ethylamine. The mother liquors from the recrystallization of XI were left at 0° for 2 weeks. White crystals of XIII separated (17 mg., 3%), m.p. 222–223°, mixture melting point with XI 206–214° dec.

Anal. Calcd. for $C_{11}H_{18}N_2O_7$: C, 45.51; H, 6.25; N, 9.65; OCH_3, 19.26. Found: C, 45.47; H, 6.14; N, 9.72; OCH_3, 19.40.

Actinamine Bisurethane Tetraacetate (XII).—Actinamine bisurethane (XI) (30 mg.) was acetylated by the sodium acetate method. No product separated on pouring the reaction mixture into water, so the aqueous solution was extracted with chloroform. Evaporation of the dried extract produced an oily solid. This was dissolved in 3:1 petroleum ether–chloroform and chromatographed on Woelm activity III alumina (2 g.). Successive elution with 3:1, 2:1, and 1:1 petroleum ether–chloroform mixtures gave a separation. The material from the 2:1 fractions was recrystallized from methanol to yield pure XII (15 mg., 33%) m.p. 202–203°.

Anal. Calcd. for $C_{20}H_{30}N_2O_{12}$: C, 48.97; H, 6.17; N, 5.71. Found: C, 49.05; H, 6.29; N, 5.65.

Treatment of I with Phosgene.—Compound I (2.403 g., 11.6 mmoles) was dissolved in aqueous sodium carbonate (2.768 g. Na_2CO_3, 22.3 mmoles, in 25 ml. of water).[18] The mixture was cooled externally to 0° in a 100-ml. standard taper joint three-neck flask equipped with mechanical stirrer, Dry Ice–acetone condenser, and soda lime trap. The cold mixture was stirred vigorously and phosgene was introduced slowly over a period of 1 hr., when the reaction mixture had pH ~ 7. After several hours at 0° the products were isolated. (i) The white crystalline deposit of XIV (0.109 g., 0.37 mmole, 3.2%) was filtered off. After recrystallization from aqueous methanol it lost water at 120–140°, darkened at 230°, and melted at 290–291° dec. (0.052 g., 48% recovery).

Anal. Calcd. for $C_{10}H_{14}N_2O_6 \cdot 2H_2O$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.84; H, 6.10; N, 9.29.

Acetylation of XIV (65 mg.) by the sodium acetate method produced crude brown crystals (73 mg. 97%). Recrystallization from 1:1 methanol–chloroform with Norit treatment produced white crystals of XV (40 mg.), m.p. >315°.

Anal. Calcd. for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.81; H, 5.28; N, 7.99.

Treatment of XV (25 mg.) with sodium methoxide[25] regenerated XIV (15 mg., 66%) identical in infrared spectrum and giving no mixture melting point depression with authentic XIV. (ii) The filtrate from the phosgene reaction was evaporated to dryness *in vacuo*. The solid residue was acetylated by the sodium acetate method. The resulting solution was concentrated to 10 ml. and water (10 ml.) was then added. Cooling to 0° produced brown crystals (0.668 g., 1.95 mmoles, 17%) which were recrystallized from 1:1 methanol–chloroform with Norit treatment to give small white crystals of XVII (0.423 g.), m.p. 255–256°.

Anal. Calcd. for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.13; H, 5.59; N, 7.93.

(iii) Compound XVII (0.423 g.) was dissolved in 1:1 methanol–chloroform and treated with 0.1 *N* sodium methoxide (0.5 ml.) overnight.[25] Removal of solvents left a colorless sticky solid which crystallized on trituration with methanol. Recrystallization from hot methanol gave colorless crystals of XVI (0.235 g., 0.91 mmole, 74%), m.p. 226–227°.

Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.56; H, 5.67; N, 10.71.

Acetylation of XVI (28 mg.) by the sodium acetate method produced XVII (19 mg., 55%) after recrystallization, no mixture melting point depression and identical in infrared spectrum with authentic XVII. (iv) Neutralization of the filtrate from the separation of XVII in (ii) with solid sodium bicarbonate caused the precipitation of crude II (1.643 g., 3.58 mmoles, 31%). Two recrystallizations from aqueous methanol gave pure II, identified by mixture melting point and infrared spectrum. Extraction of the mother liquors of the neutral aqueous solution with three 25-ml. portions of chloroform produced a further 1.207 g. (23%) of impure material of low melting point which appeared to be mostly II from inspection of its infrared spectrum.

Acknowledgment.—The authors are indebted to Abbott Laboratories, North Chicago, Illinois, for supplies of actinospectacin. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. We also wish to thank Dr. D. D. Chapman for many useful discussions.

Cleavage *vs.* Beckmann Rearrangement in α-Oximino Ketones[1]

ALFRED HASSNER, W. A. WENTWORTH, AND I. H. POMERANTZ

Department of Chemistry, University of Colorado, Boulder, Colorado

Received August 13, 1962

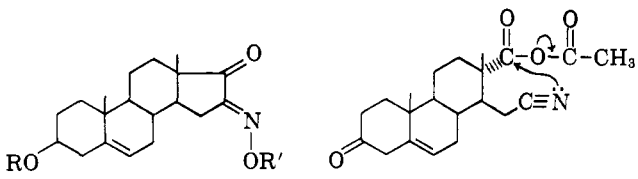
Certain cyclic α-oximino ketones under Beckmann rearrangement conditions yield the expected rearrangement products (imides), but it can be shown that the reaction proceeds first by cleavage followed by ring closure to the imides.

In a previous study[2] we have demonstrated that esters of steroidal α-oximino ketones—*e.g.*, III—undergo facile cleavage with water or alcohols rather than Beckmann rearrangement. Yet the reaction of the corresponding free oxime *anti*-16-oximino-5-androsten-3β-ol-17-one (I) with boiling acetic acid acetic anhydride gave to our surprise mainly imide VIII, a Beckmann rearrangement product. The first step in this reaction is obviously the acylation of I to III and indeed it could be shown that oxime acetate III also was converted to imide VIII under the conditions of the reaction or simply by heating with acetic acid. Based on previous findings[2] we suspected that the oxime acetate III would be cleaved by acetic acid to the mixed anhydride IV which, like the corresponding acid chloride,[2] could then cyclize, possibly *via* V, to imide VIII. When 3β-acetoxy-16-acetoximino-5-androsten-17-one (III) was heated under reflux with acetic acid for a short period of time (one hour) or at a lower temperature (50°) nitrile acid VII was formed in excellent yield but none of the anhydride IV was isolated. Under milder conditions or upon treatment with sodium acetate or propionate in polar solvents, III was recovered unchanged. It was soon established that authentic anhydride IV was much more easily converted by acetic acid to acid VII than was oxime acetate III, and therefore efforts to isolate IV from the reaction of III with acetic acid were doomed to failure.

With the evidence at hand that 3β-acetoxy-5-androstene-16,17-seco-16-nitrile-17-oic acid (VII) may be an intermediate in the conversion of I to VIII, it remained to be established that VII could ring close to imide VIII by heating with acetic acid under reflux. Indeed, heating of oxime acetate III or of nitrile acid VII in acetic acid for twenty-four hours gave an identical product consisting mainly of imide VIII and some 3β-ace-

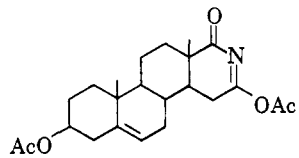
(1) Presented in part before the National Meeting of the American Association for the Advancement of Science, Denver, Colo., December, 1961.

(2) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).

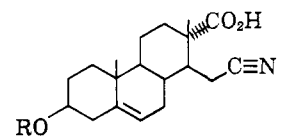


I. R = H, R′ = H
II. R = Ac, R′ = H
III. R = Ac, R′ = Ac

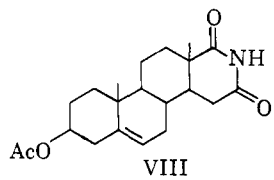
IV



V

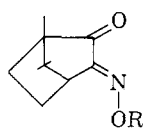


VI. R = H
VII. R = Ac

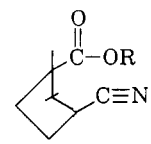


VIII

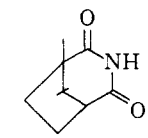
toxy-5-androstene-16,17-seco-16,17-dioic acid. Heating of III or VI, in acetic acid for one hour yielded VII or VI, respectively. Thus, it appears that cleavage of oxime acetate III to nitrile acid VII, *via* anhydride IV, precedes the formation of the Beckmann rearrangement product VIII. It is possible that an intermediate of type V is involved in the ring closure of VII to VIII. α-Camphornitrilic acid (XI), in which there is a sterically less favorable arrangement for ring closure than in VII, does not undergo ring closure to camphorimide (XIV) on refluxing with acetic acid; instead, camphoric anhydride is isolated in addition to unreacted XI. Since camphorimide (XIV) is not affected by hot acetic acid, camphoric anhydride must result from hydrolysis of nitrile XI by acetic acid. Similarly, the steroidal nitrile acid VII is in part hydrolyzed to the corresponding diacid, yet it is unusually stable[2] to basic hydrolysis.



IX. R = H
X. R = Ac



XI. R = H
XII. R = Ac



XIV

Heating of α-camphornitrilic acid XI with acetic acid–acetic anhydride does bring about ring closure to camphorimide XIV; a small amount of camphoric anhydride was also formed. Sulfuric acid likewise is effective in the cyclization of XI to XIV.[3] We felt that the effect of acetic anhydride in promoting ring closure of XI to XIV may be attributed to the formation of an intermediate, analogous to IV which could cyclize. An intermediate mixed anhydride XII was indeed isolated, except that unlike in the steroid case, it was easily converted to XIII, the dimeric anhydride of XI.

(3) W. Nagata and K. Takeda, *J. Pharm. Soc. Japan*, **72**, 1566 (1952); for a good English summary of the article see K. N. Carter, *J. Org. Chem.*, **23**, 1409 (1958).

In analogy with the steroidal oxime I, we were able to acylate *anti*-α-oximinocamphor IX to its acetate X. Both IX and X are converted by refluxing acetic acid-acetic anhydride into camphorimide XIV. Under milder conditions, or in the presence of water oxime acetate X is easily cleaved to α-camphornitrilic acid XI. Similarly, with cold concentrated sulfuric acid oxime IX is converted to acid XI and under the influence of heat to imide XIV.[3]

An earlier report[4] that oxime II undergoes Beckmann rearrangement with thionyl chloride to yield imide VIII has been shown to be incorrect, because of the mistaken identity of the starting material which had actually been nitrile acid VII rather than oxime II.[2] When the actual oxime II, prepared by selective hydrolysis of oxime acetate III, was treated with thionyl chloride at room temperature, the product isolated after digestion with methanol proved to be the methyl ester of VII. Thus, the cleavage reaction definitely predominates over Beckmann rearrangement in these α-oximino ketones,[5] although subsequent ring closure to Beckmann rearrangement products can take place.

Experimental

Melting points were taken on a Fisher melting block and are uncorrected. Analyses were performed by Pascher Laboratories, Bonn, Germany. Infrared spectra were run in potassium bromide pellets; ultraviolet spectra in methanol solution. The glacial acetic acid employed had been refluxed with and distilled from triacetyl borate.

Conversion of 16-Oximino-5-androsten-3β-ol-17-one (I) to Imide VIII.—A solution of 400 mg. of oximino ketone I,[2] m.p. 253–256°, in 10 ml. of glacial acetic acid and 15 ml. of acetic anhydride was refluxed for 18 hr. The residue, obtained upon evaporation of the solvents under reduced pressure, was washed with petroleum ether, then with water and was finally crystallized from 95% ethanol to furnish 150 mg. of 3β-acetoxy-5-androstene-16,17-seco-16,17-dioic acid imide (VIII), m.p. 251–254°, identical to authentic material.[2]

Reactions of 3β-Acetoxy-16-acetoximino-5-androsten-17-one (III).—3β-Acetoxy-16-acetoximino-5-androsten-17-one (III), m.p. 171–173°, was prepared by acetylation of I.[2] A solution of 0.1 g. of III in 10 ml. of glacial acetic acid protected from moisture by a calcium chloride tube was heated under reflux for 18 or for 24 hr. in the dark. Evaporation of the solvent under reduced pressure yielded crude imide (VIII) identified by its infrared spectrum. Crystallization from methanol gave 30 mg. of pure imide VIII, m.p. 259–261°. The mother liquor from crystallization of VIII was evaporated to dryness and the residue was extracted with 5% sodium carbonate solution. The carbonate insoluble residue furnished 20 mg. of imide VIII. Upon acidification of the carbonate extract 10 mg. of a white solid, m.p. 238–241°, was obtained. Infrared comparison identified the material as crude 3β-acetoxy-16,17-seco-5-androstene-16,17-dioic acid.[2]

Heating of acetoxime III in glacial acetic acid under reflux for only 1 hr. or at 50° for 20 hr. led to nitrile acid VII, identified by infrared and mixed melting point experiments with authentic[2] sample.

Under the following conditions acetoxime III was recovered unchanged; sometimes a trace of nitrile acid VII was also formed, as detected by infrared: at room temperature with 4 equivalents of glacial acetic acid in anhydrous pyridine, at room temperature with excess sodium acetate or potassium propionate in acetonitrile, with acetic anhydride at 50° for 24 hr., with 1 equivalent of glacial acetic acid in refluxing acetonitrile for 12 hr.

On heating of acetoxime III in dry benzene for 12 hr. under reflux, followed by evaporation of the solvent and reheating the residue for 90 min. at 140–145°, a product melting at 92–105° is obtained, the infrared of which indicates it to be impure an-

(4) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, **78**, 639 (1956).

(5) For other examples of predominance of the cleavage reaction, see R. K. Hill, *J. Org. Chem.*, **27**, 29 (1962).

hydride IV. The product could not be further purified by crystallization.

Reaction of 3β-Acetoxy-16,17-seco-5-androstene-16-nitrile-17-oic Ethanoic Anhydride (IV).—A solution of 50 mg. of mixed anhydride IV, prepared from nitrile acid as previously described,[2] in 5 ml. of glacial acetic acid was allowed to stand at room temperature for 2 hr. or for 24 hr. Work-up with cold water or with 3 *N* hydrochloric acid gave 3β-acetoxy-16,17-seco-5-androstene-16-nitrile-17-oic acid (VII), m.p. 179–183°,[2] in 70–80% yield. Refluxing with acetic acid for 17 hr. converts IV to imide VII.

Reaction of 3β-Hydroxy-16,17-seco-5-androstene-16-nitrile-17-oic Acid (VI).—Alkaline hydrolysis of acetoxime III, as previously described,[2] led to nitrile acid VI, m.p. 182–186°, which was used without further purification. A solution of 100 mg. of VI in 10 ml. of glacial acetic acid was refluxed for 24 hr. Evaporation of solvent left a residue that was identical (by infrared) to that obtained from heating of acetoxime III with acetic acid. Work-up, as described under reaction of III, furnished 50 mg. of imide VIII and 25 mg. of 3β-acetoxy-16,17-seco-5-androstene-16,17-dioic acid. Evidently acetylation of the 3-hydroxy function had occurred during the reaction. When the heating time was reduced to 1 hr., nitrile acid VI was isolated unchanged.

3β-Acetoxy-16,17-seco-5-androstene-16,17-dioic acid imide (VIII) was recovered unchanged (90%) upon refluxing for 24 hr. in glacial acetic acid; the diacid obtained from III or VI is therefore not an artifact resulting from imide VIII.

3β-Acetoxy-16-oximino-5-androsten-17-one (II).—This oxime is best prepared by dissolving acetoxime III (0.54 g.) in 3 ml. of anhydrous morpholine and after 5–10 min. pouring the solution into ice with stirring. The resulting mixture was at a pH of 10.7. The solid was collected by filtration, washed with water, and dried (0.49 g.). Crystallization from ether furnished 0.25 g. of oxime II, m.p. 238–242° dec.; lit.,[2] m.p. 221.5–222.5°. This oxime has an identical infrared spectrum as does II, m.p. 221–222° previously reported.[2]

Anal. Calcd. for $C_{21}H_{25}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.11; H, 7.90; N, 4.04.

Reaction of Oxime II with Thionyl Chloride.—3β-Acetoxy-16-oximino-5-androsten-17-one (II) (0.2 g.) was treated with excess thionyl chloride at room temperature for 1 hr. Excess thionyl chloride was removed under reduced pressure and the residue was dissolved in methanol. Addition of water precipitated methyl 3β-acetoxy-16,17-seco-5-androstene-16-nitrile-17-oate, m.p. 173–175°, identical by infrared and melting point to authentic material.[2]

***trans*-α-Oximinocamphor (IX). A. From *d*-Camphor.**—*d*-Camphor was transformed into its sodium derivative by treatment with sodium amide in dry benzene or with sodium in ether. Excess isoamyl nitrite was added and after 1 day the mixture was poured into ice–water and the aqueous layer was acidified with acetic acid. Crude α-oximinocamphor was obtained in 40–55% yield. Repeated crystallization from water and from petroleum ether (b.p. 90–100°) gave pure *trans*-*d*-oxime IX, m.p. 155–157° (lit.,[6] m.p. 152–153°); λ_{max} 240 mμ (ε 9270), on addition of dilute potassium hydroxide: λ_{max} 298 mμ (ε 12,500); ν_{max} 3440, 1735, and 1640 cm.$^{-1}$.

B. From *d,l*-Camphor.—*trans*-*d,l*-α-Oximinocamphor (IX) was prepared from *d,l*-camphor as described for the *d*-isomer. It melted at 131–133°, purified by recrystallizations from water or by chromatography over neutral alumina; ν_{max} 3440, 1735, and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.06; H, 8.08; N, 7.60.

***d,l*-α-Acetoximinocamphor (X).**—Acetylation of *d,l*-α-oximinocamphor (IX), m.p. 125–130°, with acetic anhydride at room temperature overnight gave acetoxime X in 40% yield, m.p. 91–92° upon crystallization from benzene–petroleum ether (b.p. 90–100°); λ_{max} 233 mμ (ε 9150); ν_{max} 1780, 1745, and 1645 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.38; H, 7.89; N, 6.24.

Treatment of acetoxime X with dilute sodium hydroxide or warming with aqueous solvents brings about conversion to *d,l*-α-camphornitrilic acid XI, m.p. 155–157°; ν_{max} 2650 (broad), 2240, 1690 cm.$^{-1}$.

Reaction of α-Camphornitrilic Acid (XI).—*d*-α-Camphornitrilic acid (XI), m.p. 152–154° (lit.,[3] m.p. 150–151°), ν_{max} 2650 (broad), 2240, 1700 cm^{-1}, was obtained from IX by acetylation and subsequent treatment with base. Heating under reflux of a solution of 0.1 g. of XI in 5 ml. each of acetic acid and acetic anhydride for 24 hr. yielded upon removal of solvent and usual work-up *d*-camphorimide (XIV), m.p. 238–241° (lit.,[3] m.p. 242–244°); ν_{max} 3200, 1725, and 1685 cm.$^{-1}$. A trace of *d*-camphoric anhydride was also detected by infrared.

When nitrile acid XI was refluxed for 22 hr. in excess glacial acetic acid 20% of XI was recovered unchanged together with camphoric anhydride, m.p. 220–224° (lit., m.p. 221°). The acid XI was separated from camphoric anhydride by extraction at 0° with 2% potassium carbonate solution.

Conversion of *d,l*-α-Oximinocamphor (IX) to *d,l*-Camphorimide (XIV).—A solution of 1 g. of IX in 2.5 ml. each of acetic acid and acetic anhydride was refluxed for 17 hr. The reaction mixture was treated with ice–water, made basic, and saturated with carbon dioxide. Extraction with ether and evaporation gave crude camphorimide which upon crystallization from water gave *d,l*-camphorimide (XIV), m.p. 243–245° (lit.,[7] m.p. 249°) in 47% yield. The aqueous mother liquor from crystallization of XIV was acidified and extracted with ether. Upon evaporation of the ether the residue was extracted with boiling benzene; *d,l*-camphoric acid, m.p. 211–212° (lit.,[8] m.p. 208°) was left undissolved (40 mg.).

Camphorimide XIV is recovered unchanged on heating with acetic acid for 20 hr.

***d*-α-Camphornitrilic Anhydride (XIII).**—The anhydride of *d*-α-camphornitrilic acid (XI) was prepared as follows: A solution of 0.2 g. of acid XI, 4 ml. of acetic anhydride, and 4 drops of pyridine was allowed to stand for 21 hr. The residue from evaporation of the solvents was crystallized from acetone and petroleum ether (b.p. 90–100°) to give 0.11 g. of crude anhydride. Two recrystallizations from the same solvents raised the melting point to 149.5–151.5°; ν_{max} 2250, 1810, and 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_3N_2$: C, 69.74; H, 8.19; N, 8.13; O, 13.94. Found: C, 70.30; H, 8.12; N, 8.14; O, 13.61.

Reaction of Camphornitrilic Anhydride (XIII).—Refluxing of a solution of 50 mg. of the anhydride for 18 hr. in 5 ml. of acetic acid and evaporation afforded nitrile acid XI and camphoric anhydride as described for reaction of nitrile acid XI.

Mixed *d*-α-Camphornitrilic Acetic Anhydride (XII).—*d*-α-Camphornitrilic acid (XI) (0.4 g.) was dissolved in 5 ml. of acetic anhydride containing 2 drops of pyridine and after 10 min. the solution was poured into ice-cold dilute hydrochloric acid. The solid obtained by filtration (0.16 g.) was twice crystallized from *n*-hexane to afford the mixed anhydride XII, m.p. 58–60°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.59; H, 7.63; N, 6.17.

Acknowledgment.—We are indebted to the National Institutes of Health (grant CY-4474) and to the Council on Research, University of Colorado, for financial support of this work.

(6) M. O. Forster, *J. Chem. Soc.*, **83**, 535 (1903).

(7) W. A. Noyes and P. C. Warren, *Am. Chem. J.*, **28**, 484 (1902).

(8) A. Debierne, *Compt. rend.*, **128**, 1112 (1899).