[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Base Catalyzed Autoxidation of Cyclic 1,4-Diketones to Enediones

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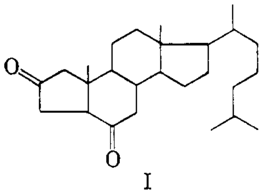
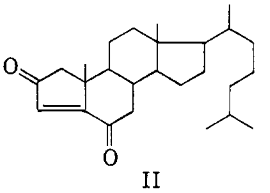
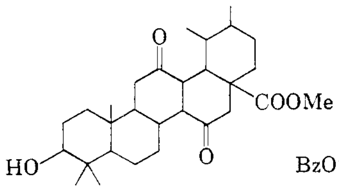
When an alkaline alcoholic solution of a cyclic 1,4-diketone is shaken with air, the compound is transformed in good yield to the corresponding enedione. The autoxidation most likely proceeds *via* an anion radical intermediate.

During the course of a study on the chemistry of A-norsteroids, the thermodynamic stability of A-norcoprostane-2,6-dione (I)[2] was investigated.


I


II

When the dione I was warmed for about five minutes in 0.5*N* ethanolic potassium hydroxide, a deep blue color developed. Upon standing at room temperature in a closed flask the color remained, but when the blue solution was swirled in air the blue color was discharged and an orange solution resulted. Upon repetition of the process, the same color sequence was again noted, and after a few such treatments the blue color no longer formed. Upon processing the reaction mixture, A-nor-3-cholestene-2,6-dione (II) was obtained in 40% yield. Such a base catalyzed autoxidation of a saturated 1,4-diketone to an enedione system has been reported previously in two cases. In 1953, Barton and de Mayo[3] found that when methyl diketopyroquinovate (III) was heated in base in the presence of air, the dehydro derivative was obtained. In 1955, Barton, McGhie, Pradhan, and Knight[4] reported that, when 7,11-dioxoeuphanyl benzoate (IV) was saponified, 7,11-dioxoeuphenol was obtained. In both of these latter two cases, the enedione system introduced was derived by removal of tertiary hydrogen atoms and was part of an internal ring system. In all three examples the yields of the reactions were good; in view of the simplicity of the reaction as compared to the use of such reagents as selenium dioxide for dehydrogenation, the base catalyzed autoxidation was further examined.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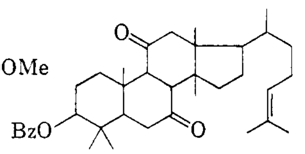
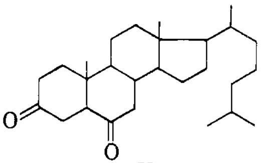

IV

When an alkaline ethanolic solution of cholestane-3,6-dione (V) was warmed in air, no blue color developed as in the A-nor series but the color of the solution went from colorless to yellow to green to red. From the reaction mixture there was obtained 4-cholestene-3,6-dione (VI) in 41% yield.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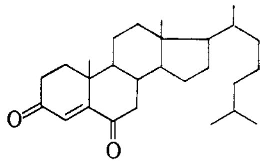
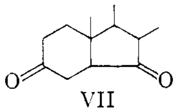
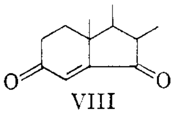
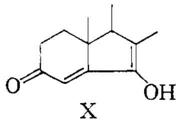
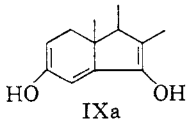

VI

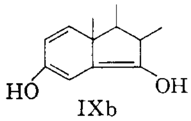
Upon similar treatment B-norcoprostane-3,6-dione (VII) did not yield the known enedione (VIII), but a new material was obtained. The pale yellow crystalline product, isolated in 62% yield, possessed the expected composition for a dehydrogenated material, but it showed no carbonyl absorption in the infrared. However, there were four bands of medium intensity in the 1650–1550 cm.$^{-1}$ region, indicating conjugated olefinic bonds, and there was a strong band at 3400 cm.$^{-1}$, characteristic of hydroxyl groups. Also, in the ultraviolet, there was a maximum at 322 mμ with an intensity of 16,300, indicating a conjugated triene system. On the basis of these data, the reaction product was assigned the structure of B-nor-2,4,6-cholestatriene-3,6-diol (IXa) or the 1,3,5-triene isomer (IXb). It has not been possible to establish the fact that no skeletal rearrangement has taken place, since when IX was allowed to react with zinc and glacial acetic acid no crystalline product could be obtained. In line with this structural assignment,


VII


VIII


X


IXa


IXb

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(1) General Electric Company Fellow in Chemistry, 1958–1959.

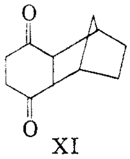
(2) A. Windaus, *Z. physiol. Chem.*, **117**, 146 (1921).

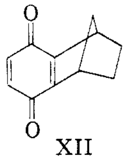
(3) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 3111 (1953).

(4) D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight, *J. Chem. Soc.*, 876 (1955).

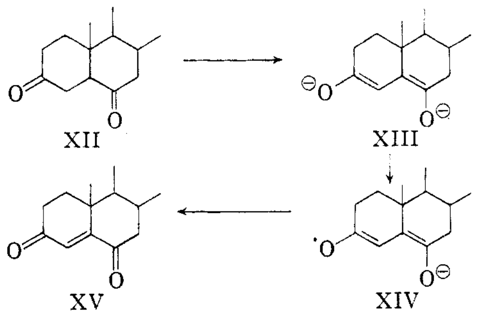
however, was the finding that when a sample of authentic B-nor-4-cholestene-3,6-dione (VIII) was allowed to stand in alkali, the same trienediol IX was obtained in 64% yield. Also, Rull and Ourisson[5] have reported that when B-nor-4-androstene-3,6-dione was passed through alumina, the material was transformed into an isomeric compound which possessed an ultraviolet spectrum similar to that reported above for IX. These workers postulated a dienone structure X for their material. Upon being informed of our results, they examined the infrared spectrum of their material and found no carbonyl absorption and now agree with our postulated trienediol structure.[6] In line with their work, when a solution of VIII was passed through a column of Woelm basic alumina, IX was isolated.

The generality of the base catalyzed autoxidation of a 1,4-dione to an enedione has not been widely examined but one nonsteroid case has been studied. When the dione XI[7] was subjected to the usual reaction conditions, the compound underwent dehydrogenation to yield the related quinone XII in 20% yield.

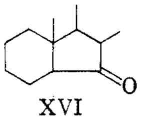

XI


XII

Finally some information with regard to the mechanism of the reaction has been obtained. First, it was found that when oxygen was excluded, no reaction occurred. Second, if the base concentration were sufficiently low (~0.02N), the rate of reaction was slow and starting material was recovered after twenty-four hours. Under identical conditions, but using 0.5N potassium hydroxide, the dehydrogenation was complete in two hours. Third, in the A-nor case, if the blue solution were flushed free of air with nitrogen, the color remained for many weeks. These data strongly suggest a mechanism similar to that postulated by Michaelis[8] for the autoxidation of hydroquinone and which involves an anion radical intermediate. Thus, in the presence of base the diketone XII is converted to the dienolate ion XIII which reacts with oxygen to generate the blue colored anion radical XIV. Finally, XIV is oxidized further to the enedione XV.



During the course of this work, the reduction of steroidal enediones with zinc and acetic acid was studied. Recently, McKenna, Norymberski, and Stubbs[9] reported that the water content of the acetic acid had an effect on such reductions. In the present study, it was found that when 4-cholestene-3,6-dione (VI) was reduced at 100° or at reflux temperature with zinc in 90% acetic acid, random reduction of the carbonyl groups as well as the reduction of the double bond occurred. In contrast, the saturated dione (V) was obtained in high yield when the reduction was conducted in glacial acetic acid at 100°. When B-nor-4-cholestene-3,6-dione (VIII) was reduced in glacial acetic acid at 100°, B-norcoprostane-6-one (XVI) was obtained. When the reaction was conducted at room temperature, following the procedure of McKenna, *et al.*,[9] the saturated 3,6-dione (VII) was formed. Recently, Schaefer[10] has found that amalgamated tin in ethanolic hydrochloric acid is an excellent reagent for the reduction of enediones. When this method was used in the B-nor series, an almost quantitative yield of the saturated dione could be isolated directly from the reaction mixture.


XVI

EXPERIMENTAL[11]

A-Nor-3(5)-cholestene-2,6-dione (II). A solution of 90 mg. (0.23 mmole) of A-norcoprostane-2,6-dione (I)[2] in 25 ml. of 0.5N methanolic potassium hydroxide was warmed in a waterbath for 5 min. The solution immediately developed a deep blue color. Upon standing overnight at room temperature, the color changed from blue to yellow-orange. The solution was diluted with water and extracted with ether. The ethereal solution was dried, the solvent evaporated, and the residue chromatographed on alumina (Act. III). Elution with petroleum ether (b.p. 30–60°)-benzene (1:1) gave 35 mg. (39%) of crystalline enedione (II), m.p. 149–152°. Recrystallization of the product from ethanol yielded A-nor-3(5)-cholestene-2,6-dione in colorless blades, m.p. 154–155°, $[\alpha]^{25}_{D}$ $-6°$ (Chf), $\lambda_{max}^{ethanol}$ 244 mμ (ϵ 10,500), $\nu_{max}^{CS_2}$ 1700, 1708 cm^{-1}.

Anal. Calcd. for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 80.75; H, 10.36.

Using 0.5N ethanolic potassium hydroxide, 150 mg. of anedione yielded 75 mg. (50%) of enedione.

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[5] T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1581 (1958).

[6] Private communication, G. Ourisson.

[7] Kindly supplied by Professor G. Wiley.

[8] L. Michaelis, *Chem. Revs.*, **16**, 243 (1935); C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, (1957), p. 457.

[9] J. McKenna, J. K. Norymberski, and R. D. Stubbs, *J. Chem. Soc.*, 2502 (1959).

[10] J. P. Schaefer, *J. Org. Chem.*, in press..

[11] Analyses by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

Reduction of 75 mg. of enedione II with 2 g. of zinc dust in 25 ml. of acetic acid followed by chromatography over alumina and recrystallization of the product from petroleum ether (b.p. 30–60°) yielded 55 mg. (73%) of A-norcoprostane-2,6-dione, m.p. 148–149°, identical in melting point and spectrum with authentic sample.

4-Cholestene-3,6-dione (VI). A solution of 1.0 g. (2.5 mmoles) of cholestane-3,6-dione[12] in 100 ml. of 1*N* ethanolic potassium hydroxide was warmed for 5 min. in a water bath. The color of the solution turned from colorless to yellow and then to green. The solution was allowed to stand at room temperature for 8 hr. during which time the solution turned bright red. The solution was diluted with water and extracted with ether. The ethereal extract was washed with cold 5% potassium hydroxide solution, water, dilute hydrochloric acid, water, and then saturated salt solution. Upon evaporation of the solvent there was obtained 768 mg. (77%) of semicrystalline yellow material which was chromatographed on 21 g. of alumina (Act. III). Elution with petroleum ether (b.p. 30–60°)-benzene (1:1) yielded 407 mg. (41%) of pale yellow crystals, m.p. 115–120°, which after recrystallization from methanol gave 4-cholestene-3,6-dione as pale yellow leaflets, m.p. 124–125°, $[\alpha]^{20}_{D}$ −38° (Chf), λ^{Chf}_{max} 252 mμ (11,600), $\nu^{CS_2}_{max}$ 1685 cm.$^{-1}$, identical in melting point and spectra with an authentic sample.[10]

B-Nor-2,4,6-cholestatriene-3,6 diol (IX). A solution of 600 mg. (1.55 mmoles) of B-norcoprostane-3,6-dione,[13] 2.8 g. of potassium hydroxide, and 50 ml. of ethanol was heated for a few minutes to effect solution. The color of the solution became yellow, then green; after standing at room temperature for 2 hr., the color was red. The solution was diluted with water and extracted with ether. The ether extracts were washed with 5% potassium hydroxide solution, then washed with water and dried. The solvent was evaporated and there was obtained 425 mg. (62%) of pale yellow crystalline material. The residue was recrystallized from ethanol to yield 400 mg. (68%) of pale yellow leaflets of B-nor-2,4,6-cholestatriene-3,6-diol, m.p. 220–225° (dec., sealed cap.), λ^{Chf}_{max} 322 mμ (16,300).

Anal. Calcd. for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 81.25; H, 11.20.

When a solution of 107 mg. (0.285 mmole) of B-nor-4-cholestene-3,6-dione,[14] 1.0 g. of potassium hydroxide, and 25 ml. of ethanol was allowed to stand at room temperature for 12 hr., there was obtained, from the neutral fraction, 80 mg. (64%) of a pale yellow solid. Recrystallization of this material from ethanol yielded pale yellow leaflets of IX, identical in all respects with that prepared above.

Autoxidation of dione XI. To a solution of 200 mg. (1.1 mmoles) of dione XI[7] (m.p. 240°, ν_{max} 1710 cm.$^{-1}$) in 100 ml. of hot ethanol, there was added, with vigorous stirring, 50 mg. of potassium hydroxide. The solution turned dark red and after 2 hr. 0.5 g. of potassium hydroxide was added. The stirring was continued for a short period and the black solution was diluted with water and acidified with dilute hydrochloric acid. The mixture was extracted with ether and after evaporation of the solvent the residual dark oil was chromatographed on alumina. Elution with benzene yielded 40 mg. of the quinone XII, m.p. 125°. The ultraviolet and infrared spectra were identical with those of the authentic material.[7]

Reduction of 4-cholestene-3,6-dione (VI) *with zinc and acetic acid.* (a) *At reflux temperature.* A solution of 100 mg. (0.25 mmole) of enedione VI in 25 ml. of 90% acetic acid was refluxed with 5.0 g. of zinc dust for 4 hr. The solution was filtered, poured into water, and the aqueous suspension extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate solution and water, dried, and the solvent evaporated. The residual colorless oil crystallized as white needles (70 mg.), m.p. 74–75°. After two recrystallizations from methanol the product melts at 86–88°, ν_{max} 1700 cm.$^{-1}$

Cholestan-3-one melts at 172° and cholestane-6-one melts at 129°.

(*b*) *At 100°.* The above experiment was repeated except that the mixture was heated on a steam bath for 2 hr. The crude product melted at 72–73°.

(*c*) *With glacial acetic acid at 100°.* A solution of 50 mg. (0.13 mmole) of enedione VI in 25 ml. of glacial acetic acid was heated on a steam bath with 2.5 g. of zinc dust. Effervescence was vigorous at first but by the end of 1 hr. it had almost stopped. After 90 min. the reaction mixture was processed as before and the crude product melted at 110–120°. Two recrystallizations from ethanol yielded 45 mg. (90%) of white needles, m.p. 155–160°, the infrared spectrum of which was almost identical with authentic cholestane-3,6-dione.

Reduction of B-nor-4-cholestene-3,6-dione (VIII) *with zinc and acetic acid.* (*a*) *With 100% acetic acid at 100°.* A solution of 43 mg. (0.11 mmole) of enedione VIII in 12.5 ml. of glacial acetic acid containing 2 drops of acetic anhydride was heated with 2 g. of zinc dust on the steam-bath for 2.5 hr. The reaction mixture was processed as above and the resulting oil crystallized upon trituration with methanol. The white needles (24 mg.) melts at 98–100°, $[\alpha]_D$ +37° and were identical with an authentic sample of B-norcoprostane-6-one.

(*b*) *At room temperature.* To a solution of 100 mg. (0.26 mmole) of enedione VIII in 50 ml. of glacial acetic acid there was added 1.7 g. of zinc dust in four equal portions at 15-min. intervals. The mixture was shaken continuously during the additions and the shaking was continued for an additional 45 min. after the final addition of zinc. The entire procedure was conducted at room temperature. The mixture was filtered, the filtrate almost neutralized with 3*N* sodium hydroxide and then extracted with ether. The ethereal extract was washed with water, dried, the solvent evaporated, and the residue chromatographed on 5 g. of basic alumina (activity III). Elution with benzene gave white needles (50 mg.), m.p. 110–111° (from methanol), which were identified as B-norcoprostane-3,6-dione by mixed melting point and infrared spectra comparison.

Reduction of B-nor-4-cholestene 3,6 dione with tin and ethanolic hydrochloric acid. A solution of 85 mg. (0.22 mmole) of enedione VIII in 10 ml. of ethanol containing 0.1 ml. of concd. hydrochloric acid was refluxed with 1 g. of amalgamated tin and a few crystals of mercuric chloride for 30 min. The mixture was filtered, poured into water, and extracted with ether. After removal of the solvent the residue crystallized spontaneously and the pale yellow needles (80 mg.) melted from 107–110° and were identical with B-norcoprostane-3,6-dione.

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(12) V. H. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 677 (1938); W. C. J. Ross, *J. Chem. Soc.*, 737 (1946).

(13) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

(14) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956).