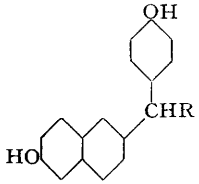
19. *New Naphthalene Derivatives Structurally Related to Stilboestrol.*

By B. J. F. Hudson.

A series of *p*-methoxyphenyl 2-methoxynaphthyl ketones are obtained by the use of Friedel–Crafts condensations. Subsequent reduction and demethylation afford dihydroxy compounds spatially related to stilboestrol. Using rats, oestrogenic activity in the compounds tested was shown to be less than one-thousandth of that of stilboestrol.

Naphthalene derivatives do not appear to have been investigated hitherto as possible oestrogenic agents, although a tetrahydronaphthalene and a hexahydrochrysene derivative were investigated by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, B, 1941, **127**, 140). The former had slight activity, but the latter was fully active in 1 mg. doses. More recently Salzer (*Z. Physiol. Chem.*, 1942, **274**, 39) has prepared 6-hydroxy-2-(*p*-hydroxyphenyl)-1-methyl-3 : 4-dihydronaphthalene, which is stated to exhibit an activity comparable with that of the natural hormones.

An account is given in the present paper of a series of naphthalene derivatives closely resembling oestradiol and the highly active synthetic oestrogens in molecular weight and spatial configuration.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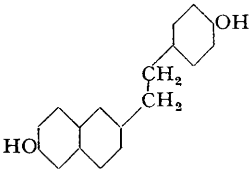
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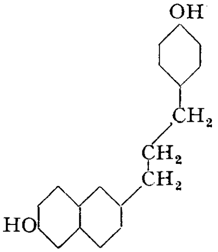
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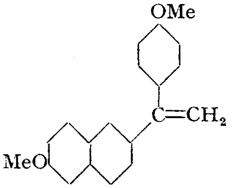
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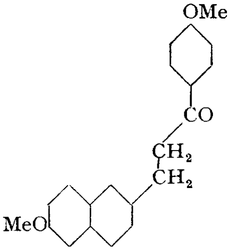
(V.)

Compounds of type (I) have now been obtained from 2-*methoxy*-6-*anisoylnaphthalene* which is derived from 2-methoxy-6-naphthoic acid by the condensation of anisole with 2-methoxy-6-naphthoyl chloride. Reduction of 2-methoxy-6-anisoylnaphthalene by Clemmensen's method yields p-*methoxyphenyl*-(2-*methoxy*-6-*naphthyl*)-*methane*, the dimethyl ether of (I, R = H). On the other hand reaction with methylmagnesium iodide leads directly to α-(p-*methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethylene* (IV) which on hydrogenation gives the dimethyl ether of (I, R = Me). Dealkylation of this ether gives no well-defined product.

It is well known that, when the solvent is cold nitrobenzene, the course of a Friedel–Crafts reaction with 2-substituted naphthalenes can be modified so that an acyl group enters the 6-position (Haworth and Sheldrick, *J.*, 1934, 865; Anderson and Johnston, *J. Amer. Chem. Soc.*, 1943, **65**, 241). The present work confirms this as far as the action of acyl chlorides on 2-methoxynaphthalene is concerned, but it has also been shown that, even in cold nitrobenzene, as well as in carbon disulphide, the anisoyl group enters the 1-position. An independent synthesis of the product, 2-*methoxy*-1-*anisoylnaphthalene*, has been achieved by the action of anisole on 2-methoxy-1-naphthoyl chloride.

Ketones leading to compounds (II) and (III) were obtained by the action of *p*-methoxyphenylacetyl chloride and β-*p*-methoxyphenylpropionyl chloride respectively on 2-methoxynaphthalene in the presence of aluminium chloride and nitrobenzene. Their structures were established by the oxidation of the reaction products to 2-methoxy-6-naphthoic acid. Reduction followed by demethylation gave (II) and (III).

A second approach to (III) has been made by condensing 2-*methoxy*-6-*naphthaldehyde*, obtained from 2-methoxy-6-naphthylmagnesium bromide by the action of ethyl orthoformate, with *p*-methoxyacetophenone, followed by hydrogenation of the resulting chalkone to the ketone (V).

Biological assay of compounds (I, R = H), (II), (III) and their diacetates was carried out by Dr. G. Brownlee of the Wellcome Physiological Research Laboratories, Beckenham. They were shown by both the uterine weight and vaginal smear methods, using rats, to have less than one-thousandth of the activity of stilboestrol.

Experimental.

(Melting points are uncorrected.)

2-*Methoxy*-6-*anisoylnaphthalene*.—2-Methoxy-6-naphthoic acid (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2840) (33·2 g.) was refluxed with excess of thionyl chloride for one hour, excess of thionyl chloride evaporated, and the resulting crystalline acid chloride gradually added to a cold stirred mixture of anisole (38 g.), dry carbon disulphide (200 c.c.), and freshly powdered aluminium chloride (52·5 g.). The deep orange-red solution was gradually heated to boiling during two hours, cooled, poured on ice, and then steam-distilled. The crude non-volatile product was recrystallised from benzene, and gave thin prisms (40 g., 91%), m. p. 146—147° (Found : C, 77·9; H, 5·6. $C_{19}H_{16}O_3$ requires C, 78·1; H, 5·5%). It formed a scarlet 2 : 4-dinitrophenylhydrazone.

2-*Methoxy*-1-*anisoylnaphthalene*.—(*a*) 2-Methoxy-1-naphthoic acid (14·5 g.) was converted into its acid chloride in the manner described above, and the latter gradually added to a cold stirred mixture of anisole (16·2 g.), carbon disulphide (80 c.c.), and aluminium chloride (22·5 g.). The product, after removal of volatile components by steam-distillation, was a brown gum which on treatment with methanol gave a solid, m. p. 154—158°. This on crystallisation from benzene gave the required product (8·0 g., 48%) in large prisms, m. p. 159—160° (Found : C, 78·2; H, 5·7. $C_{19}H_{16}O_3$ requires C, 78·1; H, 5·5%). A 2 : 4-dinitrophenylhydrazone was not formed under the usual conditions.

(*b*) Anisoyl chloride (11·5 g.) was added to a mixture of 2-methoxynaphthalene (15·8 g.), dry carbon disulphide (100 c.c.), and powdered aluminium chloride (13·5 g.). The reaction and the isolation of the product were carried out as described above; the non-volatile product (9·2 g., 40%) crystallised from benzene in large prisms, m p. 159—160°, identical with the product of (*a*).

(*c*) Anisoyl chloride (17·05 g.) was added slowly to a stirred solution of 2-methoxynaphthalene (15·8 g.) and aluminium chloride (27 g.) in dry nitrobenzene (75 c.c.) at 0°. The orange-red solution was stirred for 7 hours, decomposed by pouring on ice, and steam-distilled. The product was a thick brown oil which, after trituration with methanol, gave a solid (8·1 g., 28%), crystallising from benzene (charcoal) in stout prisms, m. p. 159—160°, identical with the products of (*a*) and (*b*).

p-*Methoxyphenyl-(2-methoxy-6-naphthyl)-methane.*—2-Methoxy-6-anisoylnaphthalene (12·0 g.), amalgamated zinc (150 g.), anisole (40 c.c.), and a mixture of concentrated hydrochloric acid (48 c.c.) and water (24 c.c.) were heated under reflux at 140—150° for 24 hours. The anisole layer was separated, washed with water and dilute sodium hydroxide, and evaporated under reduced pressure. The residual gum could not be crystallised. On distillation, it gave fractions boiling at 260—280°/6 mm. (colourless) and 280—300° (yellow) (3·6 g. in all). The residual resinous material was not volatile. On crystallisation from methanol, the first fraction gave 1·25 g., and the second 0·45 g., m. p. 100—101°. Repeated crystallisation from methanol gave 1·6 g. (14%) of thin prisms, m. p. 103—104° (Found : C, 81·75; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

p-*Hydroxyphenyl-(2-hydroxy-6-naphthyl)-methane* (I, R = H). The above dimethyl ether (2·0 g.) was heated under reflux with acetic acid (16 c.c.) and hydriodic acid (*d* 1·7, 8 c.c.) for one hour, poured into ice-water, decolourised with a trace of sodium bisulphite, collected, washed, and dried to a pink solid. After two crystallisations from benzene, the *product* (1·3 g., 70%), m. p. 159—160°, was obtained (Found : C, 81·0; H, 5·6. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·65%). The *diacetate*, obtained by treatment with acetic anhydride and pyridine, formed thin prisms, m. p. 89—90°, on crystallisation from methanol (Found : C, 75·4; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

α-(p-*Methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethylene* (IV).—To the Grignard reagent prepared from magnesium (0·66 g.) and methyl iodide (4·7 g.) in ether was added a warm solution of 2-methoxy-6-anisoyl-naphthalene (5·9 g.) in dry benzene (50 c.c.). The mixture was boiled vigorously under reflux for 6 hours, decomposed with ice, and acidified. The benzene–ether layer was separated and the solvents evaporated. The residual coarsely crystalline solid had m. p. 121—123°. After two crystallisations from ethanol or ethyl acetate, the *product* (4·4 g., 75%) was obtained in waxy leaflets, m. p. 124—125° (Found : C, 82·8; H, 6·6. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·25%).

α-(p-*Methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethane*.—The above compound (5·0 g.) was hydrogenated at room temperature and 1400 mm. in the presence of dioxan (60 c.c.) and palladised charcoal (3·0 g.). Absorption of hydrogen was complete in two hours. The solution was filtered, the catalyst washed with dioxan, and the filtrate and washings evaporated under reduced pressure. The residual white solid, on recrystallisation from ethanol, gave the product (4·4 g., 88%), m. p. 107—109°. The pure material crystallised from ethanol in clusters of needles, m. p. 109—110° (Found : C, 82·2; H, 7·2. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·9%).

Attempted demethylation of the above dimethyl ether. The following methods were employed, but in all a gummy phenolic product was formed : (*a*) refluxing with acetic acid and hydriodic acid (*d* 1·7) as already described, (*b*) heating with a slight excess of methylmagnesium iodide at 160—170°, (*c*) heating with a solution of potassium hydroxide in ethylene glycol at 225—235°. The oily products could not be obtained solid. The oily acetate, obtained by the action of acetic anhydride and pyridine, distilled over a considerable temperature range (180—250°/2 mm.) showing that the product was not homogenous. No solid diacetate could be isolated.

6-*Bromo*-2-*ethoxynaphthalene*.—In Fries and Schimmelschmidt's (*loc. cit.*) preparation of 6-bromo-2-methoxynaphthalene, the intermediate 1 : 6-dibromo-2-naphthol was converted into 6-bromo-2-naphthol by the action of granulated tin on a boiling mixture of ethanol and concentrated hydrochloric acid. A considerable non-phenolic fraction was always obtained as a solid at this state. After separating from the alkaline solution of 6-bromo-2-naphthol and washing with water, the product was dried and crystallised from methanol or ethanol, from which it separated in plates, m. p. 81—82° (Found : C, 57·3; H, 4·5. $C_{12}H_{11}OBr$ requires C, 57·4; H, 4·4%).

2-*Ethoxy*-6-*naphthoic Acid*.—6-Bromo-2-ethoxynaphthalene (98 g.) dissolved in warm dry benzene (280 c.c.) was added to a suspension of magnesium (15·0 g.) in ether (280 c.c.) which had been previously activated with a little ethyl bromide. Vigorous boiling was maintained for 20 hours, small amounts of ethyl bromide (18·5 c.c. in all) being added periodically to stimulate the formation of the Grignard reagent. The ether was evaporated and the residual thick brown oil added very slowly to a freezing mixture of ether (150 c.c.) and solid carbon dioxide. After reaching room temperature the mixture was decomposed with ice and hydrochloric acid. The colourless 2-*ethoxy*-6-*naphthoic acid* was collected, washed with ether, and crystallised from ethanol (charcoal). The pure acid (28 g., 33%) consisted of prisms, m. p. 204—205° (to an opaque liquid which cleared at 216°) (Found : C, 72·2; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%).

6-*Anisoyl*-2-*ethoxynaphthalene*.—The acid (27·4 g.) was converted to 2-ethoxy-6-naphthoyl chloride (crystals from benzene, m. p. 85—86°) in the manner described for 2-methoxy-6-naphthoic acid.

The acid chloride was submitted to the Friedel–Crafts reaction with anisole as described for 2-methoxy-6-naphthoyl chloride. The product (25 g.), after crystallisation from benzene or ethanol, was obtained in prisms, m. p. 128—129° (Found : C, 78·4; H, 5·9. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

α-(p-*Methoxyphenyl*)-α-(2-*ethoxy*-6-*naphthyl*)-*ethylene*.—A solution of the foregoing ketone (5·0 g.) in warm benzene (25 c.c.) was added to the Grignard reagent from magnesium (0·40 g.) and methyl iodide (3·5 g.) in ether (30 c.c.). The mixture was boiled for five hours and then worked up as for the 6-methoxy analogue. The product crystallised from ethanol (m. p. 116—118°). Repeated crystallisation from ethanol and ethyl acetate gave cream-coloured waxy plates (3 g.), m. p. 120—122° (Found : C, 82·4; H, 6·8. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%).

α-(p-*Methoxyphenyl*)-α-(2-*ethoxy*-6-*naphthyl*)-*ethane*.—The above compound (10 g.) was hydrogenated in dioxan (100 c.c.) in the presence of palladised charcoal (10·0 g.) at 2 atm. and room temperature. The product was worked up as described for the 2-methoxy analogue. Repeated crystallisation from ethanol and ethyl acetate yielded thin plates (4·8 g., 48%), m. p. 96—97° (Found : C, 82·3; H, 7·4. $C_{21}H_{22}O_2$ requires C, 82·3; H, 7·2%). Attempts to demethylate this ether were no more successful than in the case of the dimethyl compound; only oily phenolic mixtures were obtained.

p-*Methoxybenzyl* 2-*Methoxy*-6-*naphthyl Ketone*.—Freshly powdered aluminium chloride (34·0 g.) was slowly added to a well-stirred ice-cold solution of 2-methoxynaphthalene (20·0 g.) and *p*-methoxyphenylacetyl chloride (24·0 g.) in nitrobenzene (100 c.c.). Stirring at 0° was continued for two hours and the temperature was slowly raised to 30° during the next 4 hours. The mixture was decomposed with ice and nitrobenzene, and unchanged 2-methoxynaphthalene removed by steam-distillation. The residual sticky orange solid was collected, washed with water, and boiled with acetone. On cooling, the white solid was collected, washed with acetone, and dried (15·8 g., m. p. 165—168°). Recrystallisation from benzene gave needles (13·9 g., 36%), m. p. 167—169° (Found : C, 78·5; H, 5·9. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%). This compound formed a scarlet 2 : 4-dinitrophenylhydrazone.

The ketone (3·0 g.) was boiled for 10 hours with N-sodium hypochlorite (160 c.c.). Unchanged starting material was separated and the filtrate, on acidification with dilute hydrochloric acid, gave a white precipitate. This was collected, washed with water, and dried. It crystallised from ethanol in needles, m. p. 209° (sintering at 195°), which showed no depression in m. p. when mixed with authentic 2-methoxy-6-naphthoic acid.

α-(p-*Methoxyphenyl*)-β-(2-*methoxy*-6-*naphthyl*)-*ethane*.—The above ketone (8·0 g.) was boiled with amalgamated zinc (50 g.), concentrated hydrochloric acid (100 c.c.), and *p*-methylanisole (25 c.c.) for 16 hours at 130—140°. Solvents were removed by steam-distillation and the residual sticky solid separated from unchanged zinc, collected, washed with water and crystallised from ethanol. The separated product (3·5 g.) on crystallisation from ethyl acetate afforded colourless plates (3·15 g., 40%), m. p. 140—141° (Found : C, 81·9; H, 6·85. $C_{20}H_{20}O_2$ requires C, 82·1; H, 6·9%).

α-(p-*Hydroxyphenyl*)-β-(2-*hydroxy*-6-*naphthyl*)-*ethane* (II).—The dimethyl ether (2·0 g.) was refluxed with acetic acid (16·0 c.c.) and hydriodic acid (*d* 1·7, 8·0 c.c.) for 1½ hours, poured into water, and decolourised with sodium bisulphite; the solid was collected, washed and dried. It was twice crystallised from benzene and obtained in prisms (1·1 g., 60%), m. p. 201—202° (Found : C, 81·6; H, 6·15. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). The *diacetate*, obtained by treatment with acetic anhydride and pyridine, crystallised from methanol in needles, m. p. 138° (Found : C, 75·4; H, 5·65. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·8%).

β-(p-*Methoxyphenyl*)-*ethyl* 2-*Methoxy*-6-*naphthyl Ketone*.—A Friedel–Crafts reaction was carried out as described for the preparation of *p*-methoxybenzyl 2-methoxy-6-naphthyl ketone using β-(*p*-methoxyphenyl)-propionyl chloride (25·5 g.). The oily product was distilled and the fraction having b. p. 260—290°/2 mm., after repeated crystallisation from methanol gave the required *ketone* (7·4 g., 18%) as prisms, m. p. 100—101° (Found : C, 78·75; H, 6·5. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%). The ketone gave a scarlet 2 :.4-dinitrophenylhydrazone.

This ketone, on oxidation with boiling N-sodium hypochlorite as described above, yielded crude 2-methoxy-6-naphthoic acid, which after crystallisation from ethanol was obtained in needles, m. p. 210°, and there was no depression when mixed with authentic 2-methoxy-6-naphthoic acid.

α-(p-*Methoxyphenyl*)-γ-(2-*methoxy*-6-*naphthyl*)-*propane*.—The ketone (5·0 g.) was refluxed with amalgamated zinc 30 g.), concentrated hydrochloric acid (60 c.c.), and *p*-methylanisole (20 c.c.), at 140° for 16 hours, and worked up in the usual manner. The product (a crude yellow solid) crystallised from ethanol in prisms, m. p. 91—96°. On further crystallisation, first from ligroin (b. p. 60—80°) and then from ethanol, prisms (2·15 g., 45%), m. p. 97—99°, were obtained. They depressed the m. p. of the original ketone (Found : C, 82·05; H, 7·4. $C_{21}H_{22}O_2$ requires C, 82·3; H, 7·2%).

α-(p-*Hydroxyphenyl*)-γ-(2-*hydroxy*-6-*naphthyl*)-*propane* (III).—Demethylation was carried out as described for the homologues, using the dimethyl ether (2·0 g.), glacial acetic acid (12·0 c.c.), and hydriodic acid (*d*, 1·7, 8·0 c.c.). The *product* (0·9 g., 50%) crystallised from benzene in prisms, m. p. 126—128°, which tended to become pink on exposure to air (Found : C, 82·4; H, 7·1. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). The *diacetate*, prepared by the action of acetic anhydride and pyridine, crystallised from methanol in plates, m. p. 96° (Found : C, 76·2; H, 6·1. $C_{13}H_{22}O_4$ requires C, 76·2; H, 6·1%).

2-*Methoxy*-6-*naphthaldehyde*.—6-Bromo-2-methoxynaphthalene (45 g.) was converted into the Grignard reagent as described by Fries and Schimmelschmidt (*loc. cit.*). After 20 hours' heating, the solution was cooled and stirred and ethyl orthoformate (44 g.) added slowly during one hour, and then boiling was maintained for a further hour. Ether and benzene were evaporated, the thick brown residue heated at 100° for 1½ hours, cooled, decomposed with ice and acetic acid, and extracted with ether. The extract was washed with sodium carbonate solution and water, and the ether evaporated. The residue was shaken for several hours with saturated sodium bisulphite solution, and the solid bisulphite compound collected, washed with ether, and dried. It was then shaken with concentrated hydrochloric acid until decomposition was complete. The aldehyde was collected, washed with water, dried, and crystallised from methanol, giving prisms (6 g., 20%), m. p. 80—81°. This aldehyde yielded a scarlet 2 : 4-dinitrophenylhydrazone and its *semicarbazone* crystallised from acetic acid in leaflets, m. p. 277—280° (becoming yellow at about 250°) (Found : N, 17·5. $C_{13}H_{13}O_2N_3$ requires N, 17·3%).

α-*Benzoyl*-β-2-(6-*methoxynaphthyl*)-*ethylene*.—2-Methoxy-6-naphthaldehyde (2 g.) was treated with acetophenone (1 g.) and a solution of sodium (0·5 g.) in methanol (50 c.c.); on standing, a yellow precipitate separated. This was collected, washed with methanol and water, and dried. It crystallised from methanol in glistening pale yellow plates (2 g.), m. p. 144—145° (Found : C, 83·3; H, 5·6. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%).

α-*Anisoyl*-β-2-(6-*methoxynaphthyl*)-*ethylene*.—The reaction was carried out as above, using 2-methoxy-6-naphthaldehyde (2·0 g.) and *p*-methoxyacetophenone (1·6 g.). The solid was collected, washed, and dried. It crystallised from ethyl acetate in yellow needles (1·85 g., 60%), m. p. 166—167° (Found : C, 79·3; H, 6·2. $C_{12}H_{18}O_3$ requires C, 79·2; H, 5·7%).

p-*Methoxyphenyl* β-2-(6-*Methoxynaphthyl*)-*ethyl Ketone* (V).—The latter chalkone (1·73 g.) was hydrogenated in ethyl acetate (20 c.c.) in the presence of Adams' platinic oxide catalyst (0·25 g.) at room temperature and 1½ atm. When the necessary amount of hydrogen had been absorbed the liquid was filtered and ethyl acetate removed by evaporation from the colourless solution. The residue crystallised from methanol in colourless leaflets (1·6 g.), m. p. 104—105° (Found : C, 78·5; H, 6·75. $C_{21}H_{20}O_3$ requires C, 78·7; M, 6·4%).

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