

Anodic Decarboxylation of Carboxylic Acids¹

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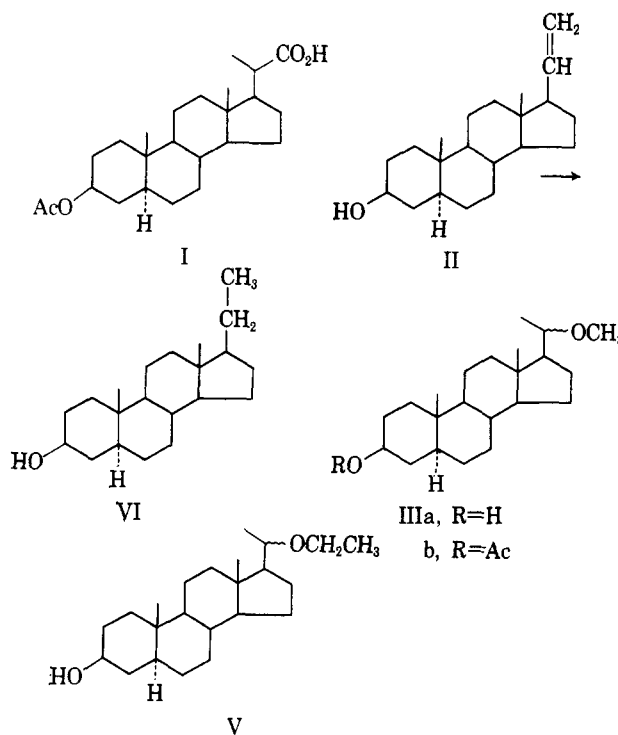
The electrolytic oxidation of 3 β -acetoxybisnorallocholanolic acid (I) in methanol at pH 11.3, 8.6, and 5.7 is described. The reaction in ethanol and 2-propanol also is discussed. The various reaction products, *i.e.*, pregnane derivatives II–V, indicate a carbonium ion intermediate is involved.

Recent investigations^{2,3} have shown that the electrolysis of carboxylic acids in methanol yielded methyl ethers, apparently from attack of solvent on a carbonium ion intermediate. The free radical evidently undergoes further oxidation at the platinum anode. We subsequently have reported¹ similar ether formation as well as olefin production (β -elimination) in the electrolytic decarboxylation of isostevic acid. An extension of the study of the anodic reaction with 3 β -acetoxybisnorallocholanolic acid (I) at various pH with different alcohols is the subject of this paper.

The anodic reaction of I in methanol at pH 11.3⁴ gave a neutral mixture in 68% yield. The reaction was carried out at 11.5–12.5° and at 130–133 ma. The neutral material consisted of three major compounds, II, IIIa, and IV (11%, 42%, and 14% yields, respectively). Compound II, m.p. 131–133°, gave a positive tetranitromethane test and the infrared spectrum showed bands at 1640 and 912 cm^{-1} , indicative of a vinyl-type olefin. This observation was supported by n.m.r., the spectrum showing multiplets centered at τ 5.05 (2 protons) and 4.46 (1 proton), the typical absorption for an olefin of this type ($\text{CH}_2=\text{CH}-$). Hydrogenation of II with palladium on charcoal in ethanol–dioxane under a pressure of 24 p.s.i. gave 5 α -pregnan-3 β -ol (VI). Its infrared spectrum showed the absence of bands at 1640 and 912 cm^{-1} . Compound IIIa, m.p. 242–243°, was identified as 20 ξ -methoxy-5 α -pregnan-3 β -ol. The compound gave a positive Zeisel test and the infrared spectrum showed a broad band at 1093 cm^{-1} (methoxyl). The n.m.r. spectrum showed a singlet at τ 6.71 (methoxyl) and an asymmetric doublet centered at τ 8.85 ($J = 7$ c.p.s.), to which was assigned the C-21 methyl absorption coupled to a proton on an adjacent carbon to which is attached oxygen ($\text{CH}_3-\text{CH}-\text{O}-$). Preliminary in-

frared and n.m.r. data on the third isolated compound (IV), m.p. 218–220°, indicated a second methoxy compound, possibly the C-20 methoxy epimer of IIIa.⁵ The 3 β -acetoxy group of I was shown to be hydrolyzed at pH 11.3 (10.5–12°) and hence the C-3 hydroxyl group did not arise from the electrolytic process, *i.e.*, cathodic reduction.

The electrolysis was then performed at other base concentrations in order to study the effect on neutral fraction yields as well as to illustrate that the olefin-



methoxy ratio is base independent. Anodic reaction of I at pH 8.6 gave a neutral mixture in 68% yield, equivalent to the experiment conducted at pH 11.3. The mixture consisted of two previously described compounds, II and IIIa (8% and 7% yields, respectively), plus a less polar compound, IIIb, in 40% yield. The infrared spectrum of IIIb showed bands at 1730 (β -acetoxy) and 1075 cm^{-1} (methoxyl). The n.m.r. spectrum, that is similar to IIIa with the exception of a band at τ 7.96 (acetate methyl), showed the presence of a singlet at τ 6.70 (methoxyl) and a doublet at τ 8.81 and 8.90 ($\text{CH}_3\text{CH}-\text{O}-$). The hydrolysis of the 3-acetoxy group was thus greatly decreased at this pH. Acetylation of IIIa gave IIIb, identical with the product obtained directly from the electrolysis (mixture melting point, infrared, and gas chromatography). The olefin-methoxy ratio did not change significantly in comparison to the electrolysis at pH 11.3. The yield of neutral material was greatly reduced to 13% when the reaction was carried out at pH 5.7. Gas and thin layer chromatography showed the presence of at least six compounds in this mixture, including II–IV.

Attention was then directed to the reaction of I in ethanol and 2-propanol. Assuming an attack of solvent on a carbonium ion, an increase in the olefin-alkoxy ratio *via* a decrease in alkoxy formation was expected because of the greater bulk of these alcohols in comparison to methanol. Anodic reaction of I

(1) Paper II concerning electrolytic reactions. For paper I, see J. A. Waters, E. D. Becker, and E. Mosettig, *J. Org. Chem.*, **27**, 4689 (1962).

(2) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Am. Chem. Soc.*, **82**, 2645 (1960).

(3) W. B. Smith and H.-G. Gilde, *ibid.*, **83**, 1355 (1961).

(4) The pH values recorded in this paper are those readings observed on a Beckman pH meter, Model G, immediately after preparing the solutions prior to electrolysis. These readings were taken for comparative purposes and no exact significance can be attributed to the stated values.

(5) A shift of the carbonium ion to the more stable C-17 position and subsequent nucleophilic attack cannot be ruled out.

in ethanol under basic conditions gave a neutral mixture in 81% yield, consisting of two major products, Δ^{20} -5 α -pregnen-3 β -ol (II) in 30% yield and 20 ξ -ethoxy-5 α -pregnan-3 β -ol (V) in 27% yield. The olefin-alkoxy ratio was increased *ca.* fivefold in this reaction over that in methanol (pH 11.3). The reaction of I in 2-propanol gave a neutral fraction in poor yield (16%), which was a mixture of at least ten compounds. The reaction was not further investigated.

The anodic oxidation of carboxylic acid I appears to proceed through a free-radical intermediate to a carbonium ion from which II (β -elimination) or IIIa, IIIb, and V (attack by solvent) may result. Products of this nature arising from a free-radical reaction are more difficult to interpret.⁶ These results are in accord with former observations.¹⁻³

The anodic decarboxylation reaction may be a useful approach to biological intermediates, *e.g.*, pregnane derivatives, such as described in this paper.

Experimental⁷

Description of the Electrolysis Apparatus.—The apparatus consisted of two smooth platinum electrodes (sheet), 9 mm. wide and 40 mm. long. The electrodes, placed parallel to each other 3–4 mm. apart, were immersed 25–30 mm. into the magnetically stirred solutions. Glass beakers (30 ml.) were used as electrolysis vessels.

Anodic Reaction of 3 β -Acetoxibisnorallocholanolic Acid (I) in Methanol at pH 11.3.—To a solution of 505 mg. of 3 β -acetoxibisnorallocholanolic acid (I) in 30 ml. of absolute methanol was added 133 mg. of metallic sodium. The pH of the resulting solution was 11.3. The solution was electrolyzed at 133 ma. and 7–8 v. for 8 hr. Methanol was added periodically to maintain the original volume. The temperature of the solution was maintained at 11–12.5° by use of an evaporating acetone bath. On completion of the electrolysis, the solvent was removed under reduced pressure and the residue dissolved in chloroform and extracted three times with 5% sodium hydroxide. After washing the chloroform extract two times with water and drying over sodium sulfate, the solvent was removed under reduced pressure. The neutral mixture, 277 mg. (*ca.* 68%) of thick oil, was subjected to preparative thin layer chromatography (silica gel G) developed continuously⁸ with dichloromethane-ether (95:5) as solvent for 3.5 hr. Inspection of the plate under short wave ultraviolet light indicated three distinct bands. Elution of each band⁹ with acetone gave 31 mg. (11%) of white solid (upper band), 128 mg. (42%) of white solid (middle band), and 43 mg. (14%) of white solid (lower band). These per cents were in good agreement with those obtained from a gas chromatogram of the neutral mixture. Crystallization of the upper band product (31 mg.) from dilute methanol gave 14 mg. of white needles, m.p. 131–133°. The product gave a positive tetranitromethane test. The infrared spectrum showed bands at 3600 (–OH), 1640, and 912 cm^{-1} ($\text{CH}_2=\text{CH}$). The n.m.r. spectrum showed multiplets centered at τ 5.05 and 4.46. Analysis of the product indicated Δ^{20} -5 α -pregnen-3 β -ol (II), $[\alpha]^{20D} 0 \pm 2^\circ$ (*c* 0.53, chloroform).

Anal. Calcd. for $\text{C}_{21}\text{H}_{34}\text{O}$: C, 83.38; H, 11.33. Found: C, 83.44; H, 11.56.

(6) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 581.

(7) Melting points were taken on a Kofler block and are uncorrected. Analyses and rotations were performed by the Analytical Services Unit, NIAMD, under the direction of Mr. H. G. McCann. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer through the cooperation of Mr. H. K. Miller and Mrs. A. H. Wright. N.m.r. spectra were obtained with a Varian HR-60 spectrophotometer. Deuteriochloroform was used as an internal reference. Gas chromatograms were obtained through the cooperation of Dr. D. F. Johnson on a Chromalab chromatograph, Model 210, using a 4-ft. column (4-mm. i.d.) of 1% SE-30 on Gaschrom P (100–120 mesh) at 215° and 30 p.s.i.

(8) R. D. Bennett and E. Heftmann, *J. Chromatog.*, **12**, 245 (1963). The author thanks Dr. Bennett for advice concerning this technique.

(9) The product eluted from each band was rechecked for homogeneity by regular thin layer chromatography in all cases throughout this paper.

Crystallization of the product from the middle band (133 mg.) from dilute methanol gave 71 mg. of crystalline product, m.p. 129–229°. Two additional recrystallizations from methanol-ether gave a sharp melting compound, m.p. 242–243° (dried at 100° under high vacuum). The compound gave a positive Zeisel test and the infrared spectrum showed a broad band at 1093 cm^{-1} (methoxyl). The n.m.r. spectrum showed the following bands: singlet at τ 6.71 (–OCH₃) and doublet centered at 8.85 (*J* = 7 c.p.s., CH₃–CH–O).

Analysis of the product indicated 20 ξ -methoxy-5 α -pregnan-3 β -ol (IIIa); $[\alpha]^{20D} -14.0 \pm 3^\circ$ (*c* 0.35, chloroform).

Anal. Calcd. for $\text{C}_{22}\text{H}_{38}\text{O}_2$, C, 78.98; H, 11.45; OCH₃, 9.31. Found: C, 79.23; H, 11.73; OCH₃, 9.62.

Crystallization of the product from the lower band from dilute methanol gave 14 mg. of white crystals, m.p. 200–210°. A second recrystallization raised the melting point to 218–220°, white needles. The infrared spectrum showed a band at 1070 cm^{-1} . The n.m.r. spectrum on a small amount of sample showed absorption similar to that of IIIa. The analytical data supported a $\text{C}_{22}\text{H}_{38}\text{O}_2$ methoxy compound (IV).

Anal. Calcd. for $\text{C}_{22}\text{H}_{38}\text{O}_2$: C, 78.98; H, 11.45. Found: C, 79.01; H, 11.79.

Hydrolysis of I at pH 11.3.—A solution of 98 mg. of 3 β -acetoxibisnorallocholanolic acid (I) in 6 ml. of methanol containing 26 mg. of metallic sodium was set at 10.5–12° for 8 hr. Approximately one-half of the solvent was then evaporated under an air stream. The solution was acidified with 5% hydrochloric acid to congo red. The white solid was removed by suction filtration, washed repeatedly with water, and air-dried. Recrystallization from a large amount of ethanol gave 51 mg. of white, crystalline compound, m.p. 273–275°. An additional recrystallization raised the melting point to 277–278°. The analytical data indicated 3 β -hydroxybisnorallocholanolic acid, $[\alpha]^{20D} 0 \pm 1.5^\circ$ (*c* 0.6, ethanol), lit.¹⁰ m.p. 270°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{36}\text{O}_3$: C, 75.81; H, 10.41. Found: C, 75.59; H, 10.67.

Anodic Reaction of I in Methanol at pH 8.6.—A solution of 505 mg. of I in 30 ml. of absolute methanol containing 69 mg. of sodium methoxide (pH 8.6) was electrolyzed for 8 hr. at 130 ma. and 12 v. Methanol was added periodically to maintain original volume. The temperature of the solution was maintained at 21–23.5°. Work-up of the reaction in the usual manner gave 291 mg. of neutral mixture (*ca.* 68%) as a thick oil. The material was subjected to preparative thin layer chromatography (silica gel G) with dichloromethane-ether (4:1) as solvent. Inspection of the plate under short wave ultraviolet light showed three definite bands. The products of the two lower bands corresponded to compounds II and IIIa by gas and thin layer chromatography. A yield of 24 mg. (8%) of II and 24 mg. (7%) of IIIa was obtained. The product of the uppermost band, 157 mg. of white solid, was further purified to remove a trace impurity using preparative thin layer chromatography (dichloromethane-ether, 95:5). Elution of the major band with acetone gave 128 mg. of white solid. Crystallization of 63 mg. of this product from methanol gave 25 mg. of white flakes, m.p. 108–118°. A second recrystallization gave 11 mg. of pure product, m.p. 122–125°. The infrared spectrum showed bands at 1730 (3 β -AcO) and 1075 cm^{-1} (methoxyl). The n.m.r. spectrum showed the following bands: singlet at τ 7.96 (acetate methyl), singlet at 6.70 (OCH₃), doublet at 8.81 and 8.90 (CH₃–CH–O). Analytical data indicated 20 ξ -methoxy-5 α -pregnan-3 β -ol acetate (IIIb), $[\alpha]^{20D} +12.0 \pm 3.0^\circ$ (*c* 0.33, chloroform).

Anal. Calcd. for $\text{C}_{24}\text{H}_{40}\text{O}_3$: C, 76.55; H, 10.71. Found: C, 76.81; H, 10.92.

Anodic Reaction of I in Methanol at pH 5.7.—To 484 mg. of carboxylic acid I in 30 ml. of absolute methanol was added *ca.* 0.6 mg. of metallic sodium. A small amount of heating was necessary to bring about solution. The cooled solution (pH 5.7) was then electrolyzed for 9 hr. at 100–110 ma. and 125 v. at a temperature of 35–38°. Work-up in the usual manner gave a low yield of neutral material, 54 mg. (*ca.* 13%), as a thick oil. Preparative thin layer (silica gel G, dichloromethane-ether, 98:2) gave six products, four of which corresponded to compounds II–IV as shown by gas and thin layer chromatography.

Anodic Reaction of I in Ethanol at pH 10.0.—To 522 mg. of I in 30 ml. of absolute ethanol was added 130 mg. of metallic sodium (pH 10.0). The solution was electrolyzed for 8 hr. at

(10) E. Fernholz, *Ann.*, **507**, 128 (1933).

130 ma. and 12–20 v. at a temperature of 14–17°. Work-up of the solution in the usual manner gave 330 mg. of neutral material (ca. 81%). The mixture was subjected to preparative thin layer chromatography developed continuously for 2.5 hr., using dichloromethane–ether (98:2) as solvent. Two distinct bands were shown under short wave ultraviolet light. Elution of these bands with acetone gave 96 mg. of II (30%) and 103 mg. of V (27%). These per cents were in good agreement with those obtained from a gas chromatogram of the neutral mixture. Compound II was recrystallized from methanol, m.p. 130–132°, identical with II previously described (mixture melting point, infrared, and gas chromatography). The second product (V), was recrystallized from acetone to give a white crystalline compound, m.p. 127–130°. A second recrystallization gave raised m.p. 137.5–139°; *trans* crystallization, m.p. 160–164°. The infrared spectrum showed a broad band at 1075 cm.⁻¹ (ethoxy). Analytical data indicated 20ξ-ethoxy-5α-pregnan-3β-ol, $[\alpha]_D^{20}$ 11.0 ± 3.0° (c 0.6, chloroform).

Anal. Calcd. for C₂₃H₄₀O₂: C, 79.25; H, 11.57. Found: C, 79.17; H, 11.81.

Attempted Anodic Reaction of I in 2-propanol.—To a solution of 457 mg. of I in 50 ml. of 2-propanol was added 28 mg. of sodium (pH of cloudy solution 8.4). The solution was electrolyzed for 10 hr. at 30–35 ma. and 135–150 v. at 18.5–23°. Work-up in the usual manner gave 60 mg. of neutral material (ca. 16%). A thin layer chromatogram (dichloromethane–ether, 4:1) showed a mixture of at least ten compounds. The reaction was not further investigated.

20ξ-Methoxy-5α-pregnan-3β-ol Acetate (IIIb).—A solution of 70 mg. of crude 20ξ-methoxy-5α-pregnan-3β-ol (IIIa) in

4 ml. of pyridine containing 0.5 ml. of acetic anhydride was refluxed for 2 hr. The cooled solution was poured into ice–water (10 ml.) and the mixture extracted with 3–5 ml. portions of chloroform. Evaporation of the solvent gave a brown crystalline solid. Recrystallization from methanol gave 21 mg. of white flakes, m.p. 111–118°. Two additional recrystallizations raised the melting point to 123–126°. A mixture melting point with IIIb obtained from the anodic reaction (methanol, pH 8.6) was 122–125°. The gas chromatographic retention times and infrared spectra of both samples were identical.

5α-Pregnan-3β-ol (IV).—To a solution of 27 mg. of Δ²⁰-5α-pregnen-3β-ol (II) in 6 ml. of ethanol–dioxane (1:1) was added 96 mg. of palladium on charcoal (10%). The mixture was hydrogenated for 6 hr. at room temperature and under a pressure of 24 p.s.i., using the Parr apparatus. Removal of the catalyst by filtration and evaporation of the solvent gave a gum. The product was subjected to preparative thin layer chromatography developed continuously for 2 hr. (silica gel G; dichloromethane–ether, 95:5). Elution of the major band with acetone gave 11 mg. of white solid, m.p. 118–128°. Recrystallization from methanol gave 2.7 mg. of 5α-pregnan-3β-ol (VI) as shiny white flakes, m.p. 138–139.5°, lit.¹¹ m.p. 138–138.4°. The infrared spectrum showed the absence of bands at 1640 and 912 cm.⁻¹.

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(11) E. P. Oliveto, L. Weber, and E. B. Hersberg, *J. Am. Chem. Soc.*, **76**, 4482 (1954).

Kolbe Electrolyses of 3-Phenyl- and 3,3-Diphenylpropanoic Acids

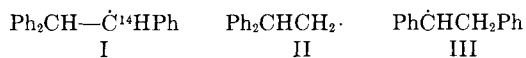
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The question of phenyl 1,2-migration of free radicals during Kolbe electrolyses has been examined by electrolyzing 3,3-diphenylpropanoic acid (1) in acetic acid containing acetate ion and (2) in methanol, and (3) by electrolyzing 3-phenylpropanoic acid in acetic acid containing acetate ion. The electrolysis products from 1 consisted of 1,1-diphenylpropane (IV), 3-phenyl-3,4-dihydrocoumarin (V), and 1,2-diphenylethyl acetate (VIII), along with smaller quantities of phenyl cinnamate (VI), 2-*O*-acetyl-1,1-diphenylethylene glycol (IX), and phenyl 3-acetoxy-3-phenylpropanoate (VII). The identified electrolysis products from 2 were 1,1,4,4-tetraphenylbutane (XIII) and methyl 1,2-diphenylethyl ether (XVIII). VIII and XVIII represent products of phenyl 1,2-migration. The electrolysis products from 3 consisted of *n*-propylbenzene and 2-phenylethyl acetate. Arguments are presented supporting the hypothesis that the unrearranged hydrocarbon products (IV and XIII) arose by coupling of free radicals prior to rearrangement and that the rearranged acetate and ether products (VIII and XVIII) resulted from anodic oxidation of unrearranged 2,2-diphenylethyl radicals to 2,2-diphenylethyl carbonium ions, followed by rearrangement of the latter to more stable benzylic 1,2-diphenylethyl carbonium ions which ultimately solvolyzed to the observed oxygenated products.

Recently, with the intention of developing a system in which the possibility of bridged radical intermediates could be critically evaluated, we have succeeded² in generating the 1,2,2-triphenylethyl-1-C¹⁴ radical (I)



by the decarbonylation of 2,3,3-triphenylpropionaldehyde-2-C¹⁴. The label redistribution in the monomeric decarbonylation product, 1,1,2-triphenylethane, indicated that radical I had undergone phenyl 1,2-rearrangement to the extent of 5–14% during its transitory existence. In considering methods by which radical intermediates might be produced to broaden the above studies, the Kolbe electrolysis reaction appeared potentially applicable. While phenyl 1,2-shifts are observed frequently and are well-documented

for radical intermediates produced by a variety of other techniques,³ the situation regarding such rearrangements during Kolbe electrolyses is less straightforward. Urry³ has reported the formation of rearranged products (isobutylbenzene, 2-methyl-3-phenyl-1-propene, and 1-phenyl-2-methyl-1-propene) along with unrearranged products (*t*-butylbenzene, ethyl β-phenylisovalerate, 2,2-dimethyl-2,2-diphenylhexane, and neophyl β-phenylisovalerate) during the Kolbe electrolysis (ca. 2 ma./cm.²) of β-phenylisovaleric acid in ethanol. More recently, on the other hand, Brederfeld and Kooyman⁴ noted specifically the absence of rearranged products on Kolbe electrolysis of β-phenylisovaleric acid under slightly different conditions (methanol and methanol–acetic acid solvents, ca. 150 ma./cm.²). Accordingly, it appeared initially pertinent to ascertain if Kolbe electrolysis would lead

(1) The authors are grateful to the National Science Foundation for a grant (G9479) which supported part of this study.

(2) W. A. Bonner and F. D. Mango, *J. Org. Chem.*, **29**, 29 (1964).

(3) W. H. Urry, Abstracts of Papers, 12th National Organic Chemistry Symposium of the American Chemical Society, Denver, Colo., 1951, p. 36.

(4) H. Brederfeld and E. C. Kooyman, *Rec. trav. chim.*, **76**, 297 (1957).