82. *Methylthio-derivatives of Benzophenone, Tetraphenylethylene, and Related Substances.*

By Ahmed Mustafa.

1-Bromo-1 : 2-diphenyl-2-*p*-methylthiophenylethylene (II) and 1-phenyl-2 : 2-bis-*p*-methylthiophenylethylene (III) were prepared and tested for oestrogenic activity.

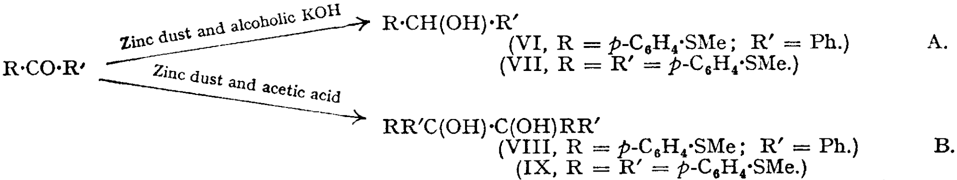
The alkaline and acid reductions of *p*-methylthiobenzophenone (IV) and bis-*p*-methylthiobenzophenone (V) (schemes A and B respectively) were studied and the photochemical behaviour of the solutions of the corresponding pinacols (VIII and IX) in acetone is described.

Some reactions of (IV), (V), and bis-*p*-methylthiobenzophenone chloride are given.

(*a*) In view of the remarkable oestrogenic activity of chlorotriphenylethylene and its analogues (Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292; Robson, Schönberg, Tadros, and

Fahim, *J.*, **1940**, 1327; Schönberg, Robson, and Tadros, *Nature*, 1942, **150**, 22) 1-*bromo*-1 : 2-*diphenyl*-2-p-*methylthiophenylethylene* (II) and 1-*phenyl*-2 : 2-*bis*-p-*methylthiophenylethylene* (III) were prepared. (II) was found to be active in doses of 1 mg. but less active than its oxygen analogue, 1-bromo-1 : 2-diphenyl-2-*p*-methoxyphenylethylene (I). (III), given either subcutaneously or by stomach tube in 1 mg. doses, produced no oestrogenic effect (oestrogenic results reported by Dr. J. M. Robson, Department of Pharmacology, Guy's Hospital, London). (II) and (III) were prepared by a method similar to that used for (I) (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2487).

(*b*) *Reduction of* p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V).—When (IV) or (V) was treated with zinc dust in the presence of alcoholic potassium hydroxide, p-*methylthiobenzhydrol* (VI) or *bis*-p-*methylthiobenzhydrol* (VII) respectively was obtained (scheme A); on the other hand, when treated with zinc dust in the presence of acetic acid, s-*bis*-p-*methylthiobenzpinacol* (VIII) or s-*tetrakis*-p-*methylthiobenzpinacol* (IX) respectively was obtained (scheme B).



(*c*) *Photochemical Behaviour of the Pinacols* (VIII) *and* (IX).—Schönberg and Mustafa (*J.*, 1944, 67; *Chem. Reviews*, 1947, **40**, 182) were unable to reduce xanthone to the corresponding pinacol by the action of *iso*propyl alcohol in sunlight, in contrast to the ready formation of benzpinacol by the action of *iso*propyl alcohol on benzophenone in sunlight (Bachmann, *Org. Synth.*, 1934, **14**, 8). They also found that, in the case of xanthopinacol and fluorenopinacol, the reverse reaction takes place. Similarly I have found that when (VIII) and (IX) were exposed to sunlight in acetone solution, (IV) and (V) respectively were formed. (IV) and (V) are stable towards *iso*propyl alcohol in sunlight. The formation of the ketones (IV) and (V) is a true photochemical reaction, the pinacols (VIII) and (IX) being stable towards acetone in the dark.

For a possible mechanism of this reverse reaction see Schönberg and Mustafa (*loc. cit.*).

(*d*) *Reactions with Benzophenone Chloride and Bis*-p-*methylthiobenzophenone Chloride*.—When benzophenone is treated with thionyl chloride, benzophenone ketochloride is obtained. This gives (i) benzophenoneanil when treated with aniline (Pauly, *Annalen*, 1887, **187**, 199), (ii) tetraphenylethylene when refluxed with diphenylmethane (Norris, Thomas, and Brown, *Ber.*, 1910, **43**, 2958), and (iii) diphenyl ketazine when treated with hydrazine hydrate (Curtius and Rauterberg, *J. pr. Chem.*, 1891, **44**, 192).

Similarly, (V) forms the corresponding keto-chloride when treated with thionyl chloride and this, by the action of thioacetic acid, yields *bis*-p-*methylthiophenylthione* (X) (Schönberg, Schütz, and Nickel, *Ber.*, 1928, **61**, 1375):

$$>C{:}O \xrightarrow{SOCl_2} >C\genfrac{}{}{0pt}{}{Cl}{Cl} \xrightarrow{CH_3\cdot CO\cdot SH} >C\genfrac{}{}{0pt}{}{Cl}{SH} \longrightarrow >C{:}S + HCl$$

With solid mercuric chloride (X) in benzene shows the colour reaction described for diphenylthione derivatives (Schönberg, *Ber.*, 1925, **58**, 1793). (X) is transformed into s-*tetrakis*-p-*methylthiophenylethylene* (XI) when its solution in xylene is refluxed with copper bronze (Schönberg, Schütz, and Nickel, *loc. cit.*).

(*e*) *Reactions of* p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V).—The ketone (IV) was converted into its *hydrazone* and *bis*-p-*methylthiophenyl ketazine*; (V) was converted into its anil and *bisphenylthiobis*-p-*methylthiophenylmethane*.

EXPERIMENTAL.

Action of Benzylmagnesium Chloride on p-*Methylthiobenzophenone* (IV).—The ketone (IV) (Schönberg, *Annalen*, 1924, **436**, 205) (10 g.) was treated with an ethereal solution of benzylmagnesium chloride [prepared from magnesium (1·4 g.), benzyl chloride (6·3 g.), and ether (75 c.c.)], and refluxed with stirring for 2 hours. The oil obtained after decomposition of the product with cold aqueous ammonium chloride was washed with light petroleum (b. p. 30—50°) and taken up in benzene from which it crystallised, after the addition of light petroleum (b. p. 30—50°), in colourless crystals, m. p. 117°. The yield was almost theoretical (Found: C, 78·5; H, 6·3; S, 10·1. $C_{21}H_{20}OS$ requires C, 78·8; H, 6·2; S, 10·0%). 2-*Hydroxy*-1 : 2-*diphenyl*-2-p-*methylthiophenylethane* was soluble in cold benzene and ethyl alcohol. It gave a deep red colour with concentrated sulphuric acid.

1-*Bromo*-1 : 2-*diphenyl*-2-p-*methylthiophenylethylene* (II).—This was prepared by adding a solution of the calculated amount of bromine in acetic acid to the hydroxy-ethane dissolved in the same solvent. The bromo-compound, which separated on cooling, recrystallised from absolute ethyl alcohol in colourless crystals, m. p. 105° (Found : C, 65·9; H, 4·4; Br, 21·5; S, 8·0. $C_{21}H_{17}BrS$ requires C, 66·1; H, 4·5; Br, 21·0; S, 8·4%). It gave a red-brown colour with sulphuric acid on standing.

2-Hydroxy-1 : 2-diphenyl-2-*p*-methylthiophenylethane was subjected to vacuum distillation in the presence of one drop of 20% sulphuric acid and gave an oily distillate which was easily soluble in alcohol, benzene, and light petroleum (b. p. 30—50°). This oily material when treated with bromine as described above gave (II), m. p. 105°, undepressed on admixture with a specimen prepared as above.

2-*Hydroxy*-1-*phenyl*-2 : 2-*bis*-p-*methylthiophenylethane*.—This was similarly prepared from bis-*p*-methylthiobenzophenone (V) (Schönberg, *loc. cit.*) (5 g.) and benzylmagnesium chloride [prepared from magnesium (0·7 g.), benzyl chloride (3·2 g.), and ether (40 c.c.)]. The *carbinol* crystallised from benzene after the addition of light petroleum (b.p. 30—50°) in colourless crystals, m. p. 118° (Found : C, 72·5; H, 6·1; S, 17·3. $C_{22}H_{22}OS_2$ requires C, 72·1; H, 6·0; S, 17·5%). It was soluble in benzene and hot ethyl alcohol, and gave a dark blue-green colour with sulphuric acid.

1-*Phenyl*-2 : 2-*bis*-p-*methylthiophenylethylene* (III).—2-Hydroxy-1-phenyl-2 : 2-bis-*p*-methylthiophenylethane (10 g.) was distilled in a vacuum in the presence of one drop of 20% sulphuric acid. The distillate was crystallised from light petroleum (b. p. 70—80°) yielding the *ethylene* in colourless crystals, m. p. 106° (Found : C, 75·9; H, 5·8; S, 18·2. $C_{22}H_{20}S_2$ requires C, 75·8; H, 5·7; S, 18·4%). It was soluble in benzene and ethyl alcohol, and difficultly soluble in light petroleum (b. p. 30—50°). The compound gave a dark blue-green colour with sulphuric acid.

Reduction of p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V) *in Alkaline Medium*.—(i) p-*Methylthiobenzhydrol* (VI). The ketone (IV) (2 g.) was treated with zinc dust (4 g.) and alcoholic potassium hydroxide (2 g. in 20 c.c.) and refluxed for 45 minutes. The hot mixture was filtered and the filtrate treated with a few drops of water and cooled, giving the *benzhydrol* which crystallised from ethyl alcohol in colourless crystals, m. p. 99° (Found : C, 72·9; H, 6·1; S, 13·5. $C_{14}H_{14}OS$ requires C, 73·1; H, 6·1; S, 13·9%). (VI) was soluble in cold benzene and hot ethyl alcohol, and gave a red colour with sulphuric acid.

(ii) *Bis*-p-*methylthiobenzhydrol* (VII). The ketone (V) (2 g.) was reduced as described above in the case of (IV). *Bis*-p-*methylthiobenzhydrol* was obtained in colourless crystals from light petroleum (b. p. 70—80°), m. p. 98° (Found : C, 65·0; H, 5·9; S, 23·0. $C_{15}H_{16}OS_2$ requires C, 65·1; H, 5·8; S, 23·2%). It was easily soluble in benzene and hot ethyl alcohol and gave a malachite-green colour with sulphuric acid.

Reduction of p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V) *in Acid Medium*.—(i) *s-Bis*-p-*methylthiobenzpinacol* (VIII). The ketone (IV) (1 g.) was dissolved in 80% ethyl alcohol (15 c.c.) and treated with zinc dust (3 g.) and glacial acetic acid (15 c.c.) (Cohen, *Rec. Trav. chim.*, 1919, **38**, 72, 113). The mixture was refluxed on the water bath for 2 hours, cooled and filtered and the solid residue washed with water, dried, and crystallised from benzene after the addition of light petroleum (b. p. 30—50°); colourless crystals, m. p. 175° (Found : C, 73·2; H, 5·7; S, 13·5. $C_{28}H_{26}O_2S_2$ requires C, 73·4; H, 5·7; S, 13·9%). The *benzpinacol* (VIII) was soluble in cold benzene and hot ethyl alcohol, and gave a malachite-green colour with sulphuric acid.

(ii) *s-Tetrakis*-p-*methylthiobenzpinacol* (IX). This was obtained by the reduction of (V) (1 g.) as described for (IV). The *benzpinacol* (IX) crystallised from benzene after the addition of light petroleum (b. p. 30—50°) in colourless crystals, m. p. 169° (Found : C, 65·2; H, 5·6; S, 22·9. $C_{30}H_{30}O_2S_4$ requires C, 65·4; H, 5·5; S, 23·3%). It was easily soluble in benzene, difficulty soluble in cold alcohol, and gave a violet colour with sulphuric acid.

Photochemical Action of Acetone on s-*Bis*-p-*methylthiobenzpinacol* (VIII).—(VIII) (2 g.) in acetone (25 c.c.) was exposed to sunlight for one month (May—June) in a sealed "Pyrex"-glass tube, from which the air had been displaced by dry carbon dioxide. The acetone was removed under reduced pressure and the solid residue of *p*-methylthiobenzophenone (IV) crystallised from benzene after the addition of light petroleum (b. p. 30—50°), m. p. and mixed m. p. 79°. The presence of *iso*propyl alcohol in the acetone solution was indicated by the formation of the *p*-nitrobenzoate (Schönberg and Mustafa, *J.*, 1943, 276).

Photochemical Action of Acetone on s-*Tetrakis*-p-*methylthiobenzpinacol* (IX).—The exposure of (IX) in acetone to sunlight for one month (May—June) gave bis-*p*-methylthiobenzophenone (V), m. p. and mixed m. p. 125°, and *iso*propyl alcohol.

Reactions of Bis-p-*methylthiobenzophenone* (V).—(i) *Bis*-p-*methylthiophenylthione* (X). Bis-*p*-methylthiobenzophenone chloride, prepared from (V) (4 g.) and thionyl chloride (30 c.c.) by heating under reflux, was dissolved in dry benzene (20 c.c.), thioacetic acid (5 c.c.) was added in a stream of dry carbon dioxide, and the mixture was refluxed for 6 hours, when a deep blue colour was observed. The excess of benzene and thioacetic acid was removed by distillation, and on addition of light petroleum (b. p. 30—50°) to the residue, *bis*-p-*methylthiophenylthione* (X) was deposited in blue crystals. It was recrystallised from benzene–light petroleum (b. p. 50—60°), m. p. 136° (blue melt) (Found : C, 61·9; H, 4·9; S, 32·9. $C_{15}H_{14}S_3$ requires C, 62·1; H, 4·8; S, 33·1%). It dissolved in hot benzene to a greenish-blue solution, was difficultly soluble in light petroleum (b. p. 30—50°), and very sparingly soluble in acetone. When mercuric chloride crystals were added to a dilute solution of the thione in benzene, they acquired a red-brown colour.

(ii) s-*Tetrakis*-p-*methylthiophenylethylene* (XI). (X) (2 g.), dissolved in xylene (30 c.c.), was refluxed with copper bronze (5 g.) for 8 hours. The hot xylene solution was filtered and concentrated; on cooling the *ethylene* (XI) separated in colourless crystals, recrystallised from benzene after the addition of light petroleum (b. p. 30—50°), m. p. 220° (Found : C, 70·0; H, 5·5; S, 24·6. $C_{30}H_{28}S_4$ requires C, 69·8; H, 5·4; S, 24·8%). It was soluble in hot benzene and difficultly soluble in alcohol.

(iii) *Bis*-p-*methylthiobenzophenoneanil*. This was obtained, from alcohol, in yellow crystals, m. p. 135° (identified by m. p. and mixed m. p.) (Schönberg, *loc. cit.*).

(iv) *Bisphenylthiobis*-p-*methylthiophenylmethane*. To a solution of the ketone (V) (1 g.) in the least amount of hot glacial acetic acid (15 c.c.), thiophenol (1 g.), and anhydrous zinc chloride (a few sticks) were added. The reaction mixture was saturated with hydrogen chloride, and kept overnight at room temperature (cf. Baumann, *Ber.*, 1885, **18**, 888). It was poured into excess of water, extracted with ether, washed with dilute aqueous sodium hydroxide, and the ether evaporated leaving colourless crystals. The *methane* was recrystallised from light petroleum (b. p. 90—100°), m. p. 119° (Found: C, 68·2; H, 5·0; S, 26·6. $C_{27}H_{24}S_4$ requires C, 68·1; H, 5·0; S, 26·9%). It was easily soluble in cold benzene and hot alcohol, and gave a violet colour with sulphuric acid.

Reactions of p-*Methylthiobenzophenone* (IV).—p-*Methylthiobenzophenone hydrazone.* This was prepared by heating a mixture of hydrazine hydrate (1·8 g.), absolute ethyl alcohol (1 c.c.), and (IV) (5 g.) in a sealed tube at 160° for 6 hours (Curtius and Rauterberg, *loc. cit.*). p-*Methylthiobenzophenone hydrazone* was obtained from alcohol in colourless crystals, m. p. 95° (Found: C, 69·2; H, 5·6; N, 11·5; S, 13·0. $C_{14}H_{14}N_2S$ requires C, 69·4; H, 5·8; N, 11·6; S, 13·2%). It was easily soluble in hot alcohol and cold benzene.

Bis-p-*methylthiophenylketazine.* This was obtained by oxidation of *p*-methylthiophenylbenzophenone hydrazone by yellow mercuric oxide, as described for xanthone hydrazone (Schönberg and Stolpp, *Ber.*, 1930, **63**, 3114), in almost colourless crystals from light petroleum (b. p. 80—90°), m. p. 156—157° (Found: C, 74·2; H, 5·0; N, 6·1; S, 13·8. $C_{28}H_{24}N_2S_2$ requires C, 74·3; H, 5·3; N, 6·2; S, 14·1%). It was easily soluble in benzene and hot ethyl alcohol.

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