[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO AND THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

THE SYNTHESIS OF 1-ETHYL-2,5-DIMETHYL-8-METHOXYPHENANTHRENE[1]

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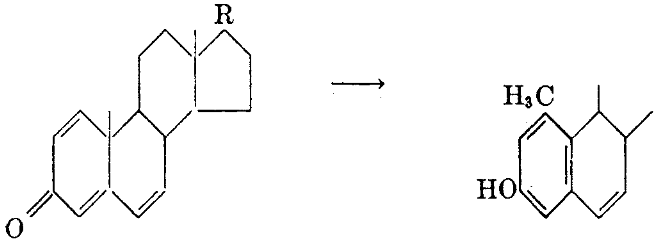
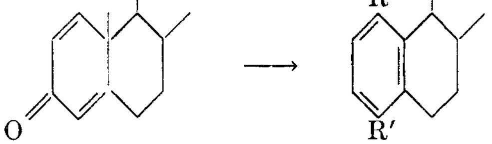
Received January 22, 1951

It has recently been reported (1, 2) that steroidal 1,4-6-trien-3-ones (I) undergo the dienone-phenol rearrangement to yield 1-methyl-3-hydroxy phenols (II) and unequivocal proof for the course of this rearrangement was provided by experiments in the naphthalene series (3). The dienone-phenol rearrangement products of steroidal 1,4-dien-3-ones (III), initially believed by Inhoffen (4) to have the 1-methyl-3-hydroxy structure, have since been termed "x-methyl-*hetero*phenols" (1, 2), since their constitution is not known with certainty. On the basis of Woodward and Singh's model studies in the naphthalene series (5), it seems likely that they possess the 1-methyl-4-hydroxy (IV) or 1-hydroxy-4-methyl (V) structure. In connection with certain degradation experiments of the "x-methyl*hetero*phenols" now being conducted by Dr. André Dreiding of the Detroit Institute for Cancer Research, there was required for comparison purposes an authentic sample of 1-ethyl-2,5-dimethyl-8-methoxyphenanthrene (XIII) and the present paper deals with an unequivocal synthesis of this previously unknown phenanthrene derivative. It is pertinent to mention at this time that the 1-ethyl-2, x-dimethyl-y-methoxyphenanthrene obtained by Dr. Dreiding is not identical with our substance (XIII), thus excluding structure IV for the "x-methyl-*hetero*phenols".



I II



III

IV R = CH_3; R′ = OH
V R = OH; R′ = CH_3

β-(2-Methoxy-5-methylbenzoyl)propionic acid (VI) (6), obtained on Friedel-

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[1] Taken from part of a thesis to be submitted by Jose Herran to the Escuela de Graduados de la Universidad Nacional Autonoma de Mexico, in partial fulfillment of the degree of Doctor en Ciencias.

Crafts succinoylation of *p*-cresol methyl ether, was reduced by the Clemmensen procedure (7) to the corresponding butyric acid (VII) and then cyclized by the Johnson-Glenn (8) inverse Friedel-Crafts method to 3,4-dihydro-5-methoxy-8-methyl-1(2*H*)-naphthalenone (VIII). Woodward and Singh (5) obtained this ketone as an oil, characterized by a dinitrophenylhydrazone, m.p. 217°, and by conversion to 4-methyl-5,6,7,8-tetrahydro-1-naphthol on Clemmensen reduction and demethylation. In our hands, the purified VIII[2] had m.p. 37°; dinitrophenylhydrazone m.p. 224°, semicarbazone m.p. 237°; and similarly gave 4-methyl-5,6,7,8-tetrahydro-1-naphthol on reduction and demethylation. On the other hand, Buu-Hoï and co-workers (9) reported m.p. 108° for this ketone and m.p. 200° for its semicarbazone (no analysis given). It seems most likely that their product possessed a different constitution (free hydroxy derivative?) and this in turn throws doubt upon the structure of their corresponding benzocarbazoles.

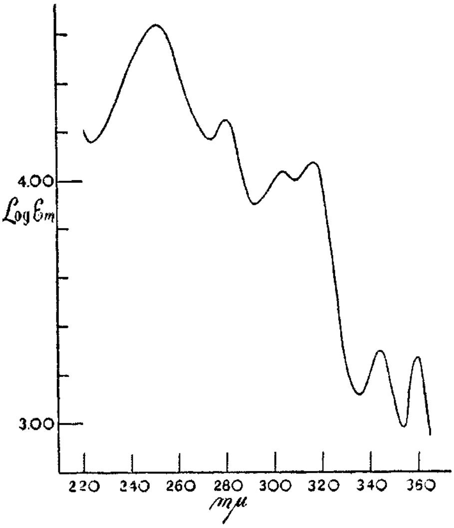

FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRUM (in 95% ethanol) OF 1-ETHYL-2,5-DIMETHYL-8-METHOXYPHENANTHRENE.

Reformatsky condensation followed by dehydration, dehydrogenation, and saponification (10) afforded the crystalline 5-methoxy-8-methyl-1-naphthaleneacetic acid (IX), which led to the crystalline alcohol (X) on lithium aluminum hydride reduction. Conversion of the latter to α-methyl-γ-(5-methoxy-8-methyl-1-naphthalene)butyric acid was patterned after a synthesis described by Wilds, *et al.* (11) for related butyric acid derivatives, while the cyclization to 1-keto-2,5-dimethyl-8-methoxy-1,2,3,4-tetrahydrophenanthrene (XII) was carried out

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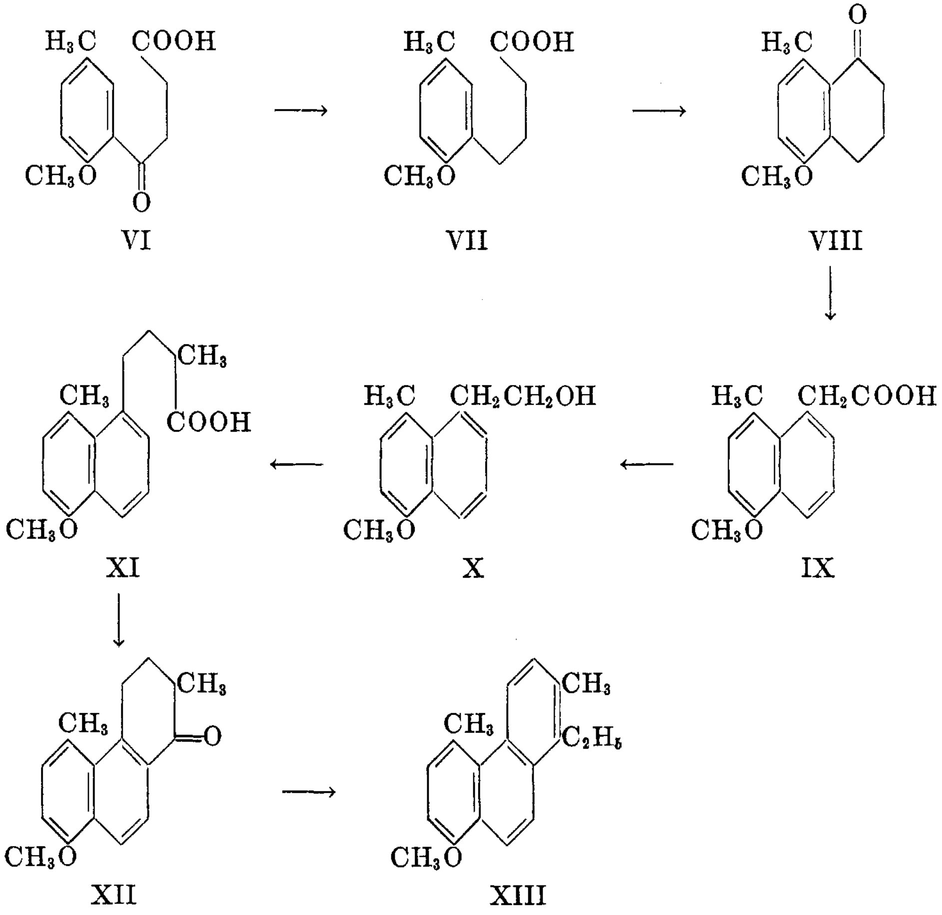
[2] After submission of this paper for publication, an article came to our attention (Cocker, Lipman and Whyte, *Chemistry and Industry*, 1950, 237) in which constants are given for the naphthalenone VIII in excellent agreement with the values found in this laboratory.

with stannic chloride (12). Treatment with ethylmagnesium bromide followed by dehydrogenation (13) led to the desired 1-ethyl-2,5-dimethyl-8-methoxyphenanthrene (XIII), m.p. 74°, further characterized by its complex with trinitrobenzene and with 2,4,7-trinitrofluorenone (14). The ultraviolet absorption spectrum of the phenanthrene derivative (XIII) is shown in Figure 1.



EXPERIMENTAL[3]

γ-(2-Methoxy-5-methylphenyl)butyric acid (VII). The Clemmensen reduction of 359 g. of β-(2-methoxy-5-methylbenzoyl)propionic acid (VI)(6), prepared in 83% yield by succinoylation of *p*-cresol methyl ether in nitrobenzene solution at 0° for three days, was carried out exactly as described by Martin (7) for β-(*p*-anisoyl)propionic acid, including the remethylation with methyl sulfate, and afforded 295 g. of the butyric acid (VII) with m.p. 63–66°, which was sufficiently pure for the next step; lit. (6), m.p. 66°.

3,4-Dihydro-5-methoxy-8-methyl-1(2H)-naphthalenone (VIII). The acid chloride was prepared by adding 315 g. of the above butyric acid (VII) in portions to 346 g. of phosphorus

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[3] Melting points are uncorrected. We are indebted to Srta. Amparo Barba of the Syntex Microanalytical Department for the analyses.

pentachloride, warming the mixture gently with swirling and then allowing the exothermic reaction to go to completion. When no more hydrogen chloride was evolved, 300 cc. of dry benzene was added and the mixture distilled at 60° under reduced pressure. This treatment was repeated twice and the residual acid chloride was dissolved in 700 cc. of dry, thiophene-free benzene and added dropwise over a period of 40 minutes to a vigorously stirred suspension of 242 g. of anhydrous aluminum chloride in 2.9 l. of benzene. The inside temperature was maintained below 10° and after adding an additional 200 cc. of benzene, the mixture was stirred for four hours, the temperature rising gradually to 25°. At the end of the reaction, 250 cc. of ether and 400 cc. of ice-cold hydrochloric acid (1:1) were added with stirring; the organic layer was separated and washed well with acid, 5% potassium hydroxide solution, and water, dried over sodium sulfate, and evaporated. Distillation of the residue at 0.15 mm. afforded 192 g. (67%) of a faintly yellowish oil boiling at 109–115°. For analysis, a sample was redistilled, b.p. 112–114° at 0.4 mm.; on cooling, the oil crystallized, m.p. 35–37°.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41.
Found: C, 75.63; H, 7.78.

The red *2,4-dinitrophenylhydrazone* exhibited m.p. 222–224° [reported (5) m.p. 215–217°], but in view of the discrepancy with Buu-Hoï's results (9), two additional derivatives were prepared. The *oxime* showed m.p. 141–142°.

Anal. Calc'd for $C_{12}H_{15}NO_2$: C, 70.23; H, 7.35.
Found: C, 69.81; H, 7.45.

The *semicarbazone* possessed m.p. 235–237° after recrystallization from chloroform-methanol. Buu-Hoï, *et al.* (9) reported that VIII had m.p. 108° and formed a semicarbazone of m.p. 200°. No analysis was given for the latter derivative.

Anal. Calc'd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99.
Found: C, 63.11; H, 6.62; N, 17.12.

For further confirmation of the structure, a sample of the naphthalenone was subjected to a Clemmensen reduction and demethylation with hydrobromic acid. It gave 4-methyl-5,6,7,8-tetrahydro-1-naphthol, exactly as described by Woodward and Singh (5).

5-Methoxy-8-methyl-1-naphthaleneacetic acid (IX). The Reformatsky condensation with ethyl α-bromoacetate and dehydrogenation (palladized charcoal instead of sulfur) was carried out as described by Bachmann. (10) for 5-ketotetrahydro-1,2-benzanthracene and after saponification gave the required acid (IX) in 57% yield. The analytical sample crystallized from methanol, m.p. 166–168°.

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13.
Found: C, 73.13; H, 6.24.

β-(5-Methoxy-8-methyl-1-naphthyl)ethyl alcohol (X). A suspension of 2.5 g. of lithium aluminum hydride in 600 cc. of anhydrous ether was treated over a period of 15 minutes with a solution of 10 g. of acid IX in 130 cc. of ether and refluxed for an additional 20 minutes. After decomposition of the excess reagent with acetone, followed by addition of dilute acid, the ether layer was separated and washed well with acid and alkali. Evaporation of the dried ether extract and trituration with hexane led to 7.4 g. of crystals, m.p. 77–80°. Further recrystallization from hexane-acetone and from methanol gave the analytical sample, m.p. 80–81°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46.
Found: C, 77.49; H, 7.62.

α-Methyl-γ-(5-methoxy-8-methyl-1-naphthalene)butyric acid (XI). The synthesis of the butyric acid (XI) from the alcohol (X) was carried out by the method of Wilds, Beck, and Close (11) without isolation of intermediates. Treatment of the alcohol (X) with phosphorus tribromide afforded the oily β-(5-methoxy-8-methyl-1-naphthyl)ethyl bromide, which was subjected to the malonic ester synthesis without purification. The intermediate malonic ester was immediately methylated (11) except that methyl iodide was used instead of methyl bromide (11). After saponification and decarboxylation, there was obtained 2.7

g. of butyric acid (XI) from 7.0 g. of alcohol (X); recrystallization from methanol gave the analytical sample, m.p. 125–126°.

Anal. Calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.37.

Found: C, 74.85; H, 7.49.

1-Keto-2,5-dimethyl-8-methoxy-1,2,3,4-tetrahydrophenanthrene (XII). The butyric acid (XI) (3 g.) was converted into the acid chloride by means of phosphorus pentachloride in benzene solution and then cyclized with stannic chloride exactly as described by Bachmann, Cole, and Wilds (12) for the corresponding intermediate in their equilenin synthesis; yield, 2.52 g., m.p. 140–142° (after recrystallization from pentane-acetone).

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13.

Found: C, 80.50; H, 7.19.

1-Ethyl-2,5-dimethyl-8-methoxyphenanthrene (XIII). A solution of 0.4 g. of the ketone (XII) in 5 cc. of benzene was treated with 2 cc. of a 6 *N* ethereal solution of ethyl magnesium bromide and left at room temperature for 20 hours. After decomposing with ammonium chloride, the organic layer was washed with water, dried, and evaporated. In one experiment, a Girard separation was carried out at this stage which indicated the complete absence of ketonic material. The ether residue, consisting of an oil, was directly dehydrogenated with 0.2 g. of palladized charcoal catalyst (15) for 20 minutes at 250–270°. The mixture was extracted with boiling benzene, evaporated to dryness, and then extracted with methanol. On cooling, there was obtained 0.23 g. of practically colorless crystals which after one recrystallization from hexane-acetone melted at 73–74°. The absorption spectrum (Fig. 1) was taken in 95% ethanol and exhibited maxima at 251 mμ (Log.ϵ 4.64), 280 mμ (Log. ϵ 4.25), 304 mμ (Log. ϵ 4.04), 317 mμ (Log. ϵ 4.07), 344 mμ (Log. ϵ 3.30) and 360 mμ (Log. ϵ 3.27).

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.32; H, 7.62.

Found: C, 86.58; H, 7.58.

The orange *trinitrobenzene complex*, prepared in methanol, crystallized from the same solvent in needles, m.p. 154–155°.

Anal. Calc'd for $C_{25}H_{23}N_3O_7$: C, 62.89; H, 4.85; N, 8.80.

Found: C, 63.14; H, 4.98; N, 8.71.

The *2,4,7-trinitrofluorenone complex* (cf. 14) crystallized from benzene-ethanol as brown crystals, m.p. 165–167°.

Anal. Calc'd for $C_{32}H_{25}N_3O_8$: C, 66.31; H, 4.35; N, 7.25.

Found: C, 66.04; H, 4.04; N, 7.43.

SUMMARY

The synthesis of 1-ethyl-2,5-dimethyl-8-methoxyphenanthrene (XIII) by way of the key intermediates, 3,4-dihydro-5-methoxy-8-methyl-1(2*H*)-naphthalenone (VIII) and 1-keto-2,5-dimethyl-8-methoxy-1,2,3,4-tetrahydrophenanthrene (XII) is described.

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