of 0.04 (and 0.094) mm. thickness were used. Calculations of percentage composition were made using the base-line technique from spectra of pure reference compounds and synthetic mixtures. Table IV lists the analytical wave lengths used.

For experiments 1–10 and 18–21 the total of unreacted hydrocarbons and products was analyzed by means of gas chromatography. A Podbielniak Chromacon[14] series 9475 apparatus was used. Sample volumes of 0.04 ml. were used with 6- and 12-ft. columns containing tricresyl phosphate on Celite or paraffin wax on 20–60 mesh firebrick; nitrogen was used as a carrier gas. Calibration runs were made for each analysis using synthetic mixtures of the starting materials and expected products in amounts which closely approximated the product composition. Calculations of composition and yield were made by comparing peak areas of the calibration and reaction product chromatograms. The results of experiments 1–10 and 17–21 are listed in Table V; good agreement between the two methods of analysis and good reproducibility of experiments is demonstrated by these results.

The Synthesis of Reference Compounds and *p*-Dialkylbenzenes.—Most of the monoalkylbenzenes and *n*-propyltoluene which were used as reference samples were prepared by means of side-chain alkylation of the appropriate alkylbenzene or xylene as described previously.[4a]

Most of the *p*-dialkylbenzenes which were used as reactants and reference compounds were prepared by means of hydrogenolysis of the appropriate substituted phenones using a copper–chromite catalyst at 210–250°. *p*-Ethyltoluene was prepared from *p*-methylacetophenone, *p*-ethylcumene from *p*-isopropylacetophenone, *p*-*n*-propylcumene from *p*-isopropylpropiophenone, *p*-*n*-propylethylbenzene from *p*-ethylpropiophenone and *p*-*t*-pentylethylbenzene from *p*-*t*-pentylacetophenone. These phenones were prepared in yields of 70–80% on a 0.25 to 1 molar scale using Friedel–Crafts acylation except for the *p*-methylacetophenone which was purchased (Eastman catalog no. 158).

Other dialkylbenzenes were prepared by means of hydrogenolysis of the appropriate benzyl alcohols using conditions similar to those used for the hydrogenolysis of phenones: *m*-ethyltoluene was prepared from 1-*m*-tolylethanol, *m*-*sec*-butyltoluene from 2-*m*-tolyl-2-butanol, *p*-*sec*-butyltoluene from 2-*p*-tolyl-2-butanol, *p*-*sec*-butylcumene from 2-*p*-cumyl-2-butanol. The *m*-isomers of these alcohols were prepared by Grignard reactions of *m*-bromotoluene with the appropriate aldehyde or ketone run on a 0.25-mole scale. The *p*-isomers were prepared by reaction of ethylmagnesium bromide with the appropriate *p*-substituted acetophenone on a 0.10-mole scale. The details of the hydrocarbon syntheses are listed in Table VI. The reference sample of *p*-*t*-pentyltoluene was kindly supplied by M. J. Schlatter of The California Research Corporation. Photographs of the spectra of these compounds may be found in the Ph.D. thesis of L. A. Schaap, Northwestern University, 1957.

TABLE VI

THE SYNTHESES OF AROMATIC HYDROCARBONS

Compound	Yield,[a] mole %	B.p. °C.	Mm.	$n^{20}D$
p-Ethyltoluene[b]	86	161.5–162.8	752	1.4942
p-Ethylcumene[c]	89	197.7–197.9	748	1.4914
p-*n*-Propylcumene	77	209–210	748	1.4895
p-Ethyl-*n*-propylbenzene	72	197–198		1.4915
p-Ethyl-*t*-pentylbenzene[d]	84	228.6		1.4960
m-Ethyltoluene	69	159		1.4961
m-*sec*-Butyltoluene	79	189.5	747	1.4919
p-*sec*-Butyltoluene	66	192–193		1.4900
p-*sec*-Butylcumene[e]	92	218		1.4890
p-*n*-Propyl-*t*-butylbenzene[f]	..	229		1.4909

[a] Based on the alcohol or ketone used. [b] The distilled material contained 3.2% of *m*-ethyltoluene. [c] The pure *p*-isomer was obtained by purification of *p*-isopropylacetophenone *via* the oxime (m.p. 72–73°) or by distillation of the hydrocarbon from the crude ketone on a Podbielniak Hypercal column.[14] Of the hydrocarbon charged, 37% was obtained as the pure *p*-isomer. [d] d^{20}_4 0.8572. *Anal.* Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44; MR_D, 58.63. Found: C, 88.67; H, 11.36; MR_D, 60.23. [e] d^{20}_4 0.8361. *Anal.* Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44; MR_D, 58.63. Found: C, 88.92; H, 11.57; MR_D, 59.64. [f] d^{20}_4 0.8582. *Anal.* Calcd. for $C_{13}H_{20}$: C, 88.56; H, 11.44; MR_D, 58.63. Found: C, 88.50; H, 11.33; MR_D, 60.51.

The commercially available *p*-*t*-butyltoluene which was used for experiment 17 contained some of the corresponding *m*-isomer, according to the infrared spectrum, so the sample which was used for experiment 10a was prepared from *p*-*t*-butylphenol using the method which was described previously[4a] for *p*-*t*-pentyltoluene. The reference sample of *p*-*n*-propyl-*t*-butylbenzene was a fraction which was distilled from the product of a reaction of the Eastman *p*-*t*-butyltoluene with ethylene and was not completely free of the *m*-isomer. The properties of this material are listed in Table VI.

Acknowledgment.—The authors wish to express their appreciation to Miss H. Beck for the elemental analyses reported in this paper.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of *dl*-Protolichesterinic Acid[1]

BY EUGENE E. VAN TAMELEN AND SHIRLEY ROSENBERG BACH

RECEIVED JUNE 24, 1957

The synthesis of *dl*-protolichesterinic acid (II) involves (i) conversion of methyl 2-hexadecenoate to methyl 3-tridecylglycidate (XVIII), (ii) ring-opening of XVIII with the anion of dimethyl malonate yielding α,β-dicarbomethoxy-γ-tridecyl-γ-butyrolactone (XVII), (iii) conversion of this lactonic diester to the monopotassium salt of the corresponding lactonic diacid XIX, and (iv) treatment of the salt with formaldehyde and diethylamine, resulting in direct formation of the natural product in the racemic form. Tentative stereoformulas for protolichesterinic acid, alloprotolichesterinic acid, as well as nephromopsinic acid and its diastereomers, are developed.

As demonstrated during recent years, the α-methylenecarbonyl group I serves as a structural feature common to certain natural products of strikingly diverse origins, for example: the antibiotic sarkomycin,[2] the amino acid γ-methyleneglutamic acid,[3] and the sesquiterpenoids alantolactone[4] and helenalin.[5] The appearance of the members in this group was prefigured by the well-known fatty acid variant present in *Cetraria islandica* (Iceland moss), protolichesterinic acid, first isolated in 1902, and assigned the currently accepted

(1) The results detailed herein were first reported in *Chemistry & Industry*, 1308 (1956).

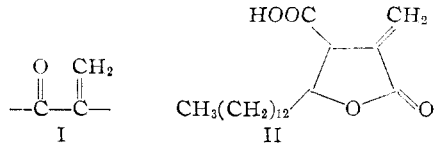
(2) I. R. Hooper, L. C. Cheney, M. J. Cron, O. B. Fardig, D. A. Johnson, D. L. Johnson, F. M. Palermiti, H. Schmitz and W. B. Wheatley, *Antibiotics & Chemotherapy*, **5**, 585 (1955).

(3) P. C. Wailes, M. C. Whiting and L. Fowden, *Nature*, **174**, 130 (1954).

(4) L. Ruzicka and P. Pieth, *Helv. Chim. Acta*, **14**, 1090 (1931).

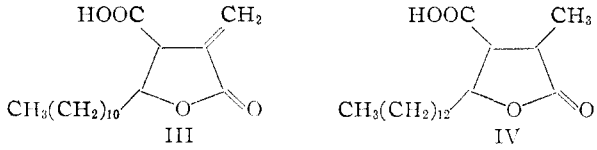
(5) G. Büchi and D. Rosenthal, THIS JOURNAL, **78**, 3860 (1956).

structure II in 1927.[6] Various relatives, *e.g.*, the



I II

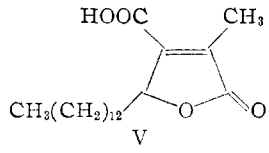
epimeric alloprotolichesterinic acid,[7] nephrosterinic acid (III)[8] and nephromopsinic acid (IV),[9] have



III IV

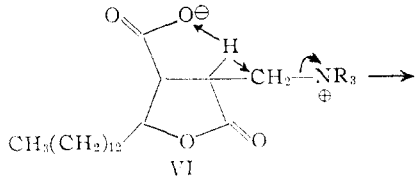
since been detected in nature, and interest in this group has been sustained by the finding that some of its members exhibit antibacterial action.[10] In this publication, we describe the first synthesis of *dl*-protolichesterinic acid.

Since protolichesterinic acid, bearing the sensitive α-methylene-β-carboxy-γ-lactone system, suffers ready isomerization to lichesterinic acid (V),[6,10,11] the latter steps in a projected synthesis

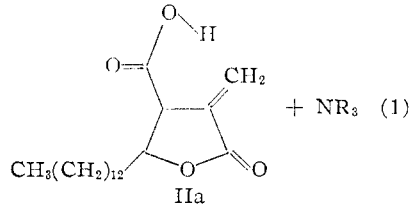


V

must be selected with some care. *It was considered that a betaine of structure VI would collapse and generate directly according to mechanism 1, the protolichesterinic acid system.*

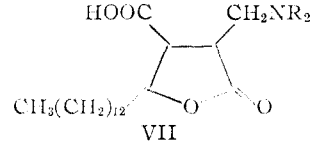


VI



IIa

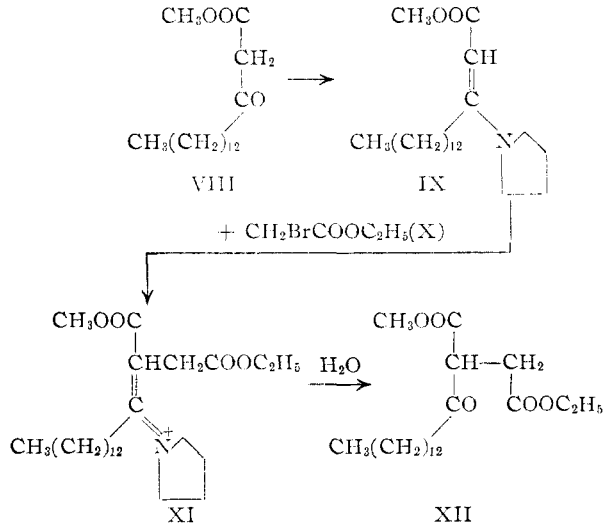
The proposal held promise because (i) being an intramolecular β-elimination process it should be facile even under mild conditions, and (ii) the reaction would provide the trialkylammonium salt of the desired material accompanied only by the solvent used for the reaction. The amino acid structure VII required appeared to be most easily accessible by means of a Mannich reaction, and consequently our efforts were directed toward the



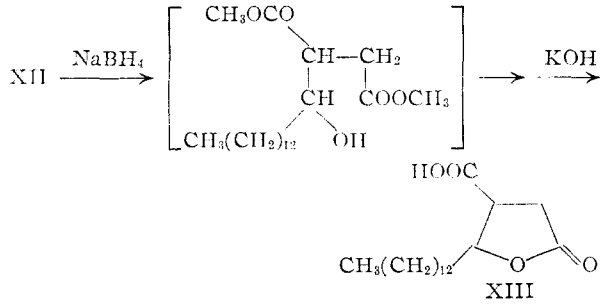
VII

preparation of a suitable active-hydrogen component for this step.

One of the routes examined called for methyl myristylacetate (VIII) as the starting material, and monoalkylation with haloacetic ester as the initial operation. Although use of the β-keto ester anion invariably led only to dialkylated product,[12] the desired product XII was prepared[13] by conversion of VIII to an enamine IX, alkylation with bromoacetic ester X, and hydrolysis of the resulting crude imine salt XI. Reduction with sodium borohydride and then saponification gave the crystalline β-carboxy-γ-tridecyl-γ-butyrolactone (XIII). All



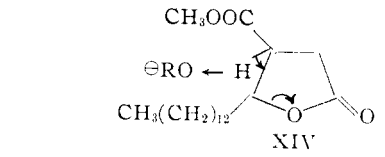
VIII IX XI XII



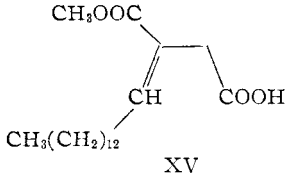
XIII

attempts to introduce into the α-position of the lactone ring a negative substituent which would provide for the projected Mannich reaction, were unavailing. Thus, although γ-butyrolactone could be converted smoothly to α-carboethoxy-γ-butyrolactone by treatment with ethyl carbonate and sodium ethoxide in absolute ethanol, attempted carboethoxylation or formylation of the β-carbomethoxy lactone XIV led only to the unsaturated half acid ester XV, or double bond isomer thereof. It is

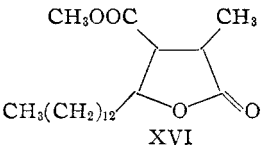
(6) Y. Asahina and M. Asano, *J. Pharm. Soc. Japan*, **539**, 1 (1927).
(7) Y. Asahina and M. Yanagita, *Ber.*, **68B**, 120 (1936).
(8) Y. Asahina, M. Yanagita and Y. Sakurai, *ibid.*, **70B**, 227 (1937).
(9) M. Asano and T. Asumi, *ibid.*, **68B**, 995 (1935).
(10) C. J. Cavallito, D. McK. Fruehauf and J. H. Bailey, THIS JOURNAL, **70**, 3724 (1948).
(11) W. Zopf, *Ann.*, **324**, 52 (1902).
(12) Contrast with the successful use of α-bromopropionic ester in this step: E. E. van Tamelen, C. E. Osborne, Jr., and S. R. Bach, THIS JOURNAL, **77**, 4625 (1955).
(13) R. Robinson, *J. Chem. Soc.*, **109**, 1038 (1916); G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).



XIV



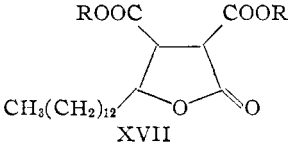
XV



XVI

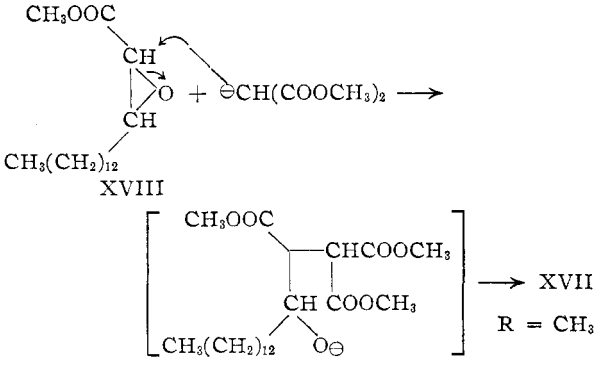
pertinent that the two known diastereoisomeric *dl*-pairs corresponding to the structure XVI, in contrast to the present case, do not suffer any detectable amount of intramolecular β-elimination of carboxylate anion when treated under conditions approximating those applied to the ester XIV. The factors determining the ease of this elimination seem to be obscure.[14]

It appeared that the desired intermediate XVII



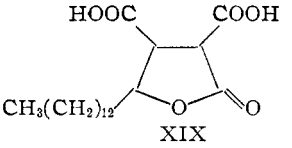
XVII

could be formed by ring-opening of methyl 3-tridecylglycidate (XVIII) with dialkyl malonate anion, in that glycidic esters have been employed in

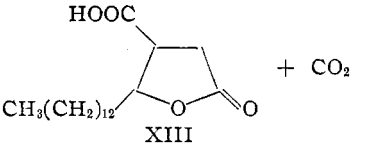


XVIII

this type of reaction,[15] and the approximate steric equivalence of the 2- and 3-positions of XVIII, but favorable electrical factors operative at the 2-position,[16] should ensure formation of the specified isomer. Accordingly, methyl 2,3-epoxy-2-hexadecenoate was prepared, smoothly and in high yield, by treatment of the unsaturated ester with peroxytrifluoroacetic acid[17]; hydrolysis of the ester resulted in formation of the epoxy acid, m.p. 86–87°.[18] Formation of the diester lactone XVII was induced by heating of sodium malonic ester and the glycidic ester XVIII in refluxing methanol, and saponification furnished a well-defined solid which analysis and titration data indicated to be the monopotassium salt XIXa of the desired α,β-dicarboxy-γ-tridecyl-γ-butyrolactone (XIX). By contrast with the



XIX



XIII

physical character of the salt, the free diacid was an unmanageable, amorphous substance. The assignment of structure was confirmed by acid-catalyzed decarboxylation, which yielded the previously obtained carboxylactone XIII.

In order to prepare the desired Mannich base, the salt XIXa was subjected to the action of formaldehyde and diethylamine in methanol for a period of two days, and the reaction mixture was separated on the basis of chloroform solubility. *The chloroform-insoluble portion of the reaction product was identified as the potassium salt of dl-protolichesterinic acid (IIa).* The chloroform-soluble material was treated first with excess methyl iodide and then with dilute sodium bicarbonate at room temperature[20]; an additional quantity of *dl*-protolichesterinic acid was obtained, increasing the total yield of this product to about 37%. The protolichesterinic acid arising directly could be generated either by (i) the decarboxylation–elimination of an intermediate α-carboxy-α-N,N-diethylaminomethyllactone (XX), or (ii) a simple β-elimination of the type XXI; however, we can offer no experimental evidence which allows a choice between these two possibilities. The chloroform-soluble product appears to be the monocarboxy Mannich base XXI, which is quaternized and eliminated according to reaction scheme 1. By carrying out the Mannich reaction with dimethylamine hydrochloride rather than the free base, it was possible to isolate, after

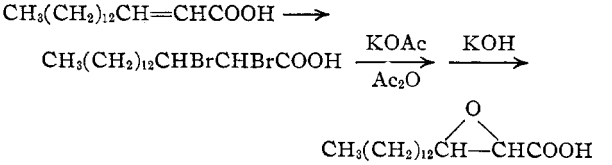
(14) An attempt to secure the diester lactone XVII by alkylating the starting ketoester VIII with chloromalonic ester (*cf.* the alkylation of acetoacetic ester with chloromalonic ester (H. Gault and L. Klees, *Bull. soc. chim. France*, [4] **39**, 1000 (1926)), followed by reduction and lactonization, failed in the first step—only starting material could be isolated.

(15) G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 2373 (1937); *C. A.*, **32**, 2099 (1938).

(16) J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

(17) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).

(18) Another reaction sequence designed to convert 2-hexadecenoic acid to the epoxy acid was investigated cursorily. Based on an approach developed by Myers (THIS JOURNAL, (a) **73**, 2100 (1951); (b) **74**, 1390 (1952)), the operation involved (i) preparation of 2,3-dibromohexadecanoic acid, (ii) displacement of halogen with potassium acetate to form the bromoacetoxy derivative and (iii) saponification and ring closure to the epoxide with ethanolic base. From the mixture of products formed, there was isolated in poor yield an epoxy-

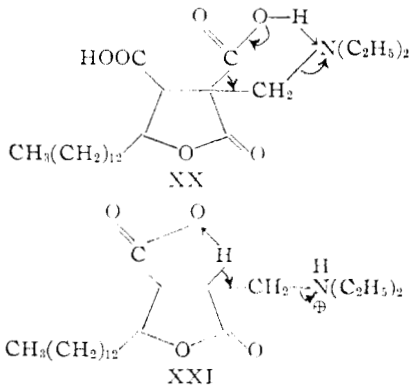


hexadecanoic acid of m.p. 70–71°. This acid is diastereoisomeric with that (m.p. 86–87°) prepared by the peroxytrifluoroacetic acid route; and since the 2-hexadecenoic acid used in both preparations must be the *trans* geometrical isomer,[18a] the higher melting epoxyacid may be regarded as *trans*, and the lower melting one, therefore, as *cis*.[19]

(19) The preparation of the *cis* isomer was carried out by Mr. Clyde E. Osborne, Jr.

(20) E. E. van Tamelen and S. R. Bach, THIS JOURNAL, **77**, 4683 (1955).

treatment with methyl iodide, a high yield of the methiodide of the amino acid XXI, thereby confirming the nature of the intermediate postulated.



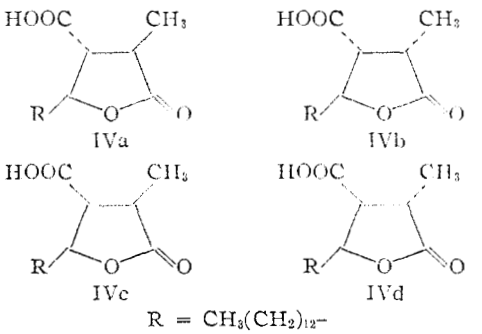
XX XXI

As expected, this methiodide afforded *dl*-protolichesterinic acid on treatment with aqueous bicarbonate at room temperature.

Although the protolichesterinic acid first obtained showed the expected ultraviolet absorption, the infrared spectra of the synthetic and natural acids in chloroform solution were similar but not identical. By suitable spectral comparisons, the disparity was traced to contamination of the racemate by some *dl*-lichesterinic acid (V), which must have formed by isomerization of the proto isomer, even under the very mild conditions employed in the synthesis. Through chromatography over silicic acid, the acids were separated; and the synthetic *dl*-protolichesterinic acid now was indistinguishable in the infrared from the natural acid. In order to provide further evidence for the nature of the synthetic product, it was (i) isomerized to *dl*-lichesterinic acid and (ii) reduced catalytically to *dl*-dihydroprotolichesterinic acid.[12] The infrared spectra of the two synthetic transformation products (in chloroform), coincided in every detail with the appropriate spectra of authentic materials. In addition, no depression was observed in the melting point of a mixture of the dihydroacid and *dl*-dihydroprotolichesterinic acid previously synthesized in this Laboratory.[12]

Stereochemistry.—In the literature there is described the conversion of the naturally occurring (from *Nephromopsis stracheyi f. ectocarpisma* Hue.) nephromopsinic acid to the diastereoisomeric dihydroprotolichesterinic acid, accomplished by saponification of methyl nephromopsinate.[21] It might be concluded, since two base-epimerizable centers are present in the dihydro- structure, that dihydroprotolichesterinic acid possesses the most stable of the possible stereochemical forms. This seems not to be the case, however, because we have determined that *both dl-dihydroproto- and dl-isodihydroprotolichesterinic acid*[12] *are in turn epimerizable, as their methyl esters, on heating with sodium methoxide in methanol.* On the basis of analysis and infrared spectral characteristics we regard the derived acid, m.p. 97–98°, as a new isomer in the dihydro- series and therefore suggest the name "neodihydroprotolichesterinic acid." Further, because of the nature of its formation, the neo-acid is, with little doubt, the most stable in the family of diastereoisomers.

By capitalizing on the new finding as well as certain observations reported in the older literature, and by making certain reasonable assumptions, stereochemical structures for proto- and alloprotolichesterinic acids as well as all the dihydro-acids, may be derived. Formulas IVa through IVd rep-



IVa IVb IVc IVd

R = $CH_3(CH_2)_{12}$–

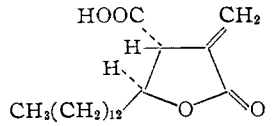
resent the four diastereoisomeric forms possible in the dihydro- series. Because of the nature of the substituents on the lactone ring, it seems reasonable that steric, rather than electrical, factors would determine the relative stabilities. Inspection of Fisher–Taylor–Hirschfelder models of the lactone ring demonstrates that the set of three (α, β and γ) bonds on the one side (or the other side) of the plane of the ring make approximately the same obtuse angle with the plane, and that consequently the overriding steric interference is that resulting from a pair of vicinal, *cis*-oriented substituents. On this basis, structure IVa, the *trans*-*trans* isomer, suffers least from steric compression and therefore represents neodihydroprotolichesterinic acid. Now, dihydroprotolichesterinic acid results from catalytic reduction of protolichesterinic acid. If it may be assumed that hydrogenation proceeds by approach of the catalyst from the least hindered side of the molecule,[22] it is then apparent that the dihydroproto-acid *cannot* possess structure IVd, *i.e.*, *if* protolichesterinic acid were the *cis* isomer, hydrogenation would be expected to give rise to IVc rather than IVd. Structure IVc, the all-*cis* possibility, must be regarded as the least stable in the series; since dihydroprotolichesterinic acid results from epimerization of two other dihydro- compounds, it therefore cannot be IVc. *The α,β-cis, β,γ-trans configuration IVb is thus reserved for dihydroprotolichesterinic acid; and protolichesterinic acid itself must then possess the trans structure XXIIa.* This assignment, it may be mentioned, is consistent with the expected steric course of the protolichesterinic synthesis. If the assumption is made that the conditions used in the reaction of sodium malonic ester with the glycidic ester are sufficiently basic to ensure enolization–equilibration at the α- and β-positions of intermediate XVII (R = CH_3), this product, and therefore the derived protolichesterinic acid, must then possess the more stable, *trans* configuration.

Turning to other known substances belonging to

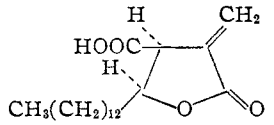
(21) M. Asano and T. Asumi, *Ber.*, **72**, 35 (1939).

(22) Production of dihydroprotolichesterinic acid cannot proceed by way of initial, heavy metal-catalyzed isomerization to lichesterinic acid followed by reduction, because lichesterinic acid, reduced independently, gives rise to a different product (ref. 12).

this group, we see that *l*-alloprotolichesterinic acid falls in the *cis* category (XXIIb). Further, since *l*-alloproto- and *l*-protolichesterinic acid both afford



XXIIa



XXIIb

l-lichesterinic acid under appropriate isomerization conditions,[6,7] the two acids must possess the same (although unknown) absolute configuration at the γ-position, as depicted in XXIIa and XXIIb. Assuming the usual steric requirements for catalytic hydrogenation to obtain, dihydroalloprotolichesterinic acid may be assigned structure IVc. Finally, nephromopsinic acid must then possess the stereochemistry represented by IVd, the only structure left unassigned.

Acknowledgment.—For financial support the authors are indebted to Eli Lilly and Co. and to the Wisconsin Alumni Research Foundation (funds administered through the Research Committee of the Graduate School).

Experimental[23]

Epimerization and Hydrolysis of Methyl *dl*-Dihydroprotolichesterinate.—A solution of sodium methoxide prepared from 5.5 ml. of methanol and 0.024 g. (1.04 mmole) of sodium was refluxed for 1 hr. with 180 mg. (0.53 mmole) of ester. The mixture was poured into water, acidified with sodium bisulfate and the oil extracted with ether. Evaporation of the ether, after drying over anhydrous sodium sulfate, left 0.129 g. (0.38 mmole) of an oily white solid. This was dissolved in 7 ml. of methanol, 1 ml. of water containing 0.0304 g. (0.76 mmole) of sodium hydroxide added, and the solution allowed to stand at room temperature for 5 days. Dilution with water and acidification with sodium bisulfate brought down 0.104 g. of a white solid, m.p. 90–95°. This product was recrystallized once from glacial acetic acid, the product washed with petroleum ether and then recrystallized again from methanol. There was obtained 0.056 g. (32.5%) of neodihydroprotolichesterinic acid, white pearly platelets, m.p. 97–98°.

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.88; H, 10.49. Found: C, 69.46, 70.22; H, 10.48, 10.46.

The methyl ester of this isomer, m. 38–39° (uncor.), was prepared *via* diazomethane. Its infrared spectrum showed bands at 5.69 and 5.79 μ.

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 69.98; H, 10.49.

Epimerization and Hydrolysis of Methyl *dl*-Isodihydroprotolichesterinate.—A solution of 0.31 g. (0.912 mmole) of ester and 10.5 ml. of dry methanol in which 0.00419 g. (1.82 mmoles) of sodium had been dissolved was refluxed for 5.5 hr. Then 1 ml. of water was added and the solution refluxed for 6.5 hr., cooled, diluted with water and acidified with sodium bisulfate. The oil which formed was taken up in ether, the ether solution dried over sodium sulfate and evaporated, leaving a partially crystalline oil. This, when extracted with cold petroleum ether, left a white solid, m.p. 94–96° which, after crystallization from aqueous methanol, left 0.070 g. (23.5%) of a white solid, m.p. 97–98°. Mixed melting point determination with the product obtained by epimerization and hydrolysis of methyl *dl*-isodihydroprotolichesterinate gave no depression.

Attempted Preparation of Ethyl β-Carbomethoxyl-γ-ketoheptadecanoate (XII).—Five grams (0.0176 mole) of methyl myristylacetate and 2.9 g. (0.0193 mole) of anhydrous finely pulverized sodium iodide were added to a solution of sodium methoxide prepared from 0.41 g. (0.0178 mole) of sodium and 10 ml. of anhydrous methanol. Over a 10-minute period, 3.0 g. (0.0166 mole) of ethyl bromoacetate was added to this mixture, which was cooled in ice a few times during the addition to keep the reaction at approximately room temperature. The mixture, which consisted of a clear yellow liquid floating on an opaque white liquid mixed with some solid, was stoppered and allowed to stand at room temperature for 2 days. The solid was then filtered and washed with water to remove inorganic salts. The rest of the reaction mixture was poured into water, acidified with sodium bisulfate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and distilled under reduced pressure. This left a yellow-orange oil which crystallized completely in 2 days, yielding 2.53 g. (33.4%) of a solid, m.p. 42–43°. This product, after crystallization from petroleum ether (b.p. 60–68°), analyzed correctly for the dialkylation product. No coloration was produced with ferric chloride solution.

Anal. Calcd. for $C_{25}H_{44}O_7$: C, 65.76; H, 9.71. Found: C, 65.59; H, 10.00.

β-Carboxy-γ-ketoheptadecanoate (XIII). (1) Pyrrolidine Enamine IX of Methyl Myristylacetate.—A mixture of 10 g. (0.0352 mole) of ketoester, 100 ml. of dry benzene and 10 g. (0.141 mole) of pyrrolidine (b.p. 86.5–87°) was refluxed for 9 hr. in a 250-ml. round-bottom flask equipped with magnetic stirrer, Cope water-separator and reflux condenser. About 0.8 ml. of water was collected (theoretical amount is 0.63 ml.). The solvent was then distilled under reduced pressure, leaving 11.5 g. (97%) of a yellow liquid, λ_{max} 287 mμ, ε 30,600, which solidified on cooling, but oiled out again at room temperature.

(2) Condensation of IX with Ethyl Bromoacetate.—A solution of 11.5 g. (0.0341 mole) of the enamine, 100 ml. of anhydrous methanol and 5.85 g. (0.035 mole) of ethyl bromoacetate was refluxed for 29 hr. The reaction was followed by observing the decrease in the optical density at 285 mμ.

After a reaction time of 30 hr., the mixture was stirred overnight with 20 ml. of water. The lower layer was separated crudely, then ether was added and a better separation was made from the water–alcohol layer by shaking with saturated sodium chloride solution. The ether layer was dried over anhydrous sodium sulfate and then removed by distillation, leaving 10 g. (73%) of a brown oil (XII) which gave no test for nitrogen.

Ten grams (0.027 mole) of XII was dissolved in 50 ml. of absolute methanol, and 8 ml. of a 1.0 *M* solution (0.008 mole) of sodium borohydride in methanol was added. After bubbling ceased, the flask was stoppered and set aside for 3 days. An additional 11 ml. of the sodium borohydride solution was then added and the solution allowed to stand for 3 hr. more. The reaction mixture was then poured into water, acidified with sodium bisulfate, and the oil which formed was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and distilled under reduced pressure. The yellow oil which remained was dissolved in a solution of 7 g. (0.125 mole) of potassium hydroxide in 110 ml. of 90% methanol and the resulting solution allowed to stand at room temperature for 1 day. The reaction mixture, which was then partially crystalline, was chilled in ice and the precipitate, presumably the potassium salt, filtered. This was acidified with 5% hydrochloric acid, digested for 1 hr. at 70° and then filtered after allowing it to stand at room temperature for several hours to effect coagulation. After drying, 5.1 g. (60%; 46% from methyl myristylacetate) of a white powder was obtained. One crystallization from benzene left 4.8 g. of a white crystalline solid, m.p. 80–83°. A neutralization equivalent determination indicated a molecular weight of 312. The infrared spectrum of a chloroform solution of XIII possessed bands at 5.71 and 5.85 μ. The spectrum taken in a potassium bromide pellet had bands at 5.75 and 5.84 μ.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.51; H, 10.46.

(23) All melting points (°C.), unless otherwise indicated, are corrected; all boiling points are uncorrected. All infrared spectra, unless otherwise indicated, were taken on the Baird automatic infrared spectrophotometer (model B). The ultraviolet spectra were taken on a Cary recording spectrophotometer (model 11 MS) in 95% ethanol in a 1-cm. cell. Unless otherwise indicated, all chromatographic separations were carried out on Mallinckrodt silicic acid which had been washed with acetone, dried for 24 hr. at 70°, and stored in a tightly closed container. The compounds were adsorbed on the column from chloroform solution (the chloroform, before use, was washed with sulfuric acid, water, dried over calcium chloride and distilled) and eluted with chloroform containing increasing amounts of methanol, usually up to 5%.

β-Carbomethoxy-γ-tridecyl-γ-butyrolactone (XIV).—An ethereal solution of diazomethane was added to 1.00 g. (3.21 mmoles) of XIII in ether. The ether was evaporated, leaving 1.03 g. (98%) of a white crystalline solid which, after crystallization from methanol, melted at 68–70°. The ester was crystallized again from petroleum ether for analysis. The infrared spectrum of a chloroform solution of the ester possessed bands at 5.65, 5.77, 8.55, 9.60, 10.06, 10.57 and 11.05 μ.

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.68; H, 10.33.

Carboethoxylation of γ-Butyrolactone.—The directions for the carboethoxylation of esters given by Wallingford[24] were followed. A mixture of 80 g. (0.677 mole) of diethyl carbonate (dried over magnesium sulfate and distilled, b.p. 124°) and 8.6 g. (0.1 mole) of butyrolactone (dried over sodium sulfate and distilled), in a 500-ml. round-bottom, three-neck flask equipped with condenser and vacuum take-off head, stirrer and dropping funnel, was heated to reflux at 125 mm. pressure. A solution of sodium ethoxide, prepared from 2.39 g. (0.104 mole) of sodium and 56 ml. of dry ethanol, was added over 1 hr. to the refluxing mixture, the alcohol being removed simultaneously with the addition. The gelatinous pale yellow mass which was left was poured into a mixture of 60 ml. of glacial acetic acid and ice. The organic product was extracted into 50 ml. of ether, the ether solution dried over anhydrous calcium chloride and the solvent removed by distillation. Distillation of the residue afforded 4.1 g. (26%) of α-carbethoxy-γ-butyrolactone, b.p. 106–109° (0.5 mm.).

The hydroxy diamide derivative was prepared by mixing an ethanolic solution of the carboethoxylactone with excess liquid ammonia and allowing the unstoppered solution to stand overnight. The solid white mass, after recrystallization from ethanol, melted at 152.5–153° (lit.[25] m.p. 150°).

Attempted Carboethoxylation of β-Carbomethoxy-γ-tridecyl-γ-butyrolactone (XIV). Run 1.—The procedure for the carboethoxylation of γ-butyrolactone was followed. A mixture of 3 g. (0.0092 mole) of XIV and 7.55 g. (0.064 mole) of diethyl carbonate (distilled over sodium hydride, b.p. 125°) was placed in a 25-ml. two-neck flask fitted with dropping funnel, magnetic stirrer and reflux condenser protected with a drying tube. A solution of sodium ethoxide, prepared from 0.212 g. (0.00922 mole) of sodium and 5.6 ml. of anhydrous ethanol, was added dropwise over 1 hr. to the stirred mixture maintained at reflux under 125 mm. pressure. The ethanol was removed continuously during the addition. At the end of the addition, the slush which remained in the flask was poured into 6 ml. of glacial acetic acid and ice and extracted into ether. The ether solution was dried over calcium chloride and the volatile material removed at reduced pressure on the steam-bath, leaving 3.4 g. of a light red oil.

From a crude chromatogram of 0.79 g. of this product on 12 g. of silicic acid, none of the desired product XVII could be obtained. Infrared spectra of chloroform solutions of the chromatogram fractions showed absorption at 5.88 and 6.08 μ, indicating the presence of a carbon-to-carbon double bond, a carboxyl group and the absence of a lactone.

Some of the crude product from the condensation was hydrolyzed to obtain the free acid. A solution of 2.37 g. of the condensation product in 20 ml. of methanol containing 1.27 g. (0.0227 mole) of potassium hydroxide was allowed to stand at room temperature for 5 days. During this time a partially crystalline material collected on the walls of the flask. The contents of the flask were acidified with 5% hydrochloric acid and the white precipitate filtered, washed with water and dried in a desiccator. This product was extracted with petroleum ether (b.p. 60–68°) to give a white powder which was crystallized from benzene, leaving 1.4 g., m.p. 133–135°, ε (220 mμ) 10,000. The infrared spectrum of a Nujol mull of this product had peaks at 5.94 (with an inflection at 5.87 and 6.11 μ), indicating the presence of a carbon-to-carbon double bond and two free carboxyl groups. A similar result was obtained through the use of potassium *t*-butoxide in *t*-butyl alcohol.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.45; H, 10.58.

(24) V. H. Wallingford, A. H. Homeyer and D. M. Jones, THIS JOURNAL, **63**, 2056 (1941).

(25) W. Traube and E. Lehmann, *Ber.*, **32**, 721 (1899).

2-Hexadecenoic Acid.—The procedure of Meyers[26] for the large-scale preparation of 2-octadecenoic acid was followed, except for the method of separation of the 2-hydroxyhexadecenoic acid from the unsaturated acid.

2-Hexadecenoic acid is very soluble in petroleum ether (b.p. 40–60°) at room temperature and at 0° only a small amount will precipitate. The hydroxy acid, $C_{14}H_{29}CH(OH)COOH$, is insoluble in this solvent at 0° and only partially soluble at room temperature. The two acids were separated by extracting the crude mixture with petroleum ether at room temperature, filtering any insoluble hydroxy acid, and then cooling to 0° and filtering again. Evaporation of the solvent followed by recrystallization of the residue from aqueous ethanol gave a 45% yield of 2-hexadecenoic acid, m.p. 47–49°.

Methyl 2-Hexadecenoate.—An ethereal solution of diazomethane was added to a solution of 5 g. (0.0197 mole) of 2-hexadecenoic acid in 50 ml. of ether until the color of the solution stayed decidedly yellow for five minutes. The excess diazomethane and the solvent were then removed by evaporation on the steam-bath, leaving 5.3 g. (100%) of the methyl ester. The infrared spectrum of a chloroform solution of the ester exhibited peaks at 5.88 and 6.07 μ. The ultraviolet spectrum in 95% ethanol showed ε (220 mμ) 8400.

Anal. Calcd. for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.56; H, 12.22.

***cis*-2,3-Epoxyhexadecanoic Acid.**—To a solution of *trans*-2-hexadecenoic acid (1.0 g., 0.004 mole) in a few ml. of carbon tetrachloride was added about 8 ml. of 5% carbon tetrachloride solution of bromine in small portions over half an hour. The color of bromine disappeared slowly after each portion was added, but the addition was stopped after about 90% of theoretical had been added because of appearance of permanent yellow color and evolution of hydrogen bromide. The solvent was then evaporated, leaving a yellow oily paste. This paste was dissolved in 10 ml. of acetic anhydride, and finely powdered and dried potassium acetate (0.5 g.) added to the solution. The mixture was refluxed for 3 hours. The product of this reaction was recovered by hydrolyzing the acetic anhydride in a large volume of ice-water and filtering off the creamy paste which separated out. In order to determine the amount of ionic bromine which had been released, the filtrate was made 0.5 *M* in nitric acid and silver nitrate (0.85 g.) was added. Then it was heated to boiling, the silver bromide filtered out and washed first with 0.01 *M* nitric acid and finally with water. After drying well, it amounted to 0.66 g., which is 89% of the expected amount based on the amount of 2-hexadecenoic acid used.

The creamy paste from the displacement reaction was dissolved in 15 ml. of 8% ethanolic potassium hydroxide and refluxed for 0.5 hr. The deep red-brown color originally present became pale red-brown after only 5 minutes of refluxing. The cooled reaction mixture was poured onto 50 g. of ice containing a slight excess of dilute sulfuric acid. A pale yellow granular solid was obtained; this was isolated by ether extraction, and the extract washed with saturated sodium chloride, and dried over sodium sulfate. Upon evaporation of the ether a pale yellow waxy solid was left, which still gave a positive Beilstein test. By trituration of this residue with a few ml. of petroleum ether for several days at room temperature, followed by suction filtration, there was obtained compound A, 0.04 g. of pure white granules giving a negative Beilstein test: m.p. 88.5–89.5°.

The filtrate from the isolation of compound A was cooled in ice; this produced a white granular precipitate which amounted to 0.30 g. of impure compound B after centrifugation and washing, m.p. 56–61.5°. This material also gave a negative Beilstein test. It apparently contained some of compound A, which was left as a residue (m.p. 77–86°) after three treatments with 10-ml. portions of petroleum ether (60–68°) at room temperature. The combined supernates were evaporated to 10 ml. and cooled to 15°, which precipitated a fine granular solid. After centrifuging and washing with a little ice-cold petroleum ether, there was obtained 0.20 g. of solid of m.p. 63–66°. Three recrystallizations from petroleum ether at 10° produced 10 mg. of pure compound B, m.p. 70.0–70.9°, fine satiny flakes, having an analysis corresponding to 2,3-epoxyhexadecanoic acid.

(26) G. S. Meyers, THIS JOURNAL, **73**, 2100 (1951).

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.15; H, 11.38.

Methyl Tridecylglycidate (XVIII).—A modification of the method of Emmons and Pagano[17] for the epoxidation of methyl methacrylate was used. A mixture of 3.5 ml. (0.125 mole) of 90% hydrogen peroxide, 21.2 ml. (0.15 mole) of trifluoroacetic anhydride (Caribou Chemical Co.) and 25 ml. of methylene chloride (dried over P_2O_5 and distilled) was cooled in ice, swirled until homogeneous and then transferred to a dropping funnel. This solution was added dropwise over a 40-min. period to a vigorously stirred refluxing mixture of 10.6 g. (0.040 mole) of methyl 2-hexadecenoate, 56.5 g. (0.40 mole) of anhydrous disodium hydrogen phosphate and 70 ml. of dry methylene chloride in a 1-l. three-neck, round-bottom flask equipped with dropping funnel, reflux condenser protected with a drying tube and Hershberg stirrer. The mixture was refluxed for 0.5 hr. after the addition was completed. Because the mixture foamed badly during the latter part of the addition and during the reflux period, a large reaction flask is recommended. The mixture was then stirred with 100 ml. of water until the salt dissolved completely. The aqueous layer was then separated and washed with 70 ml. of methylene chloride. The wash liquid was combined with the organic layer, washed with 100 ml. of 10% aqueous sodium bicarbonate, and dried overnight over anhydrous magnesium sulfate. The solvent was removed on the steam-bath, the crude product distilled, and these several fractions collected: fraction 1, b.p. 140–146° (0.4 mm.), 3.73 g.; fraction 2, b.p. 148–150° (0.4m m.), 2.62 g.; fraction 3, b.p. 150–152° (0.4 mm.), 3.73 g. The total yield was 10.8 g. (90%); however, only fractions 2 and 3, which solidified to a white wax, were used in the subsequent condensations because of the wide boiling range of the first fraction. The extinction coefficients were obtained to determine whether any unsaturated ester, ϵ (220 mμ) 8400, was present as contaminant. It was found that the increased molar ratio of trifluoroacetic anhydride to unsaturated ester was required for optimal conversion to the glycidic ester. The infrared spectrum of XVIII in chloroform solution exhibited bands at 5.80, 6.82, 7.42, 7.77 and broad bands at 9.0, 9.8 and 11.2–11.4 μ.

Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.63; H, 11.48.

A mixture of 0.2902 (0.00102 mole) of XVIII, 10 ml. of dioxane and 0.5 ml. of 10% aqueous sodium hydroxide (0.00125 mole) was hydrolyzed to the *trans*-glycidic acid by refluxing in a nitrogen atmosphere for 1.5 hr. The solution was then cooled and poured into ice-water containing 5 ml. of 5% hydrochloric acid. The mixture was extracted with ether, the ether layer dried over anhydrous sodium sulfate and evaporated, leaving a colorless oil. When 8 ml. of petroleum ether (b.p. 40–60°) was added, a fine white powder separated. The mixture was cooled in ice and filtered, leaving 0.122 g. (43.4%) of a white powder, m.p. 86–87°. Crystallization from methanol containing a small amount of water left white pearly platelets, m.p. 86–87°. The infrared spectrum of a chloroform solution of the glycidic acid showed peaks at 5.83 and 11.2 μ.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.66; H, 10.91

α,β-Dicarbomethoxy-γ-tridecyl-γ-butyrolactone.—Sodium dimethyl malonate was prepared by dissolving 0.485 g. (0.0211 mole) of sodium in 8 ml. of absolute methanol followed by addition of 2.79 g. (0.0211 mole) of dimethyl malonate in a 100-ml. three-neck, round-bottom flask equipped with Hershberg stirrer, reflux condenser protected against moisture by a drying tube, and dropping funnel. A solution of 6.00 g. (0.0211 mole) of XVIII (b.p. 151–153° at 0.3 mm.) in 10 ml. of dry methanol was added with stirring over a 10-min. period. On addition of the glycidic ester the sodium salt dissolved and after a few minutes the solution turned yellow. The solution was refluxed for 4 hr., cooled, poured into 150 ml. of an ice–water mixture, and then acidified with 5% hydrochloric acid. The mixture was extracted with chloroform and the organic layer dried over anhydrous sodium sulfate. The solvent was distilled off on the steam-bath under reduced pressure, leaving 7.85 g. of a pale yellow oil, which was chromatographed on silicic acid; 79% of the eluted product appeared in one band, fractions 2–4, and the various fractions within this band had identical infrared spectra. An example of chromatographic results is given below. In this case, 3.95 g. of the crude lactonic dimethyl ester was chromatographed on 45 g. of silicic acid.

Fraction	Weight of eluted material, g.	Eluent, % methanol in chloroform
1	0.063	1
2	2.427	1
3	0.512	1
4	.183	2
5	.053	2
6	.060	2
7	.090	2
8	.521	2

Fractions 2–4 were colorless oils which solidified on standing to white waxes. Fractions 6–8 were yellow oils and, on standing, only fraction 6 solidified. The infrared spectra of fractions 2–4, the dicarbomethoxy lactone, were nearly identical, having peaks at 3.42, 3.50, 5.64, 5.78, 6.82, 6.94, 7.27, 8.6 and 9.95 μ. The bands due to the lactone and the ester carbonyls were almost identical in intensity.

Hydrolysis of α,β-Dicarbomethoxy-γ-tridecyl-γ-butyrolactone.—To 2.1 g. (5.47 mmoles) of the dimethyl ester lactone dissolved in 40 ml. of methanol was added 5 ml. of an aqueous solution containing 1.84 g. (32.9 mmoles) of potassium hydroxide. The homogeneous solution was refluxed for 3 hr. on the steam-bath and then allowed to stand overnight at room temperature. As soon as refluxing started, the solution became cloudy and an oily material formed on the walls of the flask. After standing overnight, the liquid was poured off and the oily material on the walls of the flask was dissolved in 50 ml. of water. The aqueous solution was acidified to congo red paper with 5% hydrochloric acid and the white precipitate filtered. After drying in a vacuum desiccator over potassium hydroxide, there was obtained 1.182 g. (55%) of the white powdery potassium salt XIXa. This was crystallized from 20 ml. of hot methanol, giving 0.721 g. of a white powder, m.p. 124° dec. Only 0.59% methoxyl was found in an alkoxyl determination, indicating complete hydrolysis of the ester. Titration of the potassium salt indicated the presence of 1.1 free carboxyl groups.

Anal. Calcd. for $C_{19}H_{31}O_6K$: C, 57.87; H, 7.87. Found: C, 58.10; H, 8.33.

The mother liquor, after removal of the potassium salt, was poured into 100 ml. of water, acidified with 5% hydrochloric acid and extracted into ether. After drying over anhydrous sodium sulfate, the ether was removed by distillation under reduced pressure, leaving 0.494 g. of a white max. The infrared spectrum of a chloroform solution of this product had a peak at 5.87 μ with inflections on the left of the band at 5.83 and 5.65 μ. There is a band of medium intensity with a peak at 6.11 μ, indicating unsaturation. The spectrum is inconsistent with the presence in the mixture of any large amount of the desired dicarboxylactone XIX.

To identify the potassium salt further, 0.0394 g. (0.100 mmole) of it was refluxed with 0.5 ml. of 5% sulfuric acid for 0.5 hr. in a 3-ml. flask equipped with cold-finger condenser. The mixture was cooled and the white curdy material extracted into ether, the ether solution dried over sodium sulfate and evaporated, leaving 0.0265 g. (85%) of pearly white platelets. After recrystallization from benzene, the product melted at 87.5–94.5°. This is probably a mixture of diastereoisomers. The infrared spectrum of a chloroform solution of this product was identical with that of the carboxy lactone XIII, prepared by alkylation of methyl myristoylacetate and subsequent reduction.

A solution of 0.050 g. (0.127 mmole) of the potassium salt in 5 ml. of methanol was acidified with 5% hydrochloric acid. Water was then added and the mixture extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated at room temperature under nitrogen, leaving 0.036 g. (79.5%) of the dicarboxy lactone XIX. The infrared spectrum of a chloroform solution of this compound showed peaks at 5.66, 10.04 and a broad peak from 5.78–5.83 μ.

***dl*-Protolichesterinic Acid (IIa). A. The Reaction of XIXa with Formaldehyde and Diethylamine.**—To 0.372 g. (0.945 mmole) of the potassium salt XIXa of the diacid lactone was added 0.207 g. (2.84 mmoles) of diethylamine and 0.126 g. (1.26 mmoles) of 30% aqueous formaldehyde. Two ml. of methanol was added and the mixture heated slightly

or a minute on the steam-bath to effect complete solution. After standing for one day at room temperature, 0.126 g. (1.26 mmoles) of 30% aqueous formaldehyde was again added, and the reaction mixture allowed to stand for another day. After the addition of a few ml. of methanol, the contents of the reaction flask were transferred to a 20-ml. round-bottom flask and the solvent evaporated under reduced pressure while warming slightly on the steam-bath. The addition and removal of chloroform was carried out twice in the same manner. The white insoluble product which precipitated was allowed to stand overnight in 5 ml. of chloroform and was then filtered. The solution was used for the preparation of the methiodide, as shown below. The solid, 0.114 g. (33.4%), was dissolved in glacial acetic acid, a few drops of water added and the solution cooled to 15°. The very pale yellow powder which precipitated was filtered and washed with a few ml. of petroleum ether (b.p. 60-68°); yield 0.061 g. (19.9%), m.p. 92.5-94.5°. The infrared spectrum in chloroform solution was almost identical to that of authentic *d*-protolichesterinic acid, obtained from the extraction of *Centraria islandica*, exhibiting peaks at 5.73, 5.86, 6.05, 6.82, 7.95-84, 8.75, 8.92, 9.65 and 10.46 μ.

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.10; H, 10.14. Found: C, 69.59; H, 9.81.

The solution remaining after the separation of the potassium salt of protolichesterinic acid was evaporated, leaving a semi-solid mass whose chloroform solution showed strong absorption at 5.74 and 6.28 μ in the infrared. Other absorption maxima were at 6.82, 7.23, 8.47 and 8.93 μ. A weak band with a maximum around 4.1 μ, possibly due to NH^+, also appeared.

This product was dissolved in 2 ml. of dry benzene and 5 ml. of freshly distilled methyl iodide and allowed to stand at room temperature for 3 days. The mixture was filtered to remove a small amount of potassium iodide, and then the solvent was evaporated at about 40° under a stream of nitrogen. This left 0.338 g. (0.624 mmole) of a yellow oil which gave a positive test for iodide when dissolved in a drop of methanol and dilute nitric acid and treated with silver nitrate solution. A chloroform solution of this oil had an absorption maximum at 5.73 μ with two points of inflection on the higher wave length side of this band. The peak at 6.28 μ, present in the tertiary base, is not present in the quaternary salt.

The crude methiodide was dissolved in 4 ml. of methanol followed by the addition of 5.5 ml. of 5% aqueous sodium bicarbonate solution (3.28 mmoles). The solution was allowed to stand for three days after which it was diluted with water and extracted with ether. The aqueous solution was acidified with 5% hydrochloric acid and again extracted with ether. The ether layer was dried over anhydrous sodium sulfate and evaporated, leaving 0.0513 g. (16.8% based on the potassium salt) of a yellow powder, crude IIa. This was crystallized from acetic acid containing a little water and the cream-colored powdery product washed with petroleum ether (b.p. 60-68°); yield 0.020 g. (6.5% based on the potassium salt), m.p. 87.5-97.5°. This product lacked absorption maxima in the ultraviolet region from 220-350 mμ, but did exhibit end absorption with extinction coefficient of 6950 at 220 mμ. The infrared spectrum of a chloroform solution of this compound showed absorption maxima at 5.74, 5.86 and 6.05 μ.

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.10; H, 10.14. Found: C, 70.33; H, 9.94.

Seventy-four milligrams of the crude *dl*-acid was chromatographed on 5 g. of silicic acid. The product was placed on the column in chloroform and eluted with chloroform containing increasing amounts of methanol, up to 2%; 29% of the material placed on the column was eluted in the first band. After one crystallization from acetic acid, this melted at 114-115° and was shown to be *dl*-lichesterinic acid (V) by comparison of its infrared spectrum in chloroform solution with that of *d*-V. The next 42% eluted from the column crystallized in white pearly plates from acetic acid and melted at 100.5-101.5°. The infrared spectrum of a chloroform solution of IIa was identical with that of authentic II, and the spectrum of a potassium bromide pellet was very similar to that of II. The next 11.8% eluted from the column, after crystallization from acetic acid, melted at 98.5-100° and was probably also IIa. The last 10.7% eluted from the column melted at 91-92° after crystallization from acetic acid. The analysis of this last fraction is given below.

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.10; H, 10.14. Found: C, 69.60; H, 9.73.

Thirty milligrams (0.0926 mmole) of IIa was heated with 5 ml. of acetic anhydride for 1 hr. on the steam-bath. The solution was then cooled and water added to decompose the acetic anhydride and precipitate the product. This was crystallized from acetic acid, leaving 21 mg. (70%) of fine white needles, m.p. 113-115°. A second crystallization raised the melting point to 114-115° (lit.[7] 115°). The infrared of a chloroform solution of this product was identical to that of authentic lichesterinic acid.

Twenty milligrams (0.0618 mmole) of IIa dissolved in 10 ml. of glacial acetic acid was hydrogenated over 50 mg. of 10% palladium-on-carbon catalyst at room temperature and atmospheric pressure; 1.4 ml. of hydrogen was absorbed (calculated uptake for 1 mole, 1.38 ml.). The catalyst was removed by filtration and the product precipitated by dilution with water. After one recrystallization from acetic acid, a colorless crystalline product, m.p. 110-114°, was obtained. This was extracted with boiling petroleum ether (b.p. 60-68°) and recrystallized from acetic acid, yielding 9 mg. of fine colorless crystals, m.p. 114-116°. This did not depress in melting point on admixture with synthetic *dl*-dihydroprotolichesterinic acid. The infrared spectra of potassium bromide pellets of these two products were identical.

B. The Mannich Reaction on the Potassium Salt XIXa in Acid Solution.—To 0.3835 g. (0.974 mmole) of the potassium salt of the diacid lactone was added 3 ml. of methanol, 0.079 g. (0.974 mmole) of dimethylamine hydrochloride, 0.0873 g. (1.95 mmoles) of dimethylamine and 0.097 g. (0.970 mmole) of 30% aqueous formaldehyde solution. The stoppered mixture was allowed to stand for 2 days at room temperature after which the solution was filtered to remove a small amount of impurity. A few ml. of methanol was added, the solution transferred to a distilling flask and the solvent evaporated under reduced pressure on the steam-bath. This procedure was repeated twice with addition and removal of chloroform, leaving a waxy white solid in the flask. To this was added 3 ml. of dry benzene and 5 ml. of freshly distilled methyl iodide and the mixture allowed to stand for 3 days at room temperature. The white precipitate was filtered and the solution B was saved for later work. The precipitate is a white powder, 0.653 g., which can be crystallized from glacial acetic acid, ethanol or methanol. Crystallization from glacial acetic acid leaves 0.340 g. (68.3%) of white pearly platelets, m.p. 165° dec., which turn yellow on standing in air. The analysis indicates that this product is the methiodide desired.

Anal. Calcd. for $C_{22}H_{42}O_4NI$: C, 51.66; H, 8.28. Found: C, 51.55; H, 8.73.

The solution B, after removal of the solid methiodide, was evaporated under nitrogen, leaving 0.126 g. (0.246 mmole) of a yellow oil. This was dissolved in 2 ml. of methanol and 2.1 ml. of 5% aqueous sodium bicarbonate solution (1.25 mmoles) added. After standing for 3 days at room temperature, water was added and the solution extracted with ether. The aqueous solution was acidified with 5% hydrochloric acid, extracted with ether, the ether layer dried over anhydrous sodium sulfate and then evaporated, leaving 0.038 g. of a semi-solid wax. Extraction of this with petroleum ether (b.p. 60-68°) left a white powder, m.p. 87-99°. This was crystallized from aqueous acetic acid and the solid washed with petroleum ether, leaving 0.010 g. of white pearly platelets, m.p. 98-100°. The infrared spectra of the Nujol mull and chloroform solution of this product were identified with the β-carboxylactone XIII.

The crystalline methiodide described above also was subjected to the conditions of the Hofmann elimination; 5 ml. of methanol and 2.8 ml. of 5% aqueous sodium bicarbonate solution (1.66 mmoles) were added to 0.211 g. (0.413 mmole) of the methiodide and the solution was allowed to stand for 3 days at room temperature. After a few hours, the solution acquired an amine-like odor. The product was worked up by addition of water to the solution, extraction with chloroform, acidification of the aqueous solution and then another chloroform extraction. The chloroform was evaporated and the product crystallized from acetic acid. There was obtained 0.029 g. (21.6%) of *dl*-protolichesterinic acid, m.p. 92-95°.

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