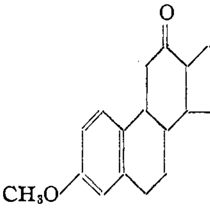
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

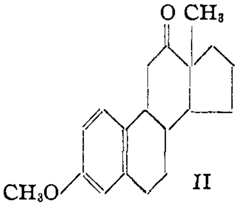
The Direct Introduction of the Angular-Methyl Group

BY ROBERT BURNS WOODWARD*

As a result of the great interest in the chemistry of the sterols and related substances, considerable effort has been expended in the past six years to elaborate methods for the synthesis of substances containing methyl groups at the bridgeheads of bicyclo-(0,3,4)-nonanes and bicyclo-(0,4,4)-decanes, the so-called angular-methyl groups. Several elegant methods have been evolved, notably those of Linstead[1a] and Robinson.[1b] With one exception, these procedures are in essence syntheses of the bicyclic systems involved from simpler compounds containing appositely substituted methyl groups. Only Robinson has in a few isolated instances introduced with difficulty an angular-methyl group in a compound already containing the bicyclic system. For example, 7-methoxy-3-keto-1,2,3,4,9,10,11,12-octahydro-1,2-cyclopentenophenanthrene[2] (I) on vigorous treatment with potassium *t*-butylate, followed by methyl iodide, is transformed into a methyl derivative in which the substituted group is presumed to be in the angular position (II).

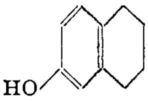


I



II

In this communication is described a method for the direct production of substances having the carbon skeleton of 9-methyl-bicyclo-(0,4,4)-decane (IV) from 6-hydroxy-1,2,3,4-tetrahydronaphthalene (III). It is at once apparent that the relationship of compounds having the skeleton (IV) to the tetralol (III) is also that which androsterone (VI) and the other male hormones bear to oestrone (V), and that these experiments may be considered as models for the conversion of oestrone into one or more of the androgenic hormones.



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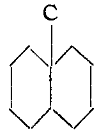

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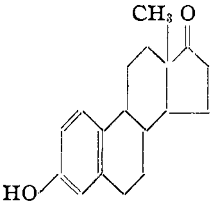

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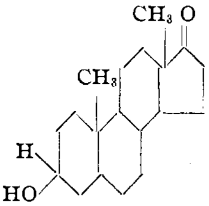
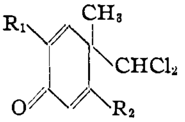
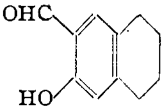


VI

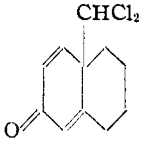
It has been shown by von Auwers[3a,b,c] and collaborators in a brilliant series of investigations that *o*- and *p*-alkyl substituted phenols, on treatment with chloroform and alkali under the conditions of the Reimer–Tiemann synthesis, are converted only in part into the expected aldehydes, the remainder being used in the formation of cyclohexadienones, the ratio of normal to abnormal products varying strikingly with the structure of the phenol. From *p*-cresol, for example, 2-hydroxy-5-methylbenzaldehyde is formed almost to the exclusion of 4-methyl-4-dichloromethyl-$\Delta^{2,5}$-cyclohexadienone-1 (VII, $R_1 = R_2 =$ H), while *ψ*-cumenol, on the other hand, gives over 80% of the abnormal product, 2,4,5-trimethyl-4-dichloromethyl-$\Delta^{2,5}$-cyclohexadienone-1 (VII, $R_1 = R_2 = CH_3$). We were led by these results to undertake the investigation of the Reimer–Tiemann reaction with 6-hydroxy-1,2,3,4-tetrahydronaphthalene (III).



VII



VIII



IX

The latter, on treatment with chloroform and 10% aqueous sodium hydroxide, was mainly converted into two products. The first, representing about 50% of the tetralol consumed in the reaction, was an aldehyde, m. p. 82°, which was found to be identical with the aldehyde obtained from the same phenol by Thom and Kross[4] through the Gattermann synthesis. Previous work[4,5] on

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(1) (a) Hibbet, Linstead and Millidge, *J. Chem. Soc.*, 476 (1936); (b) DuFeu, McQuillin and Robinson, *ibid.*, 53 (1937).

(2) Peak and Robinson, *ibid.*, 1581 (1937).

(3) (a) Von Auwers and v. Erggelet, *Ber.*, **32**, 3598 (1899); (b) v. Auwers and Winternitz, *ibid.*, **35**, 465 (1902); (c) v. Auwers and Keil, *ibid.*, **35**, 4207 (1902).

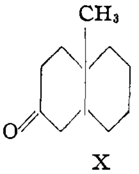
(4) Thom and Kross, *Arch. Pharm.*, **265**, 336 (1927).

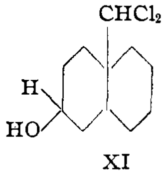
(5) Schroeter, *Ann.*, **426**, 30, *et seq.* (1922); *cf.* Robinson and Walker, *J. Chem. Soc.*, 1531 (1935).

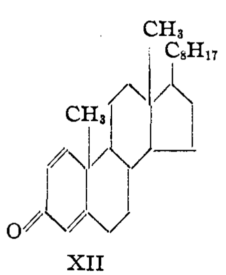
the orientation of (*ar*)-2-tetralol makes it highly probable that this aldehyde is 6-hydroxy-1,2,3,4-tetrahydronaphthalene-7-aldehyde (VIII). In our work the substance was characterized through its semicarbazone. This compound on heating undergoes an interesting change for which analogy is found in the behavior of the semicarbazone of salicylic aldehyde,[6] in that above the melting point it resolidifies in beautiful long yellow needles of the corresponding azine.

The second product of the reaction was a beautifully crystalline, non-acidic substance, m. p. 167.5–168.5°, having the formula $C_{11}H_{12}OCl_2$. While the analogy with the work of von Auwers lends strong presumptive support to the formulation of this compound as 10-dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene (IX), our work proves unambiguously that this formulation is correct.

On hydrogenation in methyl alcohol with Adams catalyst, the substance smoothly adds three moles of hydrogen with the formation of an alcohol, $C_{11}H_{18}OCl_2$, m. p. 92.5–93°, characterized by an α-naphthylurethan, m. p. 152.5–153°. Under the above conditions, it was not possible either to stop the reaction at the tetrahydro stage, or to remove the halogen atoms to an appreciable extent. However, under more drastic conditions, *viz.*, hydrogenation of the dichloro-alcohol in 10% alcoholic potassium hydroxide over palladinized barium sulfate, it was possible to remove both halogen atoms with the formation of a methyldecalol which on oxidation with chromate mixture was transformed into 10-methyl-decalone-2 (X), identical with an authentic sample prepared by the method of Robinson.[1b]


X


XI


XII

These transformations indicate clearly that the alcohol $C_{11}H_{18}OCl_2$ must be formulated as 10-dichloromethyl-2-hydroxydecahydronaphthalene (XI), and that the abnormal Reimer–Tiemann product from which it was obtained is 10-dichloromethyl-1-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene (IX).

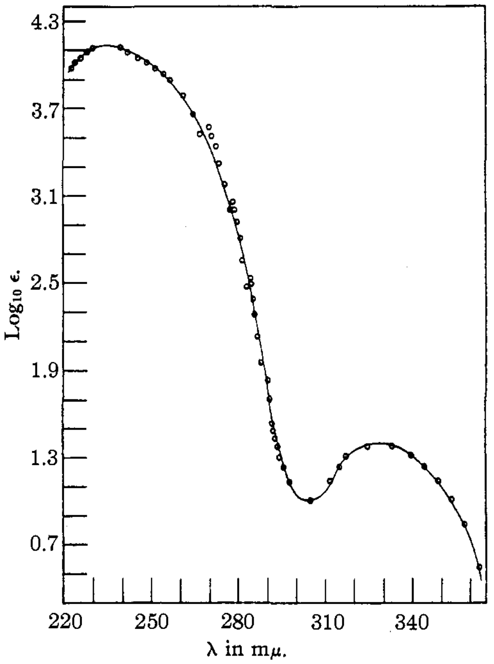


Fig. 1.—Ultraviolet absorption spectrum of 10-dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene in alcohol.

The ultraviolet absorption spectrum[7] (Fig. 1) of the latter substance gives confirmatory evidence of its structure. The maximum at 235 mμ ($\log \epsilon = 4.14$) is clearly a consequence of the conjugation of carbonyl and ethylenic double bonds, while the less intense maximum at 329 mμ ($\log \epsilon = 1.38$) must be ascribed to the carbonyl group. In this connection, it is instructive to note that cholestadiene-1,4-one-3 (XII), the only other cyclohexadienone for which ultraviolet absorption data are known, is reported by Inhoffen and Huang-Minlon[8] to have an intense band at 235 mμ ($\log \epsilon = 4.1$). It is a striking fact that both these compounds exhibit strong absorption in the same region as do those substances containing but one ethylenic bond in conjugation with the carbonyl group, as will be apparent from an inspection of Table I.

On the other hand phorone,[9] which likewise contains a cross-conjugated system, shows the expected shift of the intense band toward the red. This observation might well lead one to question the validity of the assumption of cross-conjugated systems in Inhoffen's compound and in ours. Inhoffen's degradative work,[10] however, as well as

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(6) Borsche, *Ber.*, **34**, 4299 (1901).

(7) We are indebted to Mr. D. M. Bowen of this Laboratory for the absorption measurements.

(8) Inhoffen and Huang-Minlon, *Ber.*, **71**, 1720 (1938).

(9) Bielecki and Henri, *ibid.*, **47**, 1715 (1914).

(10) Inhoffen and Huang-Minlon, *ibid*, **72**, 1686 (1939).

TABLE I

Ketone	λ max.	Log ε max.
Mesityl oxide	235	4.14[a]
Δ^4-Cholestenone	240	4.21[b]
Δ^1-Cholestenone	*ca.* 230	.. [c]
Eremophilone	243	3.90[d]
Pulegone	252	3.91[b]
α-Cyperone	251	4.28[d]
$\Delta^{1,4}$-Cholestadienone	235	4.1[c]
10-Dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene	235	4.14[e]

[a] Morton, *J. Chem. Soc.*, 719 (1926). [b] Menschick, *et al.*, *loc. cit.* [c] Inhoffen, *loc. cit.* [d] Gillam, *J. Chem. Soc.*, 676 (1936). [e] This paper.

the hydrogenation of his substance to compounds of the coprostane, rather than the cholestane, series, proves beyond doubt that his material has in fact the structure (XII).

These considerations lead us to suggest that the rule of Menschick, Page and Bossert,[11] *viz.*, that substances exhibiting strong absorption (log ε = 4.0–5.0) in the vicinity of 235–250 mμ contain an α,β-unsaturated carbonyl system, be extended to include the possibility that such absorption is a consequence of cross-conjugation of two ethylenic bonds with a carbonyl group.

Experimental

6-Hydroxy-1,2,3,4-tetrahydronaphthalene-7-aldehyde (VIII) and 10-Dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene (IX).—3.5 grams of 6-hydroxy-1,2,3,4-tetrahydronaphthalene was dissolved in 80 cc. of 10% aqueous sodium hydroxide in a flask equipped with an efficient reflux condenser and a dropping funnel. After the reaction mixture had been immersed in a water-bath at 75°, pure chloroform was dropped in slowly from the funnel. With the addition of the first few drops of chloroform, the solution turned yellow; as more was added the color gradually deepened to orange. In the course of three hours, 13.0 g. of chloroform was added. The reaction was then allowed to continue for one-half to three-quarters of an hour, when the water-bath was removed and the reaction mixture allowed to cool. More chloroform was now added, the mixture was well shaken, and the two layers separated, the neutral aqueous layer being discarded. The chloroform was evaporated on the steam-bath and the residual red oil, which crystallized partially on cooling, distilled *in vacuo* from a 10-cc. Claisen flask, b. p. 4–5 mm., *ca.* 130–150°. The distillate, a clear yellow, very sirupy liquid which deposited crystals on scratching, was triturated with 5% aqueous sodium hydroxide, the resulting solid was filtered at the pump, and washed with water until the sparingly soluble sodium salt of the hydroxy-aldehyde had been completely dissolved. The bright yellow filtrate was made neutral with dilute hydrochloric acid, the precipitated oil taken up in ether and recovered in the usual way. The oil thus obtained weighed 1.8 g., and crystallized slowly on standing as octagonal prisms, m. p. 80–82°; mixed with an authentic sample of 6-hydroxy-1,2,3,4-tetrahydronaphthalene-7-aldehyde,[4] m. p. 80–82°.

The solid remaining on the funnel after the removal of the sodium salt by washing was dissolved in methanol, the reddish solution was filtered from a small amount of amorphous material, and evaporated to a very small volume. The crystals which separated were recrystallized from cyclohexane, 0.8 g. of colorless stout hexagonal prisms, m. p. 167.5–168.5°, being obtained. (Occasionally long needles of the same m. p. were obtained on crystallization from methyl alcohol, but the above form is more common from either solvent.) Further recrystallization failed to change the melting point.

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.2; H, 5.2; Cl, 30.5. Found: C, 57.15; H, 4.91; Cl, 30.3.

10-Dichloromethyl-2-hydroxydecahydronaphthalene (XI).—150 mg. of 10-dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene was dissolved in 20 cc. of absolute methanol, a small amount of platinum oxide catalyst added, and the reaction mixture shaken with hydrogen at 30.5° and 755 mm. In five minutes 57 cc. (3.5 mols) of hydrogen had been taken up, and there was no further absorption. The clear solution was filtered to remove catalyst, evaporated to a small volume on the hot-plate, and then to "dryness" in a current of warm air. A clear, viscous oil of camphoraceous odor remained. Since it could not be crystallized on trituration with cyclohexane or petroleum ether, it was allowed to stand overnight, when it crystallized partially in waxy prisms, sintering at 67°, melting at 73–76°. The oil was then dissolved in a small amount of methanol, and the solution was allowed to stand for a few hours after enough water had been added to cause strong turbidity. At the end of this time the material had crystallized in beautiful rosets of needles. This process was repeated five times, the period necessary for crystallization becoming shorter with each repetition. 10-Dichloromethyl-2-hydroxydecahydronaphthalene finally was obtained as beautiful silky needles, m. p. 92.5–93°, extremely soluble in methanol, and giving a strong Beilstein test. The material sublimed easily in colorless rosets in high vacuum at 64°.

Anal. Calcd. for $C_{11}H_{18}OCl_2$: C, 55.70; H, 7.66. Found: C, 55.90; H, 7.73.

α-Naphthylurethan of 10-Dichloromethyl-2-hydroxydecahydronaphthalene.—The clear colorless oil obtained on hydrogenation of 130 mg. of 10-dichloromethyl-2-keto-$\Delta^{1,9;\,3,4}$-hexahydronaphthalene in the manner described above was allowed to stand overnight over phosphorus pentoxide in the vacuum desiccator. An approximately equivalent amount of freshly distilled α-naphthylisocyanate was added, the two substances were mixed completely, and the reaction mixture placed in the vacuum desiccator over phosphorus pentoxide. After six days, the flask contained a mass of prisms, and a small amount of oil. The reaction mixture was dissolved in 6–8 cc. of hot middle-boiling ligroin, and the solution filtered from a small amount of insoluble tarry material. After concentrating to 2–3 cc. on the hot-plate, the solution was allowed to stand overnight. The stout hard prisms which had separated were filtered, washed with a small amount of petroleum ether, and recrystallized twice from hot ligroin,

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(11) Menschick, Page and Bossert, *Ann.*, 495, 233 (1932).

Hard, compact glistening aggregates of plates, m. p. 152.5–153°, were formed.

Anal. Calcd. for $C_{22}H_{25}O_2NCl_2$: C, 65.0; H, 6.21. Found: C, 64.99; H, 6.42.

10-Methyl-decalone-2 (X).—220 mg. of 10-dichloromethyl-2-hydroxy-decahydronaphthalene was dissolved in 20 cc. of 10% methanolic potassium hydroxide, 0.5 g. of palladinized barium sulfate added, and the reaction mixture shaken with hydrogen for six hours at 29° and 759 mm. At the end of this time 42 cc. (1.9 mols) of hydrogen had been taken up. The reaction mixture was then poured into 60 cc. of water and extracted exhaustively with ether (6 hand extractions). The combined ethereal extracts were dried over sodium sulfate, the ether was removed, and the residual colorless viscous oil allowed to stand in the vacuum desiccator over phosphorus pentoxide. Since it did not crystallize on standing overnight, it was dissolved in 5 cc. of glacial acetic acid and oxidized directly by dropping in slowly a solution of 100 mg. of chromic oxide in 4 cc. of glacial acetic acid and 1 cc. of water. After stirring for four hours, the reaction mixture was poured into water, extracted exhaustively with ether, and the combined ethereal extracts dried over anhydrous sodium sulfate. The residual oil obtained on evaporating the ether was converted into the 2,4-dinitrophenylhydrazone in the usual manner, pale yellow needles from methyl alcohol, m. p. 151–152°, mixed with an authentic sample prepared by Robinson's method, m. p. 151–152°. On hydrolyzing this derivative with 5% sulfuric acid and working up in the usual manner, 100 mg. of a colorless oil of camphoraceous odor was obtained which solidified on standing, m. p. 46°, mixed with Robinson's ketone, m. p. 45–46°.

Summary

A novel method for the direct introduction of the angular-methyl group is described. These experiments may be considered as models for the transformation of oestrone or oestradiol into substances of the testosterone–androsterone group.

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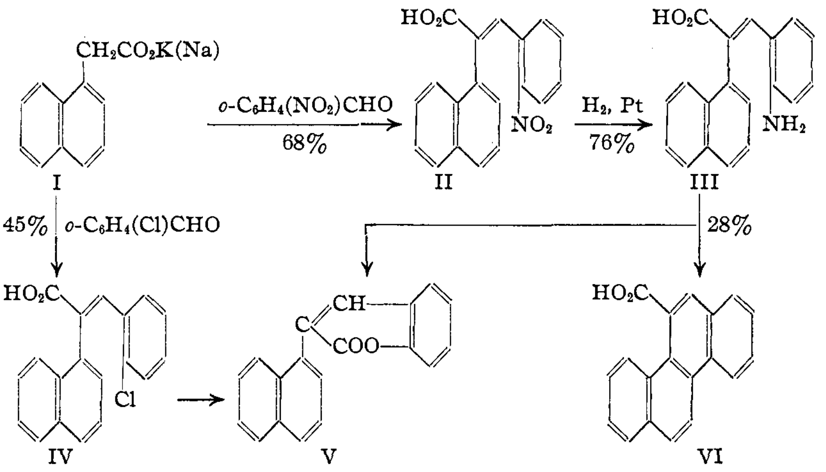
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

5-Methylchrysene

BY LOUIS F. FIESER AND LLOYD M. JOSHEL[1]

In a previous attempt to synthesize 5-methylchrysene a rearrangement was encountered in a final dehydrogenation step and the product, isolated in small yield, proved to be the 6-methyl isomer.[2] Another route not requiring a dehydrogenation now has been investigated, the plan being to obtain the 5-methyl compound from the corresponding carboxylic acid.

One scheme for obtaining the desired intermediate consisted in the condensation of α-naphthylacetic acid with *o*-chlorobenzaldehyde and fusion of the product IV with potassium hydroxide, following the synthetic method employed by Hewett.[3] The only crystalline product isolated proved to be the lactone of α-(1-naphthyl)-*o*-hydroxycinnamic acid, V. We then turned to the Pschorr synthesis, which already has been carried to the stage of the 5-acid VI by Weitzenböck and Lieb.[4] The condensation product II was obtained in improved yield and was conveniently reduced to the amine III by catalytic hydrogenation. Weitzenböck and Lieb state that the Pschorr ring closure afforded in about 20% yield a crude product which was purified with difficulty. A number of variations were tried in the present work and the best result was a 28% yield of pure chrysene-5-carboxylic acid by a procedure



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(1) Fellow of the Finney-Howell Research Foundation.

(2) Fieser, Joshel and Seligman, THIS JOURNAL, **61**, 2134 (1939).

(3) Hewett, *J. Chem. Soc.*, 1286 (1938).

(4) Weitzenböck and Lieb, *Monatsh.*, **33**, 549 (1912).