oxyamine hydrochloride had m.p. 150–151°[6]; ethoxyamine hydrochloride had m.p. 129–131°.[8]

N-Alkoxyisoindolines.—Over a period of 90 min. a solution of 0.05 mole of N-alkoxyphthalimide in dry ether was slowly added with stirring to a slurry of 0.13 mole of lithium aluminum hydride in ether. After the mixture had been stirred at room temperature for 8 hr., the reaction mixture was cooled and the complex present was decomposed by successive additions dropwise of 6.5 ml. of water, 4.5 ml. of 20% potassium hydroxide, and 10 ml. of water. The inorganic salts were removed by filtration. The filtrate was dried with magnesium sulfate and then fractionated.

N-Ethoxyisoindoline Picrate.—A colorless liquid, b.p. 145–152° (5 mm.), was obtained which became dark red on standing. The infrared spectrum of the freshly distilled, colorless liquid (neat) showed important absorption bands at 3.5 (m), 6.8 (m), 7.3 (m), 9.5 (s), 11.2 (m), and 13.4 (s) μ and no carbonyl absorption. A few drops of the freshly distilled liquid was added to a saturated solution of picric acid in 95% ethanol. The mixture was warmed over steam for a few minutes and then cooled. The yellow crystalline precipitate was filtered and recrystallized from ethanol, m.p. 170° dec. The n.m.r. spectrum of this picrate (in deuterated dimethyl sulfoxide) showed a singlet at τ 1.7 with a relative area of 2, a singlet at 2.7 with an area of 4, a singlet at 5.35 with an area of 4, a quartet at 6.0 with an area of 2, and a triplet at 9.0 with an area of 3.

Anal. Calcd. for $C_{16}H_{16}N_4O_8$: C, 48.98; H, 4.11; N, 14.27. Found: C, 48.85; H, 4.38; N, 14.78.

N-Methoxyisoindoline Picrate.—Fractionation gave a light yellow liquid, b.p. 135–140° (15 mm.), which became colorless on repeated distillations; yield, 72% of theory. On standing in the cold, the color quickly changed to dark red. The infrared spectrum (neat) had bands at 3.4 (s), 3.55 (m), 9.5 (s), 6.8 (m), and 13.4 (s) μ but no carbonyl bands. The picrate was prepared by the addition of a few drops of the freshly distilled liquid to a saturated solution of picric acid in 95% ethanol. After the solution had been warmed, it was cooled and a yellow crystalline precipitate appeared. This was filtered and recrystallized from ethanol, m.p. 104–105°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.63; H, 3.73; N, 14.80. Found: C, 47.66; H, 3.97; N, 14.61.

2-Ethoxy-3-hydroxyphthalimidine.—To 10.0 g. (0.05 mole) of N-ethoxyphthalimide suspended in 90% methanol was added a solution of 3.7 g. of sodium borohydride in methanol over a period of 1 hr. After the mixture had been stirred at room temperature for 18 hr., 5 ml. of glacial acetic acid was added. The methanol was partially removed by evaporation under reduced pressure. Water was added; the white solid which formed was filtered and then recrystallized from water: m.p. 120–121°; yield, 62% of theory. Characteristic infrared absorption bands (KBr) were found at 3.2 (s), 3.5 (m), 6.0 (s), 6.8 (m), 9.35 (s), and 13.3 (s) μ. The n.m.r. spectrum (in $CDCl_3$) showed a singlet at τ 2.0 (area 4), a doublet at 3.7 (area 1), a doublet at 6.45 (area 1), a quartet at 5.5 (area 2), and a triplet at 8.6 (area 3).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.71; N, 7.21.

Phthalide.—To 3.9 g. (0.022 mole) of N-methoxyphthalimide suspended in 90% ethanol was added a solution of 1.9 g. (0.05 mole) of sodium borohydride in 100 ml. of ethanol over a period of 1 hr. The mixture was then stirred at room temperature for 6 hr. The bases were neutralized with glacial acetic acid. The ethanol was partially removed by evaporation under reduced pressure. Water precipitated a white solid which was recrystallized from water: m.p. 73–74°; lit.[9] m.p. 73°; yield, 67% of theory. The infrared absorption spectrum (KBr) of this solid showed characteristic bands at 3.5 (w), 5.7 (s), 6.8 (m), 6.9 (m), 7.2 (m), 7.5 (m), 7.7 (m), 8.1 (m), 9.4 (s), 9.85 (s), and 13.3 (s) μ.

Anal. Calcd. for $C_8H_6O_2$: C, 71.61; H, 4.52. Found: C, 71.15; H, 4.44.

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An Improved Method for the Preparation of Volatile Epoxides

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The synthesis of the isomeric 2-butene oxides has been reported previously[2,3] and involves the conversion of *cis*- and *trans*-2-butene to the corresponding epoxides *via* the halohydrins. The halohydrins are isolated and purified before treatment with strong aqueous base to give the epoxides. The over-all yields average 44–48%.

The first one-step preparation of the isomeric 2-butene oxides was reported by Eliel and Delmonte.[4] The *trans* epoxide was prepared by treating the monotosylate (not isolated) of *meso*-2,3-butanediol with strong aqueous base. The reported yield of epoxide in this procedure is 28%.

Various investigators who have used the 2-butene oxides in research have prepared the compounds by the methods outlined above. It is of interest to note that no direct oxidations of the olefins with peracids seem to have been reported. We have observed that direct epoxidation of *cis*- or *trans*-2-butene with *m*-chloroperbenzoic acid in dioxane gives the corresponding *cis*- and *trans*-2-butene oxides in a high state of stereochemical purity and in good yield (52–60%). The experimental procedure is much simpler in that the epoxide is distilled directly from the reaction mixture without prior removal of the *m*-chlorobenzoic acid. Under these conditions the epoxides are stable in the presence of the carboxylic acid.

The general method also appears to be applicable to the preparation of higher boiling epoxides. Treatment of 1-hexene with *m*-chloroperbenzoic acid in diglyme (b.p. 162°) followed by direct distillation of the 1-hexene oxide at 116–119° gives the epoxide in 60% yield.

The greater simplicity in the experimental procedure used and the saving in time and effort makes this procedure very attractive for the preparation of volatile epoxides.

Experimental

Preparation of *cis*- and *trans*-2-Butene Oxides.—In a three-necked 1000-ml. round-bottom flask equipped with a delivery tube, magnetic stirrer, and Dry Ice–acetone reflux condenser was placed 500 ml. of anhydrous dioxane and 65.3 g. (0.322 mole) of *m*-chloroperbenzoic acid (FMC Corp., 85% minimum purity). After dissolution of the acid, the contents of the flask was cooled to 0°; 18.1 g. (0.322 mole) of *cis*- or *trans*-2-butene (Matheson Coleman and Bell, 99.0% minimum purity) was added *via* the delivery tube. The contents of the flask was stirred for 10 hr. under the Dry Ice–acetone condenser. At the end of this period of time the butene stopped refluxing. The flask was stoppered and placed in a refrigerator overnight. The mixture was subjected to distillation, collecting the fraction up to 100°. This fraction was fractionated through a 2-ft. helices-packed column giving a 52–60% yield of *cis*-2-butene oxide, b.p. 58.0–59.0° (748 mm.), and *trans*-2-butene oxide, b.p. 52.0–53.0° (748 mm.).

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The stereochemical purity of the two epoxides was shown to be greater than 99.5% by gas–liquid chromatography on a 30-ft. 20% Carbowax 20M on Chromosorb P column at 150°. The retention of the *cis* epoxide was 10.0 min. and that of the *trans* epoxide, 8.7 min.

Preparation of 1-Hexene Oxide.—A mixture of 24.4 g. (0.119 mole) of *m*-chloroperbenzoic acid (85%) and 10.0 g. (0.119 mole) of 1-hexene in 300 ml. of anhydrous diglyme was allowed to stand 24 hr. in a refrigerator. The mixture was subjected to distillation collecting the fraction up to 162°. This fraction was redistilled through a 2-ft. helices-packed column giving 7.05 g. (60%) of 1-hexene oxide, b.p. 116–119°, $n^{20}D$ 1.4051 (lit.[5] b.p. 117–119°, $n^{20}D$ 1.4060).

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The Decarboxylation of 3-Carboxy-2-isoxazolines

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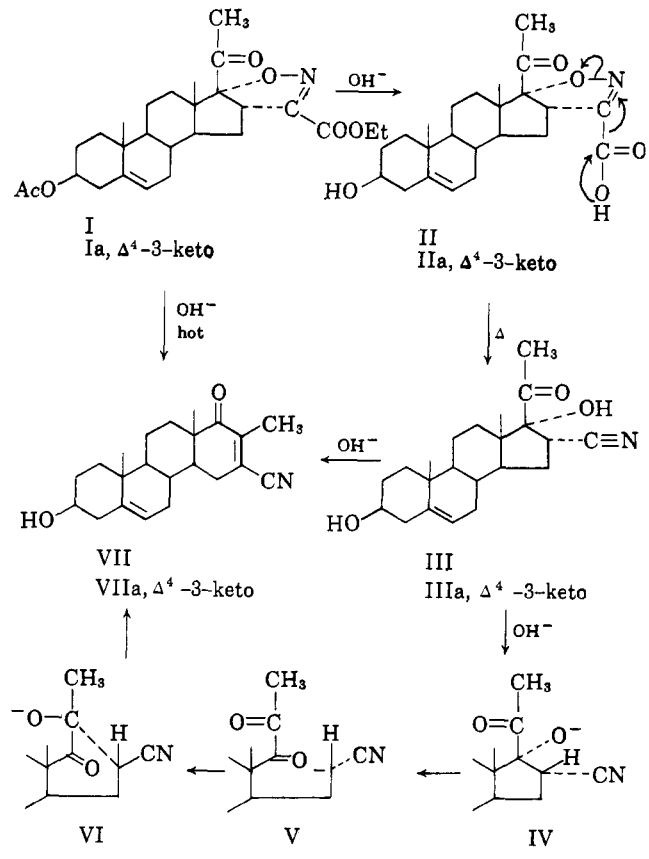
In the course of preparing a series of steroidal isoxazolines by the method of nitrile oxide addition to an olefin,[1] we found that pregna-5,16-dien-3β-ol-20-one acetate reacted smoothly in ether solution with carbethoxyformonitrile oxide[2] to yield (80%) the ethyl ester (I) of 16α,17α-[3-carboxy-3,1-(2-isoxazolino)]-pregn-5-en-3β-ol-20-one 3β-acetate ester.

Hydrolysis of this ester in methanol solution with aqueous sodium or potassium hydroxide at room temperature yielded the salt of the corresponding acid from which the free acid (II) was obtained by acidification with hydrochloric acid. The 3-acetate ester was removed simultaneously. When this hydrolysis was carried out by refluxing the ester in aqueous methanol with potassium carbonate, the acidic product (in 67% yield) was accompanied by a neutral product in 7% yield. This latter material showed infrared absorption at 2220 (cyano) and at 1680 cm.$^{-1}$ (conjugated carbonyl). The ultraviolet absorption, λ 247 mμ (ε 10,700), also indicated the presence of a conjugated ketone.

This same product (VII) was also obtained by a second process. When the free acid, 3β-hydroxy-16α,-17α-[3-carboxy-3,1-(2-isoxazolino)]-pregn-5-en-20-one (II) was heated on a hot plate at 250–280° to give a clear melt (with loss of CO_2 and initial foaming) and then cooled and crystallized, the product again showed cyano group absorption in the infrared but without conjugate absorption. Loss of the carboxyl group and isoxazoline ring opening produced the 16α-cyano-17α-hydroxy steroid (III) as a stable product. Treatment of this product (III) with base caused a dehydration and gave rise to VII. The structure of III was confirmed by analytical data, the presence of hydroxyl (3440 and 3240 cm.$^{-1}$), 20-carbonyl (1717 cm.$^{-1}$), and cyano (2267 cm.$^{-1}$) group absorption in the infrared,



and by the n.m.r. spectrum of the Δ⁴-3-keto analog (IIIa). The Δ⁴-3-keto series was obtained by the selective addition (55% yield) of carbethoxyformonitrile oxide to the Δ¹⁶ double bond of pregna-4,16-diene-3,20-dione to give Ia, followed by hydrolysis and pyrolysis to give IIa and IIIa, respectively. The Δ⁴-3-keto analog (IIIa) was sufficiently soluble in deuteriochloroform to obtain the n.m.r. spectrum, whereas the Δ⁵-3-hydroxy steroid (III) was not.

The n.m.r. spectrum of IIIa shows singlets in deuteriochloroform for the C-18 methyl (δ 0.68) and for the C-21 methyl (δ 2.28), both of which are characteristic of the normal steroid structure and which are not in accord with a D-homo structure.[3] The δ-value of 0.68 is also in better accord with a 17α-hydroxy-17β-acetyl configuration than with the "iso" structure, since the 17β-hydroxyl group tends to shift the resonance band of the C-18 methyl protons downfield in this type of structure.[4] The effects of the 16-cyano group cannot, however, be completely assessed. This interpretation of the n.m.r. data, together with the probable attack of the nitrile oxide from the α-face of the molecule, leads to the designation of III as 16α-cyano-3β,17α-dihydroxy-pregn-5-en-20-one.[4a]

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(4) Unpublished data from these laboratories. The C-18 methyl proton resonance in *epi*-testosterone has a value δ 0.70 compared with testosterone, δ 0.80. The C-18 methyl proton resonance in 3β-acetoxy-17α-hydroxy-pregn-5-en-20-one has a value δ 0.70 compared with 3β-acetoxy-17β-hydroxy-17-isopregn-5-en-20-one, δ 0.94.

(4a) NOTE ADDED IN PROOF.—The mass spectrum of compound IIIa gave additional evidence for the unrearranged steroid structure, showing a molecular ion peak at *m/e* 355 and fragments corresponding to the loss of acetyl at M − 312 and to acetyl at M − 43. The mass spectrum was determined with an Atlas CH4 mass spectrometer with an ionizing potential of 70 e.v. and an ionizing current of 18 μa. We wish to thank Dr. C. D. DeJongh of Wayne State University for determining and interpreting these results.