The substituted pteridine was purified as reported previously.[4] It showed identical ultraviolet absorption spectra as 2-amino-4-hydroxy-6-pteridinecarboxylic acid.[4]

Anal. Calcd. for $C_7H_5N_5O_3$: C, 40.59; H, 2.43; N, 33.81. Found: C, 40.21; H, 2.89; N, 34.03.

The nonpteridine compound, m.p. 160–163°, was identical with 3-iodo-4-aminobenzoylglutamic acid[3] in every respect.

Anal. Calcd. for $C_{12}H_{13}IN_2O_5$: C, 36.75; H, 3.34. Found: C, 36.82; H, 3.57.

Iodination of Pteroylglutamic Acid with Iodine Monochloride in Dimethylformamide.—The procedure differs somewhat from that for 3′-iodoaminopterin. Finely powdered pteroylglutamic acid (1.32 g., 3 mmoles) was suspended in 25 ml. of dimethylformamide and protected from light. Iodine monochloride (0.4 ml., 1.3 g., 8 mmoles) was slowly added dropwise in 10 min., accompanied by vigorous agitation at room temperature. After the addition of iodine monochloride, the agitation was continued overnight. The reaction mixture was poured with stirring into 100 ml. of water and 50 ml. of ethanol. The acidity of the mixture was adjusted to pH 5 by the addition of solid sodium acetate trihydrate, whereupon a dark yellow gelatinous precipitate started to form. The mixture was chilled at 4° for 10 hr. The precipitate was separated by centrifugation and washed with 50 ml. of ethanol followed by 50 ml. of ether. (The combined filtrate and washings, fraction A, were saved for isolation of cleavage products. See below.) The precipitate was redissolved in 10 ml. of 1 *N* sodium hydroxide, filtered, and reprecipitated with 2 ml. of glacial acetic acid. The yellow precipitate was collected by filtration and washed with water and methanol. The product weighed 1.1 g. (65%) and was identical with the iodo compound prepared by the published procedure.[2]

Identification of Cleavage Products.—Fraction A above was concentrated *in vacuo* (water pump) at 40°. The brown sirupy residue was stirred with 10 ml. of methanol and filtered. The insoluble residue was purified as described in the published procedure.[5] The pure compound was indistinguishable from an authentic sample of 2-amino-4-hydroxy-6-pteridinecarboxaldehyde.

The methanolic solution was again concentrated *in vacuo*. The residue was purified as reported previously.[3] The final product was almost colorless, m.p. 222–224° dec., undepressed by authentic 3,5-diiodo-4-aminobenzoylglutamic acid.[2]

Anal. Calcd. for $C_{12}H_{12}I_2N_2O_5$: C, 27.82; H, 2.34; I, 48.99; N, 5.41. Found: C, 28.01; H, 2.50; I, 48.55; N, 5.21.

ω-Acetyllongifolene[1]

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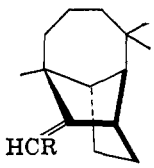
We undertook the acylation[3] of longifolene (Ia) in connection with other acylation studies being conducted in this laboratory. Acetylation of the structurally related compound, camphene, had been accomplished (5% yield) by Lipp, *et al.*,[4] with acetyl chloride and stannic chloride.

Longifolene and acetic anhydride, allowed to react at room temperature with protonic or Lewis acid catalysts, did not afford the desired acylation; however, brief reaction of longifolene at 0° with acetic anhydride



Ia, R = H
b, R = $COCH_3$
c, R = CO_2H
d, R = CO_2CH_3

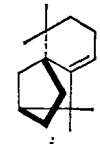
and boron trifluoride etherate gave ω-acetyllongifolene (Ib) together with a lesser amount of isolongifolene.[5] The products were separated by adsorption chromatography on silica gel, and purity of Ib was verified *via* vapor phase chromatography and ultraviolet spectroscopy.

Isolongifolene was recovered (60%) when it was subjected to the same reaction conditions, and there was no evidence for formation of Ib, showing that acylation does not *follow* isomerization.

Spectral data and conversion to a known compound (see below) provided evidence for assigning the ω-acetyllongifolene structure (Ib) to the acylation product. The spectral properties of Ib are of particular interest. In the infrared spectrum C=C and C=O stretching bands in the 6-μ region are of approximately equal intensity, indicative of an *s-cis* conjugated carbonyl system.[6] The high-intensity, long wave length ultraviolet maximum [λ_{max} 256 mμ (ε 15,000)] is similar to that of ω-formyllongifolene [λ_{max} 253 mμ (ε 15,600)].[7] This bathochromic shift from normally calculated values may be explained either by the highly strained cyclic system[8] or by the highly branched substituents on the β-carbon of the α,β-unsaturated ketone system.[9,10]

A chemical proof of structure Ib was obtained through its conversion to ω-carboxylongifolene (Ic) by means of the hypohalite reaction. Identity of Ic was established by infrared and n.m.r. comparison with an authentic sample.[7,11] However, the double bond of Ib could not be cleaved (to form longicamphenylone[12]) with ozone, chromic acid, or ruthenium tetroxide.

Finally, it was found that reaction of longifolene with boron trifluoride etherate affords a very simple method for preparation of isolongifolene. Optical rota-



i

(1) Longifolene. XII. Paper XI: D. Helminger and G. Ourisson, *Ann.*, in press. R. E. B. gratefully acknowledges the assistance provided by an Organization for Economic Cooperation and Development Science Fellowship and by a sabbatical leave from Southern Illinois University which made this investigation possible.

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(3) For a recent review, see D. P. N. Satchell, *Quart. Rev.* (London), **17**, 160 (1963).

(4) P. Lipp, P. Kuppers, and M. Holl, *Ber.*, **60**, 1575 (1927); P. Lipp and M. Quaedvlieg, *ibid.*, **62**, 2311 (1929).

(5) The structure of isolongifolene (i), which results from rearrangement during acid-catalyzed hydration of longifolene, has recently been elucidated: J. R. Prahlad, R. Ranganthan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron Letters*, 417 (1964).

(6) R. L. Erskine and E. S. Wright, *J. Chem. Soc.*, 3425 (1960); also A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

(7) U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *ibid.*, **19**, 2281 (1963).

(8) W. M. Schubert and W. A. Sweeney, *J. Am. Chem. Soc.*, **77**, 2297 (1955).

(9) P. Arnaud and M. Montagne [*Compt. rend.*, **251**, 998 (1960)] have found that a bathochromic shift of as much as 14 mμ can occur with highly branched substituents as compared to β,β-dimethyl substituents.

(10) An alternate explanation that the structure is a rearranged acylation product with an α,β,β-trialkylated and exocyclic chromophore (calcd. λ_{max} 252 mμ) is ruled out since the n.m.r. spectrum shows a vinylic proton at τ 4.13.

(11) P. Naffa and G. Ourisson, *Bull. soc. chim. France*, 1410 (1954); D. Helminger, these laboratories.

(12) V. R. Nayak and S. Dev., *Tetrahedron*, **8**, 42 (1960).

tion measurement indicates that these conditions lead to much more racemization than those of Nayak and Dev.[12]

Experimental

ω-Acetyllongifolene (Ib).—To 25 ml. of acetic anhydride and 31 ml. of boron trifluoride etherate, cooled and stirred in an ice bath, was added 10.2 g. of longifolene[13] during 5 min. The mixture slowly darkened and became almost homogeneous after an additional 5 min. at 0°. It was then added slowly to a mixture of ice and concentrated aqueous potassium hydroxide. This alkaline mixture was stirred as it warmed to room temperature. After 45 min. ether was added, the resultant emulsion was filtered from inorganic material and separated, and the aqueous phase was extracted with additional ether portions. In this way 12.0 g. of amber oil was obtained from the ether extract.

A rough separation of products was accomplished by chromatography on a column of 100 g. of silica gel to give: 3.07 g. of isolongifolene (infrared evidence) eluted with petroleum ether (b.p. 30–60°), 6.17 g. of crude Ib in the petroleum ether–ether (9:1 and 8:2) fractions, and about 1.5 g. of unidentified material in the petroleum ether–ether (7:3 and 6:4) eluates. Careful rechromatography of crude Ib on silica gel yielded 3.87 g. of product in fractions eluted with petroleum ether–ether (95:5) whose ultraviolet absorption maximum showed an $E\%$ in excess of 500.

The analytical sample was prepared from the semicarbazone (see below) by hydrolysis with 70% acetic acid at reflux for 22 hr., chromatography on silica gel, and evaporative distillation in a short-path still at 155° (20 mm.).

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.17; H, 10.63.

This material was a single component on silica gel chromatoplates (R_f 0.63 in cyclohexane–ethyl acetate, 8:2, spotted with H_2SO_4). Vapor phase chromatography (2% SE-30, temperature 170°, retention time 21.5–23 min.) also showed this product to be a single component. Other data obtained on the analytical sample or material of comparable purity are as follows: λ_{max} 256 mμ (ε 15,000) (95% ethanol); λ_{max}^{neat} 5.95 and 6.19 μ (nearly equal intensities); the n.m.r. (Varian A-60 spectrometer) showed three sharp singlets at τ 9.00, 9.06, and 9.11 for the tertiary methyl groups (τ 9.01, 9.06, and 9.10 in longifolene), a three-proton singlet at τ 7.82 for the acetyl methyl, and a one-proton singlet at τ 4.13 for the vinylic proton, in deuteriochloroform; $[\alpha]D$ +52.2° ($CHCl_3$); circular dichroism $\Delta\epsilon_{332-328} = -0.17$ in dioxane.

Semicarbazone of ω-Acetyllongifolene.—To 1.0 g. of once-chromatographed Ib in 10 ml. of 95% ethanol was added 700 mg. of semicarbazide hydrochloride dissolved in 3 ml. of water to which 10 ml. of 95% ethanol had been added. After gentle warming for 15 min. and storage in an ice chest overnight, 630 mg. of crystals, m.p. 202–206° dec., was collected. Several recrystallizations from 95% ethanol yielded a sample: m.p. 203–206° dec.[14]; λ_{max} 272 mμ (ε 21,300); λ_{max}^{KBr} 2.90, 3.15, 5.89, 6.08 (weak), and 6.32 μ. The n.m.r. showed a three-proton singlet at τ 8.05 (CH_3CO) and a one-proton singlet at τ 4.47 (vinyl H), as well as the expected tertiary methyl groups at τ 9.0–9.1 in deuteriochloroform.

Anal. Calcd. for $C_{18}H_{29}N_3O$: C, 71.24; H, 9.63; N, 13.85. Found: C, 71.09; H, 9.68; N, 14.29.

ω-Carboxylongifolene (Ic).—To 125 mg. of Ib in 8 ml. of methanol was added 2.0 ml. of 1.53 M sodium hypochlorite solution. After an initial exothermic reaction the mixture was refluxed on a steam bath for 15 hr. It was cooled, water was added, and the mixture was extracted with ether. The ether extract was washed with aqueous sodium thiosulfate, dried, and concentrated to give 52 mg. of neutral product as an oil.

From the ether extract of the acidified initial aqueous phase 25 mg. of crystalline acid product was obtained. Recrystallization from ether–petroleum ether and then from 95% ethanol gave pure Ic, m.p. 223–224° (subliming slowly above 210°). This product was proved to be the same as ω-carboxylongifolene[11] by the identity of infrared spectra in chloroform and n.m.r. spectra in deuteriochloroform.

(13) We thank Dr. E. Klein (Dragoco, Holzminden) for the gift of longifolene used in this study.

(14) All melting points were taken on a Kofler micro hot stage.

The neutral product after chromatography on silica gel appeared to be ω-carbomethoxylongifolene (Id),[15] as evidenced by spectral data: λ_{max} 235 mμ, $E\%$ 528 (95% ethanol); methyl ester protons at τ 6.30 and a vinyl proton at τ 4.50. However, the optical rotation, $[\alpha]D$ +44.6° ($CHCl_3$), is quite different from that reported,[7] $[\alpha]D$ +104° (neat), for this compound by Dev and co-workers. There is, of course, the possibility of *cis–trans* mixtures.

Isolongifolene.—To 1.0 g. of longifolene in 5 ml. of sodium-dried ether was added 3 ml. of boron trifluoride etherate and the mixture was refluxed for 1 hr. on the steam bath. The resultant dark brown mixture was added cautiously to excess potassium hydroxide and ice. The mixture was stirred at room temperature for 1.5 hr., at the end of which time the ether phase became straw yellow in color. Separation, further extraction, water wash, and evaporation of ether left 980 mg. of light yellow oil. This material was essentially identical with authentic isolongifolene by infrared comparison, and vapor phase chromatography showed it to be about 90% pure isolongifolene. When this oil was passed through a column of 40 g. of silica gel the eluate contained 689 mg. of isolongifolene as a colorless oil, $[\alpha]D$ −14.9° (*c* 1.39, $CHCl_3$), in the first fraction and 143 mg., $[\alpha]D$ −3.9° (*c* 0.76, $CHCl_3$), in the second fraction.[12]

(15) We have been unable to find a precedent for this unusual esterification reaction in the presence of sodium hypochlorite.

N-Acylation of Cysteine

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Inconsistent yields and complex procedures characterize the indirect preparation[1-3] of N-acetyl-L-cysteine from L-cystine. Acetylation of two mercapto starting materials, L-cysteine ester[4] and anilide,[5] with acetic anhydride gave N,S-diacetyl derivatives. By acylating cysteine with acyl halides, good yields of S-acylated cysteines[6,7] and unspecified yields of N-acylated derivatives[8] were obtained.

We have prepared N-acetyl-L-cysteine in 65–80% yields directly from L-cysteine using 1 equiv. of acetic anhydride and a variety of acid acceptors in aqueous tetrahydrofuran. N-Propionyl and N-succinoyl derivatives were obtained in yields of 61 and 22%, respectively, by this simple, direct method.

Experimental[9]

N-Acetyl-L-cysteine.—A suspension of 35.2 g. (0.2 mole) of L-cysteine hydrochloride monohydrate in 87 ml. of 91% aqueous tetrahydrofuran (THF) was stirred under nitrogen at room temperature and treated with 54.4 g. (0.4 mole) of sodium acetate trihydrate. The sodium acetate addition lowered the internal temperature to 9° and produced a curdy mass. After

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(7) L. Zervas, J. Photaki, and N. Ghelis, *ibid.*, **85**, 1337 (1963).

(8) A. L. Sheffner, U. S. Patent 3,091,569 (May 28, 1963).

(9) All melting points are uncorrected. The infrared spectra of all the described compounds were consistent with the assigned structures. We wish to thank Dr. Donald L. Timma and associates of these laboratories for the analytical and physical data. The sulfhydryl determination was performed potentiometrically with mercuric chloride using a gold indicating electrode [R. Cecil, *Biochim. Biophys. Acta*, **18**, 154 (1955)].