tion were carried out simultaneously. A large amount of hydrogen sulfide was liberated. The rotation fell and leveled off at $[\alpha]D+18°$ after 19 hr. The solution was filtered and stripped under reduced pressure. The crude residue exhibited no characteristic absorption from 220–320 mμ. A portion of the crude solid was esterified with diazomethane and gas chromatographed on Versamide-900 at 240°. A single peak was observed of emergence time identical with that of an authentic sample of methyl dehydroabietiate. The cyclohexylamine salt of the crude residue was prepared in acetone and recrystallized from 95% ethanol; yield 4.88 g. The filtrate was concentrated to give a black, noncrystallizable oil. The salt was regenerated using dilute phosphoric acid and ether.[2] The crude acid was chromatographed on 92 g. of silicic acid and eluted with benzene. The eluate was crystallized from 95% ethanol to give 0.69 g. of dehydroabietic acid, $[\alpha]D$ +61.8° (*c* 0.6, 95% ethanol), λ_{max} 268 mμ (α 2.21) and 276 (α 2.34), infrared spectrum essentially identical with an authentic sample. A second crop of 0.32 g. was obtained, λ_{max} 268 mμ (α 2.51) and 276 (α 2.60), for a total of 1.01 g. or 13% over-all yield. The remainder of the material from the column could not be crystallized.

Blank Runs in 95% Ethanol.—A series of runs was made in 100-ml. Pyrex reactors,[2] 0.01 *M* in resin acid, and 0.01 *M* in sulfur, and followed by means of the change in rotation and/or ultraviolet spectrum for 7 hr. A 15-w. daylight fluorescent bulb was used as a light source. No reaction occurred in the case of levopimaric acid under nitrogen, on aeration in the dark, or on aeration in the absence of sulfur. In the presence of air, light, and sulfur, the reaction with levopimaric acid was over in less than 12 hr. No reaction occurred in the presence of air, light, and sulfur when levopimaric acid was replaced with palustric, neoabietic, abietic, dehydroabietic, pimaric, or isopimaric acids.

Isomerization of Levopimaric Acid in Carbon Disulfide.—A 0.011 *M* solution of levopimaric acid in carbon disulfide was charged to a 100-ml. Pyrex reactor[2] open to the air and irradiated with a 15-w. daylight fluorescent lamp. The original rotation of −200° fell to −116° after 8 hr. At this point the light was turned off and the reactor was stored in the dark. After an additional 16 hr. the rotation was +20° (abietic acid exhibits $[\alpha]^{25}D$ +20° in carbon disulfide), and the ultraviolet spectrum showed a single major peak at λ_{max} 241 mμ (α 69). The product was esterified with diazomethane and analyzed *via* g.l.c. The yield of abietic acid was 83%. The reaction proceeded more slowly under nitrogen. The presence of dissolved sulfur did not affect the reaction. No reaction occurred in the dark over the same period of time.

3′-Iodopteroylglutamic Acid (Iodofolic Acid)

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Several chloro and bromo derivatives of pteroylglutamic acid have been described in the literature.[2] The iodo derivatives, except 3′-iodo-4-amino-4-deoxypteroylglutamic acid (3′-iodoaminopterin),[3] are not as well studied. Iodination of 1 mole of pteroylglutamic acid with 2 moles of iodine monochloride in hydrochloric acid yielded a substance which, on the basis of nitrogen and iodine analyses alone, seemed to be the 3′-iodopteroylglutamic acid.[2b] However, this substance, prepared by identical procedure, was claimed by the same authors as the 3′,5′-diiodo derivative in patent literature.[2c,d] In either case structural proof was lacking.

We repeated this reaction. In addition, we prepared a magnesium salt of the iodinated compound. Both displayed correct analyses of all elements for monoiodopteroylglutamic acid and the magnesium salt, respectively. Moreover, oxidation of the iodinated product with potassium permanganate in dilute alkali degraded it to two fragments, separately identified as 2-amino-4-hydroxy-6-pteridinecarboxylic acid[4] and 3-iodo-4-aminobenzoylglutamic acid,[3] thus definitely establishing the structure of the iodo compound as 3′-iodopteroylglutamic acid.

The iodination of pteroylglutamic acid with iodine monochloride was also carried out in dimethylformamide. In this case, iodination was accompanied by cleavage of pteroylglutamic acid into 3,5-diiodo-4-aminobenzoylglutamic acid[2] and 2-amino-4-hydroxy-6-pteridinecarboxaldehyde,[5] similar to the case with aminopterin.[3]

Experimental[6]

3′-Iodopteroylglutamic Acid.—The published procedure[2] was faithfully followed. For the preparation of the magnesium salt, the free iodinated acid (100 mg.) was dissolved in a minimal amount of a saturated solution of sodium bicarbonate and mixed with 100 mg. of anhydrous magnesium sulfate powder. To the thick paste was added 5 ml. of water, and the mixture was centrifuged. The precipitate was washed with 5 ml. of water and recrystallized from 50 ml. of boiling water. The yellow magnesium salt was collected and washed with water and alcohol. The yield was 100 mg.

Anal. Calcd. for $C_{19}H_{16}IMgN_7O_6$: C, 38.70; H, 2.74; I, 21.52; Mg, 4.13; N, 16.63. Found: C, 38.69; H, 2.83; I, 20.76; Mg, 3.99; N, 16.90.

Reconversion of the magnesium salt into the free acid was easily achieved by dissolving the former (100 mg.) in 2 ml. of concentrated hydrochloric acid and diluting with 20 ml. of water. The precipitate was collected by filtration and washed with water and methanol. It weighed 40 mg.

Anal. Calcd. for $C_{19}H_{18}IN_7O_6$: C, 40.23; H, 3.20; I, 22.37; N, 17.28. Found: C, 40.03; H, 3.18; I, 22.22; N, 17.06.

The ultraviolet absorption spectra of 3′-iodopteroylglutamic acid bear close resemblance to those of 3′-iodoaminopterin,[3] differing by the absence in 3′-iodopteroylglutamic acid of an absorption maximum at 336 mμ in dilute acid. The characteristics are: in 0.1 *N* sodium hydroxide, λ_{max} 223 mμ (log ε 4.77), 255 (4.48), 282 (4.38), and 366 (4.12); in 0.1 *N* hydrochloric acid, λ_{max} 223 mμ (log ε 4.48) and 301 mμ (log ε 4.28).

Oxidative Degradation of 3′-Iodopteroylglutamic Acid.—The procedure was exactly the same as for the oxidation of 3′-iodoaminopterin.[3] From 100 mg. of the iodo compound were obtained 25 mg. of a substituted pteridine and 15 mg. of a nonpteridine moiety.

(1) Supported in part by Public Health Service Research Grants CY-3335 and C-6516 from the National Cancer Institute, National Institutes of Health.

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(6) Melting points were determined on a Fisher-Johns apparatus. Ultraviolet absorption spectra were recorded with a Cary spectrophotometer, Model 14. All analyses were performed by Dr. William C. Alford and staff of the National Institute of Arthritis and Metabolic Diseases, to whom we express our gratitude.

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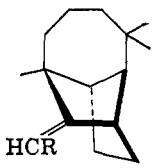
We undertook the acylation[3] of longifolene (Ia) in connection with other acylation studies being conducted in this laboratory. Acetylation of the structurally related compound, camphene, had been accomplished (5% yield) by Lipp, *et al.*,[4] with acetyl chloride and stannic chloride.

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

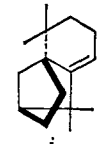
and boron trifluoride etherate gave ω-acetyllongifolene (Ib) together with a lesser amount of isolongifolene.[5] The products were separated by adsorption chromatography on silica gel, and purity of Ib was verified *via* vapor phase chromatography and ultraviolet spectroscopy.

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

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