methanol and 70 ml. of water saturated with octanol. Spots were detected by spraying with a saturated solution of antimony trichloride in chloroform and 20% thionyl chloride. Ozonolysis yielded dihydronorparthenone, m.p. 220°. Hydrogenation gave dihydroisoparthenin, m.p. 200–202°.

A sample of leaves and petioles identified as *Ambrosia artemisiifolia* L. var *elatior*, collected by Dr. B. H. Braun in the vicinity of Cincinnati, Ohio, in 1956, was extracted in the same manner but did not furnish crystalline material.

Two samples of *Ambrosia trifida* L. were extracted. One of leaves and petioles only, collected by Dr. B. H. Braun near Cincinnati in 1956, 1000 g., yielded 2.1 g. of gum which gave no crystalline fractions on chromatography. A second, large sample, 40 kg., collected in September 1959, on the outskirts of Tallahassee during the flowering period, gave 55 g. of gum which could not be separated into crystalline fractions.

A 600-g. sample of *Ambrosia bidentata* Michx., collected by Dr. B. H. Braun near Lamar, Missouri, in August 1959, gave 28 g. of gum which appeared to be quite polar. Chromatography over alumina failed to yield crystalline material.

Extraction of Parthenium incanum H.B.K. A 2380-g. sample of the above, collected by Dr. H. F. L. Rock in July 1960, near El Paso, Texas, was ground and extracted with chloroform for 2 days. The extract was concentrated; the residue taken up in 200 ml. of hot ethanol, 300 ml. of hot water containing 15 g. of lead acetate, and a few ml. of acetic acid. After 1 day the mixture was filtered, the filtrate concentrated *in vacuo*, extracted with chloroform, and dried. Removal of chloroform gave 45 g. of gum which was dissolved in 35 ml. of chloroform, diluted with 80 ml. of benzene, and chromatographed over 400 g. of alumina. The first fractions (benzene-chloroform 4:1) eluted some gum. This was followed by 14 g. of crystalline material in the benzene-chloroform and chloroform fractions. Recrystallization from acetone–diisopropyl ether gave 8.3 g. of colorless crystals, m.p. 175–178°, raised to 178–180° by further purification, $[\alpha]_D^{24}$ −32.5° (*c* 4.3, ethanol), $[\alpha]_D^{22}$ −5.7°(*c* 5.1, chloroform). The substance was indistinguishable from coronopilin in infrared spectrum and paper chromatography.

A finely ground sample of the same plant, wt. 1420 g., collected by Mr. R. J. Barr in September 1960, near Portal, Cochise County, Arizona, was extracted with chloroform. The usual work-up gave 32 g. of an orange-yellow gum which was taken up in 30 ml. of chloroform and diluted with 70 ml. of benzene. Chromatography over 350 g. of alumina with benzene (eight 100-ml. fractions), benzene-chloroform (10 fractions, 10:1), chloroform (21 fractions) and chloroform-methanol (20 fractions, 50:1) gave no crystalline material. The second benzene fraction was taken up in benzene and diluted with ligroin to incipient cloudiness. Some benzene was added to clear the solution. On standing there precipitated 0.15 g. of crystalline material which was recrystallized from benzene-ligroin. The colorless needles melted at 145–146°, $[\alpha]_D^{20}$ −15.4° (*c*, 0.925, chloroform), ultraviolet maxima at 218 mμ, ε 13,900, and 325 mμ, ε 38. The infrared spectrum exhibited bands at 1770 cm.$^{-1}$ (γ-lactone), 1718 (cyclopentenone), 1660 (double bond conjugated with lactone), and 1595 cm.$^{-1}$ (cyclopentenone double bond). The NMR spectrum reported previously[3] confirmed the assignments. These properties suggested that the material was ambrosin which was confirmed by comparison with an authentic sample.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37; O, 19.49. Found: C, 72.84; H, 7.57; O, 19.29.

Rechromatography of the gummy fractions did not result in crystalline material.

Acknowledgment. We are indebted to Dr. B. H. Braun, Dr. H. F. L. Rock, and Mr. R. J. Barr for plant collections and to Professor R. K. Godfrey for valuable discussions.

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER]

Chemistry of Edulin, Neorautone, and Related Compounds from *Neorautanenia edulis C.A. Sm.*

B. L. VAN DUUREN

Received June 9, 1961

Four of the compounds isolated in an earlier study from *N. edulis* were subjected to chemical and spectroscopic examination. A structure is proposed for edulin and a partial structure is derived for neorautone. One new compound, substance vii, was isolated from extracts of the tuber of this plant and examined in this work. Substance vii and edulin are structurally closely related to the reduced isoflavanes pterocarpin and homopterocarpin and to the angular rotenoids pachyrrhizone and pachyrrhizine.

In a previous report[1] the isolation of six new substances from the tuber of *Neorautanenia edulis C.A. Sm.* was described. A study of the chemical constituents of the tuber of this plant became of interest in view of the use of the tuber as a fish poison by natives in the Northern Transvaal region of Southern Africa.[2] Of the six compounds isolated, two were found to be toxic to goldfish.[3] On the basis of elemental analyses and molecular weight determinations molecular formulas were assigned to the six compounds[1] but chemical studies were not described. The present report gives the results of chemical studies on some of these compounds of which larger quantities were available for investigation.

In the isolation of these compounds from the tuber[1] large amounts of dark brown resins were obtained; these resins were examined with the purpose of improving the yields of the compounds obtained from the tuber. Three of the compounds

(1) B. L. Van Duuren and P. W. G. Groenewoud, *J. S. African Chem. Inst.*, **3**, (2), 29 (1950).

(2) J. M. Watt and M. G. Breyer-Brandwijk, *Medical and Poisonous Plants of Southern Africa*, Livingstone, Edinburgh, 1932, p. 77.

(3) B. L. Van Duuren and P. W. G. Groenewoud, *J. S. Afr. Chem. Inst.*, **3**, (2), 35 (1950).

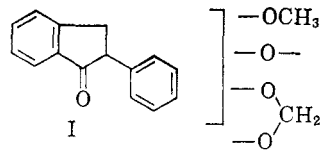
previously isolated[1] were obtained from the resin by solvent fractionation and column chromatography. In addition, one new compound, labeled substance vii, was obtained from the resin. Furthermore, the resin yielded a sterol which had an analysis corresponding to $C_{28}H_{48}O$. This material, from its melting point, rotation, and infrared spectrum, consisted mainly of stigmasterol; other isomeric sterols could not be removed by repeated crystallization. Catalytic hydrogenation yielded stigmastanol; the melting point of this product was not depressed on admixture with an authentic sample. A discussion of the results obtained in this study on some of the seven compounds of unknown structure from *N. edulis* follows.

Neorautone. The name neorautone is suggested for the light yellow compound, m.p. 207°, earlier[1] labeled substance i. New analytical data suggest the molecular formula $C_{17}H_{12}O_6$ for this compound. Neorautone shows no measurable optical activity; it fluoresces brilliantly under ultraviolet light, does not give a coloration with ferric chloride and does not react with diazomethane. This substance has one methoxyl group and does not contain carbon-methyl groups. It is insoluble in alkali and is stable to boiling 10% aqueous ethanolic (1:1) potassium hydroxide. This behavior excluded the possibility that neorautone contains the γ-pyrone ring which is characteristic of the rotenone group of fish poisons.[4] Neorautone gives a positive Labat test[5] for methylenedioxyphenyl and decolorizes alkaline permanganate. Its infrared absorption spectrum shows an intense peak at 1730 cm.$^{-1}$ The insolubility of neorautone in alkali excludes the presence of carboxylic acid, anhydride, ester, or lactone carbonyls, so that this band must be due to keto carbonyl.

The ultraviolet absorption spectrum suggested a conjugated carbonyl; this can be reconciled with the position of the carbonyl peak in the infrared only by concluding that the keto carbonyl is present in a five-membered ring conjugated to a benzene ring.[6,7]

Neorautone does not show hydroxyl absorption but shows bands that can be ascribed to aromatic structures and methylenedioxyphenyl groups.[8] The pertinent infrared absorption bands of neorautone and the other compounds described in this report are given in the Experimental section.

The ultraviolet absorption spectrum of neorautone suggests a substituted desoxybenzoin chromophore,[9-12] so that the partial structure I can be written for neorautone.



I

Neorautone was hydrogenated with a rhodium-on-alumina catalyst to dihydroneorautone. This alkali-insoluble compound shows in its infrared absorption spectrum two bands in the carbonyl region, *viz.*, at 1750 and 1710 cm.$^{-1}$ This suggests that the double bond hydrogenated is adjacent to the cyclic carbonyl groups.

Hydrogenation of neorautone with a palladium catalyst in acetic acid gave a second dihydroneorautone. The carbonyl band in the infrared spectrum of this compound is at essentially the same position as in neorautone and it does not show hydroxyl absorption.

The NMR spectrum of neorautone was measured in deuterochloroform with tetramethylsilane as internal standard. This spectrum showed a signal at 226 c.p.s. which is characteristic of a methoxyl group attached to a resonant ring. A signal at 358 c.p.s. is typical of a methylenedioxy group attached to a benzene ring. Integration results based on the signals from the methylenedioxy and methoxyl protons confirmed a total of twelve protons in the molecule. Furthermore, signals were obtained which are very characteristic of three adjacent protons on a benzene ring. The NMR spectrum indicates that there are no hydrogens other than the methoxyl and methylenedioxy which are not directly bonded to benzene rings or conjugated double bonds; also there are no *ortho*-hydrogens other than the three adjacent protons on one benzene ring. Although unlikely on the basis of other data, the NMR also excluded the presence of a methyl ketone which characteristically gives rise to a signal at about 130 c.p.s.

Edulin. Substance vi, m.p. 225°, was described earlier[1] and the molecular formula $C_{18}H_{14}O_6$ assigned to it. New analytical data suggest the molecular formula $C_{18}H_{12}O_5$; the name edulin is suggested for this compound.

(4) K. Venkataraman, *Progress in the Chemistry of Organic Natural Products*, L. Zechmeister, ed., Springer Verlag, Vienna, 1959, Vol. 17, p. 2.

(5) J. A. Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).

(6) W. M. Shubert and W. A. Sweeney, *J. Am. Chem. Soc.*, **77**, 4172 (1955).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley & Sons, Inc., New York, 1958, 2nd ed., p. 138.

(8) (a) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 4807 (1955); (b) C. K. Briggs, P. F. Highet, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 2899 (1956); (c) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957); (d) H. Tschamler and R. Leutner, *Monatsh.*, **83**, 1502 (1952); (e) H. Suginome, *J. Org. Chem.*, **24**, 1655 (1959).

(9) P. Crabbe, P. R. Leeming, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 5258 (1958).

(10) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, J. Wiley & Sons, Inc., New York, 1951, No. 135.

(11) H. Bickel and H. Schmid, *Helv. Chim. Acta*, **36**, 664 (1953).

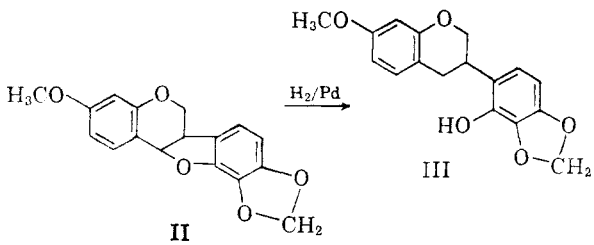
(12) M. A. P. Meisinger, F. A. Kuehl, E. L. Rickers, N. G. Brink, K. Folkers, M. Forbes, F. Zilliken, and P. Gyorgy, *J. Am. Chem. Soc.*, **81**, 4979 (1959).

Edulin is optically active, gives a positive Labat test for methylenedioxyphenyl, decolorizes alkaline permanganate and does not contain methoxyl or carbon-methyl groups. The infrared absorption spectrum does not show any hydroxyl or carbonyl absorption; the presence of aromatic ether structures and methylenedioxyphenyl groups[8] is indicated.

Oxidation of edulin with 5% nitric acid gave styphnic acid as the only isolable product; permanganate oxidation gave oxalic acid only. Traces of other oxidation products were obtained in insufficient quantities for further investigation. Edulin is stable to refluxing 20% aqueous ethanolic alkali and is recovered unchanged on alkaline fusion at 250°. With hydriodic acid, edulin is rapidly degraded to give dark colored resinous products.

Edulin contains one readily reducible double bond, as hydrogenation with palladium in acetic acid gave a neutral dihydro compound. The infrared spectrum of this compound is very similar to that of edulin. Dihydroedulin could be further hydrogenated with the same catalyst to tetrahydroedulin. Tetrahydroedulin is soluble in alkali and shows hydroxyl absorption at 3400 cm.$^{-1}$ in the infrared spectrum. Hydrogenation of edulin with a rhodium-on-alumina catalyst gives a neutral octahydro derivative which does not show hydroxyl absorption in the infrared spectrum.

The formation of a phenol, tetrahydroedulin, in the hydrogenation of edulin with two moles of hydrogen can be accounted for by the opening of a dihydrobenzofuran structure. Robertson and coworkers[13,14] found that pterocarpin, II, undergoes a similar hydrogenolysis to the phenol, III. The



same type of hydrogenolysis has been observed in the rotenone series.[15]

A comparison of the infrared spectra of edulin and pterocarpin (Fig. 1) suggests a close structural similarity between these two compounds. Pterocarpin, like edulin, gave styphnic acid on nitric acid oxidation[13] which suggests that edulin contains a *meta*-dioxybenzene residue.

The ultraviolet absorption spectra of pterocarpin

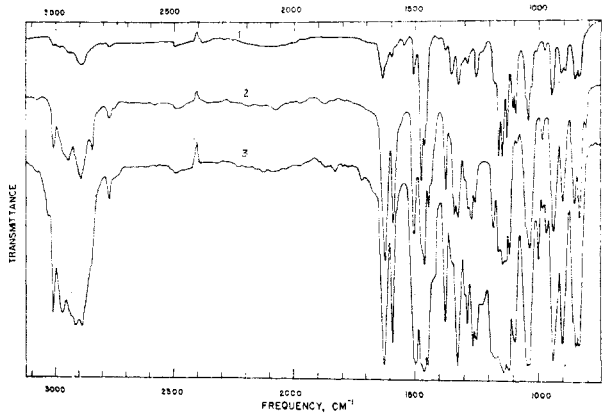


Fig. 1. Infrared absorption spectra in chloroform solution, 0.1 mm. thickness: 1, edulin, 2.5% solution; 2, pterocarpin, 5% solution; 3, substance (vii), 10% solution

and the related compound homopterocarpin[13] were compared with those of edulin and its hydrogenation products (Figs. 2 and 3). All these

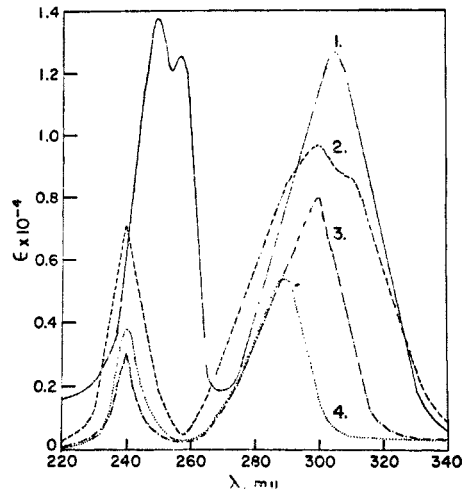


Fig. 2. Ultraviolet absorption spectra: 1, ———, edulin; 2, – – – –, dihydroedulin; 3, – · – · –, tetrahydroedulin; 4, ... , octahydroedulin; solvent chloroform

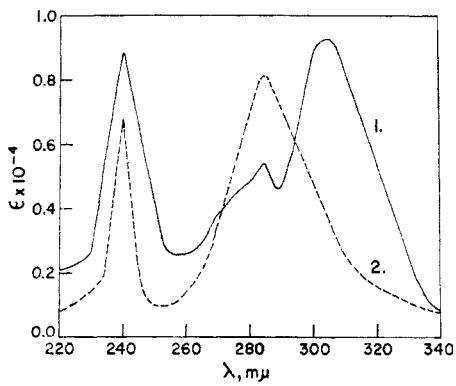


Fig. 3. Ultraviolet absorption spectra: 1, ———, pterocarpin; 2, – – – –, homopterocarpin, solvent chloroform

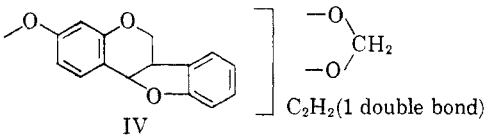
compounds, except edulin, show a peak at 240 mμ. The peaks at 250 and 257 mμ in edulin are replaced by a single peak at 240 mμ in its hydrogenation

(13) A. McGookin, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 787 (1940).

(14) A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1440 (1954).

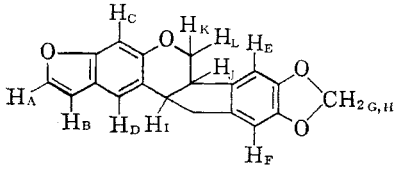
(15) F. B. LaForge and L. F. Smith, *J. Am. Chem. Soc.*, 51, 2574 (1929).

products. This shift must be associated with the saturation of the easily reducible double bond. The ultraviolet absorption spectra of dihydroedulin and pterocarpin are very similar which suggests that, whereas these two compounds probably have the same chromophore, there is additional conjugation in edulin. Both edulin and pterocarpin have large negative specific rotations, which suggests that these two compounds have similar asymmetric centers. On this basis it became possible to postulate a partial structure IV for edulin.



IV

The readily reducible double bond cannot be placed between the two heterocyclic rings since this would give a diphenylethylene chromophore which is expected to show significantly different ultraviolet absorption from that observed for edulin. Diphenylethylene shows a broad ultraviolet absorption maximum at 297 mμ (ϵ_{max} 27,000). Anhydrosophorol,[8e] which contains a diphenylethylene chromophore, shows an ultraviolet absorption spectrum significantly different from that of edulin. The ultraviolet absorption spectral data and the presence of the readily reducible double bond are best explained if the two remaining carbon atoms are present in a benzofuran structure. The plausibility of such a structure was strengthened by the NMR spectrum shown in Fig. 4; the assignments for the various protons are indicated in the diagram. The lack of spin coupling between H_E and H_F also fixes the position of the methylenedioxy group as shown in the proposed structure for edulin given in Fig. 4.



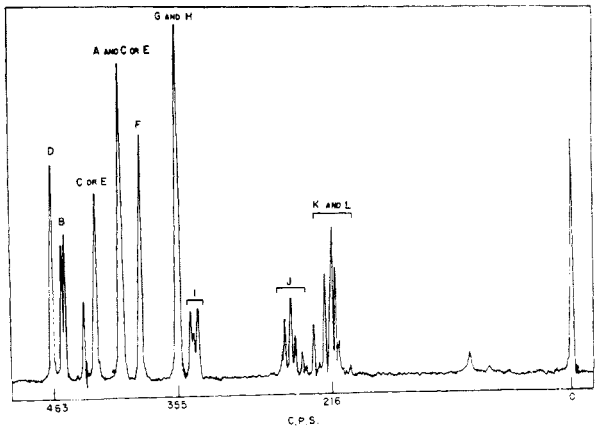


Fig. 4. NMR spectrum of edulin in deuterochloroform with tetramethylsilane as internal 0 reference; 60 mc.

Robinson[16] has discussed the biogenesis of pterocarpin and homopterocarpin and points out that they are related to the isoflavones, exemplified by genistein[17] and related natural products such as angolensin.[18]

The evidence given in the present work indicates a close structural relationship between edulin, pterocarpin, homopterocarpin and substance vii, which is discussed below. Moreover, the similarities between the structure proposed here for edulin and that of pachyrrhizone and pachyrrhizine[11,19] are striking and suggest similar biogenetic pathways.

Substance vii. This compound, m.p. 122–123°, was isolated for the first time in the present work. Analytical data on substance vii and its hydrogenation product suggest the molecular formula $C_{18}H_{18}O_4$ for substance vii; it contains one or, more probably, two carbon-methyl groups and does not contain any methoxyl groups. As in the case of edulin and pterocarpin, substance vii is optically active and shows a large negative specific rotation. The infrared spectrum of substance vii (Fig. 1) indicates the absence of hydroxyl and carbonyl bands. This spectrum shows a close agreement in most bands with that of pterocarpin; furthermore their ultraviolet absorption spectra suggest the presence of the same chromophore in these two compounds. Catalytic hydrogenation of substance vii gave a tetrahydro derivative which is soluble in alkali and shows a strong hydroxyl band at 3400 cm.$^{-1}$ in the infrared spectrum. The formation of a phenolic hydrogenation product is ascribed to the presence in vii of a dihydrobenzofuran residue, as described above for edulin.

Neorautenone. The name neorautenone is suggested for substance iii, m.p. 179°, described earlier.[1] The molecular formula, $C_{19}H_{14}O_6$, assigned for this compound[1] is supported by new analytical data on neorautenone and its derivatives. Neorautenone does not contain methoxyl or carbon-methyl groups, does not give a coloration with ferric chloride and is insoluble in aqueous alkali. The material is soluble in, but stable to, refluxing aqueous ethanolic alkali. Neorautenone gives a positive Labat test for the methylenedioxyphenyl grouping[5] and decolorizes aqueous alkaline permanganate. The infrared absorption spectrum of neorautenone indicates the absence of hydroxyl groups; a strong carbonyl band appears at 1680 cm.$^{-1}$ This band is ascribed to a keto carbonyl group conjugated to an aryl group. The carbonyl

(16) R. Robinson, *The Structural Relations of Natural Products*, Oxford University Press, London, 1955, p. 41.

(17) A. G. Perkin and L. H. Horsfall, *J. Chem. Soc.*, **77**, 1310 (1900).

(18) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 1920 (1952).

(19) O. A. Stamm, H. Schmid, and J. Büchi, *Helv. Chim. Acta*, **41**, 2006 (1958).

group must then be either a six-membered ring fused to the aromatic residue or in an open-chain conjugated system.[20] The presence of one or more methylenedioxyphenyl groups, indicated by a positive Labat test is supported by the infrared data. The considerable intensities of the aromatic bands at 1630, 1585, and 1550 cm.$^{-1}$ are ascribed to conjugation with the carbonyl group. The ultraviolet absorption spectrum shows an intense peak at 242 mμ which is ascribed to the conjugated carbonyl group.[21] Neorautenone gives a red crystalline 2,4-dinitrophenylhydrazone. The ultraviolet absorption maxima of this derivative is characteristic for such a derivative when the carbonyl group is conjugated to an aromatic group or carbon-carbon double bond. Neorautenone is readily brominated to give two isomeric dibromides.

Hydrogenation of neorautenone with palladium in acetic acid solution leads to the absorption of three moles of hydrogen. When the hydrogenation is stopped after the absorption of one mole of hydrogen, a dihydroneorautenone is obtained. The carbonyl peak and aromatic absorption bands in the infrared spectrum of dihydroneorautenone remain unchanged from that of the parent compound. The absence of hydroxyl absorption in the infrared spectrum of dihydroneorautenone and its insolubility in alkali suggests that, unlike edulin, this compound does not contain a dihydrobenzofuran system. Furthermore, the bromination and hydrogenation products suggest the presence of a readily reducible double bond, not alpha to the carbonyl group.

The product obtained when neorautenone is hydrogenated in acetic acid with palladium as catalyst with the absorption of three moles of hydrogen does not have an analysis corresponding to a hexahydroneorautenone. Instead, repeated analyses confirm an empirical formula $(C_4H_4O)_n$ for this compound; it does not show carbonyl or hydroxyl absorption in the infrared spectrum. Further studies were not carried out on this compound.

When neorautenone is hydrogenated with rhodium-on-alumina as catalyst a total of 5.2 moles of hydrogen was absorbed after twenty-four hours. The oily product gave, after column chromatography, two new products. The infrared spectra show that in both compounds the carbonyl group of neorautenone was reduced to hydroxyl.

Substance iv. On the basis of a carbon-hydrogen analysis and molecular weight determination the molecular formula $C_{17}H_{14}O_5$ was earlier assigned to this compound.[1] Substance iv was not isolated from the resins that were fractionated in the present study, so that extensive further investigations were not carried out on it. However, its ultraviolet and infrared absorption spectra showed striking similarities to those of neorautenone, which suggests a close similarity in structure between these two compounds. Substance iv gives a crystalline 2,4-dinitrophenylhydrazone. New elemental analyses of substance iv and this derivative support the originally assigned molecular formula, $C_{17}H_{14}O_5$.

(20) Ref. 7, p. 137.

(21) H. S. French, *J. Am. Chem. Soc.*, **74**, 5114 (952).

EXPERIMENTAL[22]

Fractionation of resin. Ether extraction of the powdered tuber of *N. edulis* gave a dark brown solution from which crystalline material was obtained on evaporation. The fractionation of this product was described in an earlier paper.[1] Evaporation of the mother liquors left after crystallization yielded large quantities of dark brown resin. It is the fractionation of this resin which was undertaken in the present work. The resin, 290 g., was repeatedly extracted with boiling petroleum ether (b.p. 30–60°) to yield 36.7 g. of petroleum ether–soluble material. The petroleum ether–insoluble material, 254 g., yielded by chromatography on alumina small quantities of the compounds isolated earlier.[1] The petroleum ether–soluble fraction gave on evaporation 8.6 g. of a yellow resin (fraction B) and 27.5 g. of petroleum ether–soluble oil (fraction A). Fractions A and B were chromatographed on activated alumina; both fractions gave the same series of compounds. The column chromatographic separation of fraction A is described here. The entire fraction A was chromatographed on 270 g. of activated alumina. (Alcoa activated alumina, grade F-20, reactivated by heating at 210° for 16 hr.) In all, eighteen fractions were collected, but these were recombined on the basis of their infrared absorption spectra and melting points into six fractions.

Fraction i, *sterol.* This fraction, eluted with 1 l. of petroleum ether (b.p. 30–60°)–ether (1:1) gave 4.20 g. of a yellow oil. This oil was rechromatographed on 250 g. of activated alumina and eluted with petroleum ether (b.p. 30–60°)–ether (1:1), 1.4 l., then with ether, 1 l., and finally with chloroform, 1.2 l. All these fractions gave oily residues. The oil from the chloroform eluate, 0.30 g., gave colorless flakes, m.p. 130–140° (uncorr.), on crystallization from ethanol. The product was recrystallized from ethanol and vacuum sublimed at 130°/0.10 mm., m.p. 155–156° (reported[23] m.p. for stigmasterol, 170–171°).

Anal. Calcd. for $C_{28}H_{48}O$: C, 84.00; H, 12.00. Found: C, 84.19; H, 11.89.

Rotation. Seven milligrams in 1.2 ml. of chloroform gave α_D −0.16°, l = 1, at 25°, $[\alpha]_D^{25}$ −27.6° (reported[23] rotation for stigmasterol $[\alpha]_D^{17}$ −45.8°). This sterol gave an infrared absorption spectrum very similar to that of stigmasterol. With acetic anhydride it gave a crystalline acetate, m.p. 133–134°, $[\alpha]_D^{25}$ −43.9° in chloroform (reported[24] for stigmasterol acetate: m.p. 140–141°, $[\alpha]_D^{20}$ −50.3°). On hydrogenation of the sterol 2.0 moles of hydrogen was absorbed to give a stanol, m.p. 136–137°, undepressed on admixture with stigmastanol (reported[25] m.p. 137°). The infrared spectra of the unknown and authentic compounds were identical. The other fractions from the rechromatography of fraction i did not give solids on attempted crystallizations and were not examined further.

Fraction ii, *edulin.* This fraction, also eluted with petroleum ether (b.p. 30–60°)–ether (1:1), yielded 4.1 g. of a tan

(22) Except where stated otherwise, melting points are corrected and infrared absorption spectra were obtained with potassium bromide pellets. Ultraviolet absorption data are given in mμ followed by molecular extinction values in parentheses.

(23) J. C. E. Simpson and N. E. Williams, *J. Chem. Soc.*, 737 (1937).

(24) R. J. Anderson, *J. Am. Chem. Soc.*, **46**, 1450 (1924).

(25) D. Larsen and F. W. Heyl, *J. Am. Chem. Soc.*, **56**, 2663 (1934).

colored crystalline material. The product was triturated with petroleum ether (b.p. 30–60°) and the petroleum ether–insoluble residue recrystallized from chloroform-ether to give 0.65 g. of colorless needles, m.p. 225°, undepressed on admixture with edulin, earlier[1] labeled substance vi.

Anal. Calcd. for $C_{18}H_{12}O_5$: C, 70.19; H, 3.93. Found: C, 69.83, 70.19, 69.88; H, 4.26, 3.86, 4.14; C—CH_3, 1.10; O—CH_3, 0.0.

Rotation. Twenty-six milligrams of edulin made up to 1 ml. in chloroform gave α_D −6.90°, l = 1, $[\alpha]_D^{25}$ −265.3°.

Ultraviolet absorption spectrum in chloroform (see also Fig. 2): 250 (13,680), 257 (12,500), 305 (12,600).

Infrared absorption maxima (see also Fig. 1): 1645, 1639, 1626, 1608, 1548, 1511 (aromatic), 1166, 1040, 915 cm.$^{-1}$ (methylenedioxyphenyl).

Fraction iii, *neorautenone and substance* vii. The third fraction from the chromatography of fraction A was eluted with ether, 800 ml., to give, after removal of solvent 2.1 g. of oily crystals. Trituration with petroleum ether (b.p. 30–60°) gave 1.1 g. of a petroleum ether–insoluble solid. Recrystallization from ether gave 200 mg. of white prisms, m.p. 179°, undepressed on admixture with neorautenone, earlier[1] labeled substance iii. Neorautenone was purified for analysis by vacuum sublimation at 145°/0.05 mm.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 67.45; H, 4.10. Found: C, 67.26, 67.44; H, 4.44, 4.35; O—CH_3, 0.0; C—CH_3, 0.51.

Ultraviolet absorption spectrum in chloroform: 242 (40,000), 260 (shoulder, 9300), 275 (5800), 302 (6000), 337 (3500).

Infrared absorption maxima: 1680 (carbonyl), 1630, 1585, 1550 (aromatic), 1192, 1042, 930 cm.$^{-1}$ (methylenedioxyphenyl).

Neorautenone sometimes crystallized in an isomorphous form, m.p. 139–140°, when ether was used as solvent. When this form was heated above its melting point, cooled, and the melting point determined again, it then melted at 179°.

The petroleum ether–soluble triturate, from which neorautenone separated, gave 1.0 g. of a white solid on evaporation to dryness. This residue, m.p. 100–110° (uncorr.) gave, after repeated recrystallization from petroleum ether (b.p. 30–60°)–ether, 0.3 g. of colorless needles m.p. 122–123°, unchanged by vacuum sublimation. This compound, not isolated in the earlier study was labeled substance vii.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.54; H, 6.09; C—CH_3, 5.24; mol. wt., 298. Found: C, 72.88, 72.67; H, 6.31, 6.31; C—CH_3, 4.97, 5.39; O—CH_3, 0.00; mol. wt., 314.

Ultraviolet absorption in chloroform: 240 (5,992), 292, (4,494), 310 (5,671).

Infrared absorption maxima (see also Fig. 1): 1620, 1590 (aromatic), 1190, 1035, 910 cm.$^{-1}$ (methylenedioxyphenyl).

Rotation. Twenty-eight milligrams of substance vii dissolved in 0.50 ml. of chloroform gave α_D −12.95° at 25°, l = 1, $[\alpha]_D^{25}$ −232.1°.

Fraction iv. This fraction was obtained from the chromatography of fraction A by continued elution with ether, 400 ml.; the residue gave a small yield of a tan solid, m.p. 160–165° (uncorr.), which was not investigated further.

Fractions v *and* vi. These fractions were obtained by elution with chloroform and ethanol, respectively, and gave on evaporation minute quantities of crystalline material which were not investigated further.

Purification of neorautone. This material obtained in the earlier study[1] was purified by chromatography on activated alumina followed by crystallization from chloroform-ethanol to give light yellow needles, m.p. 207° (reported[1] m.p. 211°).

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.98; H, 4.09; O—CH_3, 10.47. Found: C, 68.94, 68.91, 68.90; H, 3.67, 3.80, 3.64; O—CH_3, 8.95; C—CH_3, 0.51.

Ultraviolet absorption in chloroform: 246 (41,500), 291 (20,000), 350 (16,750).

Fluorescence excitation max. 380 mμ, fluorescence emission max. 485 mμ.

Infrared absorption maxima: 1730 (carbonyl), 1620, 1580, 1540, 1500 (aromatic), 1190, 1036, 922 cm.$^{-1}$ (methylenedioxyphenyl).

Hydrogenation of neorautone. (a) *With palladium as catalyst.* Neorautone, 150 mg., was hydrogenated with 0.25 g. of palladium-on-charcoal as catalyst (10% Baker and Co., Inc.) in glacial acetic acid. One mole of hydrogen was absorbed. The product was crystallized from chloroform-ethanol, m.p. 215–216°. This product is insoluble in alkali.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.74. Found: C, 68.27; H, 4.57.

Ultraviolet absorption in chloroform: 250 (6350), 300 (6146), 350 (9866).

Fluorescence excitation max. 360 mμ, fluorescence emission max. 490 mμ.

Infrared absorption maxima: 1725 (carbonyl), 1637, 1590 cm.$^{-1}$ (aromatic).

(b) *With rhodium-on-alumina as catalyst.* A solution of 100 mg. of neorautone in 20 ml. of prereduced tetrahydrofuran was hydrogenated with 200 mg. of rhodium-on-alumina (5%) as catalyst. Two moles of hydrogen was absorbed. The oily product was chromatographed on activated alumina and eluted successively with ether, chloroform, and ethanol. The ether and ethanol eluates left small amounts of resinous residues which were not examined further. The chloroform eluate gave a white crystalline residue, 0.05 g., which was crystallized from chloroform-ethanol to give white needles, m.p. 215–216°. This product was insoluble in alkali and gave a 10° depression of melting point on admixture with the product obtained from the palladium-catalyzed hydrogenation.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.74. Found: C, 68.13, 68.06; H, 4.76, 4.77.

Ultraviolet absorption in chloroform: 240 (8382), 297 (8741), 352 (2724).

Fluorescence excitation max. 360 mμ, fluorescence emission max. 490 mμ.

Infrared absorption maxima: 1750, 1710 (carbonyl), 1625, 1589 (aromatic), 1190, 1035, 915 cm.$^{-1}$ (methylenedioxyphenyl).

Oxidative degradation of edulin. (a) *With aqueous nitric acid.* Edulin, 0.5 g., was heated at 100° with 50 ml. 5% aqueous nitric acid for 16 hr. The aqueous solution was extracted with benzene. The residue from this extraction was recrystallized from chloroform, m.p. 177°. This material gave no depression of melting point on admixture with styphnic acid (m.p. 178°) and their infrared absorption spectra were identical.

(b) *With permanganate.* Edulin, 0.5 g., was oxidized with potassium permanganate in acetone. Neutral oxidation products were not obtained. The acidic product was extracted with ether and crystallized from benzene-ether to give colorless crystals, m.p. 189°, undepressed on admixture with oxalic acid. The infrared absorption spectrum was identical with that of oxalic acid.

Hydrogenation of edulin. (a) *Dihydroedulin.* Edulin, 0.10 g., in 5 ml. of tetrahydrofuran was added to 0.25 g. of prereduced palladium-on-charcoal (10%) catalyst in 15 ml. of glacial acetic acid and hydrogenated at atmospheric pressure. One mole of hydrogen was absorbed and the product obtained was crystallized from carbon tetrachloride, m.p. 213–215° dec.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.74; H, 4.55. Found: C, 69.46; H, 4.89.

Ultraviolet absorption in chloroform (see also Fig. 2): 240 (7052), 287 (shoulder, 8750), 300 (9632), 309 (shoulder, 8600).

Infrared absorption maxima: 2980, 2960, 2930, 2900 (aliphatic CH), 1637, 1620, 1608 (aromatic), 1160, 1040, 910 cm.$^{-1}$ (methylenedioxyphenyl).

(b) *Tetrahydroedulin.* Hydrogenation of edulin with 2.0 moles of hydrogen or hydrogenation of dihydroedulin with 1.0 mole of hydrogen using the same catalyst and solvent as described under dihydroedulin above gave tetrahydroedulin, which was recrystallized from chloroform and purified by

vacuum sublimation at 130°/0.1 mm. to give white needles, m.p. 213° (dec.).

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.29; H, 5.17. Found: C, 69.38; H, 5.11.

Ultraviolet absorption in chloroform (see also Fig. 2): 240 (3444), 300 (7896).

Infrared absorption maxima: 3400 (hydroxyl), 2990, 2960, 2930, 2900 (aliphatic CH), 1639, 1610 (aromatic), 1180, 1040, 910 cm.$^{-1}$ (methylenedioxyphenyl).

This product is soluble in aqueous alkali and can be recovered unchanged by acidification and extraction with chloroform.

(c) *Octohydroedulin.* Edulin, 100 mg., was hydrogenated in tetrahydrofuran with prereduced rhodium-on-alumina, 150 mg., as catalyst until there was no further uptake of hydrogen. Four moles of hydrogen was absorbed within 1 hr. The product was worked up in the usual manner and yielded, after two crystallizations from chloroform-ether, 40 mg. of long colorless needles, m.p. 198–199°. This material was purified by chromatography on activated alumina, eluted with ether-chloroform (1:1) and recrystallized as before, m.p. 199–200°.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.41; H, 6.38. Found: C, 67.88; H, 6.40.

Ultraviolet absorption in chloroform: (see also Fig. 2): 240 (3950), 290 (5846).

Infrared absorption maxima: 2995, 2960, 2900 (aliphatic CH), 1630, 1610 (aromatic), 1190, 1035, 910 cm.$^{-1}$ (methylenedioxyphenyl).

The mother liquors from the crystallization of octahydroedulin gave an oil which resisted crystallization. Unlike tetrahydroedulin, octahydroedulin is insoluble in aqueous alkali.

Hydrogenation of substance vii. Substance (vii) was hydrogenated with palladium-on-charcoal (10%) as catalyst in acetic acid as described above for tetrahydroedulin. A total of 2.2 moles of hydrogen was absorbed. The product, worked up as usual, was crystallized from ether–petroleum ether (b.p. 30–60°) to give white needles, m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.58; H, 7.34. Found: C, 71.62; H, 7.30.

Ultraviolet absorption in chloroform: 241 (5180), 293 (7920).

Infrared absorption maxima: 3400 (hydroxyl), 1620, 1590 cm.$^{-1}$ (aromatic).

The product is soluble in alkali and is precipitated unchanged upon acidification.

Hydrogenation of neorautenone. (a) *Rhodium-on-alumina catalyst.* The hydrogenation was carried out under the same conditions described above for neorautone. Hydrogen absorption was slow and after 24 hr. a total of 5.0 moles of hydrogen had been absorbed. The product was crystallized from dioxane ether to give white prisms, m.p. 202–203°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.33; H, 5.86. Found: C, 65.66; H, 5.78.

Ultraviolet absorption in chloroform: 240 (8500), 295 (10,000).

Infrared absorption maxima: 3450 (hydroxyl), 1630, 1600 cm.$^{-1}$ (aromatic).

From the mother liquors a small amount of second product was obtained, m.p. 131–132°. This product was not investigated further; however its infrared spectrum was obtained and this showed hydroxyl absorption at 3250 cm.$^{-1}$

(b) *Adams' catalyst.* Hydrogen absorption was very slow with this catalyst. After 48 hr. a total of 2.0 moles of hydrogen had been absorbed. The product, m.p. 202–203°, gave no depression on admixture with the product of the same melting point obtained from the rhodium-catalyzed hydrogenation.

(c) *Palladium catalyst.* Neorautenone, 200 mg., was hydrogenated in dioxane–glacial acetic acid in the presence of 150 mg. of palladium-on-charcoal (10%) catalyst until 1.0 mole of hydrogen was absorbed. The product was worked up as usual and purified by crystallization from chloroform-ether to give 150 mg. of white crystals, m.p. 224–226°. This product is insoluble in aqueous alkali.

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.11; H, 4.74. Found: C, 67.42; H, 4.64.

Ultraviolet absorption in chloroform: 242 (29,000), 276 (13,710), 310 (12,650).

Infrared absorption maxima: 1680 (carbonyl), 1625, 1590, 1550 (aromatic), 1190, 1035, 930 cm.$^{-1}$ (methylenedioxyphenyl).

When the hydrogenation of neorautenone with palladium catalyst in dioxane–acetic acid was allowed to go to completion a total of 3.0 moles of hydrogen was absorbed. The product which is also insoluble in alkali was purified by crystallization from chloroform-ether to give colorless needles, m.p. 182°.

Anal. Calcd. for $(C_4H_4O)n$: C, 70.65; H, 5.93. Found: C, 70.51, 70.75, 70.46; H, 5.96, 5.74, 5.70.

Ultraviolet absorption in dioxane: 230 ($E^{1\%}_{1\,cm.}$ 316.0), 300 ($E^{1\%}_{1\,cm.}$ 340.0).

Infrared absorption maxima: 1631, 1608 (aromatic), 1195, 1037, 935 cm.$^{-1}$ (methylenedioxyphenyl).

Bromination of neorautenone. Neorautenone, 150 mg., in 5 ml. of chloroform was treated with bromine in chloroform solution at 0° until the solution was light yellow in color. The solution was then kept at 0° for 1 hr., evaporated to dryness under a stream of nitrogen and crystallized from ether–petroleum ether (b.p. 30–60°) to give white prisms, m.p. 131–132° dec.

Anal. Calcd. for $C_{19}H_{14}Br_2O_6$: C, 45.82; H, 2.84; Br, 32.10. Found: C, 45.22; H, 3.38; Br, 32.41.

Ultraviolet absorption in chloroform: 246 (30,000), 306 (9000).

Infrared absorption maxima: 1680 (carbonyl), 1620, 1575 cm.$^{-1}$ (aromatic).

In another experiment the bromination product was allowed to stand at 4° for 24 hr. in the presence of a slight excess of bromine. Evaporation of the solvent under a stream of nitrogen followed by recrystallization from chloroform-ether gave a white solid, m.p. 171–172°.

Anal. Calcd. for $C_{19}H_{14}Br_2O_6$: C, 45.82; H, 2.84; Br, 32.10. Found: C, 46.48; H, 2.56; Br, 31.38.

Ultraviolet absorption in chloroform: 249 (37,800), 306 (17,800).

Infrared absorption maxima: 1650 (carbonyl), 1632, 1620, 1600 cm.$^{-1}$ (aromatic).

Neorautenone-2,4-dinitrophenylhydrazone. Neorautenone in dioxane was treated with the reagent in ethanol solution in the usual manner to give, after recrystallization from dioxane-ethanol, long red needles, m.p. 286–287° dec.

Anal. Calcd. for $C_{25}H_{18}N_4O_9$: C, 57.96; H, 3.49; N, 10.82. Found: C, 58.16; H, 4.01; N, 11.00.

Ultraviolet absorption in dioxane: 393 (18,720).

Purification of substance iv. This compound, obtained in the earlier study[1] was purified for elementary analysis by crystallization from chloroform-ethanol to give straw-colored prisms, m.p. 149°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.51; H, 4.74. Found: C, 68.54; H, 4.30.

Ultraviolet absorption in chloroform: 244 (26,000), 260 (shoulder, 8500), 274 (5500), 302 (5400), 337 (3480).

Infrared absorption maxima: 1680 (carbonyl), 1630, 1585, 1550 (aromatic), 1190, 1042, 930 cm.$^{-1}$ (methylenedioxyphenyl).

2,4-Dinitrophenylhydrazone of substance iv. This product, made in the usual manner was recrystallized from dioxane-ethanol to give red prisms, m.p. 268–269°.

Anal. Calcd. for $C_{23}H_{16}N_4O_8$: N, 11.72. Found: N, 11.46.

Ultraviolet absorption in dioxane: 302 (11,472), 392 (23,900).

Acknowledgment. NMR spectra were measured and interpreted by Mr. L. F. Johnson of Varian

Associates, Palo Alto, Calif. The author is indebted to Professor W. B. Whalley of the University of Liverpool, England, for kindly supplying small samples of pure pterocarpin and homopterocarpin for spectroscopic examination.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

Norsteroids. III. Preparation of B-Norcholestane Derivatives by an Ester Condensation of a 5,6-*seco*-Cholestane Keto Ester[1]

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Received May 1, 1961

Condensation of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate with sodium methoxide in methanol gave methyl B-norcholest-3-en-5-ol-6-carboxylate (61%). The use of sodium hydride in toluene gave the same compound in 43% yield, while sodium *t*-butoxide in *t*-butyl alcohol gave B-norcholesta-3,5-diene (30%) and B-norcholesta-3,5-diene-6-carboxylic acid (24%). Evidence that elimination of the 3-acetoxy group preceded condensation was obtained. The structures of the condensation products were proved by conversion to known B-norsteroids by unequivocal reactions.

Although a variety of methods has been employed for the preparation of ring-norsteroids, very little use has been made of the ester condensation of the esters of *seco* acids or *seco*-keto acids, which is somewhat surprising in view of the ready availability of these types of compounds. Rull and Ourisson[3] obtained 2,11,20-triketo-A-norpregnane by a Dieckmann condensation (followed by hydrolysis and decarboxylation) from the dimethyl ester of the corresponding 2,3-*seco* acid, but Jacobs and Takahashi were[4a] unable to cyclize the dimethyl ester of the 2,3-*seco* acid from cholestenone. However, Fuchs and Loewenthal[4b] successfully condensed the methyl esters from the saturated 2,3-*seco*- and 1,2-*seco*-compounds and obtained good yields of the 3-carboxy and 2-carboxy derivatives, respectively.

The ready availability of 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oic acid (I, R^1 = Ac, R^2 = H) suggested its use for the synthesis of B-norsteroids by an ester condensation. Treatment of this compound with benzoyl chloride and pyridine had been shown previously[5] to lead to B-norsteroids, thus making available for comparison purposes B-norcholestanes of known structure.

When methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R^1 = Ac, R^2 = CH_3) was heated with sodium methoxide in methanol for 144 hours, the major product was methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) (61%), accompanied by trace amounts of what was presumably methyl B-norcholestane-3,5-diol-6-carboxylate (IV). Although III could not be obtained crystalline, its structure was established on the basis of its reactions, infrared spectrum, and conversion to known B-norsteroids, as described below. No evidence for the presence of isomers in the oily III could be obtained by careful and extensive chromatography on alumina. The use of sodium hydride in toluene as the condensation reagent gave (after forty-eight hours under reflux) a 43% yield of III, R = CH_3. The use of sodium *t*-butoxide in *t*-butyl alcohol gave (after forty minutes under reflux) a 30% yield of B-norcholesta-3,5-diene (VI), accompanied by 24% of oily B-norcholesta-3,5-diene-6-carboxylic acid (V, R = H). Apparently under the latter conditions condensation was followed by dehydration, ester hydrolysis, and in part, decarboxylation.

While various condensation products could be envisaged for the reaction, the most likely ones were considered to be those containing a five- or a seven-membered ring, as shown. The infrared spectrum of the product indicated the presence of an ester grouping, and therefore hydrolysis and decarboxylation were carried out for the initial proof of structure. The methyl ester III was very resistant to hydrolysis with sodium hydroxide in boiling aqueous methanol, but was saponified with sodium hydroxide in boiling aqueous *n*-amyl alcohol to give, after acidification, B-norcholest-3-en-5-ol-6-carboxylic acid (III, R = H) (46% yield). The acid was noncrystalline, but when it was heated to

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(1) For the previous paper in this series see N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959).

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