Acid-catalysed Decomposition of β,γ-Unsaturated Diazo-ketones: Preparation of 4,4-Dimethyl-D-nor-steroidal Systems from Pimaradiene and Sandaracopimaradiene Precursors [1]

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4,4-Dimethyl-17-nor-5α,13α-androst-8-en-16-one (9) and 3β-acetoxy-4,4-dimethyl-17-nor-5α-androst-8-en-16-one (19) have been prepared by the acid-catalysed intramolecular cyclization of 16-diazopimar-8(14)-en-15-one (7) and 3β-acetoxy-16-diazoisopimar-7-en-15-one (16) prepared from pimara-8(14),15-diene (5) and isopimara-7,15-dien-3β-ol acetate (10), respectively.

OVER the past 18 years the preparation of D-nor-steroids has attracted the attention of several research groups.[2] This interest has largely been motivated by the hope of discovering hormone analogues with modified biological activities and by an interest in exploring carbonium ion reactions of cyclobutane rings held in a rigid framework.

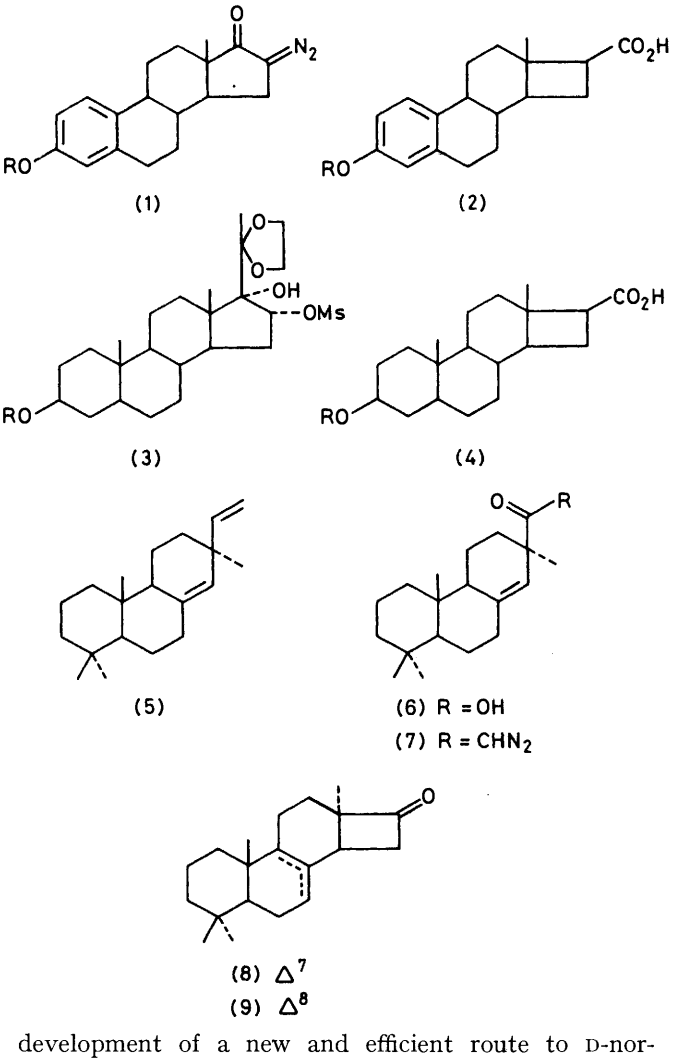
The preparation of D-nor-steroids has been achieved by two synthetic routes, the first one involving the photolysis of 16-diazo-17-keto-steroids [*e.g.* (1) ⟶ (2)] while a more recent method is based on the pinacol-type rearrangement of 16-methanesulphonate derivatives of 16α,17α-dihydroxy-17β-ethyl steroids [*e.g.* (3) ⟶ (4)].[2j,†]

We have developed an alternative route for the preparation of the D-nor-steroidal skeletal type which involves the non-carbenoid, acid-catalysed intramolecular cyclization of olefinic diazo-ketones (7) and (17) prepared from pimaradiene (5) and sandaracopimaradiene (13), respectively.

The possibility of a rapid eliminative cyclization as the consequence of the close proximity between an olefinic double-bond β,γ [3] or γ,δ [4] to the electrophilic carbon adjacent to the diazo-group has been widely employed for the incorporation of the bicyclo-[3.2.1]- and -[2.2.1]-octanone entities into a variety of systems. One reported case, in which the acid-catalysed decomposition of a β,γ-unsaturated diazoketone led selectively to the formation of a cyclobutanone derivative [5] caught our attention and led us to explore the possibility of employing this method for the preparation of the 4,4-dimethyl derivatives (9) and (19) *via* the acid-catalysed decomposition of the corresponding β,γ-unsaturated diazoketones (7) and (17). In our case two factors should, predictably, favour their regioselective formation. (a) The preferential intermediacy of the more stable, incipient tertiary carbonium ion at C-8 (generated as the consequence of the electrophilic attack of the olefinic double bond to the carbonyl α to the diazo-group) and the impossibility of the alternative, less-favoured secondary carbonium ion at C-14 leads to collapse to an olefin because of the absence of α hydrogens.

(b) The non-bonding interactions which disallow the π-bond participation needed for the C(16)–C(8) carbon–carbon bond formation.

The end result of the above considerations was the development of a new and efficient route to D-nor-steroids such as (9) and (19). Treatment of pimaradiene (5) ‡ with a catalytic amount of potassium



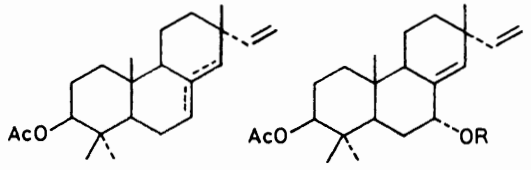
† In both synthetic routes the D-ring contraction occurs with retention of the original C/D ring fusion.

‡ The pimaradiene (5) was prepared starting from pimaric acid following the procedure reported for the preparation of abietatriene from abietic acid.[6]

permanganate in a buffered solution of sodium metaperiodate [7] served to convert (5) into the carboxylic acid (6). Sequential treatment of the acid (6) with oxalyl chloride and diazomethane [8] gave the expected diazo-ketone (7). A solution in benzene of (7) was then poured through a column of silica gel, giving in the eluate good yields of a *ca.* 1 : 1.2 mixture of the two isomeric cyclobutanones (8) and (9).*

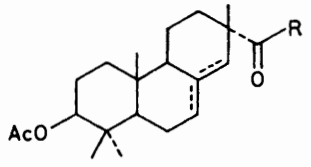
After unsuccessful attempts to separate the cyclobutanones (8) and (9) the mixture was treated with hydrogen chloride gas in chloroform,[9] yielding the more stable cyclobutanone (9) as the only product. The 4,4-dimethyl-D-nor-steroidal ketones (8) and (9) possess a C/D *cis*-ring fusion. The assignment of the stereochemistry of the newly created chiral centre at C-14 was based upon an examination of molecular models, which led us to exclude the possibility of a cyclization leading to the *trans* C/D ring-fused product.

We next turned our attention to the preparation by the above described method of the isomeric cyclobutanone (19). The key intermediate, the olefinic

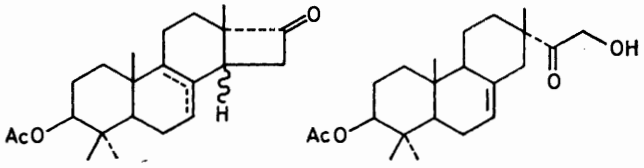


(10) Δ^7
(13) $\Delta^{8(14)}$

(11) R = H
(12) R = Ac



(14) Δ^7 R = OH
(15) $\Delta^{8(14)}$ R = OH
(16) Δ^7 R = CHN_2
(17) $\Delta^{8(14)}$ R = CHN_2

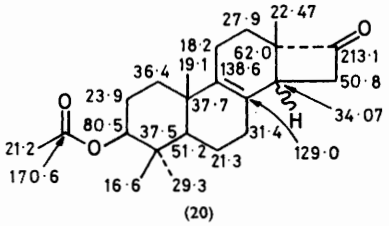


(18) Δ^7
(19) Δ^8

(20)

diazo-ketone (17) was prepared from the isopimaric diene † (10) by the synthetic sequence described below.

Photo-oxygenation of compound (10) followed by reduction with sodium iodide in methanol of the hydroperoxide initially formed, cleanly gave the allylic alcohol (11).[10] Eliminative reduction of the corresponding acetate (12) with lithium in ammonia,[11] followed by reacetylation afforded an inseparable mixture of olefinic compounds (13) and (10) in a ratio 2.5 : 1. The malpositioning of the double bond of (10) was



(20)

initially ignored and the mixture was oxidized as previously described to give a mixture of acids (14) and (15) which by sequential treatment with oxalyl chloride and diazomethane was converted into a mixture of olefinic diazo-ketones (17) and (16) in the ratio 2.5 : 1.

Sulphuric acid-promoted cyclization gave the isomeric cyclobutanones (19) and (18) as well as the alcohol (20). The cyclobutanones (18) and (19) were easily isolated by column chromatography from the alcohol (20) and their mixture treated with hydrogen chloride in chloroform in order to convert (18) into the more stable isomeric cyclobutanone (19). The attribution of the stereochemistry at C-14 was not as straightforward as in the case of (9). Indeed, the α-equatorial orientation of the two-carbon chain at C-13 of (17) could allow both *cis*- and *trans*-cyclization; the former, however, appears to be greatly favoured by the absence of non-bonding interactions in the transition state of the cyclization process and by the minor strain of the resulting *cis*-fused bicyclo[4.2.0] system. The ^{13}C n.m.r. data of the cyclobutanone (19), shown on formula (21), seems to confirm this assignment, but in the absence of the corresponding values for adequate model compounds this evidence falls short of that necessary to furnish conclusive proof for the stereochemistry assigned by us to the C-14 chiral centre.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (ν/cm^{-1}) were obtained with a Beckmann Acculab 5 spectrophotometer in carbon tetrachloride solution. ^1H N.m.r. spectra were recorded with a JEOL INM-L-60 HL spectrometer and ^{13}C n.m.r. spectra were recorded with a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode (solutions in deuteriochloroform with internal tetramethylsilane as standard). Column chromatography was performed with Merck silica gel (0.063—0.200 mm particle size).

Oxidation of Pimara-8(14),15-diene (5).—A solution of pimaradiene (5) (2 g) in t-butyl alcohol (0.5 l) was treated with a solution of sodium metaperiodate (9.5 g) and potassium permanganate (0.15 g) in water (1 l). The stirred solution was kept at pH 8 by the addition of 5% aqueous potassium carbonate solution, and the mixture was stirred

* Similar results are obtained by the acid promoted (PTSA, or N-sulphuric acid in ether) cyclization of compound (7).

† This compound was prepared from virescenol B according to a reported procedure.

for 3 h. The solution was acidified with 2N-sulphuric acid and extracted with ether. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1.8 g) on silica gel and elution with benzene–ethyl acetate (10 : 1) gave starting material (5) (0.4 g) and the acid (6) (1.2 g), $\nu_{max.}$ 1 705 (CO_2H); δ 0.70, 0.85, 0.88, 1.25 (each s, Me_4), and 9.35 (m, CO_2H) (Found: C, 78.2; H, 10.6. $C_{19}H_{30}O_2$ requires C, 78.57; H, 10.41%).

4,4-*Dimethyl*-17-*nor*-5α,13α-*androst*-7-*en*-16-*one* (8) *and* 4,4-*Dimethyl*-17-*nor*-5α,13α-*androst*-8-*en*-16-*one* (9).— The acid (6) (0.5 g) was added to freshly distilled oxalyl chloride (5 ml). The frothing mixture was stirred for 2 h, and then the excess of oxalyl chloride was removed by vacuum distillation. A solution of the resulting crystalline acid chloride in dry ether (100 ml) was added dropwise during 4 h to an ice-cold, well-stirred, ethereal solution of diazomethane (5.0 mmol). The solution was stirred at 0 °C for an additional 4 h and kept at room temperature for 12 h. The excess of diazomethane was blown off under a stream of nitrogen and the solution concentrated to give the solid diazo-ketone (7), $\nu_{max.}$ 2 110s (N_2CH), 1 630s (C=O), which was decomposed on a silica-gel column in benzene to give a mixture (45 : 55) of cyclobutanones (8) (0.18 g, 36%); $\nu_{max.}$ 1 778s (C=O); δ 0.80, 0.93, 0.98, 1.18 (each s, Me_4), and 5.53 (m, 7-H); and (9) $\nu_{max.}$ 1 778s (C=O); δ 0.88, 0.93, 0.98, and 1.15 (each s, Me_4) (Found: C, 83.4; H, 10.7. $C_{20}H_{30}O$ requires C, 83.86; H, 10.56%).

4,4-*Dimethyl*-17-*nor*-5α,13α-*androst*-8-*en*-16-*one* (9).—A solution of a mixture of the cyclobutanones (8) and (9) (0.15 g) in chloroform saturated with hydrogen chloride (70 ml) was kept at room temperature for 24 h. It then was poured into ice–water (150 ml), and the organic layer separated. The latter was washed with saturated sodium hydrogencarbonate solution and water and then dried (Na_2SO_4) and evaporated. Chromatography of the residue (0.14 g) on silica gel and elution with benzene–ethyl acetate (19 : 1) yielded a solid (0.13 g) which crystallized from n-hexane to give the cyclobutanone (9), m.p. 103—105 °C (*vide supra*).

Sandaracopimaradiene-3β,7α-*diol Acetate* (12).—A 2.0 g sample of (10) in ethanol (150 ml) was placed in a gas-washing bottle and hematoporphyrin (30 mg) was added. The mixture was irradiated with a tungsten 250 W lamp, while a stream of oxygen was passed though the solution, for 48 h. The mixture was treated with a solution of sodium iodide (0.8 g) in ethanol (40 ml) and the resulting mixture was stirred for 4 h. The mixture was diluted with water and extracted with ether. The organic phase was washed with saturated sodium thiosulphate solution and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1.8 g) on a silica-gel column and elution with benzene–ethyl acetate (9 : 1) gave starting material (10) (0.6 g) and the alcohol (11) (1.1 g). The latter was quantitatively converted into the corresponding diacetate (12) by the standard procedure, δ 0.87 (s, Me_2), 0.91, 1.05 (each s, Me_2), 2.0, 2.05 (each s, 2 × $OCOCH_3$), 5.32 (t, 7-H, *J* 3 Hz), and 5.65 (s, 14-H) (Found: C, 74.0; H, 9.45. $C_{24}H_{36}O_4$ requires C, 74.19; H, 9.34%).

Li–NH_3 *Reduction of the Sandaracopimaradiene*-3β,7α-*diol Acetate* (12).—A solution of the diacetate (12) (0.9 g) in tetrahydrofuran (20 ml) was added during 20 min to a solution of lithium (0.15 g) in liquid ammonia (100 ml) and the reaction mixture was stirred at −40 °C for 10 min. A few drops of bromobenzene were added to the mixture, the ammonia was evaporated in a stream of nitrogen and a 0.5N-sulphuric acid solution (20 ml) was added to the residue. The resulting mixture was extracted with chloroform and the combined organic layers were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue (0.8 g) was treated with acetic anhydride in pyridine for 12 h at room temperature, and then poured into water. The mixture was acidified with 2N-sulphuric acid and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (0.78 g) on a silica-gel column and elution with benzene–ethyl acetate (19 : 1) gave a mixture (30 : 70) of (10) and (13) (0.7 g); the latter compound was identified by its n.m.r. spectrum: δ 0.82, 0.85, 0.90, 1.05 (each s, Me_4), 2.05 (s, $OCOCH_3$), 4.5 (m, H-3), and 5.18br (s, H-14) (Found: C, 80.0; H, 10.1. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.37%).

Oxidation of Isopimara-7,15-*dien*-3β-*ol Acetate* (10) *and Sandaracopimaradien*-3β-*ol Acetate* (13).—The mixture of (10) and (13) (0.7 g) in t-butyl alcohol (180 ml) was treated with a solution of sodium metaperiodate (2.5 g) and potassium permanganate (0.07 g) in water (360 ml). The stirred solution was kept at pH 8 by the addition of 5% aqueous potassium carbonate solution and the mixture was stirred for 3 h. Work-up as above and column chromatography of the crude product (0.68 g) on silica gel, followed by elution with chloroform–methanol (30 : 1) yielded starting material (0.2 g) and a mixture of the isomeric acids (14) and (15) (0.4 g), $\nu_{max.}$ 1 690 (C=O of CO_2H) (Found: C, 71.5; H, 9.85. $C_{27}H_{32}O_4$ C, 71.96; H, 9.78%).

3β-*Acetoxy*-16-*diazoisopimar*-7-*en*-15-*one* (16) *and* 3β-*Acetoxy*-16-*diazosandaracopimaren*-15-*one* (17).—The mixture of the two isomeric acids (14) and (15) (0.4 g) was added to freshly distilled oxalyl chloride (5 ml). The frothing mixture was stirred for 2 h and then the excess of oxalyl chloride was removed by vacuum distillation. A solution of the resulting crystalline acid chlorides in dry ether (100 ml) was added dropwise during 4 h to an ice-cold, well stirring ethereal solution of diazomethane (5 mmol). Work-up as above and chromatography on silica gel, followed by elution with chloroform–methanol (30 : 1), yielded the diazoketones (16) and (17) (0.3 g); $\nu_{max.}$ 2 120 (N_2CH) and 1 640 (C=O).

3β-*Acetoxy*-4,4-*dimethyl*-17-*nor*-5α-*androst*-7-*en*-16-*one* (18) *and* 3β-*Acetoxy*-4,4-*dimethyl*-17-*nor*-5α,14-*androst*-8-*en*-16-*one* (19).—A solution of sulphuric acid (0.25 ml) in ether (5 ml), was added to a stirring ethereal solution of the isomeric diazoketones (16) and (17) (0.2 g). The mixture was stirred at room temperature for 30 min. Water (10 ml) was then added and the organic layer washed with saturated sodium hydrogencarbonate solution, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the crude residue (0.18 g), on silica gel and elution with benzene–ethyl acetate (19 : 1) gave a mixture of isomeric cyclobutanones (18) (0.1 g, 53%) [$\nu_{max.}$ 1 768s (cyclobutanone C=O); δ 0.85, 0.90, 0.97, 1.13 (each s, Me_4), 2.02 (s, $OCOCH_3$), 4.48 (m, 3-H), and 5.60 (m, 7-H)] and (19) [$\nu_{max.}$ 1 768s (cyclobutanone C=O); δ 0.90, 0.90, 0.99, 1.25 (each s, Me_4), and 4.48 (m, 3-H)] (Found: C, 76.8; H, 9.25. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36); further elution with the same solvents gave the keto-alcohol (20) (0.05 g), $\nu_{max.}$ 3 480s (OH) and 1 700 (C=O, ketone); δ 0.87, 0.87, 0.97, 1.05 (each s, Me_4), 2.02 (s, $OCOCH_3$),

4.40 (s, CH_2OH), 4.45 (m, 3-H), and 5.41 (m, 7-H) (Found: C, 72.6; H, 9.6. $C_{22}H_{34}O_4$ requires C, 72.89; H, 9.45%).

3β-*Acetoxy*-4,4-*dimethyl*-17-*nor*-5α,14-*androst*-8-*en*-16-*one* (19).—A solution of a mixture of the cyclobutanones (18) and (19) (0.1 g) in chloroform saturated with hydrogen chloride gas (50 ml) was kept at room temperature for 24 h. Work-up as above and column chromatography of the crude product (0.09 g) on silica gel, followed by elution with benzene–ethyl acetate (19 : 1) yielded the cyclobutanone (19) (0.07 g) (*vide supra*).

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