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THE ACID-CATALYSED REARRANGEMENT OF 4,4a,5,6,7,8-HEXAHYDRO-5-HYDROXY-4a-METHYL-2(3H)-NAPHTHALENONE

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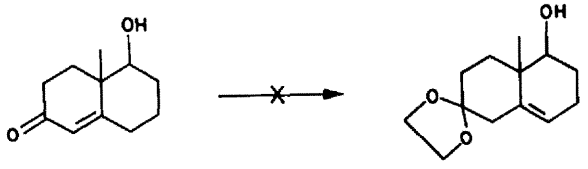
Abstract—The rearrangement of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (I) by acid to derivatives of 4-methyl-5,6,7,8-tetrahydro-1-naphthol is described.

During the course of some work with 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (I), an attempt was made to prepare the corresponding ethylene ketal (II) by *p*-toluenesulfonic acid catalysed condensation with ethylene glycol.[1] Instead of II, however, a mixture of products was obtained which was shown to be aromatic by UV and IR spectroscopy.



I II

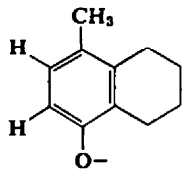
Before attempting to determine the structure of these products, we decided to study the effects of acid on I in the absence of ethylene glycol. When I was heated in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, water was formed and removed azeotropically. The major product was readily separated in about 40% yield. Analytical data indicated a molecular formula of $C_{22}H_{28}O_2$. It readily formed a 2,4-dinitrophenylhydrazone and a semicarbazone. Its IR spectrum showed bands at 1660 cm^{-1} (C=C—C=O), 1640 cm^{-1} (C=C) and 1580 cm^{-1} (aromatic C=C). There was no band corresponding to a hydroxyl group. The UV spectrum confirmed the presence of an α,β-unsaturated ketone [λ_{max} 234 mμ. (ϵ = 18,690)] and also indicated an aromatic moiety [λ_{max} 275 mμ. (ϵ = 2,000)]. Since one of the oxygen atoms of the molecule was present in a carbonyl group and the compound contained no hydroxyl group, the second oxygen had to be an ether linkage.

The NMR of the product showed a quartet centered at 3·25τ corresponding to two protons with a coupling constant of 8 c/s. This resonance must be attributed to two *ortho*-nonequivalent aromatic protons. No other aromatic protons were evident in the spectrum. Other distinguishing features in the NMR spectrum were a single olefinic proton (singlet at 4·13τ), a single proton next to oxygen (multiplet centered at 6·03τ),

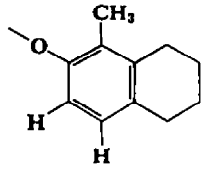
[1] E. J. Salmi, *Ber. Dtsch. Chem. Ges* **71**, 1803 (1938).

a methyl group on unsaturated carbon (singlet at 7·8τ) and a methyl group on saturated carbon (singlet at 8·57τ).

The product must therefore contain the partial structure III or IV. Of the two structures III would appear to be more reasonable since the methyl group and oxygen

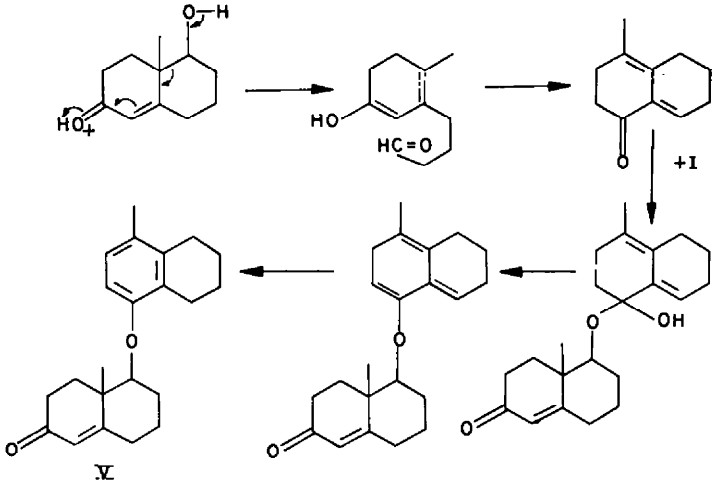


III



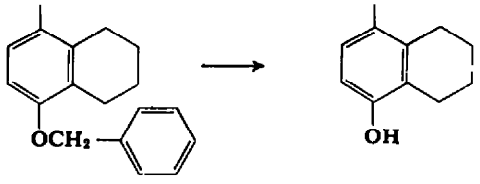
IV

functions are already *p*-oriented in I. One way by which such a structure could arise from I would involve a ring-opening followed by an alternative ring-closure.



V

That structure V was probably correct was indicated by a series of related experiments. When I was treated with benzyl alcohol in the presence of *p*-toluenesulfonic acid, an aromatic compound was isolated in high yield. By analogy with the reactions discussed above, the product should have structure VI. This was proven by catalytic

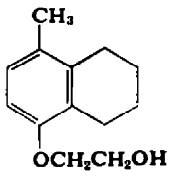


VI VII

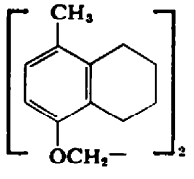
reduction of VI to a crystalline phenol identical in all respects with an authentic sample of 5,6,7,8-tetrahydro-4-methyl-1-naphthol, VII.[2]

[2] M. S. Newman and A. B. Mekler, *J. Amer. Chem. Soc.* **82**, 4039 (1960). We thank Prof. Newman for sending us a sample of 5,6,7,8-tetrahydro-4-methyl-1-naphthol.

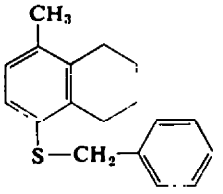
It was then possible by careful chromatography to isolate two products from the reaction of I with ethylene glycol. The major product was the ether VIII. This was shown by analysis, infrared and ultraviolet spectra and particularly by its NMR spectrum which showed the two *ortho* aromatic protons as a quartet centered at 3·48τ with a coupling constant of 8 c/s. Final proof for the structure came from cleavage of VIII with 57% hydriodic acid to the phenol VII. Analysis and spectral data indicate the minor component to be IX. Similarly, treatment of I with α-toluenethiol in the presence



VIII



IX



X

of *p*-toluenesulfonic acid gave in good yield the thioether X, analytical and spectral data being consistent with the structure.

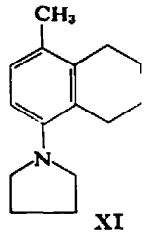
The experiments described above clearly indicate that the aromatic moiety of the rearranged product derived from I is as shown in V. Attempts to cleave the ether bond by acid were completely unsuccessful. Cleavage of V by sodium in pyridine[3] yielded a small amount of phenolic material having the same mobility as VII on thin-layer chromatography. The non-aromatic portion of V requires further comment. There is ample evidence for the presence of the α,β-unsaturated ketone. The UV spectrum of V shows λ_{max} 234 mμ which is certainly lower than would be expected. There is, however, a definite shoulder at about 245 mμ. The peak at 234 mμ is thus a summation of two peaks—one due to the unsaturated ketone, the other to the substituted phenyl ether.[4] All the spectral data are thus in agreement with V. Since both benzyl alcohol and ethylene glycol reacted with I to give phenolic ethers, it is a reasonable assumption that I, as an alcohol would react with the rearranged product of I to yield V.

Further indirect evidence for the structure V was provided by a high dilution experiment. When I was treated with the same concentrations of *p*-toluenesulfonic acid as before, but in twenty times the volume of benzene, the IR spectrum of the crude product indicated a high yield of phenolic material. In order to achieve a complete separation of phenolic and neutral products, an ether solution had to be extracted six times with equal volumes of 4 N potassium hydroxide. In this way I gave a 74% yield of crystalline phenol VII and a 21% yield of crystalline neutral product V. In other words, when the concentration of alcohol is low, the rearrangement gives predominantly the phenol VII. That V did not arise from the reaction of phenol VII with I was shown by the reaction of I with plain phenol in the presence of *p*-toluenesulfonic acid. The crude product was identical with that formed from the reaction of I with *p*-toluenesulfonic acid alone.

To complete the series, the reaction of I with an amine, pyrrolidine, was examined. By analogy with the other reactions, it was anticipated that the aromatic amine XI would be formed. That the *p*-toluenesulfonic acid was superfluous was established by

[3] V. Prey, *Ber. Dtsch. Chem. Ges* **76B**, 156 (1943).

[4] *p*-Methylanisole is reported to have λ_{max} 223 mμ (ε = 8,500). J. C. Dearden and W. F. Forbes, *Canad J. Chem.* **37**, 1305 (1959).

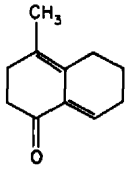


XI

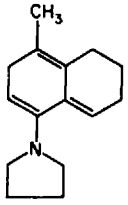
carrying out two experiments, one with and one without acid. These yielded identical products. The crude product was hydrolysed by the method of Johnson *et al.*[5] to convert any enamine of I that might be present back to I. No basic material remained and a high yield of neutral product was obtained.

The IR spectrum of this neutral product showed carbonyl absorption at 1690 cm^{-1} and strong bands at 1640 and 1600 cm^{-1}. The UV spectrum showed maxima at 298 mμ (ϵ = 3,300) and 228 mμ (ϵ = 11,600). The presence of a carbonyl group was confirmed by the preparation of 2,4-dinitrophenylhydrazone and semicarbazone derivatives. These derivatives indicated that the molecular formula of the original ketone was $C_{11}H_{14}O$. The distilled ketone was shown by gas chromatography to be contaminated by another compound in amounts varying from 8–13%. This impurity could not be eliminated by repeated distillations. A pure sample of the ketone was obtained by preparative gas chromatography. The NMR spectrum of this sample showed a methyl group (singlet at 8·2τ) and a single olefinic proton (triplet centered at 3·3τ with a coupling constant of 5 c/s). Reduction of the ketone with sodium borohydride gave an alcohol having no carbonyl absorption in the IR and showing λ_{max} 207 and 243 mμ. (ϵ = 11,740) in the UV, suggesting a hetero annular diene.[6] Treatment of the ketone with benzyl alcohol in benzene with a catalytic amount of *p*-toluenesulfonic acid gave in high yield the benzyl ether VI. This reaction was rapid compared to the reaction of benzyl alcohol with I. When the ketone was treated with *p*-toluenesulfonic acid alone in benzene, a high yield of the phenol VII was obtained.

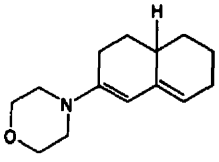
These reactions establish that the methyl group and oxygen function are again *p*-oriented. If a heteroannular diene is to be accommodated with only one olefinic proton, the only possible structure for the ketone is XII. The structure of the primary product from I and pyrrolidine was originally thought to be XIII. The material how-



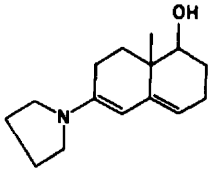
XII



XIII



XIV



XV

ever shows λ_{max} 270 mμ in the UV spectrum, identical with that reported[7] for the enamine XIV, suggesting that the enamine obtained had structure XV. Formulation of

[5] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *J. Amer. Chem. Soc.* **78**, 430 (1956).

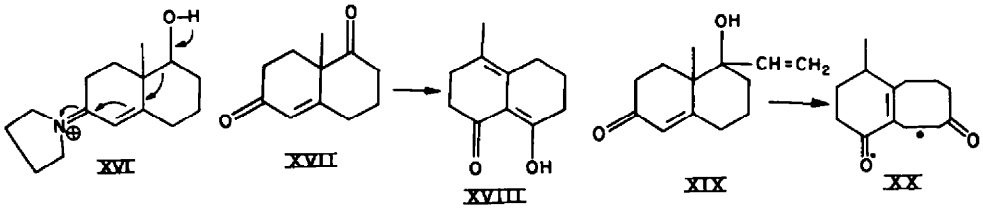
[6] L. Fieser and M. Fieser, *Steroids.* p. 17. Reinhold, N.Y. (1959).

[7] G. Stork and G. Birnbaum, *Tetrahedron Letters* 313 (1961).

the primary product as the enamine XV is further supported by analytical data. When the ketone XII is reacted with pyrrolidine in the presence of *p*-toluenesulfonic acid, the crude product has λ_{max} 237 mμ in the UV spectrum and rapidly reverts to the starting ketone on hydrolysis. Apparently the enamine XIII is formed and is stable to the acid in benzene whereas the parent ketone XII is not.

The question remains as to how the starting material I is converted to the ketone XII via the enamine XV. The possibility that the enamine XV was merely converted back to I, when hydrolysed by a mixture of water, methanol, sodium acetate and acetic acid, and that I was rearranging under these conditions was eliminated when a control experiment established that I was stable under these conditions. It is probable, therefore, that the ring-opening stage of the rearrangement occurs when the enamine is protonated during hydrolysis as shown in XVI. Hydrolysis of the enamine intermediate followed by ring closure would then give the ketone XII. This mechanism parallels that proposed for the rearrangement of I, the salt here replacing the protonated carbonyl form of I.[8]

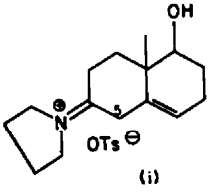
Several examples are to be found in the literature of base-catalyzed ring-opening-ring-closure reactions in related systems but none, to our knowledge, of similar acid-catalyzed reactions. The base-catalyzed conversion of XVII to XVIII has been described by Newman and Mekler[2] and that of XIX to XX by Swaminathan *et al.*[9]



EXPERIMENTAL[10]

4,4a,5,6,7,8-*Hexahydro*-4a-*methyl*-5-(5,6,7,8-*tetrahydro*-4-*methyl*-1-*naphthyloxy*)-2(3H)-*naphthalenone* (V). A solution of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (3·60 g, 0·02 mole) in benzene (100 ml) containing *p*-toluenesulfonic acid (250 mg) was heated under reflux under a Dean-Stark water separator filled with anhydrous $CaSO_4$ for 17 hr. The cooled solution was washed with $NaHCO_3$ aq, dried and the solvent removed *in vacuo*. The residue was dissolved in hexane and chromatographed on 70 g neutral alumina. A 1:1 mixture of hexane

[8] It is not immediately obvious why XV rearranges in the aqueous acidic medium but not in benzene solution in the presence of *p*-toluenesulfonic acid. Possibly XV is protonated at C_5 in benzene solution to form the tight ion-pair (i). Alternatively, protonation could occur on nitrogen. In



(i)

either case, rearrangement would be prevented. In the aqueous acidic medium, equilibration of (i) to XVI, followed by rearrangement would probably be much more rapid than in benzene. (Cf. the protonation of enolates of α,β-unsaturated ketones. See H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters* 669 (1962).)

[9] S. Swaminathan, J. P. John and S. Ramchandaran, *Tetrahedron Letters* 729 (1962).

[10] M. ps are corrected, b. ps uncorrected. UV spectra were taken in MeOH using a Cary Model 11 M Recording Spectrophotometer.

and benzene and pure benzene eluted 1·4 g V, m.p. 139–142°. Recrystallization from an acetone–hexane mixture and then EtOH gave analytical sample with m.p. 153–155°. (Found: C, 81·56; H, 8·75; Mol. W, 352, 341. Calc. for $C_{22}H_{32}O_3$: C, 81·44; H, 8·70%; Mol. W, 324.)

The 2,4-dinitrophenylhydrazone, prepared in the usual way, was recrystallized from a mixture of $CHCl_3$ and EtOH and had m.p. 177–189°. (Found: C, 66·28; H, 6·33; N, 11·32. Calc. for $C_{28}H_{32}O_5N_4$: C, 66·65; H, 6·39; N, 11·10%.)

The semicarbazone prepared in the usual way and recrystallized from EtOH had m.p. 207–208°. (Found: C, 72·05; H, 8·49; N, 10·72. Calc. for $C_{23}H_{31}O_2N_3$: C, 72·02; H, 8·67; N, 10·96%.)

5-(*Benzyloxy*)-1,2,3,4-*tetrahydro*-8-*methylnaphthalene* (VI). A mixture of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (3·6 g, 0·02 mole), benzyl alcohol (4·32 g, 0·04 mole) and *p*-toluenesulfonic acid (250 mg) in benzene (100 ml) was heated under reflux under a Dean-Stark water separator overnight. After cooling, the benzene solution was washed with $NaHCO_3$ aq, water, and sat. brine, dried and evaporated *in vacuo*. A solution of the residue in hexane was percolated through a short plug of neutral alumina. The alumina was further washed with hexane, the hexane evaporated and the residue crystallized from hexane at 0° to give 5-(benzyloxy)-1,2,3,4-tetrahydro 8-methylnaphthalene (2·05 g) m.p. 59·5–61°. The analytical sample obtained by further crystallizations from the same solvent had m.p. 60·5–61·5°. (Found: C, 86·25; H, 8·03. Calc. for $C_{18}H_{20}O$: C, 85·67; H, 7·99%.)

Hydrogenolysis of 5-(*benzyloxy*)-1,2,3,4-*tetrahydro*-8-*methyl-naphthalene*. A solution of 5-(benzyloxy)-1,2,3,4-tetrahydro-8-methylnaphthalene (504 mg; 2 mmole) in EtOH (40 ml) was hydrogenated at room temp and atmo. press. in the presence of 200 mg 10% Pd–C. Reduction was complete in 1·5 hr (50 ml H_2 absorbed). The catalyst was removed by filtration and the EtOH removed *in vacuo*. The residue was crystallized from hexane to give a quantitative yield of VII, m.p. 88·5–89·5°, identical in all respects with an authentic sample.[3]

5-(*Benzylthio*)-1,2,3,4-*tetrahydro*-8-*methylnaphthalene* (X). A mixture of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (3·6 g; 0·02 mole), α-toluenethiol (4·96 g; 0·04 mole) and *p*-toluenesulfonic acid (250 mg) in benzene (100 ml) and heated under reflux under a Dean-Stark water separator overnight. The cold solution was than washed with sat. $NaHCO_3$ aq, water, and sat. brine solution, dried and the solvent removed *in vacuo*. The residue was fractionally distilled, the main fraction having b.p. 147–158° at 0·15 mm. This fraction was redistilled to give 5-(benzylthio)-1,2,3,4-tetrahydro-8-methylnaphthalene (3·5 g) b.p. 147–150° at 0·03 mm. (Found: C, 80·67; H, 7·53; S, 11·96. Calc. for $C_{18}H_{20}S$: C, 80·56; H, 7·51; S, 11·93%.)

2-(5,6,7,8-*Tetrahydro*-4-*methyl*-1-*naphthyloxy*)*ethanol* (VIII) *and* 1,2-*bis*(5,6,7,8-*tetrahydro*-4-*methyl*-1-*naphthyloxy*)*ethane* (IX). A solution of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (3·6 g; 0·02 mole), ethylene glycol (2·48 g; 0·01 mole) and *p*-toluenesulfonic acid (250 mg) in benzene (100 ml) were heated under reflux under a Dean-Stark water separator filled with anhydrous $CaSO_4$ for 17 hr. The cooled solution was washed with $NaHCO_3$ aq, water, dried and the solvent removed *in vacuo*. The residue was chromatographed on 70 g neutral alumina. A 1:1 mixture of benzene and hexane eluted IX (0·55 g). Recrystallization from acetonitrile gave an analytical sample with m.p. 169–170·5°. λ_{max} 275 mμ. (ε = 2,200). (Found: C, 82·20; H, 8·80. Calc. for $C_{24}H_{30}O_2$: C, 82·24; H, 8·63%.)

Further elution with the same solvent and pure benzene gave VIII (1·3 g), m.p. 72·5–74°. Recrystallization from ether-hexane gave an analytical sample with m.p. 73–74°. λ_{max} 275 mμ (ε = 2,160) and a shoulder at 220 mμ (ε = 12,360). The NMR spectrum (in CCl_4) showed a quartet centered at 3·48τ (2H, J = 8 c/s), singlet at 6·19τ (4H), singlet at 7·0τ (1H), multiplet at 7·48τ (4H), singlet at 7·92τ (3H), and a multiplet at 8·32τ (4H). (Found: C, 75·88; H, 8·29. Calc. for $C_{18}H_{18}O_2$: C, 75·69; H, 8·80%.)

The 3,5-dinitrobenzoate of IX was prepared in pyridine in the usual way and was recrystallized from EtOH to give an analytical sample with m.p. 126·5–127·5°. (Found: C, 60·01; H, 5·03; N, 6·54. Calc. for $C_{30}H_{30}O_7N_2$: C, 59·99; H, 5·04; N, 7·00%.)

4-*Methyl*-3,5,6,7-*tetrahydro*-1(2H)-*naphthalenone* (XII). A mixture of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (11·88 g; 0·066 mole), pyrrolidine (8·52 g; 0·12 mole), and *p*-toluenesulfonic acid (0.5 g) in benzene (450 ml) was heated under reflux under a Dean-Stark water separator for 1 hr. The water separator was then filled with anhydrous $CaSO_4$ and heating continued overnight. The mixture was cooled, washed successively with dil. $NaHCO_3$ aq, water, sat. brine, dried and the solvent evaporated. The residue, a pale yellow oil, was dissolved in MeOH

(240 ml), acetic acid (24 ml) and water (24 ml) and sodium acetate (27 g) added. The mixture was heated under reflux for 4 hr. Most of the MeOH was removed *in vacuo*, water added to the residue and thoroughly extracted with ether. The ether was washed with 2 N HCl, water and sat. $NaHCO_3$ aq. The ethereal solution was dried and the solvent evaporated. The residue, a pale yellow oil, was distilled *in vacuo*. The bulk of the material distilled at 80° at 0·1 mm (7·5 g; 77%). This material had λ_{max} 228 mμ. (ε = 11,600) and 298 mμ. (ε = 3,300). Gas chromatographic analysis (1% Carbowax 20 M, 110°) showed that the product contained 13% of a second component reduced to 9% by a second distillation.

The 2,4-dinitrophenylhydrazone obtained in the usual way was recrystallized from $CHCl_3$–EtOH and melted at 199–200°. (Found: C, 59·59; H, 5·12; N, 15·97. Calc, for $C_{17}H_{18}N_4O_4$: C, 59·64; H, 5·30; N, 16·37%.)

The semicarbazone prepared in the usual way and recrystallized from EtOH had m.p. 175–176°. (Found: C, 65·82; H, 7·90; N, 19·02. Calc. for $C_{12}H_{17}N_3O$: C, 65·72; H, 7·81; N, 19·16%.) A pure sample of XII was prepared by preparative gas chromatography on a 6′ column of 2% Carbowax 20 M on Diatoport S at 190°. The NMR spectrum (in $CDCl_3$) showed a triplet centered at 3·29τ (1H, J = 5 c/s) and a singlet at 8·22τ (3H).

Action of benzyl alcohol on 4-methyl-3,5,6,7-tetrahydro-1(2H)-naphthalenone. A mixture of 4-methyl-3,5,6,7-tetrahydro-1(2H)-naphthalenone (1 g), benzyl alcohol (1 g) and *p*-toluenesulfonic acid (100 mg) in benzene (100 ml) was heated under reflux under a Dean-Stark water separator for 4 hr. The mixture was cooled, washed with $NaHCO_3$ aq, water and brine, dried and the solvent removed *in vacuo*. The residue was crystallized from hexane at 0° to give 800 mg 5-(benzyloxy)-1,2,3,4-tetrahydro-8-methylnaphthalene m.p. 60–61°, identical with that prepared from 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone as described above.

The action of p-toluenesulfonic acid on 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone in dilute solution. A mixture of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (1·8 g; 0·005 mole) and *p*-toluenesulfonic acid (2·5 g) in benzene (1 l.) was heated under reflux under a Dean-Stark water separator overnight. The cold solution was washed with $NaHCO_3$ aq, dried and the solvent removed *in vacuo*. The residue was dissolved in a small volume of ether and exhaustively extracted with 4 N KOH. The ether was washed with water, dried and the solvent evaporated. The residue was crystallized from hexane to give 350 mg of V identical with that obtained previously.

The KOH-extracts were acidified with conc. HCl and then extracted with ether. The ether extract was washed with water, dried and the solvent evaporated. The residue crystallized completely to give 1·2 g of phenol VII identical with that obtained from the hydrogenolysis of the benzyl ether VI.

Isomerization of 4-methyl-3,5,6,7,-tetrahydro-1(2H)-naphthalenone. A solution of 4-methyl-3,5,6,7-tetrahydro-1(2*H*)-naphthalenone (2 g) and *p*-toluenesulfonic acid (2·5 g) in benzene (1 l.) was heated under reflux under a Dean-Stark water separator overnight. After cooling, the solution was washed with dil. $NaHCO_3$ aq, dried and evaporated. The residue was dissolved in a small volume of ether and extracted 5 times with equal volumes of 5 N KOH. The combined basic extracts were acidified with conc. HCl and extracted with ether. The ether extract was washed with water, dried and evaporated. The residue (1·56 g) which crystallized completely was identical with a sample of VII.

The enamine of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (XV). A solution of 4,4a,5,6,7,8-hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (3·92 g), pyrrolidine (2·84 g) and *p*-toluenesulfonic acid (250 mg) in 150 ml benzene was heated under reflux under a Dean-Stark water separator overnight. The solvent was removed *in vacuo* and the residue distilled. The product distilled at 130–134° at 0·02 mm, λ_{max} 277 mμ. (ε = 9,200). (Found: C, 78·16; H, 8·82; N, 5·78. Calc. for $C_{15}H_{23}NO$: C, 77·88; H, 9·15; N, 6·05%.)

Sodium borohydride reduction of 4-methyl-3,5,6,7-tetrahydro-1(2H)-naphthalenone. To a solution of the naphthalenone (200 mg) in 20 ml 50% aqueous EtOH was added 200 mg $NaBH_4$ and the mixture left at room temp for 2 hr. The solution was diluted with water and extracted with ether. The ether extract was washed with water, dried and evaporated. The residue, an oil, showed no carbonyl absorption in the IR spectrum but a strong hydroxyl band. The UV spectrum showed λ_{max} 243 mμ. (ε = 11,700).

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