212. *Substitution Reactions of Triphenylethylene and its Derivatives. A Contribution to the Problem of Synthetic Analogues of Progesterone.*

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In the course of an investigation on the synthesis of compounds which may exhibit progestational activity, the chemistry of triphenylethylene has been explored. From this hydrocarbon and from 1 : 2-diphenyl-1-*p*-chlorophenylethylene, monoketones were readily obtained, and the acyl group in these compounds is shown to be located in the 2-phenyl nucleus. Other reactions leading to amino- and to nitro-derivatives of triphenylethylene and some of its halogenated derivatives are also described. The physiological properties of the new compounds are mentioned and discussed.

During the last five years, numerous attempts have been made to build synthetic substances having progestational activity by introducing the characteristic acetyl group of progesterone into a molecule which would be related to artificial oestrogenic compounds. For instance, Robinson and Jaeger (*J.*, 1941,744) prepared 4-hydroxy-4′-acetyl-αβ-diethyl- and -α-methyl-β-ethyl-stilbene, but these compounds still retained a strong oestrogenic activity; the same remark may be applied to 4′-hydroxy-4-methoxy-3′-acetyl-αβ-diethylstilbene and other similar derivatives made by Brownlee and Duffin (B.P. 550,262), although progesterone-like properties have been claimed for 4-methoxy-4′-acetyl-αβ-diethyldibenzyl. As phenolic substituents are known to enhance oestrogenic properties, Ross (*J.*, 1945, 536) expressed the view that the kind of substances most likely to bear luteal hormone-like activity without perturbating oestrogenic side-effects would be non-phenolic ketones related to stilbene, dibenzyl, or triphenylethylene. This author, however, could not obtain monoketones from any of these or similar hydrocarbons by means of the Friedel–Crafts reaction. In every case, pure products could not be obtained unless acetyl chloride was used in excess, polyacetylated compounds being thus obtained; from triphenylethylene, only a triacetyl compound could be isolated. As progesterone is a monoketone, polyketonic substances would hardly be expected to exhibit luteal hormone activity, and, in fact, these have been found to be inactive. But as there still remained some hope that monoacetylated oestrogenic hydrocarbons would bear some activity, we examined more thoroughly the behaviour of triphenylethylene towards Friedel–Crafts reactions.

We found that 1 mol. of acetyl chloride at 0° gave rather good yields of a mono-substituted ketone which could easily be isolated by vacuum distillation. The crystalline compound thus obtained was homogeneous and may be formulated as 1 : 1-*diphenyl*-2-p-*acetylphenylethylene* (I; X = H, Y = Ac), as substitution on the 1-phenyl nuclei would be expected to produce a mixture of two stereoisomeric compounds. By replacing acetyl chloride with propionyl or *n*-valeryl chloride, the analogous *ketones* (I; X = H, Y = COEt) and (I; X = H, Y = COBu) could similarly be prepared. (From the results of classical work upon substituted derivatives of benzene, the possibility of *o*- and of *m*-substitution can be ignored.)

$CPh_2{:}CX{\cdot}C_6H_4Y$ (*p*) (I.) $\qquad$ $CPh(C_6H_4Cl){:}CX{\cdot}C_6H_4Y$ (II.)

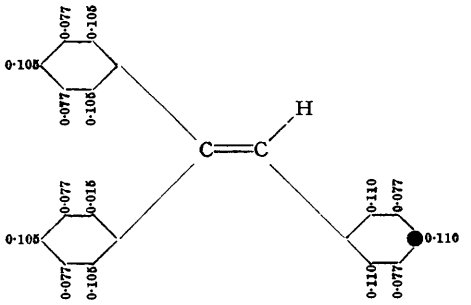
The first two ketones gave crystalline *oximes* which readily underwent Beckmann's transposition into the corresponding 1 : 1-*diphenyl*-2-p-*acylamidophenylethylene* (I; X = H, Y = NHAc or NH·COEt). In view of the potent carcinogenicity of 2-acetamidofluorene (Wilson, Cox, and de Eds, *Cancer Res.*, 1941, **1**, 595) and of several aminostilbenes (Haddow, Harris, and Kon, *Biochem. J.*, 1945, **39**, 2), the first of these derivatives is under test for similar biological properties.

From 1 : 2-*diphenyl*-1-p-*chlorophenylethylene* (II; X = Y = H), prepared by dehydration of the tertiary alcohol obtained from *p*-chlorobenzophenone and benzylmagnesium chloride, a ketone which was probably 1-*phenyl*-1-p-*chlorophenyl*-2-p-*acetylphenylethylene* (II; X = H, Y = COMe) could also be synthesized.

Triphenylethylene and 1 : 2-diphenyl-1-*p*-chlorophenylethylene readily underwent mononitration, and the homogeneous compounds thus obtained may be formulated respectively as 1 : 1-*diphenyl*-2-p-*nitrophenylethylene* (I; X = H, Y = NO_2) and 1-*phenyl*-1-p-*chlorophenyl*-2-p-*nitrophenylethylene* (II; X = H, Y = NO_2).

From the potent oestrogenic and anticarcinogenic 1-bromotriphenylethylene (Y.59) (cf. *Lancet*, 1947, **253**, 172) and from 1-*bromo*-1 : 2-*diphenyl*-2-p-*chlorophenylethylene* (II; X = Br, Y = H), 1-*bromo*-2 : 2-*diphenyl*-1-p-*nitrophenyl*- (I; X = Br, Y = NO_2) and 1-*bromo*-2-*phenyl*-2-p-*chlorophenyl*-1-p-*nitrophenyl-ethylene* (II; X = Br, Y = NO_2) could similarly be prepared, although the presence of bromine rendered the nitration somewhat more difficult.

The fact that substitution of triphenylethylene occurs in the lone phenyl nucleus may be accounted for on the basis of the electronic theory of substitution. The distribution of the density of π-electrons around each atom of carbon in triphenylethylene has been estimated by Daudel *et al.*, by means of the method of " molecular diagrams " based upon mesomerism (Daudel and Pullman, *J. Phys. Radium*, 1946, **59**, 74, 105; Daudel *et al.*, *Rev. Sci.*, 1946, **84**, 489; *Compt. rend.*, 1946, **223**, 947; cf. also Coulson and Daudel, *Rev. Sci.*, 1947, **85**, 29), to be as shown below, from which it will be seen that the " free valency number " of the *p*-carbon atom in the lone phenyl nucleus is definitely greater than that of the corresponding atoms in the other phenyl nuclei.



Physiological Properties.—1 : 1-Diphenyl-2-*p*-acetylphenylethylene and its 1-*p*-chloro-derivative are far more toxic than the parent hydrocarbons, but at the tolerated doses of 20 mg. (in injection), both failed to produce any luteal hormone-like effect in female rabbits. p-*Acetyl*-αβ-*diethylstilbene*, (*p*)C_6H_4Ac·CEt:CEt·C_6H_5, obtained from αβ-diethylstilbene by means of our technique of monoacetylation, proved also to be toxic, as well as completely inactive at the tolerated doses.

Some of the new substances described in this work have been examined for oestrogenic properties. Activities determined upon female spayed rats by means of the Allen–Doisy test are listed below :

Compound.	M.E.D., mg. (single injection).	Compound.	M.E.D., mg. (single injection).
(I; X = H, Y = Ac)	0·1	(I; X = Br, Y = NO_2)	0·1
(I; X = H, Y = COEt)	1	(II; X = Br, Y = H)	5
p-Acetyl-αβ-diethylstilbene	1		

It is noteworthy in this respect that acetylation leaves the activity of triphenylethylene almost unchanged, and that even nitration of 1-bromotriphenylethylene (Y.59) does not suppress its oestrogenic potency.

From consideration of the above-mentioned results, and of the work of Robinson and Jaeger (*loc. cit.*) and of Ross (*loc. cit.*), it appears to be very doubtful whether progesterone-like substances with a sufficient order of potency will ever be found in the field of purely aromatic molecules (see also Dodds, *Chem. and Ind.*, 1947, 373).

Note added June 20th, 1948.—Work by Bergmann, Dimant, and Japhe (*J. Amer. Chem. Soc.*, 1948, **70**, 1618), which appeared while this paper was in the press, suggests that the nitrotriphenylethylene described above might be 1-nitro-1 : 2 : 2-triphenylethylene, since it differs from 1 : 1-diphenyl-2-*p*-nitrophenylethylene synthesised by the Meerwein coupling of *p*-nitrobenzenediazonium salts with ββ-diphenylacrylic acid. This is still in accord with the molecular diagram of triphenylethylene, which also ascribes a high " free valency number " (0·140) to the lone carbon atom.

Experimental.

Acetylation of Triphenylethylene.—The most convenient method of preparing triphenylethylene is the dehydration of diphenylbenzylcarbinol (obtained from benzophenone and benzylmagnesium chloride) by means of anhydrous formic acid or acetyl chloride. An attempt to extend the Gattermann–Skraup synthesis of 2 : 2-diarylethylenes (Gattermann, *Ber.*, 1889, **22**, 1130; Skraup and Nieten, *Ber.*, 1924, **57**, 1300) to phenylacetyl chloride and benzene resulted in formation of only minute quantities of triphenylethylene. A mixture of triphenylethylene (20 g.) dissolved in carbon disulphide (150 c.c.) with finely powdered aluminium chloride (10 g.) was cooled to 0°, and treated gradually (15 mins.) with a solution of acetyl chloride (7 g.) in carbon disulphide (10 g.). A smooth reaction took place, and the mixture was then kept for 2 hours at room temperature. After decomposition with cold dilute hydrochloric acid, the organic layer was separated, washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). After removal of the solvent, the greenish oily residue was submitted to vacuum-distillation. After some triphenylethylene (7 g.) had been recovered (mixed with traces of a green impurity), a fraction, b. p. 261—262°/10 mm., was collected; it solidified on standing, and was crystallised twice from alcohol–benzene, giving 1 : 1-*diphenyl*-2-p-*acetylphenylethylene* (8 g.) as fine, silky, colourless needles with a greenish shade, m. p. 125°, which dissolved in sulphuric acid with a yellow halochromic coloration (Found : C, 88·1; H, 6·2. $C_{22}H_{18}O$ requires C, 88·2; H, 6·0%). A solution of this ketone (2·2 g.) in alcohol (30 c.c.) was refluxed during 24 hours with hydroxylamine hydrochloride (1·6 g.) and sodium carbonate (1·1 g.) dissolved in water (5 c.c.). After cooling, the mixture was poured into an excess of water, and the solid precipitate collected, and twice recrystallised from alcohol; the *oxime* (2 g.) formed colourless prisms, m. p. 160° (Found : N, 4·6. $C_{22}H_{19}ON$ requires N, 4·4%), which dissolved in sulphuric acid with an intense yellow coloration.

1 : 1-*Diphenyl*-2-p-*acetamidophenylethylene.*—The foregoing oxime (0·3 g.) was dissolved in a mixture of glacial acetic acid (2 c.c.) and sulphuric acid (2 c.c.), and the solution heated al 95—100° until the yellow halochromic coloration disappeared (10 mins.). After cooling, the mixture was poured into ice-water; the flocculent precipitate obtained was collected, thoroughly washed with water, and recrystallised twice from alcohol, giving 1 : 1-*diphenyl*-2-p-*acetamidophenylethylene* (0·2 g.) in colourless prisms, m.p. 202—203° (decomp.) (Found : N, 4·2. $C_{22}H_{19}ON$ requires N, 4·4%). Alkaline saponification of this amide afforded 1-*p*-aminotriphenylethylene, which could not be obtained pure owing to its great solubility in alcohol and benzene.

Propionylation of Triphenylethylene.—The Friedel–Crafts reaction between triphenylethylene (12 g.), propionyl chloride (4·5 g.), and aluminium chloride (6 g.) was performed in carbon disulphide (120 c.c.) in the same manner as described above. 1 : 1-*Diphenyl*-2-p-*propionylphenylethylene* (6·5 g.) was obtained as a viscous, yellowish oil, b. p. 267—268°/10 mm., which slowly solidified on cooling, and formed fine, silky, colourless needles, m. p. 85°, from alcohol (Found : C, 88·7; H, 6·5. $C_{23}H_{20}O$ requires C, 88·4; H, 6·4%). The *oxime* (0·7 g.), obtained from the ketone (0·8 g.), hydroxylamine hydrochloride (0·55 g.), and sodium carbonate (0·3 g., dissolved in a few drops of water) in alcohol (25 c.c.), crystallised from alcohol in brilliant, colourless plates, m. p. 155° (Found : N, 4·6. $C_{23}H_{21}ON$ requires N, 4·3%). Beckmann's transformation, performed upon this oxime in the same way as for the lower homologue, yielded 1 : 1-*diphenyl*-2-p-*propionamidophenylethylene*, which formed minute colourless needles, m. p. 147° (sintering above 140°), from dilute aqueous alcohol (Found : N, 4·2. $C_{23}H_{21}ON$ requires N, 4·3%).

1 : 1-*Diphenyl*-2-p-n-*valerylphenylethylene.*—Triphenylethylene (12 g.), *n*-valeryl chloride (5·6 g.), and aluminium chloride (6·5 g.) were condensed in carbon disulphide (120 c.c.) as above, giving a liquid *ketone* which could not be induced to crystallise. After two redistillations in a vacuum, it formed a thick, yellowish oil (5 g.), b. p. 274—276°/10 mm., $n_D^{13°}$ 1·6570 (Found : C, 88·2; H, 7·2. $C_{25}H_{24}O$ requires C, 88·3; H, 7·0%), which did not solidify even after 6 months. The corresponding oxime also could only be obtained as an oil.

1 : 2-*Diphenyl*-1-p-*chlorophenylethylene.*—The crude crystalline carbinol obtained from benzylmagnesium chloride and *p*-chlorobenzophenone was dehydrated by dissolution in warm anhydrous formic acid. After dilution with water, the yellow oil obtained was extracted with benzene, the benzene layer washed with an aqueous solution of sodium carbonate, then with water, and dried (Na_2SO_4). After removal of the solvent and vacuum-distillation of the residue, a yellow oil, b. p. 231—232°/10 mm., was obtained, which slowly solidified into a crystalline cake; 1 : 2-*diphenyl*-1-p-*chlorophenylethylene* (yield 80%) formed long, silky, colourless needles, m. p. 89°, from acetic acid (Found : C, 82·4; H, 5·3. $C_{20}H_{15}Cl$ requires C, 82·6; H, 5·2%). Treatment of this compound (5 g.) dissolved in carbon disulphide (25 c.c.) with bromine (2·8 g., dissolved in 5 c.c. of carbon disulphide) in the cold yielded 1-*bromo*-1 : 2-*diphenyl*-2-p-*chlorophenylethylene* (5 g.), which crystallised from glacial acetic acid in long, colourless, glistening prisms, m. p. 157° (Found : C, 65·0; H, 4·0. $C_{20}H_{14}ClBr$ requires C, 64·9; H, 3·7%).

1-*Phenyl*-1-p-*chlorophenyl*-2-p-*acetylphenylethylene.*—A Friedel–Crafts reaction was performed with the foregoing chlorotriphenylethylene (15 g.), acetyl chloride (5·5 g.), and aluminium chloride (7 g.) in carbon disulphide (120 c.c.) as with triphenylethylene. The resulting *ketone* was purified by vacuum-distillation b. p. 282°/10 mm.); after two recrystallisations from acetic acid and then from alcohol–benzene, it formed long, colourless needles, m. p. 137° (Found : C, 79·1; H, 5·2. $C_{22}H_{17}OCl$ requires C, 79·4; H, 5·1%). The corresponding *oxime* crystallised from alcohol in fine, silky, colourless needles, m. p. 148° (Found : N, 4·2. $C_{22}H_{18}ONCl$ requires N, 4·0%).

Acetylation of αβ-Diethylstilbene.—Friedel–Crafts condensation of αβ-diethylstilbene (15 g.) in carbon disulphide (150 c.c.) with acetyl chloride (6·5 g.) in the presence of aluminium chloride (9 g.) afforded an orange-red mixture; this was decomposed by ice-cold dilute hydrochloric acid, and the organic layer worked up in the usual manner. After two redistillations in a vacuum, p-*acetyl*-αβ-*diethylstilbene* (2 g.) was obtained as a pale yellow, viscous oil, b. p. 205—210°/10 mm. (Found : C, 86·7; H, 8·2. $C_{20}H_{22}O$ requires C, 86·3; H, 7·9%). The diethylstilbene used was prepared according to Ramart-Lucas and Anagnostopoulos (*Compt. rend.*, 1928, **186**, 1626), and is therefore probably a mixture of stereoisomers.

Nitration of Triphenylethylene.—A suspension of triphenylethylene (10 g.) in cold glacial acetic acid (40 c.c.) was treated dropwise with concentrated nitric acid (*d* 1·52; 7 c.c.), and the mixture thus obtained

was heated at 80° on a water-bath for 2—3 mins. The thick, crystalline mass, which set rapidly on cooling, was filtered off and thoroughly washed with water. After recrystallisation from acetic acid, and then from alcohol–benzene, 1 : 1-*diphenyl*-2-p-*nitrophenylethylene* (6·5 g.) formed pale yellow, silky needles, m. p. 173° (Found : N, 4·8. $C_{20}H_{15}O_2N$ requires N, 4·6%).

Nitration of 1 : 2-*Diphenyl*-1-p-*chlorophenylethylene*.—A solution of this compound (5 g.) in glacial acetic acid (40 c.c.) was treated with concentrated nitric acid (*d* 1·52; 3·5 c.c.) in the same manner as above. The *mononitro*-compound (2 g.) thus obtained was recrystallised three times from acetic acid and formed brilliant yellow prisms, m. p. 166° (Found : N, 4·4. $C_{20}H_{14}O_2NCl$ requires N, 4·1%).

Nitration of 1-*Brominated Triphenylethylenes*.—(a) A suspension of 1-bromotriphenylethylene (Y.59) (5 g.) in a mixture of glacial acetic acid (25 g.) and nitric acid (*d* 1·52; 4 c.c.) was heated for ½ hour on a water-bath at *ca.* 80°, then cooled; the resulting yellow precipitate was collected, washed with water, and recrystallised first from acetic acid and then from alcohol. 1-*Bromo*-2 : 2-*diphenyl*-1-p-*nitrophenylethylene* (2 g.) was thus obtained as long, glistening, yellow needles, m. p. 180° (Found : N, 3·8. $C_{20}H_{14}O_2NBr$ requires N, 3·6%).

(b) 1-*Bromo*-2-*phenyl*-2-p-*chlorophenyl*-1-p-*nitrophenylethylene* (0·8 g.) was similarly obtained from 2 g. of the un-nitrated compound and concentrated nitric acid (2 c.c.); after crystallisation from glacial acetic acid, and then from alcohol, it formed fine, bright yellow, prismatic needles, m. p. 163° (Found : N, 3·5. $C_{20}H_{13}O_2NClBr$ requires N, 3·3%).

The reduction of those nitro-derivatives will be described later.

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