Halogenated o- *and* p-*Phenolic Ketones.*

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Synthesis, by various methods, of a wide series of *o*- and *p*-phenolic ketones bearing halogen substituents (F, Cl, Br, I) is reported; bromination of 4-hydroxyacetophenone and its homologues takes place in the benzene nucleus or in the side chain, according to the experimental conditions. These halogenated ketones and a series of derived indoles were prepared for biological testing.

Phenolic ketones bearing halogen atoms in the nucleus are of manifold biological interest. Chloro- and bromo-diaryl ketones frequently display high tuberculostatic activity *in vitro* (cf. Buu-Hoï, *Compt. rend.*, 1945, **221**, 202; *Rec. Trav. chim.*, 1949, **68**, 769; Kuhn *et al.*, *Ber.*, 1952, **85**, 72); 4-hydroxyacetophenones bearing halogen substituents in the 3- and the 5-position are structurally related to antagonists of thyroxine (cf. Lerman and Harington, *J. Clin. Invest.*, 1948, **27**, 546; Wilkinson, Sheehan, and Maclagan, *Biochem. J.*, 1951, **48**, 188; **49**, 710); a substance such as 4-hydroxy-3 : 5-di-iodohexanophenone would be very similar in shape to the biologically active *n*-butyl 4-hydroxy-3 : 5-di-iodobenzoate (Barker, Dirks, Garlick, and Klitgaard, *Proc. Soc. Exper. Biol. Med.*, 1951, **78**, 840), recently described as a pituitary inhibitor. A broad investigation was therefore undertaken of the synthesis of hydroxy-ketones containing one or more atoms of fluorine, chlorine, bromine, or iodine.

o-Fluoroanisole readily underwent Friedel–Crafts acylation with both aliphatic and aromatic acid chlorides, to give a series of 4-acyl-2-fluoroanisoles, which were converted into the corresponding 4-acyl-2-fluorophenols by means of pyridine hydrochloride. Bromination of these phenols in aqueous acetic acid gave 4-acyl-2-bromo-6-fluorophenols. The fluorinated ketones, listed in Table 1, bear structural resemblance to compounds such

Table 1. *Fluoro-ketones.*

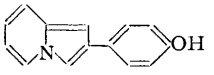
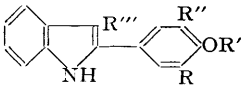
Ketone	M. p	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-Fluoro-4-methoxyvalerophenone [a]	liquid	$C_{12}H_{15}O_2F$	68·5	7·2	68·6	7·1
3-Fluoro-4-hydroxyvalerophenone	49°	$C_{11}H_{13}O_2F$	67·0	6·4	67·3	6·6
3-Fluoro-4-methoxyhexanophenone	62	$C_{13}H_{17}O_2F$	69·4	7·5	69·6	7·6
3-Fluoro-4-hydroxyhexanophenone [b]	64	$C_{12}H_{15}O_2F$	68·6	7·3	68·6	7·1
1-Decanoyl-3-fluoro-4-methoxybenzene [c]	72	$C_{17}H_{25}O_2F$	73·1	8·8	72·9	8·9
1-Decanoyl-3-fluoro-4-hydroxybenzene [d]	67	$C_{16}H_{23}O_2F$	72·0	8·6	72·2	8·6
3-Fluoro-4-methoxybenzophenone	97	$C_{14}H_{11}O_2F$	73·1	4·8	73·0	4·8
3-Fluoro-4-hydroxybenzophenone	123	$C_{13}H_9O_2F$	72·0	4·3	72·2	4·2
3-Fluoro-4-methoxy-1-phenacetylbenzene	113	$C_{15}H_{13}O_2F$	73·7	5·2	73·8	5·3
3-Fluoro-4-hydroxy-1-phenacetylbenzene	140	$C_{14}H_{11}O_2F$	73·1	4·8	73·0	4·8
3-Bromo-5-fluoro-4-hydroxyacetophenone	173	$C_8H_6O_2BrF$	41·4	2·9	41·2	2·6
3-Bromo-5-fluoro-4-hydroxypropiophenone	114	$C_9H_8O_2BrF$	43·9	3·5	43·7	3·2
3-Bromo-5-fluoro-4-hydroxybutyrophenone	97	$C_{10}H_{10}O_2BrF$	45·7	3·9	46·0	3·8
3-Bromo-5-fluoro-4-hydroxyvalerophenone	87	$C_{11}H_{12}O_2BrF$	47·8	4·7	48·0	4·4
3-Bromo-5-fluoro-4-hydroxyhexanophenone	95	$C_{12}H_{14}O_2BrF$	49·5	4·8	49·8	4·8
1-Decanoyl-3-bromo-5-fluoro-4-hydroxybenzene	68	$C_{16}H_{22}O_2BrF$	55·6	6·5	55·6	6·4
3-Bromo-5-fluoro-4-hydroxybenzophenone	187	$C_{13}H_8O_2BrF$	53·1	2·9	52·9	2·7
3-Bromo-5-fluoro-4-hydroxy-1-phenacetylbenzene	165	$C_{14}H_{10}O_2BrF$	54·4	3·5	54·4	3·2

[a] B. p. 198—201°/32 mm., n_D^{28} 1·5350. [b] B. p. 200°/15 mm. [c] B. p. 232—233°/20 mm. [d] B. p. 233—234°/20 mm.

as 3-fluoro-4-hydroxypropiophenone (Buu-Hoï, Xuong, and Lavit, *J. Org. Chem.*, 1953, **18**, 910), 3-fluorotyrosine (Schiemann, "Die organischen Fluorverbindungen," 1950, Steinkopf, Frankfurt a.M.), and 3-fluoro-4-hydroxyphenylacetic acid, which are active in Graves–Basedow's disease (May, "Die Basedowsche Krankheit, Jod und Fluor," 1950, Editio Cantor, Aulendorf i.W.). The same sequence of reactions was used for preparing 3-bromo-5-chloro-4-hydroxypropiophenone *via* 3-chloro-4-hydroxypropiophenone.

An interesting observation was made during the study of bromination of 4-acylphenols.

4-Hydroxyacetophenone reacting with one molecule of bromine in acetic acid gave ω-bromo-4-hydroxyacetophenone, whose constitution was determined by the formation of 2-*p*-hydroxyphenylpyrrocoline (I) in the reaction with 2-picoline (cf. Tschitschibabin, *Ber.*, 1927, **60**, 1607); 4-hydroxypropiophenone similarly gave α-bromo-4-hydroxypropiophenone, in whose molecule the halogen atom was proved to be on the side chain by removal with aniline; under the same conditions, 3-bromo-4-hydroxypropiophenone

(I)  (II) 

(Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1363) was unchanged. In aqueous acetic acid 3 : 5-dibromo-4-hydroxyacetophenone (Priestley and Moness, *J. Org. Chem.*, 1940, **5**, 358) and 3 : 5-dibromo-4-hydroxypropiophenone were obtained; a compound prepared by Goldzweig and Kaiser (*J. pr. Chem.*, 1891, **43**, 86) from 4-hydroxypropiophenone and aqueous bromine was found to consist mainly of the latter compound. Further nuclear bromo-ketones synthesised in the course of this work are listed in Table 2; ketones containing bromine in the side chain were not intermediates in the nuclear halogenation, as no rearrangement took place in acidic or in basic media.

TABLE 2. *Bromo- and Chloro-ketones.*

Ketone [a]	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3 : 5-Dibromo-4-methoxybutyrophenone	53°	$C_{11}H_{12}O_2Br_2$	39·2	3·8	39·3	3·6
3 : 5-Dibromo-4-hydroxybutyrophenone	117	$C_{10}H_{10}O_2Br_2$	37·5	3·0	37·3	3·1
3 : 5-Dibromo-4-hydroxyvalerophenone	75	$C_{11}H_{12}O_2Br_2$	39·1	3·5	39·3	3·6
3 : 5-Dibromo-4-hydroxyhexanophenone	68	$C_{12}H_{14}O_2Br_2$	40·8	4·2	41·1	4·0
3 : 5-Dibromo-4-hydroxyheptanophenone	71	$C_{13}H_{16}O_2Br_2$	43·0	4·2	42·9	4·4
1-Decanoyl-3 : 5-dibromo-4-hydroxybenzene	54	$C_{16}H_{22}O_2Br_2$	47·4	5·2	47·3	5·4
3 : 5-Dibromo-4-hydroxy-1-phenacetylbenzene [b]	144	$C_{14}H_{10}O_2Br_2$	45·1	2·8	45·4	2·7
3-Bromo-5-chloro-4-methoxypropiophenone	57	$C_{10}H_{10}O_2BrCl$	43·0	3·8	43·2	3·6
3-Bromo-5-chloro-4-hydroxypropiophenone	125	$C_9H_8O_2BrCl$	40·7	3·0	41·0	3·0
2-Bromo-4-2′-thenoyl)anisole	127	$C_{12}H_9O_2BrS$	48·2	3·2	48·5	3·0
2-Bromo-4-2′-thenoyl)phenol	183	$C_{11}H_7O_2BrS$	46·4	2·6	46·6	2·5
2-Bromo-4-(5-methyl-2-thenoyl)anisole	142	$C_{13}H_{11}O_2BrS$	50·0	3·4	50·2	3·5
2-Bromo-4-(5-methyl-2-thenoyl)phenol	188	$C_{12}H_9O_2BrS$	48·1	3·1	48·5	3·0
2-Chloro-4-2′-thenoylanisole [c]	124	$C_{12}H_9O_2ClS$	56·9	3·5	57·0	3·6
2-Chloro-4-2′-thenoylphenol	180	$C_{11}H_7O_2ClS$	55·0	3·0	55·3	2·9
2-Chloro-4-(5-methyl-2-thenoyl)anisole [d]	143	$C_{13}H_{11}O_2ClS$	58·2	4·0	58·5	4·1
2-Chloro-4-(5-methyl-2-thenoyl)phenol	183	$C_{12}H_9O_2ClS$	56·8	3·8	57·0	3·6
3 : 4′-Dichloro-4-methoxybenzophenone [e]	125	$C_{14}H_{10}O_2Cl_2$	59·4	3·4	59·7	3·6
3 : 4′-Dichloro-4-hydroxybenzophenone	168	$C_{13}H_8O_2Cl_2$	58·2	3·2	58·4	3·0
2′ : 3-Dichloro-4-methoxybenzophenone [f]	131	$C_{14}H_{10}O_2Cl_2$	59·4	3·6	59·7	3·6
2′ : 3-Dichloro-4-hydroxybenzophenone	156	$C_{13}H_8O_2Cl_2$	58·3	3·3	58·4	3·0
4-Chloro-2-2′-furoylanisole [g]	—	$C_{12}H_9O_3Cl$	60·6	3·8	60·9	3·8
4-Chloro-2-2′-furoylphenol	96	$C_{11}H_7O_3Cl$	59·2	3·1	59·3	3·1
3 : 4′-Dichloro-6-methoxybenzophenone	131	$C_{14}H_{10}O_2Cl_2$	59·5	3·5	59·7	3·6
2′ : 3-Dichloro-6-methoxybenzophenone	108	$C_{14}H_{10}O_2Cl_2$	59·5	3·8	59·7	3·6
2′ : 5-Dichloro-2-hydroxy-4-methylbenzophenone	105	$C_{14}H_{10}O_2Cl_2$	59·6	3·4	59·7	3·6

[a] In the case of Friedel–Crafts reactions involving 2-furoyl, 2-thenoyl, and 5-methyl-2-thenoyl chloride, the contact with aluminium chloride was reduced to 2—4 hours. The ketones derived from aliphatic acid chlorides were recrystallised from benzene–ligroin; those derived from aromatic and heterocyclic acid chlorides were recrystallised from methanol or ethanol. [b] An *x* : *x*′-dibromo-4-hydroxydeoxybenzoin, m. p. 138—142°, prepared by Glassner (*Monatsh.*, 1907, **28**, 291) by bromination of 4-hydroxydeoxybenzoin-3-carboxylic acid, was probably an impure sample of the present compound. [c] B. p. 240°/13 mm. [d] B. p. 250°/13 mm. [e] B. p. 252°/13 mm. [f] B. p. 243°/13 mm. [g] B. p. 220°/13 mm.

Halogenation of 4-hydroxypropiophenone with iodine and yellow mercuric oxide in ethanol yielded 4-hydroxy-3 : 5-di-iodopropiophenone, which was kindly tested by Mrs. Pitt-Rivers (at the National Institute for Medical Research, London) and shown to have no antithyroxine action as assayed by the method of goitre prevention in rats; several higher homologues of this compound were prepared in the same way.

Most of the nuclear-halogenated ketones described in this work retained their halogen

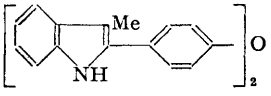
atoms when heated with phenylhydrazine, and Fischer cyclisation of the resulting hydrazones yielded a series of indoles (II) (see Table 3), together with some non-halogenated compounds; bis-indoles could also be prepared in the same way, 4 : 4′-di-propionyldiphenyl oxide giving 4 : 4′-di-(3-methyl-2-indolyl)diphenyl oxide (III).

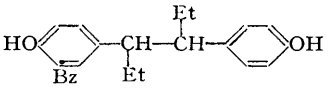
TABLE 3. 2 : 3-*Disubstituted indoles.*

Substituents	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-Ethyl-2-*p*-hydroxyphenyl-[a]	122°	$C_{16}H_{15}ON$	81·2	6·4	81·0	6·3
2-*p*-Hydroxyphenyl-3-phenyl-	152	$C_{20}H_{15}ON$	84·0	5·2	84·2	5·3
2-(3-Fluoro-4-hydroxyphenyl)-3-methyl-	90	$C_{15}H_{12}ONF$	75·0	5·3	74·7	5·0
2-(3-Fluoro-4-hydroxyphenyl)-3-phenyl-	139	$C_{20}H_{14}ONF$	79·2	4·5	79·2	4·6
2-(3-Chloro-4-hydroxyphenyl)-3-methyl-[b]	104	$C_{15}H_{12}ONCl$	69·8	4·7	69·9	4·7
2-(3-Bromo-4-hydroxyphenyl)-3-methyl-[c]	109	$C_{15}H_{12}ONBr$	59·9	4·3	59·6	4·0
2-(3-Chloro-4-methoxyphenyl)-3-methyl-[d]	151	$C_{16}H_{14}ONCl$	70·5	5·2	70·7	5·2
2-(3-Bromo-4-methoxyphenyl)-3-methyl-	155	$C_{16}H_{14}ONBr$	60·5	4·6	60·8	4·4
2-(3-Fluoro-4-methoxyphenyl)-3-phenyl-	135	$C_{21}H_{16}ONF$	79·3	5·1	79·5	5·0
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-methyl-	168	$C_{15}H_{11}ONBr_2$	47·5	2·9	47·2	2·9
2-(3-Bromo-5-chloro-4-hydroxyphenyl)-3-methyl-	151	$C_{15}H_{11}ONBrCl$	53·6	3·3	53·4	3·3
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-ethyl-[e]	144	$C_{16}H_{13}ONBr_2$	48·5	3·5	48·6	3·3
2-(3 : 5-Dibromo-4-hydroxyphenyl)-	151	$C_{20}H_{13}ONBr_2$	54·3	3·1	54·2	2·9
2-(3-Bromo-5-fluoro-4-hydroxyphenyl)-3-phenyl-	162	$C_{20}H_{13}ONBrF$	63·0	3·2	62·8	3·4
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-*n*-octyl-	70	$C_{22}H_{25}ONBr_2$	55·3	5·5	55·1	5·2

[a] Deep brown picrate, m. p. 136°. [b] Dark brown picrate, m. p. 148°. [c] Dark brown picrate, m. p. 158°. [d] Brown-violet picrate, m. p. 120°. [e] Brown-violet picrate, m. p. 121°.

The halogenated hydroxybenzophenones and heterocyclic furan and thiophen analogues, obtained by pyridine hydrochloride demethylation of the corresponding methyl ethers (prepared by Friedel–Crafts reaction with halogenated anisoles and homologues), showed notable tuberculostatic activity *in vitro*, which, however, was considerably reduced

(III) 


(IV)

or suppressed in the presence of blood serum. For similar biological investigation, 3-benzoylhexœstrol (IV) was synthesised by pyridine hydrochloride demethylation of the methyl ether obtained in Friedel–Crafts benzoylation of hexœstrol dimethyl ether; 3-*p*-anisoylhexœstrol dimethyl ether was also prepared.

EXPERIMENTAL (with M. R. KHENISSI).

Preparation of Intermediates.—*o*-Fluoroanisole was prepared from *o*-anisidine by the Schiemann reaction. *p*-Acylphenols were prepared by refluxing for 30 min. a mixture of the *p*-acylanisole (1 part) and redistilled pyridine hydrochloride (3—4 parts); after addition of water, the product was taken up in chloroform and purified by vacuum-distillation. *p*-Acylanisoles were prepared by Friedel–Crafts reaction with aluminium chloride and the acid chloride in carbon disulphide; as by-products, ethylenic compounds were obtained (cf. Xuong and Buu-Hoï, *J.*, 1952, 3741). 1 : 1-*Di*-p-*anisoylhept*-1-*ene*, from heptanoyl chloride and anisole, formed a pale yellow oil, b. p. 250—252°/15 mm., n_D^{23} 1·5810 (Found : C, 81·1; H, 8·5. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%); 1 : 1-*di*-p-*anisoylhex*-1-*ene*, from hexanoyl chloride and anisole, was also a pale yellow oil, b. p. 242—244°/15 mm., n_D^{22} 1·5950 (Found : C, 81·0; H, 8·2. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%).

3-*Chloro*-4-*hydroxypropiophenone*.—(a) *By demethylation.* A mixture of 3-chloro-4-methoxypropiophenone (50 g.) and redistilled pyridine hydrochloride (200 g.) was refluxed for 15 min.; the *phenol* obtained in 75% yield on dilution with water was purified by vacuum-distillation; it formed shiny colourless prisms, m. p. 114°, from aqueous acetic acid (Found : C, 58·2; H, 5·1. $C_9H_9O_2Cl$ requires C, 58·5; H, 4·9%).

(b) *By chlorination.* 4-Hydroxypropiophenone was best prepared in bulk by saturating a mixture of equal parts of phenol and propionic acid with boron trifluoride at 70—75°; the ketone, obtained in 65—70% yield, was characterised as the *semicarbazone*, needles, m. p. 183° (from ethanol) (Found : N, 20·0. $C_{10}H_{13}O_2N_3$ requires N, 20·3%), oxime, prisms, m. p. 141°

(from aqueous methanol), and 2 : 4-dinitrophenylhydrazone, red needles, m. p. 254—255° (from acetic acid).

4-*Propionyloxypropiophenone* (prepared by use of propionyl chloride) formed colourless prisms, m. p. 68°, from ligroin (Found : C, 69·8; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%); 4-n-*butyryloxypropiophenone* formed prisms, m. p. 52°, from ligroin (Found : C, 70·7; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), and 4-*benzoyloxypropiophenone* formed needles, m. p. 116°, from methanol (Found : C, 75·5; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

To a suspension of 4-hydroxypropiophenone (50 g.) in cold acetic acid (800 c.c.), a solution of chlorine (24 g.) in acetic acid (850 c.c.) was added in small portions; the clear solution obtained was kept overnight, concentrated in a vacuum, and diluted with water, giving 35 g. of 3-chloro-4-hydroxypropiophenone.

Action of Bromine on 4-*Hydroxyacetophenone.*—(a) *Side-chain bromination.* To a cooled solution of 4-hydroxyacetophenone (5 g.) in acetic acid (150 c.c.), a solution of bromine (5·9 g.) in acetic acid (30 c.c.) was added in small portions with stirring. The mixture was kept for 1 hr. at room temperature, concentrated in a vacuum, and poured into water; the precipitated oily ω-bromo-4-hydroxyacetophenone gradually solidified, and formed from benzene needles (5 g.), m. p. 130°, highly lachrymatory and irritant (Found : C, 44·4; H, 3·2. $C_8H_7O_2Br$ requires C, 44·6; H, 3·2%).

(b) *Nuclear bromination.* A solution of 4-hydroxyacetophenone (4·5 g.) in aqueous acetic acid (25 c.c. of acid and 65 c.c. of water) was treated with a solution of bromine (10·6 g.) in 80% aqueous acetic acid (25 c.c.) in small portions; on addition of water, 3 : 5-dibromo-4-hydroxyacetophenone (6 g.), m. p. 181°, was obtained (Priestley and Moness, *loc. cit.*); substantial amounts of the same ketone were also obtained when one mol. of bromine was used.

2-p-*Hydroxyphenylpyrrocoline* (I).—A solution of ω-bromo-4-hydroxyacetophenone (1·2 g.) and α-picoline (0·5 g.) in ethanol (15 c.c.) was heated at 60° for 30 min.; the quaternary picolinium bromide precipitated on addition of ether was treated with boiling water (50 c.c.) containing hydrogen sodium carbonate (4 g.). The precipitate crystallised from ethanol as grey-tinged prisms, m. p. 243°, which lost one mol. of water only on prolonged heating above 100° (Found : C, 80·0; H, 5·5. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3%).

Action of Bromine on 4-*Hydroxypropiophenone.*—(a) *Side-chain bromination.* Obtained as for the lower homologue, α-*bromo*-4-*hydroxypropiophenone* formed from aqueous acid colourless, lachrymatory needles, m. p. 98°, which gave a precipitate of aniline hydrobromide when heated with aniline (Found : C, 47·5; H, 4·1. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%). 3-Bromo-4-hydroxypropiophenone, m. p. 124° (Hoán and Buu-Hoï, *loc. cit.*), after treatment with boiling aniline, was recovered unchanged.

(b) *Nuclear bromination.* 3 : 5-*Dibromo*-4-*hydroxypropiophenone* (6·5 g.), obtained in the treatment of 4-hydroxypropiophenone (5 g.) with bromine (10·6 g.) in aqueous acetic acid, formed colourless needles, m. p. 114°, from the same solvent (Found : C, 35·0; H, 2·9. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%); this ketone was stable in aqueous potassium hydroxide, and treatment with methyl sulphate gave 3 : 5-*dibromo*-4-*methoxypropiophenone*, needles, m. p. 59° (from ethanol) (Found : C, 37·2; H, 3·2. $C_{10}H_{10}O_2Br_2$ requires C, 37·3; H, 3·1%). The *x* : *x'*-dibromo-4-hydroxypropiophenone, m. p. 100°, described by Goldzweig and Kaiser (*loc. cit.*) could be mainly converted into the same methyl ether, and contained a component with labile bromine (aniline test).

Preparation of Fluoro-ketones.—Friedel–Crafts acylations of *o*-fluoroanisole were performed with acid chlorides and aluminium chloride in carbon disulphide in the usual way; the methoxy-ketones were purified by vacuum-distillation and recrystallisation from ligroin, and were in general obtained in better yields (75—85%) than with anisole. The corresponding hydroxy-ketones were purified by vacuum-distillation and recrystallisation from aqueous acetic acid or aqueous ethanol, and were all colourless prisms; nuclear bromination of the fluorohydroxy-ketones was performed in aqueous acetic acid.

3-*Benzoylhexœstrol* [3-(3-*Benzoyl*-4-*hydroxyphenyl*)-4-p-*hydroxyphenylhexane*] (IV).—To a well-cooled solution of hexœstrol dimethyl ether (50 g.) and benzoyl chloride (25 g.) in redistilled nitrobenzene (200 c.c.), finely powdered aluminium chloride (25 g.) was added portion-wise; the mixture was kept at 5° overnight, then treated with ice, and the nitrobenzene removed by steam; the residue gave on vacuum-fractionation a portion, b. p. 305—308°/20 mm. (37 g.), which was a thick resin, giving on treatment with boiling pyridine hydrochloride 3-*benzoyl-hexœstrol*, crystallising as colourless needles, m. p. 201—202°, from benzene (Found : C, 80·5; H, 6·8. $C_{25}H_{24}O_3$ requires C, 80·6; H, 6·5%); the substance gave yellow alkaline solutions.

3-p-*Anisoylhexœstrol Dimethyl Ether.*—Similarly prepared by Friedel–Crafts reaction from

hexœstrol dimethyl ether (50 g.), anisoyl chloride (30 g.), and aluminium chloride (25 g.) in nitrobenzene (200 c.c.), this *ketone* formed colourless needles (60 g.), m. p. 112°, b. p. 328—330°/15 mm., from methanol (Found : C, 77·6; H, 7·5. $C_{28}H_{32}O_4$ requires C, 77·8; H, 7·4%).

4-*Hydroxy*-3 : 5-*di-iodopropiophenone*.—To a mixture of 4-hydroxypropiophenone (5 g.), yellow mercuric oxide (14·4 g.), and ethanol (100 c.c.), iodine (17 g.) was added in small portions with stirring; after the iodine had disappeared, the mixture was filtered by suction and the solid mass treated with dilute aqueous potassium hydroxide; after filtration, the alkaline solution was neutralised with hydrochloric acid, and the precipitate repeatedly recrystallised from benzene–ligroin. 4-*Hydroxy*-3 : 5-*di-iodopropiophenone* formed colourless needles, m. p. 124° (Found : C, 27·3; H, 2·1. $C_9H_8O_2I_2$ requires C, 26·9; H, 2·0%); 3 : 5-*di-iodo*-4-*methoxypropiophenone*, prepared by heating for 1 hr. the foregoing compound (2 g.) with methyl iodide (1 g.) and potassium hydroxide (0·3 g.) in ethanol (30 c.c.), formed colourless needles, m. p. 104°, from ethanol (Found : C, 29·0; H, 2·4. $C_{10}H_{10}O_2I_2$ requires C, 28·8; H, 2·4%).

4-*Hydroxy*-3 : 5-*di-iodobutyrophenone*, prepared from 4-hydroxybutyrophenone (10 g.), yellow mercuric oxide (26·3 g.), and iodine (31 g.) in ethanol, formed colourless needles, m. p. 106°, from aqueous acetic acid (Found : C, 29·0; H, 2·3. $C_{10}H_{10}O_2I_2$ requires C, 28·8; H, 2·4%); 3 : 5-*di-iodo*-4-*methoxybutyrophenone* formed colourless prisms, m. p. 79°, from ethanol (Found : C, 31·0; H, 3·0. $C_{11}H_{12}O_2I_2$ requires C, 30·7; H, 2·8%). 4-*Hydroxy*-3 : 5-*di-iodohexanophenone* formed colourless prisms, m. p. 69° (Found : C, 32·8; H, 3·0. $C_{12}H_{14}O_2I_2$ requires C, 32·4; H, 3·1%). 4-*Hydroxy*-3 : 5-*di-iodoheptanophenone* formed colourless needles, m. p. 50°, from ligroin (Found : C, 33·8; H, 3·2. $C_{13}H_{16}O_2I_2$ requires C, 34·1; H, 3·5%).

Friedel–Crafts Reactions with Diphenyl Oxide.—(a) *With propionyl chloride*. The reaction of propionyl chloride (1·5 mol.) with diphenyl oxide (1 mol.) in carbon disulphide in the presence of aluminium chloride (1·2 mol.) gave, in addition to 4-propionyldiphenyl oxide, b. p. 210—212°/13 mm., crystallising as colourless leaflets, m. p. 36°, from methanol (Dilthey *et al.*, *J. pr. Chem.*, 1927, **117**, 359, described this substance as a liquid), some 4 : 4′-*dipropionyldiphenyl oxide*, b. p. 270—272°/15 mm., crystallising as colourless needles, m. p. 100°, from methanol (Found : C, 76·5; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

(b) *With higher aliphatic acid chlorides*. 4-iso*Butyryldiphenyl oxide* formed a pale yellow oil, b. p. 223—224°/21 mm., n_D^{23} 1·5741 (Found : C, 80·0; H, 6·9. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); 4-*hexanoyldiphenyl oxide* had b. p. 236—238°/15 mm., and formed lustrous leaflets, m. p. 39°, from ligroin (Found : C, 80·5; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%); 4-*octanoyldiphenyl oxide*, b. p. 250—252°/15 mm., formed silky needles, m. p. 35°, from ligroin (Found : C, 81·3; H, 8·2. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%).

Preparation of Indoles.—The 2-*arylindoles* listed in Table 3 were prepared by heating at 110—120° a mixture of phenylhydrazine and the appropriate ketone until steam ceased to be evolved, and boiling for a few minutes the crude hydrazone thus formed with acetic acid saturated with hydrogen chloride; the precipitate obtained on addition of water was collected, washed with water, and recrystallised several times from ligroin (for the phenolic compounds) or ethanol (for the methoxy-compounds). These indoles generally retained crystallisation-solvents very strongly, and must be carefully dried in vacuum for analysis.

4 : 4′-*Di*-(3-*methyl*-2-*indolyl*)*diphenyl Oxide* (III).—Prepared as above from phenylhydrazine (2 mol.) and 4 : 4′-dipropionyldiphenyl oxide (1 mol.), this *ether* crystallised as colourless prisms, m. p. 210°, from ethanol, giving a deep violet picrate (Found : N, 6·4. $C_{30}H_{24}ON_2$ requires N, 6·5%).

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