hydrogen (6β-hydroxyl) and the 17α-hydrogen (17β-acetoxyl). A peak for a 17α-hydrogen (17β-hydroxyl) which should have appeared at 6.35 was not present.

6β,17β-Dihydroxy-1,4-androstadien-3-one.—17β-Acetoxy-6β-hydroxy-1,4-androstadien-3-one, 3.0 g., was mixed with 1/3 l. of methanol and twelve pellets of sodium hydroxide. The mixture was stirred until homogeneous. After 18 hr. the base was neutralized with acetic acid and the solution was concentrated to dryness. Water and methylene chloride were added to the residue and the mixture was filtered. The solid was crystallized from methylene chloride–acetone to give 6β,17β-dihydroxy-1,4-androstadien-3-one, 2.1 g., with the following properties: m.p. 194–195°, $\lambda_{max}^{CH_3OH}$ 246 mμ ε 16,300, [α]D 21 ± 2° (methanol).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.22; H, 8.56.

4-Androstene-3,12-,17-trione.—12α-Hydroxy-4-androstene-3,17-dione,[13] 0.20 g., in acetone was oxidized with chromium trioxide-sulfuric acid solution by the method of Jones and Djerassi.[26] The product was crystallized from acetone–ether to give 4-androstene-3,12,17-trione, 0.10 g., m.p. 212.5–214°.

Hydroxylation of Testololactone.—The steroid, 6.5 g., was fermented with *Penicillium* sp., A.T.C.C. 12,556, under conditions similar to those described for the fermentation of 16α,17α-epoxyprogesterone.

The methylene chloride solution was filtered and evaporated. The residue was dissolved in benzene and chromatographed on silica gel.

From the later fractions of 30% ethyl acetate in benzene, 2β-hydroxy-testololactone was obtained. After the material was crystallized twice from acetone-ether it weighed 0.33 g. and had the following properties: m.p. 180–182°, $\lambda_{max}^{CH_3OH}$ 240.5 mμ ε 14,750, [α]D −182 ± 2°, ΔMD (2βOH − 2βH) = −706°.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.56; H, 8.31.

(26) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Glutarimide Antibiotics. I. The Synthesis of Actiphenol

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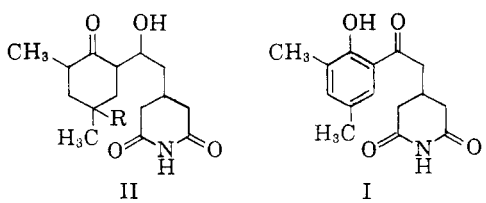
A synthesis of actiphenol is described.

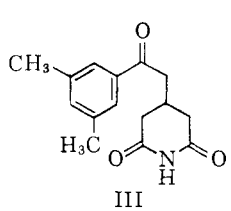
As part of a program aimed at the synthesis of naturally occurring glutarimide compounds we report in this paper a synthesis of actiphenol (I). This substance, which to date is the simplest member of this class of compounds, was first isolated and characterized by Prelog and Highet.[1] They effected its partial synthesis in minute yield by the aromatization of the cyclohexane ring of cycloheximide (II, R=H) with N-bromosuccinimide.

Independently, I was isolated by Rao[2] who gave it the trivial designation C-73. He also came to the same conclusion regarding its structure by relating it to a derivative (III) of E-73 (II, R=OAc). Our synthetic results confirm these findings.



II

I



III

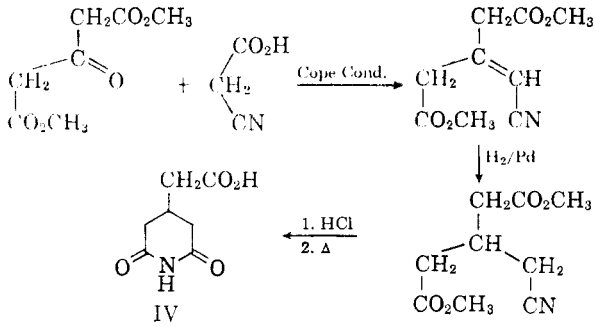
The common intermediate, 3-carboxymethylglutarimide (IV), desired for synthetic approaches to compounds of this glutarimide class has been prepared previously by Phillips, *et al.*,[3] and Lawes.[4] In our hands, however, the former procedure suffered from the capriciousness of the yield in the final cyclization step,[5] while the latter involved the preparation of the somewhat inaccessible methanetriacetic acid.[6,7]

We have found that the desired material can be prepared conveniently using the three step reaction sequence shown in Chart I.

Cope condensation[8] of dimethyl acetonedicarboxylate with cyanoacetic acid in a benzene–acetic acid medium using ammonium acetate as the catalyst afforded dimethyl 3-cyanomethyleneglutarate[9] in 54% yield. Hydrogenation of this material in ethanol over a palladium–charcoal catalyst led to 90% of the expected dimethyl 3-cyanomethylglu-

(1) R. H. Highet and V. Prelog, *Helv. Chim. Acta*, **42**, 1523 (1959).
(2) K. V. Rao, *J. Org. Chem.*, **25**, 661 (1960).
(3) D. D. Phillips, M. A. Acitelli, and J. Meinwald, *J. Am. Chem. Soc.*, **79**, 3517 (1957).
(4) B. C. Lawes, *ibid.*, **82**, 6413 (1960).
(5) M. A. Acitelli, Ph.D. thesis, Cornell University (1957).
(6) E. P. Kohler and G. H. Reid, *J. Am. Chem. Soc.*, **47**, 2803 (1925).
(7) E. C. Kornfeld, R. G. Jones, and T. V. Parke, *ibid.*, **71**, 150 (1949).
(8) A. C. Cope, C. M. Hoffman, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941).
(9) T. Okuda of the Tanabe Saiyaku Co., Tokyo, Japan, has informed us that they also have prepared this material by this method—private communication.

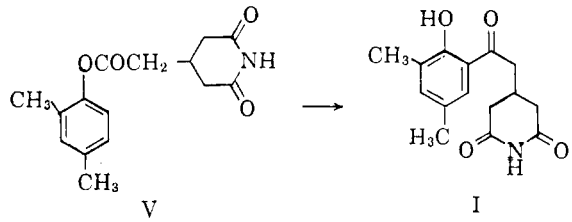
Chart I



tarate. The latter compound was refluxed with moderately strong hydrochloric acid and the resulting homogeneous solution evaporated to small bulk. The residual opaque viscous sludge was then heated slowly to 235° and held at this temperature until a clear quiescent liquid was obtained. The melt crystallized on cooling and when recrystallized from water gave an excellent yield of II. This acid was prepared by several other routes. These included (a) the fusion of 3-carboxymethylbutyrolactone with potassium cyanide followed by acid hydrolysis and heating at 230° and (b) the acid hydrolysis of triethyl α-cyanomethanetriacetate followed by heating the total products to 235°. None, however, proved as satisfactory as the method described above.

It first was thought that I might be prepared directly by the acylation of 2,4-dimethylphenol with the anhydride of II. The latter was prepared by the action of acetic anhydride on II or better by treating II with ethyl chloroformate in the presence of base followed by decomposing the mixed anhydride at 100°. However, treatment of 2,4-dimethylphenol with the anhydride at 90° in the presence of boron trifluoride etherate afforded only the ester V without further rearrangement. Attention was turned therefore to the Fries rearrangement of V. Larger quantities of the latter material were prepared by a more conventional route. Conversion of II to the corresponding acid chloride was accomplished in excellent yield by refluxing the finely powdered II with a large excess thionyl chloride for a short period, (extended refluxing times led to a considerable loss of yield). Treatment of 2,4-dimethylphenol in pyridine with the acid chloride then afforded the ester V.

Fries rearrangement of V to actiphenol proved troublesome. The use of boron trifluoride in methylene chloride, acetic acid, or nitromethane at 90°, proved to be ineffective while aluminum chloride in refluxing tetrachloroethane, nitromethane, or nitrobenzene left V unaffected or led to unidentifiable products. Subsequently it was found that the rearrangement could be carried out in 55% yield by simply heating V with an excess of finely powdered aluminum chloride for a short period at 150–160°. Above this temperature range the yield drops off rapidly while below 125° little rearrangement takes place. The product of the reaction was shown to be identical with actiphenol by a mixed melting point with an authentic specimen, (no depression). Their infrared and ultraviolet spectra were also identical. The acetates of the natural and synthetic products also showed the same congruity.



Experimental

Melting points were determined on a Fisher–Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model 4–55 as films or as Nujol mulls, while n.m.r. data were obtained from a Varian A-60 spectrometer.

Dimethyl 3-Cyanomethyleneglutaronitrile.—Cyanoacetic acid (1275 g.; 15.0 moles; crude Kay-Fries product) and dimethyl acetonedicarboxylate (1740 g.; 10 moles; Pfizer material), were added to a mixture of ammonium acetate (154 g.), acetic acid (600 ml.), and benzene (4.0 l.) in a 12-l. flask. The contents of the flask were then gently refluxed and water removed azeotropically using a water separator. After 72 hr. the reaction appeared complete and 255 ml. of water had been collected. The reaction solution was cooled, washed consecutively with water (5 l.), saturated sodium hydrogen carbonate solution (1 l.), and water (500 ml.). The wash liquids were extracted with benzene (1 l.) and the latter combined with the main organic solution. This was dried over anhydrous magnesium sulfate and, after filtration, the benzene removed by distillation. The residual liquid (1745 g.) was distilled through a fractionating column (25 cm.) at 0.35–0.45 cm. The fraction boiling at 112–132° was collected (1110 g.) and redistilled through a similar column. Pure dimethyl 3-cyanomethyleneglutarate (1069 g.) was collected at 124–127° (0.48 mm.), $n^{25}D$ 1.4700; yield 54%. The infrared spectrum of the material showed bands at 4.45, 5.75, and 6.10 μ.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.8; H, 5.6; N, 7.1. Found: C, 55.0; H, 5.6; N, 7.0.

Dimethyl 3-Cyanomethylglutarate.—Dimethyl 3-cyanomethyleneglutarate (1065 g.) was mixed with a palladium–charcoal catalyst (25 g.; 5% Pd) and hydrogen sparged through the ice-cooled reaction flask. The latter was equipped with sensitive input and output flowmeters. After 5 hr., absorption of hydrogen ceased and the catalyst was removed by filtration and washed with a little ethanol. The filtrate was distilled under reduced pressure and that fraction (963 g.; yield 89%) distilling at 131–133° (0.42 mm.) collected. A sample was distilled at the same temperature and pressure for analysis, $n^{25}D$ 1.4460. Its infrared spectrum showed absorption at 4.41 and 5.76 μ.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.3; H, 6.6; N, 7.0. Found: C, 54.4; H, 6.7; N, 7.0.

3-Carboxymethylglutarimide.—Dimethyl 3-cyanomethylglutarate (200 g.) was added to hydrochloric acid (500 ml., sp. gr. 1.2), diluted with water (200 ml.), and the mixture refluxed until homogeneous (overnight). The solution then was concentrated under reduced pressure on a steam bath until no more volatile materials could be removed. The flask containing the viscous white sludge was transferred to

an oil bath and slowly heated to 235° and maintained at this temperature until no further gases were evolved and the contents of the flask were clear and quiescent (application of a little water pump vacuum towards the end expedites complete removal of the volatiles). The melt crystallized on cooling and was recrystallized from dioxane–ethyl acetate. The resulting tan-colored crystals of 3-carboxymethylglutarimide (157 g.; yield 91%) m.p. 172–174° were purified by one further crystallization from ethanol containing 10% water. This afforded material of m.p. 176–178° (reported[3,4] m.p. 172–173°). The yield of pure 3-carboxymethylglutarimide was 143 g. (83%). Its infrared spectrum exhibited bands at 3.08, 5.80, 5.99, and 12.62 μ.

3-Glutarimidylacetic Anhydride.—(a). A solution of IV (3.4 g.) and triethylamine (2.1 g.) in tetrahydrofuran (90 ml.) was treated dropwise at −10° with ethyl chloroformate (2.2 g.) in the same solvent (10 ml.). The precipitate was removed by filtration and washed with water. The small amount of insoluble material was retained. The organic filtrate was concentrated to dryness on a steam bath and heated for 30 min. at 100°. This product and the water insoluble material from above were combined (3 g.) and recrystallized with good recovery from dioxane–heptane, m.p. 229–232°. A sample recrystallized for analysis had m.p. 232–234°. Its infrared showed absorption at 5.49, 5.76, and 5.90 μ.

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.9; H, 5.0; N, 8.6. Found: C, 52.0; H, 5.0; N, 8.9.

(b). The acid IV (0.5 g.) was refluxed with acetic anhydride (15 ml.) for 1 hr. Removal of acetic anhydride by distillation followed by crystallization of the residue from nitromethane afforded the anhydride (0.3 g.) m.p. 231–233° whose infrared spectrum was identical with that of the material from (a) above.

Crystallization from methylene chloride–ether, of the material from the mother liquors led to a small amount of a second compound, m.p. 93–94°, whose infrared and elemental analysis indicated it to be the mixed anhydride of 3-carboxymethylglutarimide and acetic acid. Its spectrum showed bands at 3.11, 3.23 (imide NH), 5.50, 5.72, 5.79, and 5.91μ.

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.7; H, 5.2. Found: C, 51.0; H, 5.1.

3-Glutarimidylacetyl Chloride.—Finely powdered 3-carboxymethylglutarimide (3.42 g.) was added to pure thionyl chloride (40 ml.). The mixture was gently refluxed until all of the acid had dissolved (30 min.) and the excess thionyl chloride then removed under reduced pressure at < 40°. The highly crystalline residue was washed with a little dry benzene to remove traces of thionyl chloride. This slightly yellow solid (3.6 g.), m.p. 136° (reported[3] 130–132°), was generally used as such in further reactions, for crystallization from acetone–petroleum ether (b.p. 30–60°) did not improve its properties. 3-Glutarimidylacetyl chloride showed absorption in the infrared at 3.15, 3.22 (imide NH), 5.48 (acid chloride), and 5.90 μ (imide carbonyl). The band in the infrared at 12.62 μ characteristic of the starting material was completely absent. The acid chloride was generally stored over phosphorus pentoxide due to its extreme sensitivity to moisture.

2,4-Xylyl 2,6-Dioxo-4-piperidineacetate (V).—(a). The acid chloride (from 5 g. of II) was dissolved in pyridine (35 ml.) and 2,4-dimethylphenol (5 g.) added in one portion. The mixture was heated on a steam bath for 2 hr., then poured into a mixture of water (250 ml.) and methylene chloride. Some unwanted black material separated at this stage and this was removed by filtration through diatomaceous earth. The organic layer in the filtrate was washed with dilute hydrochloric acid (2 *N*; 2 × 125 ml.) then water, and dried over anhydrous magnesium sulfate. Isolation of the product in the usual way followed by crystallization from methylene chloride–ether gave V (6.05 g.), m.p. 154–157°. A sample crystallized thrice for analysis had m.p. 160°. Its infrared spectrum showed absorption at 5.74, 5.82, and 5.89 μ.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.5; H, 6.0; N, 5.0.

(b). 3-Glutarimidylacetic anhydride (2.0 g.) suspended in a solution of 2,4-dimethylphenol in boron trifluoride etherate was stirred at 90° for 2.5 hr. The homogeneous solution was poured into 20% sodium acetate solution (200 ml.) and the solid precipitate (1.5 g.) removed by filtration. Crystallization of this material from methylene chloride–ether gave pure V with good recovery, m.p. 160°.

Actiphenol (I).—A flask containing the finely ground ester V (5.0 g.) intimately mixed with pulverized aluminum chloride (10 g.) was placed in an oil bath at 100° and the temperature raised to 155° in 15 min. The oil bath was held at this temperature for 2 hr., and the reaction mixture then was allowed to cool. The resulting fused mass was ground in a mortar and added to hydrochloric acid (500 ml.; 2 *N*) and methylene chloride (200 ml.). After stirring for a short period, the organic layer was removed and processed as usual. The resulting solid was recrystallized from methylene chloride–methanol to give actiphenol (2.7 g.) m.p. 196–200°. One further recrystallization gave the pure substance, m.p. 200–202°, as white fluffy needles. A mixed melting point with an authentic specimen of actiphenol showed no depression; mixed m.p. 200–203°. The synthetic material showed absorption in the infrared at 3.15, 3.25, 5.80, 5.90, and 6.09 μ, while its n.m.r. spectrum had peaks at 132 and 135 c.p.s. corresponding to two methyl groups on a benzene ring. The analogous compound 2-acetyl-4,6-dimethylphenol showed absorption at 129 and 132 c.p.s. (measurements relative to TMS at 0 c.p.s.).

Anal. Found: C, 65.5; H, 6.1; N, 5.0.

Actiphenol acetate was prepared by heating actiphenol (0.1 g.) with pyridine (2 ml.) and acetic anhydride (1 ml.) on a steam bath for 1 hr. Isolation of the product by standard procedures led to the acetate (90 mg.) m.p. 148–150°. Two recrystallizations from methylene chloride–ether afforded the pure material m.p. 155–155.5°. A mixed melting point with an authentic specimen (m.p. 155–156°) showed no depression; mixed m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{19}NO_5$: N, 4.4. Found: N, 4.4.

Acknowledgment.—The author would like to thank Professor V. Prelog and Dr. K. V. Rao who supplied samples of actiphenol and its acetate for comparison. Thanks are also due to Dr. Paul Hinkamp (Dow High Pressure Laboratory, Midland, Michigan) for running the large scale hydrogenation, to Dr. C. K. Fitz for elemental analyses, and to Mr. A. A. Carlson for technical assistance.