed that elimination of carbon monoxide is not always followed by combination with the aromatic component; the alkylated phenylacetic acid chlorides yield in addition a small proportion of the hydrocarbon which would result from the decarboxylation of the acid; however, as judged from the volume of carbon monoxide isolated, its presence should be attributed to a secondary reaction. The matter is discussed further in Part V.

EXPERIMENTAL.

Apparatus.—The Friedel–Crafts reactions described in this and the succeeding papers were carried out in a three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser, and a ground-in dropping funnel, by means of which the acid halide could be run in. For experiments in which the solid catalyst was added to a solution of the acid derivative, the funnel was replaced by a ground joint connected to the neck of a distilling flask by means of wide-bore pressure tubing; this flask, through the side-arm of which dry nitrogen could be passed, contained the catalyst, and the latter could be added in small portions to the reaction mixture. A delivery tube from the top of the condenser led through a calcium chloride guard-tube to 1-l. measuring cylinders which were inverted over water. Before the start of the reaction, the whole apparatus was swept through with dry nitrogen, and again after its completion.

Determination of Carbon Monoxide.—The evolved gases were kept over water for 1 day, and a measured volume washed with, successively, water, concentrated potassium hydroxide solution, and bromine water. The residual gas was then shaken with a freshly prepared ammoniacal cuprous chloride solution contained in a Hempel pipette until no further contraction in volume took place. Lastly it was shaken

again with a fresh solution of the reagent to confirm the completeness of the absorption of the carbon monoxide.

<div align="center">*Preparation of the Substituted Acetic Acids.*</div>

a-*Phenyl*iso*butyric Acid.*—Benzyl cyanide was methylated by methyl iodide and freshly prepared sodamide obtained by dissolving sodium in liquid ammonia in the presence of hydrated ferric nitrate (Haller and Bauer, *Compt. rend.*, 1912, **155**, 1582; Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and the 2-phenyl-2-propyl cyanide so obtained was hydrolysed. Other methods for the preparation of this acid offered no advantage. Phenyldimethylcarbinol, for instance, could not be converted into the cyanide owing to elimination of hydrogen chloride from the intermediate chloride on distillation or when mixed with a metallic cyanide; in either case isopropenylbenzene, b.p. 60—61°/17 mm., was formed (Found : C, 91·3; H. 8·7. Calc. for C_9H_{10} : C, 91·5; H, 8·5%). On the other hand, a Friedel–Crafts condensation of ethyl a-bromoiso*butyrate* with benzene (Wallach, *Chem. Zentr.*, 1899, II, 1047) afforded not more than a 19% yield which was smaller when the ester was replaced by acid (Brander, *Rec. Trav. chim.*, 1918, **37**, 681).

1 : 1-*Diphenylpropionic Acid.*—2 : 2-Diphenylpropaldehyde, obtained by the rearrangement of 1 : 2-diphenylpropane-1 : 2-diol (Tiffineau and Dorlencourt, *Ann. Chim.*, 1909, [viii], **16**, 254) with 20% sulphuric acid (yield 54%), was oxidised by alkaline potassium permanganate (yield 53%). Warming an ethereal solution of the acid with thionyl chloride and a drop of pyridine gave a 72% yield of the acid chloride.

Triphenylacetic acid, obtained by passing carbon dioxide through ethereal triphenylmagnesium chloride (Gilman, *J. Amer. Chem. Soc.*, 1929, **51**, 1576, 3493; Rule and Bain, *J.*, 1930, 1901), was converted into the acid chloride with thionyl chloride (yield 82%).

β-*Phenyl-aa-dialkylpropionic Acids.*—The best methods for the preparation of these acids were those of Haller and Bauer (*loc. cit.*) and are outlined below. In order to confirm the location of the alkyl groups, however, other methods leading to unambiguous structures were initially employed.

(i) An ethereal solution of benzoyl chloride was condensed with the sodio-derivatives of the appropriate dialkylacetic esters prepared by the use of sodio-triphenylmethane (Hudson and Hauser, *J. Amer. Chem. Soc.*, 1941, **63**, 3156; *Org. Synth.*, Coll. Vol. 2, p. 269, note 2; p. 609, note 3), the yield of the benzoyl esters being 60%. The Clemmensen reduction in a hydrocarbon solvent (compare Martin, " Organic Reactions," Vol. 1, p. 155), followed by fractionation through an electrically heated, packed column, yielded the esters (50%) which were hydrolysed to the required acids by alcoholic potash.

(ii) A Reformatsky condensation of trioxymethylene with ethyl a-bromoiso*butyrate* was accomplished by a modification of the method of Blaise and Marcilly (*Bull. Soc. chim.*, 1904, [iii], **31**, 110). A three-necked flask fitted with a mercury-sealed stirrer and a condenser was connected to a flask containing the trioxymethylene. Dry benzene (120 g.), zinc turnings (35 g.), and the bromo-ester (40 g.) were placed in the main flask, and to them was added a mixture of the reactants in a test-tube, the reaction having been started by warming. The main bulk was now warmed gently and a further quantity of the ester (40 g.) added. The trioxymethylene (12 g.) contained in the external flask was vapourised, by heating the latter in an oil-bath, at such a rate as to maintain a moderate reaction. After the product had been boiled for 30 minutes and set aside overnight, it was mixed with a slight excess of dilute acid, and the benzene layer separated, washed with dilute ammonia to remove unchanged trioxymethylene, and dried (Na_2SO_4). The ethyl hydroxypivalate (yield 51%) was then hydrolysed and the acid mixed with six times its weight of hydrobromic acid, saturated at 0°. The liquid was warmed for 10 hours at 80° and a further 10 hours at 100° (McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 806; Kohn and Schmidt, *Monatsh.*, 1904, **25**, 1056). The bromo-acid (yield 59%) was re-esterified and condensed with benzene, using aluminium chloride. The maximum yield obtainable was, however, 12%.

(iii) The steps in Haller and Bauer's synthesis consist of the alkylation of indan-1-one by the appropriate alkyl halide in conjunction with sodamide, the latter reagent also being used for breaking the ring and yielding the phenyldialkylpropionamide; finally the acid is prepared by the action of nitrous acid. Use of freshly prepared solutions of sodamide in liquid ammonia instead of the usual suspension of the powdered reagent for both the alkylations and for ring-fission resulted in greatly improved yields. The phenylpivalic acid was obtained in this way in 83% yield from the amide, and crystallised in white needles, m. p. 57° (Found : C, 74·1; H, 7·9. Calc. for $C_{11}H_{14}O_2$: C, 74·1; H, 7·8%). It was identical (m. p. and mixed m. p.) with the specimens prepared by the first two methods. Very much the same yields were isolated of the diethyl homologue.

β-*p*-*Nitrophenylpivalic Acid.*—The direct interaction of *p*-nitrobenzyl chloride with the Grignard compound of ethyl a-bromoiso*butyrate* failed and consequently this acid was prepared by the nitration of phenylpivalic acid. The acid (1 g.) was heated on the steam-bath with concentrated nitric acid (1 c.c.) for 3 hours and then mixed with ice. The yellow solid was crystallised twice from ethyl acetate, whence it separated in pale lemon-coloured plates, m. p. 134° (Found : C, 58·7; H, 5·8; N, 5·6. $C_{11}H_{13}O_4N$ requires C, 59·1; H, 5·8; N, 6·2%). This β-*p*-*nitrophenylpivalic acid* is identical with that obtained by Haller and Bauer as a by-product in the decomposition of phenylpivalamide to the acid, but these workers failed to orient their product. The above structure follows from the formation of *p*-nitrobenzoic acid on oxidation.

γ-2 : 4-*Dinitrophenyl-aa-dimethylbutyric Acid.*—β-Benzoyl-aa-dimethylpropionic acid (4 g.) was reduced with zinc amalgam (20 g.), water (12 c.c.), concentrated hydrochloric acid (30 c.c.), and toluene (15 c.c.) (yield 74%). The product was heated with three times its weight of concentrated nitric acid on the steam-bath for 2½ hours, and the γ-2 : 4-*dinitrophenyl-aa-dimethylbutyric acid* precipitated with ice–water; this acid separated from ethyl acetate–ligroin in prisms, m. p. 111° (Found : C, 51·2; H, 4·9; N, 9·3. $C_{12}H_{14}O_6N_2$ requires C, 51·1; H, 4·9; N, 9·8%). 2 : 4-Dinitrobenzoic acid was obtained on oxidation.

γ-4-*Methoxy-3-diphenylylbutyric Acid.*—4-Aminodiphenyl was diazotised (Schlenk, *Annalen*, 1909, **368**, 303; Kaiser, *ibid.*, 1890, **257**, 101), and the mixture was boiled to yield the phenol (76%). Methylation with alkali and methyl sulphate yielded 4-methoxydiphenyl from which γ-keto-β-4-methoxy-3-

diphenylylbutyric acid was obtained by treatment with succinic anhydride and aluminium chloride (Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1936, **58**, 1738). The methyl ester was then reduced by the ordinary Clemmensen method. The acid chloride did not react with aluminium chloride and benzene.

β-*Mesitoylpivalic Acid.*—Aluminium chloride (24 g., 2·1 mols.) was added in small portions to a stirred mixture of *as*-dimethylsuccinic anhydride (10 g.) and mesitylene (39 g.) at 0°. The mixture was heated very gradually until the temperature reached 80—100° and maintained there for 1 hour. A white solid (crude yield, 21 g.) was isolated from the resulting dark red complex. β-*Mesitoylpivalic acid* separated from ligroin in small white crystals, m. p. 105—106° (yield, 70%) (Found : C, 72·3; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·0%). It was not possible to reduce the acid.

Reactions of Acid Chlorides.

Cyclisation of Phenylpivaloyl and 3-*Benzylpentane*-3-*carboxyl Chloride.*—By use of benzene and 2 molecules of aluminium chloride, 66% and 73% yields, respectively, of the corresponding 2 : 2-dialkyl-indan-1-ones were obtained (Haller and Bauer employed 1·1—1·2 mols. of the catalyst, ligroin being the solvent; the yield in each case was 80%). The yields of carbon monoxide were 2·5% and 3·5% for the two reactions.

Reaction of p-*Nitrophenylpivaloyl Chloride with Benzene.*—*p*-Nitrophenylpivalic acid (10 g.) was converted into the acid chloride by purified thionyl chloride (9 g.). Excess of the reagent was removed by heating the mixture to 100° in a vacuum, and then thiophen-free benzene (80 c.c.) was added, followed by resublimed aluminium chloride (15 g.) in small portions. The liquid was then boiled under reflux for 3 hours. Carbon monoxide (347 c.c., 44·5%) was evolved. The liquid product containing much tarry material was identified as 2-*phenyl*-1-p-*nitrophenylisobutane* since nitration with a mixture of fuming nitric acid and concentrated sulphuric acid gave the 2 : 2' : 4 : 4'-*tetranitro*-compound which crystallised from ethyl acetate in pale yellow plates, m. p. 250—251° (Found : C, 48·9; H, 3·6; N, 13·7. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6; N, 14·2%). Oxidation afforded 2 : 4-dinitrobenzoic acid. Moreover, 1 : 2-di-phenyl*iso*butane, synthesised from *iso*butene dibromide, benzene, and aluminium chloride (Bodreaux, *Compt. rend.*, 1901, **132**, 1335), was nitrated to the identical tetranitro-compound.

Reaction of γ-2 : 4-*Dinitrophenyl*-αα-*dimethylbutyryl Chloride with Benzene.*—The acid chloride, prepared from the acid (8·4 g.) with thionyl chloride, was dissolved in benzene (80 c.c.), and aluminium chloride (2·5 mols.) ᵃadded. The resulting 2-*phenyl*-4-2' : 4'-*dinitrophenyl*-2-*methylbutane* separated from ethyl acetate in pale yellow prisms, m. p. 135° (Found : C, 65·0; H, 5·8; N, 9·3. $C_{17}H_{18}O_4N_2$ requires C, 64·9; H, 5·6; N, 8·9%). The yield of carbon monoxide was 51·5%.

Attempted Cyclisation of 2-p-*Nitrophenylpropionyl Chloride.*—The acid chloride (from 5 g. of acid) was boiled for 1 hour with benzene (60 c.c.) and aluminium chloride (1·2 mols.). About 81% of the original acid was recovered unchanged. The carbon monoxide eliminated corresponded to 2·5% of that theoretically possible. Repetition in carbon disulphide solution afforded a substance containing sulphur as well as nitrogen, and separating from absolute alcohol in white leaflets, m. p. 128—129° (Found : C, 59·5, 59·6; H, 4·2, 4·0; N, 4·9; S, 12·2%). Repeated recrystallisation failed to remove the sulphur.

Condensation of α-*Phenylisobutyryl Chloride with Benzene.*—A suspension of aluminium chloride (13·5 g., 1·5 mols.) in benzene (120 c.c.) was stirred at room temperature during the gradual addition of the acid chloride (12·3 g.) in the same solvent. Immediate evolution of gas took place, and stirring was continued for a further 2 hours. The following products of the reaction were identified. (i) *iso*Propylbenzene, b. p. 60—65°/20 mm. (yield, 1·2 g., 15%) (Found : C, 90·0; H, 9·9. Calc. for C_9H_{12} : C, 90·0; H, 10·0%), identified by comparison (m. p. and mixed m. p.) of its trinitro-derivative with that of cumene. (ii) 2 : 2-Diphenylpropane, b.p. 180—185°/12 mm. (yield, 6 g., 45%), not obtained pure (Found : C, 89·3; H, 7·9. Calc. for $C_{15}H_{16}$: C, 91·8; H, 8·2%); the *dinitro*-derivative, recrystallised from ethyl acetate and ligroin, had m. p. 133—134° (Found : C, 62·7; H, 5·1; N, 9·5. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%). (iii) A small quantity of unidentified residue, b. p. above 200° (decomp.)/0·1 mm. No trace of α-phenyl*iso*butyrophenone could be detected. The yield of carbon monoxide was nearly 85%.

Condensation of αα-*Diphenylpropionyl Chloride with Benzene.*—The reaction carried out in the same way as the previous experiment, with aluminium chloride (7 g., 1·8 mols.), benzene (100 c.c.), and αα-diphenylpropionyl chloride (7 g.), furnished an orange-red complex, carbon monoxide being rapidly liberated. The following products were isolated. (i) αα-Diphenylethane, b. p. 97—98°/0·2 mm. (yield, 1·7 g., 32·6% theory) (Found : C, 92·8; H, 7·3. Calc. for $C_{14}H_{14}$: C, 92·3; H, 7·7%). Nitric acid in acetic acid solution afforded the dinitro-derivative, m. p. 148° (Anschütz and Romig, *Ber.*, 1883, **18**, 664, 935; *Annalen*, 1886, **233**, 340), whilst oxidation by chromic acid gave benzophenone. (ii) A *hydrocarbon*, b. p. 180—220°/0·6 mm., separating from ethyl alcohol in small crystals, m. p. 143—144° (yield, 2·5 g.). The empirical formula, $C_{10}H_9$, is the same as that for triphenylethane, but the m. p. is very much greater than that of either of the isomers [Found : C, 93·0; H, 7·0. $(C_{10}H_9)_x$ requires C, 93·0; H, 7·0%]. The yield of carbon monoxide was 86%.

Condensation of Triphenylacetyl Chloride with Benzene.—Aluminium chloride (5·1 g., 2 mols.) was added in small portions to a stirred solution of triphenylacetyl chloride (5·9 g.) in benzene (80 c.c.), the mixture being cooled in ice. The yield of carbon monoxide was 59%. The substance isolated crystallised from alcohol as a white solid, m. p. 80°. This could correspond to the labile form of triphenylmethane, m. p. 81°, and oxidation with nitric acid (Schwartz, *Amer. Chem. J.*, 1904, **31**, 848) yielded pure triphenylcarbinol. Analysis of the compound, m. p. 80°, indicated that it could possibly be a mixture of the hydrocarbon and the carbinol (Found : C, 87·1; H, 6·6. Calc. for $C_{19}H_{16}$: C, 93·4; H, 6·6%) and in fact reduction of an alcoholic solution with tin and hydrochloric acid furnished pure triphenyl-methane, m. p. 92—93°.

The University, Leeds.