[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Chemistry of Ring C in α-Amyrin

BY IRVING ALLAN KAYE,[1] MARY FIESER AND LOUIS F. FIESER

RECEIVED JUNE 7, 1955

α-Amyrin and derivatives react with ozone or peracetic acid to form 12,13-oxides, which are isomerized by mild acid treatment to 12-ketones having an unstable configuration at C_{13}. More drastic acid treatment rearranges either the oxides or the unstable 12-ketones to stable 12-ketones. Various reactions of these products are described. A new method for separation of α- and β-amyrin has been developed.

The original objective of this investigation was the preparation of 3β-hydroxyursane and of ursane, the saturated dihydro derivatives of α-amyrin (3-hydroxy-Δ^{12}-ursene) and of α-amyrene (Δ^{12}-ursene). Work directed to this end was dropped when we were informed that these substances have been prepared in Ruzicka's laboratory.[2] One of the routes considered in this Laboratory involved 12-keto derivatives of ursane. According to the literature[3,4] these are prepared by acid rearrangement of "12,13-oxides," obtained from α-amyrin and derivatives by oxidation with either peracetic acid (100°) or ozone (25°). These products were formulated as oxides mainly because they are isomerized to 12-ketones in the presence of acids. We have observed, however, that the so-called "α-amyrin acetate oxide" shows a typical ketone band in the infrared ($\lambda_{max}^{CS_2}$ 5.86 μ, λ_{max}^{KBr} 5.85 μ); recently additional evidence (reduction by lithium aluminum hydride) that this "oxide" is actually a ketone has been presented by Spring.[5] The true oxides, however, can be obtained if the oxidation products are purified by crystallization without recourse to chromatography. The oxides are stable on neutral or somewhat alkaline alumina but rearrange on acid-washed alumina. The formation of oxides by ozonization of hindered double bonds is not without precedent.[6] We examined the behavior of the oxide toward reduction by lithium aluminum hydride, with the hope of determining the configuration.[7] The oxide is recovered when treated for many hours at 85° with the reagent. Under more vigorous conditions (refluxing N-ethymorpholine, 139°), the product is α-amyrin, presumably formed by dehydration of the desired alcohol.

The two ketones differ in configuration at the adjacent bridgehead position C_{13}, since both ketones are converted by treatment with acetic anhydride–sodium acetate (reflux) into the same enol diacetate, 3,12-diacetoxy-Δ^{12}-ursene.[3] Moreover two different enol diacetates were obtained when the ketones were treated with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. These must be derivatives of Δ^{11}-enols differing in configuration at C_{13}, and they are the first known derivatives of ursane containing a double bond in the 11,12-position. The Δ^{11}-enol diacetates, like the Δ^{12}-enol diacetate, are not hydrogenated (huge excess of freshly prepared prereduced PtO_2 in ethanol, 90°, 50–54 lb. pressure); but they are evidently less hindered than the Δ^{12}-enol diacetate since they add bromine readily in the absence of illumination to give isomeric bromoketones, from which hydrogen bromide is eliminated with formation, in both cases, of the known α,β-unsaturated keto acetate, 3β-acetoxy-12-keto-$\Delta^{9(11)}$-ursene.

The isomeric 12-ketones absorb at slightly different positions in the infrared. The unstable ketones absorb at 5.85 μ, whereas the stable ketones absorb at 5.93 μ. The shift to longer wave length may be indicative of greater hindrance.[8] The two ketones also differ in behavior on reduction with lithium aluminum hydride. The 13-stable 12-ketone yields a mixture of the 3β,12β- and 3β,12α-diols. The configurations at C_{12} are assigned on the basis of acetoxylation experiments. The latter diol (12-axial) forms a monoacetate under conditions which convert the former (12-equatorial) into a diacetate.[9] The unstable 12-keto acetate is reduced by the reagent to a single, different 3,12-diol; we assign the β-equatorial configuration to the 12-hydroxyl group of this diol because of its ready acylation. Spring[5] has assigned the 13α-configuration (C/D *cis*) to the unstable ketone and the 13β-configuration (C/D *trans*) to the stable ketone; but we do not feel that the evidence warrants stereochemical conclusions. Thus our three 12-hydroxy derivatives undergo ready dehydration with formation of a 12,13-double bond, even the diol, which according to Spring would have the 12β-OH, 13β-H configuration, and which should be more stable than the 12-epimer to dehydration. Consequently we prefer to refer to compounds in the unstable series as 13-isoursane derivatives.

Experimental[10]

Isolation of α-Amyrin Benzoate.—The only convenient source of α-amyrin is *Manila elemi* resin, where it is accom-

(1) On leave from Brooklyn College, Brooklyn 10, N. Y.; Research Fellow, National Institutes of Health (1953–1955).

(2) T. Lyssey, Dissertation, E. T. H., Zurich, 1955.

(3) L. Ruzicka, O. Jeger, J. Redel and E. Volli, *Helv. Chim. Acta*, **28**, 199 (1945).

(4) J. McLean, G. A. Silvertone and F. S. Spring, *J. Chem. Soc.*, 935 (1951).

(5) G. G. Allan, J. M. Beaton, J. I. Shaw, F. S. Spring, R. Stevenson, J. L. Stewart and W. S. Strachan, *Chemistry and Industry*, 281 (1955). We thank Prof. Spring and Dr. Stevenson for informing us of their results prior to publication.

(6) The acetate of methyl morolate (morolic acid = Δ^{18}-oleanolic acid) forms an oxide on ozonization. This oxide is rearranged to dienes by acid [D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951)]. Other examples are the oxide of camphene [W. J. Hickenbottom and D. G. M. Wood, *ibid.*, 1906 (1953)] and of 2,2,3,3,5,5-hexamethylhexene-3 [J. J. Backer, *Chem. Weekblad*, **36**, 214 (1939)].

(7) Oxides are reduced so that the C–OH and C–H bonds are both axial; *cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(8) *Cf.* M. Stiles, Ph.D. Thesis, Harvard University, 1953.

(9) Neither diol is identical with an "α-amyranediol" prepared by reduction of the two 13-isomeric 3β-acetoxy-12-ketoursanes with sodium and amyl alcohol [D. E. Seymour, K. S. Sharples and F. S. Spring, *J. Chem. Soc.*, 1075 (1939), and ref. 4]. We were unable to isolate a solid product on repetition of this experiment.

(10) All melting points are corrected. Higher and sharper melting points were often observed when taken in evacuated capillaries. The values reported are ranges from first sintering to complete clearing of the melt. Unless otherwise noted all rotations are recorded for chloroform solutions. Analyses by S. M. Nagy and associates.

panied by β-amyrin. Although we had no difficulty separating the bulk of the β-amyrin (as the benzoate) by the procedure of Vesterberg and Westerlind,[11] we were unable to effect complete separation of the amyrin benzoates either by crystallization or by chromatography. We then took advantage of the fact that α-amyrin benzoate is inert to oxidation with selenium dioxide, whereas β-amyrin benzoate is readily dehydrogenated to the 11,13(18)-diene. This dienyl benzoate differs sufficiently from α-amyrin benzoate so that separation is readily effected by chromatography.

In a typical run the crude amyrins (296 g.) were isolated from the resin (2 kg.) by the standard extraction with 85% ethanol–water and then converted into the benzoates (crude, 390 g.).[11] The major portion of the β-amyrin benzoate was separated readily by virtue of its lesser solubility in ether; crystallized from methyl ethyl ketone, it was obtained in slightly impure form as white flakes, m.p. 226–232°, α_D +98.2° (*c* 2.48), 55.7 g. The residue (326 g.), in 160-g. portions, was dissolved in glacial acetic acid (2 l.) and treated with selenous acid (43.6 g.) or selenium dioxide (37.5 g.) dissolved in about 40 ml. of water. After a one-hour reflux period, anhydrous sodium acetate (300 g.) was added in portions to the hot reaction mixture, which was then refluxed again for 15 min. The product was precipitated by pouring the reaction solution into water (10–12 l.) and dried well on the steam-bath. The black selenium was removed when the organic product was dissolved in refluxing petroleum ether (1.5 l.). The solution was concentrated to about 800 ml. and transferred to acid-washed alumina (2600 g.). α-Amyrin benzoate was removed from the column by continuous extraction for 4–5 days with petroleum ether; as the effluent was received, the solvent was removed by distillation and the distillate collected at the head of the column. The diene fraction was then removed by stripping the column by a similar 24-hr. extraction with benzene–petroleum ether (1:4). The column, after thorough washing with petroleum ether (2.4 l.), could be used for another separation, but becomes ineffective after several runs. The α-amyrin benzoate fraction was crystallized from acetone, m.p. 195.5–197.1°, α_D +97.1° (*c* 2.04), 102.7 g. The diene fraction (24.4 g.) was crystallized from methyl ethyl ketone; about 10–11 g. of pure β-amyradienyl-II benzoate ($\Delta^{11,13(18)}$-oleandienyl benzoate) could be isolated, m.p. 250–251.5°, α_D −30.8° (*c* 1.77).

α-Amyrin itself was obtained in 96–98% yield either by saponification[12] or by treatment with excess lithium aluminum hydride. In either case, the product had a lower melting point [m.p. 174.5–176.6°, α_D + 87.5° (*c* 1.93)] than that (m.p. 186°) listed in Elsevier.[13] Crystallization, vacuum sublimation, or chromatography has little or no effect on the melting point. Our preparations of α-amyrin, however, could be converted into various derivatives, all of which agreed in physical properties with those expected from the literature.

α-Amyrin trifluoroacetate was prepared in quantitative yield by treating α-amyrin (10 g.) in benzene solution (100 ml.) with trifluoroacetic acid (7 ml.) for 5 min. at room temperature. The solvent was removed in vacuum and the derivative crystallized from acetone; m.p. 208.3–210.6°, α_D +72.7° (*c* 2.82), λ_{max}^{KBr} 5.61 μ(s).

Anal. Calcd. for $C_{32}H_{40}FO_2$ (522.71): C, 73.52; H, 9.45. Found: C, 73.44; H, 9.51.

The ester was readily cleaved at room temperature by base, such as diethylamine. The recovered alcohol, after crystallization, melted at 175.9–179° with complete clearing at about 186°.

α-Amyrin *p*-Toluenesulfonate.—α-Amyrin (1.71 g.) in 3 ml. of hot pyridine was treated with *p*-toluenesulfonyl chloride (840 mg.) and then allowed to stand at 25° overnight. Addition of methanol precipitated the derivative, which was then washed well with the same solvent; m.p. 129.8–129.9°, α_D +70° (*c* 2.30), $\lambda_{max}^{CHCl_3}$ 8.55 μ(s), 88% yield. The ester is extremely thermolabile.

Anal. Calcd. for $C_{37}H_{56}O_3S$ (580.88): C, 76.50; H, 9.72; S, 5.52. Found: C, 76.28; H, 9.78; S, 5.37.

The methanesulfonate was prepared similarly by use of methanesulfonyl chloride; m.p. 102.2–102.4°, α_D +67.0° (*c* 1.56), λ_{max}^{KBr} 8.52 μ(s), 92% yield.

Anal. Calcd. for $C_{31}H_{52}O_3S$ (504.79): C, 73.76; H, 10.38. Found: C, 73.74; H, 10.39.

α-Amyradienyl Benzoate ($\Delta^{10,12}$-Ursadienyl Benzoate).—This diene has been prepared[14] by the reaction of α-amyrin benzoate with N-bromosuccinimide. We were able to obtain higher yields by bromination with catalysis by ultraviolet light followed by dehydrobromination with collidine. Thus α-amyrin benzoate (258.1 mg.) in carbon tetrachloride solution reacts readily with bromine (80 mg.) under irradiation. After discharge of the bromine color, the solvent was removed in vacuum and the dark-colored residue refluxed for 22 hr. in freshly distilled collidine. The product was worked up in the usual way and crystallized from isopropyl alcohol–acetone, m.p. 171.5–173°, m.m.p. with authentic dienyl benzoate not depressed; yield 205 mg.

Lithium–Ammonia Reduction.—About 100 ml. of liquid ammonia was added to a stirred solution of 1.0 g. of the dienyl benzoate in 30 ml. of thoroughly dried 1,2-dimethoxyethane. About 1.0 g. of lithium (wire) was added, in small portions and over a space of 30 min., when the blue color disappeared. Acetone was added after an additional 15 min. to decompose excess lithium. Solvent was evaporated in a current of air and the product extracted in the usual way with ether. After acetylation and crystallization from acetone, α-amyrin acetate was isolated as the only product, m.p. and m.m.p. 220–224°, α_D +79.7° chf. (*c* 2.57), yield 0.675 g.

α-Amyrin Acetate Oxide (3-Acetoxy-12,13-epoxyursane).—A stream of oxygen containing about 2% ozone was passed at a fairly rapid rate through a solution of 37.9 g. of α-amyrin acetate[15] in 197 ml. of dry carbon tetrachloride until the solution no longer gave a yellow color with tetranitromethane (about 4.5 hr.). The solvent was removed *in vacuo* to give a white powder, α_D +76.1° (*c* 2.63), 39.0 g. On three crystallizations (10 g.) from acetone white needles of the oxide were obtained, m.p. 220–223° (evac.), α_D +63.9° (*c* 2.36), yield about 5 g.

Anal. Calcd. for $C_{32}H_{52}O_3$ (468.74): C, 79.28; H, 10.81. Found: C, 79.13; H, 10.67.

α-Amyrene Oxide (12,13-Epoxyursane).—This was prepared from α-amyrene (Δ^{12}-ursene)[16] by the procedure described above for the 3β-acetoxy derivative. The analytical sample was crystallized from methanol–ether, m.p. 142–144°, α_D +69.4° (*c* 2.03), no C=O absorption in the infrared.

Anal. Calcd. for $C_{30}H_{50}O$ (426.70): C, 84.44; H, 11.81. Found: C, 84.50; H, 11.77.

Isomerization of α-Amyrin Acetate Oxide and of α-Amyrene Oxide.—A solution of the uncrystallized acetate oxide (32.8 g.) in benzene was treated with 246 g. of acid-washed alumina at room temperature overnight. The alumina was removed by filtration through diatomaceous earth and the filtrate evaporated to a small volume. Methanol was added to incipient precipitation and after cooling the solid product weighed 24.9 g., m.p. 196.8–201°, α_D +122° (*c* 2.22). After several crystallizations from methanol–ether the **13-iso-ketoacetate** melted at 201–203°, α_D +124.3° (*c* 1.85)[17]; λ_{max}^{KBr} 5.78 μ (s), 5.85 μ (s), $\lambda_{max}^{CHCl_3\ EtOH}$ 249.5–250.0 (*E* 256). The unusual position of absorption in the ultraviolet (for a ketone) may be due to a trace of diene. The ultraviolet absorption of the stable 12-keto acetate is also unusual ($\lambda_{max.}$ 282, log *E* 2.25[3]) in that the

(11) K. Vesterberg and S. Westerlind, *Ann.*, **428**, 243 (1922).

(12) P. Horrmann, *Arch. Pharm.*, **268**, 64 (1930).

(13) *Elsevier's Encyclopaedia*, **14**, 529 (1940); L. Ruzicka, H. Leuenberg and H. Schellenberg [*Helv. Chim. Acta*, **20**, 1271 (1937)] report constants similar to ours for α-amyrin prepared by hydrolysis of the benzoate, but a melting point of 186–188° for material obtained by catalytic hydrogenation of α-amyrenonol (3β-hydroxy-11-keto-Δ^{12}-ursene).

(14) L. Ruzicka, O. Jeger and J. Redel, *Helv. Chim. Acta*, **26**, 1235 (1943).

(15) Prepared by heating α-amyrin in acetic anhydride under reflux (3.5 hr.); m.p. (evac.) 225.6–226.6°, α_D +88.4° (*c* 2.08); 98.8% yield.

(16) Prepared according to L. Ruzicka, G. Muller and H. Schellenberg, *Helv. Chim. Acta*, **22**, 758 (1939), or by desulfurization (25% yield) of the ethylene thioketal of 3-keto-Δ^{12}-ursene, m.p. 248–250°, α_D +71.0° (*c* 2.35). Found: C, 76.73; H, 10.47; S, 1.280. Calcd. for $C_{32}H_{52}S_2$ (500.87): C, 76.26; H, 10.28; S, 12.80. An analytically pure sample of the hydrocarbon had the constants, m.p. 121.5–123.3°, α_D +96.7° (*c* 1.81).

(17) G. C. Allen, *et al.*,[5] report for this compound m.p. 207–209°, α_D +114°.

intensity is greater than expected. The oxide is stable to ordinary or neutral[18] alumina.

The oxide of α-amyrene was isomerized by alumina in the same way to 12-keto-13-isoursane, α_D +131.2° (*c* 2.16), $\lambda_{max}^{CS_2}$ 5.87 μ(s), $\lambda_{max}^{CHCl_3-C_2H_5OH}$ 251 mμ (*E* 92.8). This material evidently corresponds to the "α-amyrene oxide" of McLean, *et al.*,[4] α_D +135°.

These unstable 12-ketones were isomerized to the stable 12-ketones by treatment with a solution of concentrated hydrochloric acid in chloroform–acetic acid.[3] Since the stable ketones have a characteristically less positive optical rotation, the isomerization can be followed conveniently by this property.

Attempted Reductions of 3β-Acetoxy-12-ketoursane.—We subjected the ketoacetate to the drastic Wolff–Kishner conditions used successfully to reduce 3β-benzoyloxy-4,4,-14-trimethyl-15-keto-Δ⁷-cholestene[19]; a mixture was obtained, which on chromatography yielded various fractions, all of which showed carbonyl bands in the infrared. Clemmensen reduction under a variety of conditions, even those used in reduction of hindered 11-ketones in the lanosterol series,[20] were likewise unsuccessful (starting material recovered).

Enol Acetylation of 12-Ketones.—α-Amyranonol enol diacetate was obtained when either of the 13-epimeric 3β-hydroxy-12-ketoursanes was refluxed in acetic anhydride in the presence of sodium acetate according to the procedure already described for the stable ketone,[3] m.p. 251.5–256.5°, α_D +64.2° (*c* 2.03); $\lambda_{max}^{CS_2}$ 5.72 μ, 5.77 μ (s), 5.97 μ (w-m); strong yellow color with tetranitromethane.

Anal. Calcd. for $C_{34}H_{54}O_4$ (526.77): C, 77.52; H, 10.33. Found: C, 77.25; H, 10.23.

The isomeric Δ¹¹-enol diacetates were prepared in the following way. A solution of 2.0 g. of the hydroxy ketone and 0.3 g. of *p*-toluenesulfonic acid in 100 ml. of isopropenyl acetate was distilled slowly until the temperature reached 98° (2 hr., 10 ml. distillate). The reaction was then refluxed for 17 hr., and then distilled until a total of 76 ml. of liquid was obtained. Sodium bicarbonate (2 g.) was then added and the residual liquid removed at 30°, 10 mm. pressure. Water and benzene were added and the benzene layer worked up in the usual way; yield 85–88%.

3β,12-Diacetoxy-Δ¹¹-ursene crystallized as white needles from ether–isopropyl alcohol; m.p. 247–250°, α_D +85.9° (*c* 2.00); $\lambda_{max}^{CS_2}$ 5.72 μ, 5.76 μ (s), 6.01 μ (w-m).

Anal. Calcd. for $C_{34}H_{54}O_4$ (526.77): C, 77.52; H, 10.33. Found: C, 77.22; H, 10.14.

3β,12-Diacetoxy-Δ¹¹-13-isoursene after crystallization melts at 169.5–173°, α_D −37.1° (*c* 2.12); $\lambda_{max}^{CS_2}$ 5.75 μ, 5.76 μ (s), 6.02 μ (w-m).

Anal. Calcd. for $C_{34}H_{54}O_4$ (526.77): C, 77.52; H, 14.33. Found: C, 77.17; H, 10.10.

Attempted hydrogenation (PtO_2, ethanol, 24 hr. at 90° and 50–54 lb.) of either Δ¹¹-enol acetate gave mixtures of starting material and the stable keto acetate.

Bromination of the Δ¹¹-Enol Acetates.—A solution of 200.3 mg. of 3β,12-diacetoxy-Δ¹¹-13-isoursene in 1 ml. of carbon tetrachloride was treated with the theoretical amount of a bromine solution in the same solvent in the absence of light. Decolorization was rapid, but the mixture was allowed to stand overnight. Methanol (10 ml.) was then added and the clear solution was kept in the dark for another 26 hr.[21] during which time the bromo ketone separated. Recrystallized twice from methanol–ether; m.p. 230.2–230.7° (dec., evac.), α_D +145.5° (*c* 2.09, CCl_4); $\lambda_{max}^{CS_2}$ 5.76 μ (s), 5.82 μ (s). The displacement of the carbonyl band toward shorter wave length is indicative of an equatorial α-bromo ketone, and hence the product is **3β-acetoxy-11α-bromo-12-keto-13-isoursane.**

Anal. Calcd. for $C_{32}H_{51}BrO_3$ (563.65): C, 68.19; H, 9.30. Found: C, 68.25; H, 9.24.

Bromination of the 13-isomer of the above enol diacetate in glacial acetic acid (absence of light, 1 mole Br_2, room temperature) gave a bromo ketone, m.p. 226–239°; λ_{max}^{KBr} 5.76 μ (s). 5.90 μ (w-m), whose infrared spectrum is indicative of an axial α-bromo ketone. On crystallization from acetone, hydrogen bromide is lost to give the known α,β-unsaturated ketone, iso-α-amyrenoyl acetate, m.p. 265–271°, m.p. 290.5–293° (evac., α_D +92.2° (*c* 1.83). This compound was obtained directly (79.2% yield) by bromination under ultraviolet light. This α,β-unsaturated ketone does not react with bromine (ultraviolet light catalysis) or with sulfuryl chloride (benzoyl peroxide catalysis).

3β,12-Diacetoxy-Δ⁹(¹¹),¹²-ursadiene.—3β,12-Diacetoxy-Δ¹³-ursene (α-amyranonol enol diacetate) does not react with bromine in the dark. On exposure of a mixture of the enol diacetate (255.9 mg.) and bromine in carbon tetrachloride solution to ultraviolet light the bromine color bleaches rapidly and hydrogen bromide is evolved. On evaporation of the solvent a residue is obtained which gives a positive Beilstein test. The compound lost hydrogen bromide on standing in methanol (40 ml.)–carbon tetrachloride (4 ml.) solution or 46 hr. After removal of the solvents the product was obtained as short white needles from acetone–methanol, m.p. 240–252.5°, $\lambda_{max}^{C_2H_5OH}$ 276 mμ,[22] 200 mg. After seven recrystallizations, m.p. 257–259.3°, m.p. 258.8–259.6° (evac.), α_D +260° (*c* 1.52); $\lambda_{max}^{CS_2}$ 5.69 μ (s), 5.76 μ (s).

Anal. Calcd. for $C_{34}H_{52}O_4$ (524.76): C, 77.82; H, 9.99. Found: C, 77.88; H, 10.21.

Reduction of 3β,12-Diacetoxy-Δ¹³-ursene with $LiAlH_4$.—A mixture of the enol diacetate (500 mg.) and lithium aluminum hydride (equal weight) in ether (dried over the reagent) was stirred for 10 hours. Ethyl acetate–benzene was added dropwise without cooling with subsequent volatilization of the ether. Water was added until the gray suspension changed to a white precipitate, removed by filtration through dicelite. The filtrate was evaporated to an oily residue which crystallized from ligroin (m.p. 179–183°, 380 mg.); obtained from this solvent as large translucent crystals, m.p. 181–183°, α_D +90.6° (*c* 2.86, C_6H_6), end absorption at 220 mμ; $\lambda_{max}^{CS_2}$ 2.77 μ (m), 4.91 μ (m), 5.98 μ (m-s); red-brown color → deep yellow with tetranitromethane, deep green color with ferric chloride.

Anal. Calcd. for $C_{30}H_{50}O_2$ (442.79): C, 81.39; H, 11.38. Found: C, 81.43; H, 11.33.

On acetylation with acetic anhydride–pyridine (17 hr., room temp.) the original enol diacetate is obtained. On treatment with hydrochloric acid (glacial acetic acid solution. 3 hr., room temp.) a product is obtained whose infrared spectrum is indicative of a mixture of the two 12-keto acetates.[23] No change occurs on treatment with acid-washed alumina.

These various reactions indicate that the product of reaction with lithium aluminum hydride is not a normal reduction product; the analysis, ferric chloride test and behavior on acetylation suggest that it is the free enol, 3β,12-dihydroxy-Δ¹²-ursene.

Reduction of 3β-Acetoxy-12-ketoursane.—The stable ketone (5 g.) was treated with lithium aluminum hydride according to the procedure described above for the enol diacetate (40 hr. stirring). The oily product was dissolved in isopropyl alcohol, from which a solid separated after 24 hr. at 0°, m.p. 250–254°, 0.40 g. This diol (3β,12α-dihydroxyursane) was recrystallized twice from acetone–methanol; m.p. 258.4–259.2° (evac.), α_D +17.4° (*c* 2.19), λ_{max}^{KBr} 2.94–2.97 (s), no C=O band, 9.65 μ, 9.79 μ, 10.04 μ, 10.21 μ.

Anal. Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.86; H, 11.72.

The diol formed a **monoacetate** when treated with acetic anhydride–pyridine either at 100° for 16 min or at room temperature for 18 hr.; purified by crystallization from ether–ethanol, m.p. 283.5–287.5°, α_D +30.3 (*c* 1.32); λ_{max}^{KBr} 2.75 μ (w), 2.93 μ (w), 5.79 μ (s), 9.69 μ, 9.79 μ (s), 9.91 μ (s), 10.04 μ (s), 10.18 μ (s).

Anal. Calcd. for $C_{32}H_{54}O_3$ (486.75): C, 78.96; H, 11.18. Found: C, 78.46; H, 10.89.

The isopropyl alcohol mother liquors from this diol were

(18) Alumina washed with ethyl acetate and then dried for four hours at 120°.

(19) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, THIS JOURNAL, **76**, 2852 (1954); we thank the authors for detailed directions for this method.

(20) W. Voser, *et al.*, *Helv. Chim. Acta*, **33**, 1907 (1950).

(21) If the bromination is conducted in acetic acid, this step is not necessary.

(22) A similar compound in the β-amyrin series shows an absorption maximum at 278 mμ [R. Budziarek, *et al.*, *J. Chem. Soc.*, 3019 (1951)].

(23) α-Amyrin is also acetylated under these conditions.

evaporated, and the oily residue dissolved in ligroin. The isomeric diol (3β,12α-ursanediol) separated on chilling, m.p. 165.8–167°, 3.59 g. The analytical sample was obtained from ether–ligroin, large white blades, m.p. 169.9–170.4° (evac.), α_D +10.2° (*c* 1.87); λ_{max}^{KBr} 2.92–2.97 μ (s), no C=O band, 9.75 μ (s), 9.99–10.03 μ (s), 10.14 μ (m), 10.25 μ (m).

Anal. Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 81.19; H, 12.07.

The diol forms a diacetate under conditions where the above 12-isomeric diol forms a monoacetate; translucent crystals from methanol, m.p. 205.2–206.4° (evac.), α_D −1.2° (*c* 2.11), λ_{max}^{KBr} 5.77 μ (s).

Anal. Calcd. for $C_{34}H_{56}O_4$ (528.79): C, 77.22; H, 10.67. Found: C, 77.26; H, 10.58.

A mixture of the 3-mono- and 3,12-diacetates was obtained if acetylation was conducted at 100° for 8 min. These are separable by chromatography. The monoacetate was purified by crystallization from methanol–benzene, m.p. 274.4–276.2° (evac.), α_D +17.8° (*c* 1.49); λ_{max}^{KBr} 2.82 μ (s), 5.78 μ (s), 9.79 μ (s), 9.95 μ (s), 10.10 μ (w).

Anal. Calcd. for $C_{32}H_{54}O_3$ (486.75): C, 78.96; H, 11.18. Found: C, 78.53; H, 10.90.

Under conditions which convert α-amyrin into the mesylate, this monoacetate affords α-amyrin acetate.

Reduction of 3β-Acetoxy-12-keto-13-isoursane.—The unstable keto acetate (1.0 g.) was reduced with lithium aluminum hydride by the method described for the stable keto acid to give a **3,12-diol**, m.p. 189.8–190.6°, 0.545 g. Crystallized ether–ligroin, m.p. 191.6–192.8° (evac.), α_D +52.0° (*c* 2.03); λ_{max}^{KBr} 2.98 μ (s), no C=O band, 9.73 μ (s), 10.08 μ (s).

Anal. Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.90; H, 11.82.

The same diol was obtained on reduction of 3β-benzoyloxy-12-keto-13-isoursane ("α-amyrin benzoate oxide"[4]).

On acetylation, acetic anhydride–pyridine, at room temperature for 25 hr., a mixture of 3-mono- and 3,12-diacetates resulted, separable by chromatography. **The 3,12-diacetate**, eluted with 3:1 and 2:1 petroleum ether–benzene, was purified by crystallization from methanol; m.p. 163–165.5°, α_D +49.7° (*c* 1.96), λ_{max}^{KBr} 5.76 μ (s).

Anal. Calcd. for $C_{34}H_{56}O_4$ (528.79): C, 77.22; H, 10.67. Found: C, 76.76; H, 10.37.

The 3-monoacetate, eluted with 2:1 petroleum ether–benzene, formed white needles from methanol, m.p. 234–236° (evac.), α_D +62.7° (*c* 2.13[24]); λ_{max}^{KBr} 2.83 μ (s), 5.77 μ (s), 9.81 μ (s), 10.01 μ (s), 10.20 μ (w).

Anal. Calcd. for $C_{32}H_{54}O_3$ (486.75): C, 78.96; H, 11.18. Found: C, 78.91; H, 11.02.

(24) Literature m.p. 234–235°, α_D +66° (*c* 1.7).[5]

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

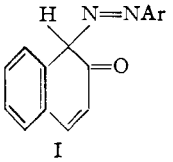
Benzothiophene Chemistry. VII. Substitution Reactions of 5-Hydroxy- and 5-Aminobenzothiophene Derivatives

BY F. G. BORDWELL AND HUGO STANGE[1]

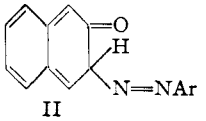
RECEIVED MARCH 12, 1955

Electrophilic substitution in 5-hydroxy-, 5-acetamido-, and 5-aminobenzothiophene was found to occur at the 4-position. This is analogous to the behavior of similarly substituted naphthalene derivatives. Unlike 2-naphthol, 5-hydroxybenzothiophene undergoes reactions at both positions *ortho* to the hydroxyl group under nearly the same conditions. When the sulfur atom in benzothiophene is oxidized to the sulfone stage, orientation in the benzene ring is changed from predominant 4-substitution to predominant 6-substitution. The results are rationalized in terms of current theory.

The strong preference for α-substitution by electrophilic reagents observed in naphthalene, β-naphthol and many other naphthalene derivatives is well known.[2] This orientation appears to be best correlated at present with the relative stability of possible intermediate addition complexes formed in such reactions.[3] For example, the much greater rate of coupling of β-naphthol at the 1-position as compared to the 3-position corresponds to a greater stability for the intermediate I as compared to II.



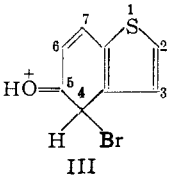
I



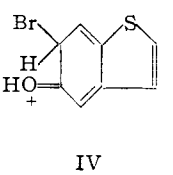
II

This difference in stability can be used to account not only for the position of coupling, but also for the formation of 1,1-dichloro-2-keto-1,2-dihydronaphthalene rather than 1,3-dichloro-2-naphthol in the chlorination of 1-chloro-2-naphthol, and for the expulsion of Br^+ from an intermediate similar to I rather than H^+ from an intermediate similar to II in coupling reactions of 1-bromo-2-naphthol.[4] The difference in stability of I and II is presumably dependent on the aromatic system in type I as compared to the conjugated polyene system of type II.[3]

It seemed worthwhile to us to compare the reactions of 5-hydroxybenzothiophene and related compounds with those of the corresponding naphthalene derivatives to see whether or not strong preferential orientation effects would also be found in this system. Preferential 4-substitution in 5-hydroxybenzothiophene might be anticipated since, for example, in bromination the stability of intermediate III, which contains a thiophene ring, should exceed that of IV, which contains a conjugated triene system.



III



IV

The necessary 5-substituted benzothiophenes

(1) Heyden Chemical Corp. Fellow, 1946–1948; Northwestern University Fellow, 1948–1949.

(2) See the data given by L. F. Fieser and M. Fieser in "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1944, pp. 760–770.

(3) See the discussion by M. J. S. Dewar in "Electronic Theory of Organic Chemistry," Oxford University Press, New York, N. Y., 1949, pp. 173–176.

(4) T. Hewitt and H. V. Mitchell, *J. Chem. Soc.*, **89**, 1167 (1906).