Tetrahedron, 1963, Vol. 19, pp. 1611 to 1616. Pergamon Press Ltd. Printed in Northern Ireland

A STEREOSPECIFIC SYNTHESIS OF *TRANS*-1β-HYDROXY-7-METHOXY-11-METHYL-1,2,3,4,9,10,11,12-OCTAHYDROPHENANTHRENE

C. SOMESWARA RAO and D. K. BANERJEE
Department of Organic Chemistry, Indian Institute of Science, Bangalore, India

(*Received* 26 *July* 1963)

Abstract—The potassium salt of 2-β-(*m*-methoxyphenyl)-ethylcyclohexane-1,3,dione (I) has been methylated with methyl iodide and the resulting product (II) cyclized to give the tricyclic unsaturated ketone (III). Catalytic hydrogenation of III gave the *trans*-octahydrophenanthrone (IV) stereospecifically. The *trans*-configuration of IV has been unequivocally established by degradation to the known *trans*-1-oxo-8-methyl-4,5-(4′-methoxybenzo)-hydrindane (XI). Sodium borohydride reduction of IV gave *trans*-1β-hydroxy-7-methoxy-11-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (XII), also obtainable from the unsaturated ketone (III) by borohydride reduction followed by catalytic hydrogenation.

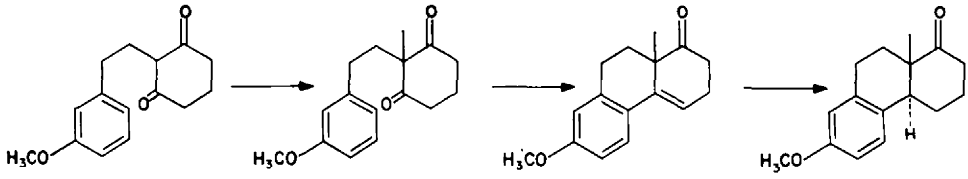
A TOTAL stereospecific steroid synthesis, following the hydrochrysene approach, was investigated by the synthesis of a tricyclic benzodecalin (hydrophenanthrene) intermediate comprising the B, C, D-rings of a D-homosteroid with an aromatic ring B, an angular methyl group at C-13, an ethylenic linkage between C-14 and C-15, and a functionalized 17a-position. Such a system, on catalytic hydrogenation, may be expected to give rise to a C/D *trans*-junction stereospecifically and it also lends itself to easy synthetic manipulation both as regards the contraction of the D-homoring and other potentiating structural modifications.

A similar attempt was made earlier by Birch and Smith,[1] but they found that a monoalkylated dihydroresorcinol dimethyl ether could not be further alkylated. Robinson and Thompson[2] in an attempt to synthesize the tetracyclic unsaturated ketone (V) found that the condensation reaction between γ-1-naphthyl-α- methylbutyryl chloride and ethyl sodioacetyl glutarate, on hydrolysis, yielded naphthylbutyric acid instead of the required long chain ketoacid. Chaung *et al.*[3] recorded a similar failure in the corresponding methoxy series. The tetracyclic unsaturated ketone (V) was earlier synthesized by Burnop *et al.*[4] utilizing the cyclopentenyl approach[5] and later by Chang Chin.[6] We have now studied the dialkylation of cyclohexane-1,3-dione with a view to preparing the required benzodecalin system.

2-β-(*m*-Methoxyphenyl)-ethylcyclohexane-1,3-dione (I), was prepared according

[1] A. J. Birch and H. Smith, *J. Chem. Soc.* 1882 (1951).
[2] R. Robinson and J. M. C. Thompson, *J. Chem. Soc.* 1739 (1939).
[3] C. K. Chaung, Ch. M. Ma and Y. T. Huang, *Ber. Dtsch. Chem. Ges.* **72**, 949 (1939).
[4] V. C. E. Burnop, G. H. Elliott and R. P. Linstead, *J. Chem. Soc.* 727 (1940).
[5] G. H. Elliott and R. P. Linstead, *J. Chem. Soc.* 660 (1938).
[6] Chang Chin, *Scientia Sinica* **4**, 547 (1955).

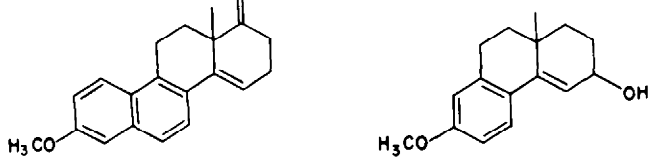
to the method of Birch *et al.*[7] Following the directions of Stetter and Klanke,[8] the β-diketone (I) was methylated with methyl iodide and potassium ethoxide. In view of its likely instability, the crude reaction product (II) was directly cyclized with *p*-toluene-sulphonic acid to give the tricyclic unsaturated ketone (III) with the expected UV maximum. Consistent yields of about 40% could be obtained only when a concentrated solution of the potassium salt of the starting β-diketone in ethanol was used in methylation and when the product isolated by avoiding aqueous conditions and immediately cyclized. Alkylation involving treatment of the potassium salt of 2-methyl-cyclohexane-1, 3-dione with β-*m*-methoxyphenylethyl bromide in t-butanol or DMF was not promising.



I II III IV

The tricyclic unsaturated ketone (III) was hydrogenated over 6% palladium-on-strontium carbonate catalyst to furnish trans-1-oxo-7-methoxy-11-methyl-1,2,3,4,9,-10,11,12-octahydrophenanthrene (IV) in an almost quantitative yield. A yellow 2,4-dinitrophenylhydrazone was obtained for this ketone.

Formation of IV as the single product of catalytic hydrogenation showed clearly the stereospecific nature of the reaction. There is analogy in the literature that catalytic hydrogenation of systems similar to III proceeds by *cis*-addition of hydrogen to the double bond resulting in a *trans*-ring juncture. Thus the tetracyclic unsaturated ketone (V) gave on hydrogenation D-homoequilenin methyl ether[4] as the only product, conversion of which to equilenin was accomplished by Chin.[6] Such a stereospecificity was also observed[9] in the case of the tricyclic unsaturated alcohol (VI). Robinson[9]



V VI

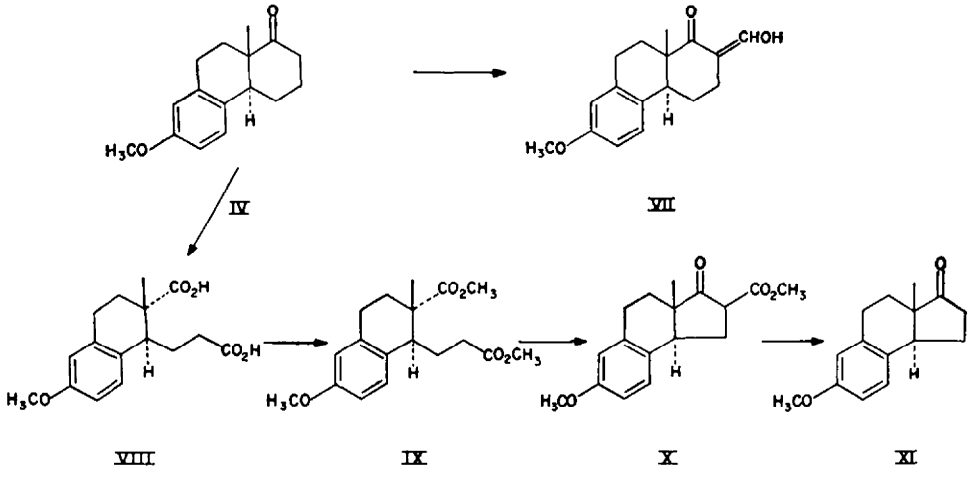
rationalized these findings on the basis of the concept of catalyst hindrance[10,11] assuming that the proposed 6-membered transition complex resembles more the reactant than the product. In the present case the *trans*-configuration was definitely

[7] A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.* 1339 (1957).
[8] H. Stetter and E. Klanke, *Ber.* **86**, 513 (1953).
[9] M. J. T. Robinson, *Tetrahedron* **1**, 49 (1957).
[10] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942).
[11] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 1855 (1949); W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. De Walt, *J. Amer. Chem. Soc.* **78**, 6302 (1956).

established by degrading the saturated ketone (IV) to the known *trans*-1-*oxo*-8-*methyl*-4, 5-(4'-*methoxybenzo*)-*hydrindane* (XI) prepared earlier by Bachmann and Thomas[12] and by Banerjee *et al.*[13]

To this end we first prepared the 2-hydroxymethylene derivative (VII) of the saturated ketone (IV). The formylation reaction proved to be unusually difficult. Attempted condensation of IV with ethyl formate using sodium ethoxide or potassium isopropoxide and by keeping the reaction mixture for 1 to 5 days at room temperature yielded unreacted starting material. Only when a refluxing benzene solution of IV was treated for a prolonged period with sodium hydride and excess ethyl formate, could a 70% yield of VII be obtained. But oxidative degradation of VII in alcohol with alkaline hydrogen peroxide gave only a small amount of an acidic material which could not be purified.

Later the dicarboxylic acid (VIII), which was a semisolid, was obtained directly from IV by oxidative cleavage with potassium hypoiodite following the method of Heer *et al.*[14] This on esterification with diazomethane afforded the dimethyl ester (IX), synthesized earlier by Bachmann and Thomas[12] form 6-methoxytetralone. Dieckmann cyclization of IX using alcohol-free potassium t-butoxide[15] as the base furnished

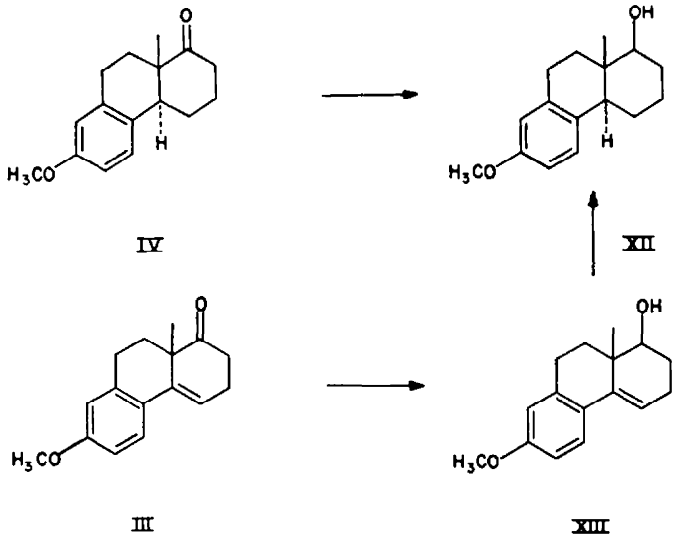


the cyclic β-ketoester (X). Following essentially Bachmann's directions,[16] the β ketoester (X) was decarbomethoxylated using a mixture of glacial acetic acid and concentrated hydrochloric acid. The neutral reaction product was purified by distillation in vacuum followed by crystallization to afford the pure benzohydrindane derivative (XI). Mixture melting point and IR spectra established its identity with an authentic specimen.[13]

The *trans*-saturated ketone (IV) gave a saturated alcohol (XII) in 90% yield on reduction with sodium borohydride in methanol. The same alcohol was obtained from the unsaturated ketone (III) by borohydride reduction followed by catalytic hydrogenation, as was evidenced by identical IR spectra. The β-configuration was

[12] W. E. Bachmann and D. G. Thomas, *J. Amer. Chem. Soc.* **64**, 94 (1942).
[13] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Amer. Chem. Soc.* **78**, 3769 (1956).
[14] J. Heer, J. R. Billeter and K. Miescher, *Helv. Chim. Acta* **28**, 991 (1945).
[15] W. S. Johnston, B. Bannister and R. Pappo, *J. Amer. Chem. Soc.* **78**, 633 (1956).
[16] W. E. Bachmann, W. Cole and A. L. Wilds, *J. Amer. Chem. Soc.* **62**, 835 (1940).

assigned to both the alcohols (XII and XIII) derived from the saturated and unsaturated ketones on the basis of Barton's generalization[17] that unhindered ketones are reduced chiefly to equatorial alcohols by metal hydrides and also on the basis of Dauben's postulate[18] of product development control.



Work is on hand for the elaboration of ring A on the tricyclic *trans*-saturated alcohol (XII). Structural and functional modifications which might lead to enhanced physiological activities are also being explored.

EXPERIMENTAL*

1-Oxo-$\Delta^{4(12)}$*-7-methoxy-11-methyl-1,2,3,9,10,11-hexahydrophenanthrene* (III)

To a solution of potassium ethoxide, prepared from potassium (1·26 g) and dry ethanol (10 ml), 2-*β*-(*m*-methoxyphenyl)-ethylcyclohexane-1,3-dione (I; 8·15 g) was added and the mixture refluxed for ½ hr. To the clear, cooled solution methyl iodide (3·5 ml) was added and after refluxing for 1½ hr additional methyl iodide (6 ml) was added followed by refluxing for another 2 hr (reaction mixt. neutral to red litmus). The filtrate, free from precipitated KI, was diluted with dry ether causing further KI to separate. After filtration, the solvent mixture was evaporated (red. press.), and the residue dissolved in dry ether leaving a small quantity of undissolved gummy substance. The ether solution was filtered through a fluted filter paper and the ether evaporated leaving an oil (7·38 g) which was practically insoluble in dil. NaOH. This material was used in the following cyclization reaction.

To a solution of the crude diketone (II) in dry benzene (100 ml), *p*-toluenesulphonic acid (1·4 g) was added and the mixture refluxed for 6 hr in a Dean-Stark apparatus. The benzene solution was diluted (equal vol. ether) and washed with dil. NaOH (2%) and then with water. Removal of the solvent afforded a solid (6·5 g), m.p. 85–87°. Crystallization from pet ether using a little norite gave

* All m.ps. are uncorrected. The UV absorption spectra were studied in 95% ethanolic solution The pet ether used in this section had b.p. 40–60°. Microanalyses were carried out by Messrs. B. R. Seetharamia and D. P. Bose of this department.

[17] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).

[18] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78,** 2579 (1956); W. G. Dauben, E. J. Blanz, J. Jiu and R. A. Michelli, *Ibid.* **78,** 3752 (1956).

a pale yellow solid (3·5 g), m.p. 90–93°. Recrystallization furnished pure III, m.p. 98–99°. (Found: C, 79·2; H, 7·15. $C_{16}H_{18}O_3$ requires: C, 79·34; H, 7·43%). UV λ_{max} 262 mμ (log ε 4·22) IR (CCl_4) Peaks at 1718 cm^{-1} (C=O); 6·05 μ (conjugated C=C).

trans-1-*Oxo*-7-*methoxy*-11-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (IV)

A solution of the unsaturated ketone (IV; 0·12 g) in 95% ethanol (50 ml) containing 6% Pd–$SrCO_3$ catalyst (50 mg) was stirred in an atm. of hydrogen (1 mole H_2 absorption). The catalyst was separated by filtration (F-grade sintered glass funnel) and distillation of the alcohol (red. press.) furnished a pale yellow solid, m.p. 87–90°, yield 0·11 g. A single crystallization from pet ether gave pure IV, m.p. 89–90°. (Found: C, 78·48; H, 8·23. $C_{16}H_{20}O_2$ requires: C, 78·68; H, 8·20%). UV λ_{max} 278 mμ (log ε 3·305); 285·5 mμ (log ε 3·25) IR ($CHCl_3$) Peaks at 1721 cm^{-1} (C=O); 1613 cm^{-1} (aromatic ring).

The 2,4-*dinitrophenylhydrazone* crystallized from ethyl acetate as bright yellow powder, m.p. 228–230°. (Found: N, 13·56. $C_{22}H_{24}O_5N_4$ requires: N, 13·2%).

Methyl 6-methoxy-2-methyl-2-carbomethoxy-1,2,3,4-*tetrahydronaphthalene*-1-*propionate* (IX)

(a) *By direct oxidation of the saturated ketone* (IV) *followed by esterification.* A solution of the saturated ketone (IV, 0·1 g) in methanol (8·5 ml) was treated alternately with 6 drops of a solution of iodine (0·3 g) in methanol (5 ml) and 2 drops of a solution of KOH (0·54 g) in water (1·1 ml) and methanol (3 ml) with vigorous shaking. The reaction mixture was kept at room temp for 24 hr under a N_2 atm. The total volume was then reduced to about 5 ml by removing the methanol under suction, 10% KOH solution (6 ml) was added and the mixture heated on a boiling water-bath for 3½ hr. Most of the alcohol was removed under suction and the residue, after dilution with warm water (100 ml), was filtered into 1:1 HCl (50 ml) when a deep yellow turbidity developed. The neutral portion on the filter paper amounted to 7·5 mg. The acidified mixture was extracted with ether and the ether extract washed free of acid with brine water. Removal of the ether, after drying the extract, furnished an acidic material (0·106 g) as a thick deep yellow gum. The acidic material (0·336 g) collected from 3 similar experiments was chromatographed over silica gel (activated at 150–160°/25–30 mm for 3 hr). Elution with a 1:1 mixture of benzene ether furnished 0·263 g dicarboxylic acid (VIII) and all attempts to crystallize it failed.

This crude acidic material was esterified with an ethereal solution of diazomethane, prepared from nitrosomethyl urea (5 g). Purification by short-path distillation at 150–170° (0·5–0·7 mm) afforded the pure IX as a yellow viscous oil (0·2 g). (Found: C, 67·76; H, 7·56. $C_{18}H_{24}O_5$ requires: C, 67·51; H, 7·50%).

(b) *By oxidation of the hydroxymethylene derivative* (VII).[19] The hydroxymethylene derivative (VIII) of the saturated ketone (IV) was prepared as follows: A solution of the saturated ketone (IV; 0·1 g) in dry benzene (50 ml), containing sodium hydride (50 mg) and ethyl formate (0·2 g), was refluxed for 11 hr under a N_2 atm. Ice and water were added to the mixture under N_2 and the organic layer separated and washed with ice-cold 2% NaOH solution (3 × 20 ml). The aqueous solution and the alkali extract were combined and acidified with 2N H_2SO_4 when a yellow precipitate was obtained. This was filtered, washed, and dried, m.p. 105–108°, yield 77 mg. From the benzene solution 15 mg of the saturated ketone was recovered. The formyl derivative gave a reddish violet colour with alcoholic ferric chloride. All of the starting material was recovered unchanged when the above reaction was carried out at room temp for 5 days.

To a solution of the crude hydroxymethylene derivative (75 mg) in ethanol (1·8 ml), 2N NaOH (2 ml) and 30% hydrogenperoxide (0·6 ml) were added and the mixture kept at room temp for 1 hr followed by heating under reflux for 2 hr. The reaction mixture was treated twice as above with hydrogen peroxide. The solvent was removed (red. press.) and the aqueous solution of the residue, after one extraction with ether, was acidified with ice-cold, dil. HCl. The acidic product, isolated by ether extraction, amounted to 10 mg. only and it could not be crystallized.

trans-1-*Oxo*-8-*methyl*-4,5-(4′-*methoxybenzo*)-*hydrindane* (XI)

To dry alcohol-free potassium t-butoxide, prepared from potassium (1·023 g), a solution of the dimethyl ester (IX; 0·18 g) in dry benzene (80 ml) was added under an O_2-free N_2 atm. and the reaction mixture refluxed with stirring for 5 hr and then left at room temp for 10 hr. Glacial acetic acid (5 ml) was added, followed by water (20 ml). The mixture was shaken thoroughly in a separatory

[19] F. von Gautschi, O. Jeger, V. Prelog and R. B. Woodward, *Helv. Chim. Acta* 296 (1955).

funnel, the aqueous layer removed and the organic layer washed with water, dil. $NaHCO_3$ aq and finally with brine water. The benzene extract was clarified by shaking with a few pieces anhydrous $CaCl_2$ and filtered. The solvent was removed in a current of air at 35°. The residue gave a greenish violet colouration with alcoholic ferric chloride.

To the above crude β-ketoester (X), glacial acetic acid (10 ml), conc HCl (5 ml), and water (1 ml) was added and the mixture heated under reflux (N_2 atm) for 1½ hr. The acetic and hydrochloric acids were removed under suction. The residue was treated with 2·5% NaOH solution (32 ml) in methanol containing water (3 ml) under reflux (N_2 atm) for 2 hr. The methanol was removed (red. press.) and water (80 ml) was added to the residue. The aqueous mixture was extracted with ether and the ether extract washed with brine water. Removal of the solvent after drying (Na_2SO_4) furnished a viscous oil. On short-path distillation at 130°/5 × 10^{-3} mm a pale yellow liquid was obtained which solidified on scratching, m.p. 100–106°, yield 50 mg. Two recrystallizations from n-hexane gave the pure XI, m.p. 112–113°. On admixture with an authentic specimen the m.p. was not depressed. The IR spectra of this and an authentic specimen in CCl_4 solution were superimposable. (Found: C, 78·34; H, 7·83. $C_{15}H_{18}O_2$ requires: C, 78·27; H, 7·83%).

1β-*Hydroxy*-7-*methoxy*-11-*methyl*-1,2,3,9,10,11-*hexahydrophenanthrene* (XIII)

To a solution of the tricyclic unsaturated ketone (III; 0·1 g) in methanol (25 ml), $NaBH_4$ (50 mg) was added. The resulting solution was kept at room temp for 24 hr and then poured into ice-cold 1:1 HCl (200 ml) causing precipitation of a colourless fluffy solid. This was extracted with ether, and the ether extract washed with brine water till free of acid and dried (Na_2SO_4). Removal of the solvent afforded XIII as a pale yellow solid (0·1 g), m.p. 125–130°. Crystallization from benzene–pet ether gave pale yellow flakes, m.p. 129–131°. (Found: C, 78·70; H, 8·19. $C_{16}H_{20}O_2$ requires: C, 78·68; H, 8·196%). UV λ_{max} 260·5 mμ (log ε 4·25) IR (CCl_4) Peaks at 3774 cm^{-1} (OH); 1639 cm^{-1} (conjugated C=C).

trans-1β-*Hydroxy*-7-*methoxy*-11-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (XII)

(a) *By sodium borohydride reduction of the saturated ketone* (IV). A solution of the saturated ketone (IV; 0·1 g) in methanol (25 ml) was treated with $NaBH_4$ (50 mg) and the resulting solution kept at room temp for 24 hr. On working up as in the case of the unsaturated alcohol (XIII) a semisolid (90 mg) was obtained which on crystallization from pet ether gave XII as colourless needles, m.p. 99–100°, yield 80 mg. (Found: C, 77·96; H, 8·81. $C_{16}H_{22}O_2$ requires: C, 78·05; H, 8·94%).

(b) *By catalytic hydrogenation of the unsaturated alcohol* (XIII). A solution of the unsaturated alcohol (XIII; 50 mg) in 95% ethanol (50 ml) containing 6% Pd–$SrCO_3$ catalyst (30 mg) was stirred in an atm of H_2 (rapid uptake of 1 mole H_2). The catalyst was separated by filtration and removal of the alcohol (red. press.) gave XII as a colourless solid (45 mg), m.p. 96–100°. A single crystallization from pet ether furnished colourless needles, m.p. 99–100°.

The alcohols obtained from both experiments were identical as shown by the undepressed mixed m.p. and superimposable IR spectra.