1-butanol. The extracts were worked up as described in the preceding experiment. The yield of thyroxine based on the amount of 4-hydroxy-3,5-diiodophenylpyruvic acid-U-C^{14} present in the ether extract used as a starting material was 17%. The yields in a number of experiments varied from 12 to 20%.

The Synthesis of Dihydrotriacanthine[1]

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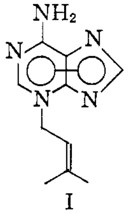
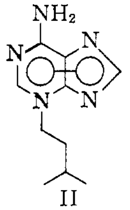
Received December 8, 1961

3-Isopentyladenine has been synthesized and shown to be identical with dihydrotriacanthine (II).

In a companion article[2] we have provided physical and chemical evidence that the structure of triacanthine, naturally occurring in the new leaves of *Gleditsia triacanthos* L., is 6-amino-3-(γ,γ-dimethylallyl)purine (I). Moreover, we have reported a synthesis, novel but equivocal, of I, along with syntheses of the isomeric 6-amino-7-(γ,γ-dimethylallyl)- and 6-amino-9-(γ,γ-dimethylallyl)purines,[3] all by the alkylation of adenine. An unequivocal synthesis of triacanthine or one of its derivatives was desirable for final structure proof, and we elected to synthesize dihydrotriacanthine (II) following a method which Elion[4] had established as unambiguous for 3-methyladenine.[5]

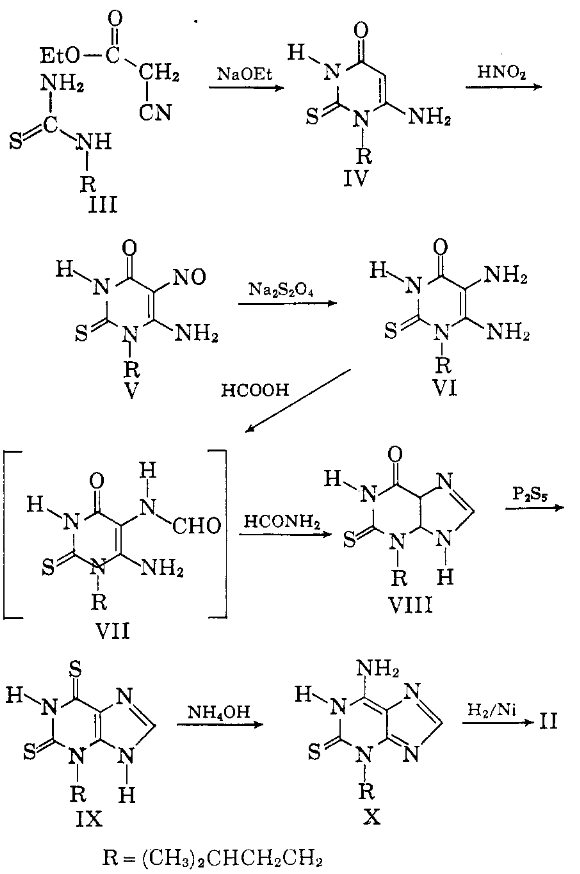


I



II

6-Amino-1-isopentyl-2-thiouracil (IV) was prepared according to the general method of Traube and Winter,[6] by the almost unidirectional condensation of isopentylthiourea (III) with ethyl cyanoacetate, followed by nitrosation to give 6-amino-1-isopentyl-5-nitroso-2-thiouracil (V, a possible equilibrium of tautomeric forms is recognized). Reduction of V with sodium hydrosulfite[7-9] yielded 5,6-diamino-1-isopentyl-2-thiouracil (VI). The imidazole ring was closed by formic acid and/or formamide, and



R = $(CH_3)_2CHCH_2CH_2$

the product, 3-isopentyl-2-thioxanthine (VIII), was converted to 3-isopentyl-2,6-dithioxanthine (IX) using phosphorus pentasulfide.[4] Replacement of the sulfur at C-6 by an amino group to give 3-isopentyl-2-mercaptoadenine (X) and hydrogenolysis of the C-2 sulfur linkage by means of Raney nickel completed the synthesis of 3-isopentyladenine (6-amino-3-isopentylpurine) (II). Yields at each stage averaged 80%. The only

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[1] This investigation was supported in part by a research grant (USPHS-RG5829) from the National Institutes of Health, U. S. Public Health Service.

[2] N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, in press.

[3] 6-(γ,γ-Dimethylallyl)aminopurine has also been made in this laboratory (Dr. T. Fujii, research in progress).

[4] (a) G. B. Elion, "Ciba Foundation Symposium on the Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, eds., Little, Brown and Co., Boston, 1957, p. 39; (b) G. B. Elion, private communication; article now in press, *J. Org. Chem.*

[5] Another method of synthesis of 3-methyladenine and of triacanthine (I) will be reported independently by R. Denayer, A. Cavé, and R. Goutarel, *Compt. rend.*, in press. The authors are grateful to Dr. Goutarel for providing a copy of this note prior to publication.

[6] W. Traube and F. Winter, *Arch. Pharm.*, **244**, 11 (1906).

[7] M. T. Bogert and D. Davidson, *J. Am. Chem. Soc.*, **55**, 1667 (1933).

[8] G. B. Elion, E. Burgi, and G. H. Hitchings, *ibid.*, **74**, 411 (1952).

[9] G. Levin, A. Kalmus, and F. Bergmann, *J. Org. Chem.*, **25**, 1752 (1960).

other possible isomeric product of this synthetic sequence might have been 1-isopentyladenine, but the final compound did not show similarity in spectral or dissociation constant data with the 1-methyladenine of Brookes and Lawley,[10] whereas it was similar in these properties[2,4] to the authentic 3-methyladenine of Elion. Moreover, the product of our reaction sequence was stable to heating with ammonia, as is 3-methyladenine, while Brookes and Lawley have reported that 1-methyladenine undergoes rearrangement to 6-methylaminopurine upon such treatment.

Synthetic 3-isopentyladenine was identical by the criteria of infrared, ultraviolet and NMR spectra, melting and mixture melting points, and X-ray powder patterns with dihydrotriacanthine. Accordingly, the structure of triacanthine is confirmed as that of 6-amino-3-(γ,γ-dimethylallyl)purine (I).

Experimental[11]

6-Amino-1-isopentyl-2-thiouracil (IV).[6]—To a solution of sodium ethoxide prepared by dissolving 4.1 g. (0.18 g.-atom) of sodium in 110 ml. of absolute ethanol, were added 25 g. (0.17 mole) of isopentylthiourea (III),[12] m.p. 91.5–92.5°[13,14] and 20.1 g. (0.18 mole) of ethyl cyanoacetate. The solution was heated under reflux for 4 hr., and the ethanol was removed under vacuum. About 200 ml. of 2 *N* acetic acid was added to the viscous residue, and the precipitate which formed was collected and recrystallized from aqueous ethanol as fluffy, feather-like crystals, m.p. 251–252°, yield 31.9 g. (88%).

Anal. Calcd. for $C_9H_{15}N_3OS$: C, 50.68; H, 7.08; N, 19.70. Found: C, 50.94; H, 7.15; N, 19.42.

The compound could also be made from its isomeric precursor, *3-cyanoacetyl-1-isopentylthiourea* [$(CH_3)_2CHCH_2$-$CH_2NHCSNHCOCH_2CN$], m.p. 124–126°, ν_{max}^{KBr} 3230 (NH), 3050 (CONH), 2240 ($C{\equiv}N$), 1677 cm.$^{-1}$ (CO), prepared from III.

Anal. Calcd. for $C_9H_{15}N_3OS$: C, 50.68; H, 7.08; N, 19.70. Found: C, 50.87; H, 7.21; N, 19.39.

6-Amino-1-isopentyl-5-nitroso-2-thiouracil (V).[6]—To a solution of 3.5 g. (0.051 mole) of sodium nitrite, 10.0 g. (0.047 mole) of 6-amino-1-isopentyl-2-thiouracil (IV), and 1.9 g. (0.047 mole) of sodium hydroxide in 150 ml. of water was added 30 ml. of acetic acid. The initially pink precipitate became gray-green after stirring the mixture at 25° for 5 hr. and on the steam bath for 3 hr. The solid was collected by filtration, washed with water, and recrystallized from aqueous ethanol as shiny, violet leaflets that became green after a few days, dec. (violent) *ca.* 200°, yield 7.7 g. (68%).

5,6-Diamino-1-isopentyl-2-thiouracil (VI).—Ammonium hydroxide was added to a stirred suspension of 5.0 g. (0.021 mole) of 6-amino-1-isopentyl-5-nitroso-2-thiouracil (V) in 50 ml. of water until the mixture became bright orange. The mixture was heated to about 80°, and 7.2 g. (0.042 mole) of sodium hydrosulfite was added over a period of 5 min.[8] Stirring was continued an additional 5 min., the mixture was cooled, and the tan precipitate was collected by filtration. Purification was accomplished by dissolving the solid in 40 ml. of 2 *N* sodium hydroxide, treating with charcoal, and adding the filtered solution to 40 ml. of 2 *N* acetic acid. The yield of product (4.7 g.) obtained in this way was nearly quantitative. Recrystallization from ethanol gave small, slightly tan needles, dec. 234–237°.

Anal. Calcd. for $C_9H_{16}N_4OS$: C, 47.34; H, 7.06; N, 24.54. Found: C, 47.38; H, 7.34; N, 24.34.

3-Isopentyl-2-thioxanthine (VIII).—A solution of 4.65 g. (0.0204 mole) of 5,6-diamino-1-isopentyl-2-thiouracil (VI) in 42 ml. of 98% formic acid was heated under reflux for 2 hr.[8] Excess formic acid was removed under vacuum, and the solid residue was purified as in the case of VI (see above). The solid was then heated in 35 ml. of formamide for 2 hr. at 180°.[4,15] After the formamide had been removed under vacuum, the residue was recrystallized from ethanol as tiny, colorless plates, m.p. 312–314°, yield 2.95 g. (61%). The compound could also be obtained from I *via* the same reaction sequence but without the isolation of intermediates.

Anal. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.40; H, 5.92; N, 23.51. Found: C, 50.27; H, 5.99; N, 23.28.

3-Isopentyl-2,6-dithioxanthine (IX).—A mixture of 2.94 g. (0.0123 mole) of 3-isopentyl-2-thioxanthine (VIII), 17 g. of technical phosphorus pentasulfide and 150 ml. of anhydrous pyridine was heated under reflux for 3 hr.[4] Evaporation of the pyridine left a yellow solid, which was then heated with 150 ml. of water for 15 min. Hydrogen sulfide was removed by applying vacuum. The solution was adjusted to about *p*H 6 with ammonium hydroxide and the solid was collected by filtration. The compound was purified by solution in sodium hydroxide, treatment with charcoal, and acidification with acetic acid. Recrystallization from ethanol afforded 2.43 g. (74%) of small yellowish needles, m.p. 256–258°.

Anal. Calcd. for $C_{10}H_{14}N_4S_2$: C, 47.21; H, 5.55; N, 22.03. Found: C, 47.02; H, 5.43; N, 21.58.

3-Isopentyl-2-mercaptoadenine (X).—A solution of 2.24 g. (8.5 mmoles) of 3-isopentyl-2,6-dithioxanthine (IX) in 50 ml. of concd. ammonium hydroxide was heated in a glass-lined steel bomb at 140° for 18 hr.[4] After the excess ammonia had been removed by distillation under vacuum, the solution was acidified to *p*H 6 with acetic acid. The solid which separated was recrystallized from ethanol as colorless, fluffy leaflets, m.p. 311–313°, yield 2.0 g. (95%).

Anal. Calcd. for $C_{10}H_{15}N_5S$: C, 50.61; H, 6.37; N, 29.51. Found: C, 50.43; H, 6.23; N, 29.20.

3-Isopentyladenine (**6-Amino-3-isopentylpurine; Dihydrotriacanthine**) (II).—A mixture of 2.24 g. (9.46 mmoles) of 3-isopentyl-2-mercaptoadenine (X), 15 ml. of concd. ammonium hydroxide, 180 ml. of water, 20 ml. of ethanol, and 8 ml. of settled Raney nickel catalyst, activity W-2,[16] was heated at reflux for 2.5 hr.[4] The catalyst was removed by filtration and washed several times with ethanol. The filtrate and washings were concentrated to about one-half volume to remove most of the ethanol. The resulting solution was made basic with ammonium hydroxide (*p*H 10) and extracted with three 60-ml. portions of chloroform. Drying the solution and evaporation of the solvent were followed by recrystallization of the residue from water as colorless needles, m.p. 230–231°, yield 1.4 g. (72%). The compound sublimed at 170° (0.025 mm.).

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.62; H, 7.26; N, 33.90.

A mixture of synthetic 3-isopentyladenine and dihydrotriacanthine from triacanthine, m.p. 230–231°, showed no melting point depression. The infrared spectra determined in potassium bromide disk were identical, as were the X-ray powder patterns (7-cm. camera radius; wave length, 1.5418 Å.) and the NMR spectra (20% in sulfur dioxide). The ultraviolet spectra of 3-isopentyladenine showed the following values: λ_{max}^{water} (*p*H 1) 274 (19,500) and (*p*H 8) 272 mμ (ϵ 13,700); λ_{min}^{water} (*p*H 1) 236 (2980) and (*p*H 8) 243 mμ (ϵ

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(10) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(11) Melting points are corrected. We are indebted to Mr. Josef Nemeth and his associates at the University of Illinois for the microanalyses.

(12) Prepared from isopentylamine *via* isopentyl isothiocyanate following the method of M. L. Moore and F. S. Crossley, *Org. Syntheses*, Coll. Vol. III, 599 and 617 (1955), for methylthiourea.

(13) G. M. Dyson and R. F. Hunter, *Rec. trav. chim.*, **45**, 421 (1926).

(14) A. E. Dixon, *J. Chem. Soc.*, **67**, 556 (1895).

(15) Ring closure appears to take place in formic acid, but the latter step, heating in formamide, was carried out to insure complete closure.

(16) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 181 (1955).

3270); and, in direct comparison with the spectral curves of Deyrup[17]:

pH 1	Dihydrotriacanthine	Synthetic 3-Isopentyladenine
$\lambda_{max}^{C_2H_5OH}$	277 mμ (ε 18,700)	277 mμ (ε 17,500)
$\lambda_{min}^{C_2H_5OH}$	239 (3,350)	238 (3,400)
pH 7		
$\lambda_{max}^{C_2H_5OH}$	273 (12,700)	274 (12,600)
$\lambda_{min}^{C_2H_5OH}$	247 (3,240)	246 (3,170)

Acknowledgment.—The authors are happy to record particular appreciation to Miss Gertrude B. Elion, Burroughs Wellcome and Co., Tuckahoe, N. Y., for providing us with details for the synthesis of 3-methyladenine.

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[17] J. A. Deyrup, Ph.D. thesis, University of Illinois, 1961.

Model Compounds for Comparison with Native Lignin. II. 3-Phenyl-1-propyl α-Ethylbenzyl Ether and 3-Phenyl-1-propyl α-Ethylveratryl Ether[1]

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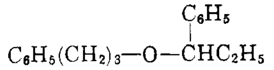
Received October 20, 1961

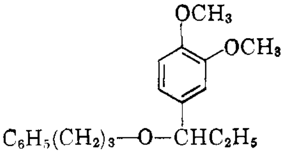
The difference in reactivity of 3-phenyl-1-propyl α-ethylbenzyl ether (I) and 3-phenyl-1-propyl α-ethylveratryl ether (II) is ascribed to the activating influence of the 3,4-dimethoxy substitution present in II. Lignin, in which the 3-methoxy-4-hydroxyphenyl nucleus is prominent, has a chemical reactivity closely approached by 3-phenyl-1-propyl α-ethylveratryl ether (II) in the studies that have been made. The presence of this benzyl γ-propyl ether structure in lignin may be regarded as a definite possibility.

There is general agreement among the investigators of the structure of lignin that the fundamental unit present is a substituted benzene ring with a three carbon atom side chain. However, the mode of linkage of the units has not been determined. Numerous types of linkage have been proposed and this prior work has been summarized by Brauns.[3] Although the ether linkage has been suggested as a possibility, substituted dipropyl ethers linked in the α, β, or γ positions have not been synthesized. The present investigation concerns the synthesis of ethers with linkages between the α-carbon of one propyl group and the γ-carbon of another propyl group. Model compounds of this type, specifically 3-phenyl-1-propyl α-ethylbenzyl ether (I) and 3-phenyl-1-propyl α-ethylveratryl ether (II), were selected for study in order to compare their properties with those recorded in the literature for lignin. This particular type of ether was selected because hydrogenolysis of II should yield 3-phenyl-1-propanol and 1-(3,4-dimethoxyphenyl)propane. The selective hydrogenolysis of the α-ether linkage has been shown by Beets and Van Essen.[4,5] Such a structure would be in agreement with the hydrogenolysis products obtained from lignin.[3] A possible polymeric structure incorporating these α,γ-ether linkages is the following:

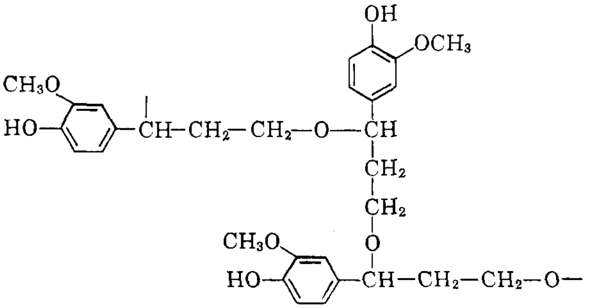


$C_6H_5(CH_2)_3-O-CH(C_6H_5)C_2H_5$

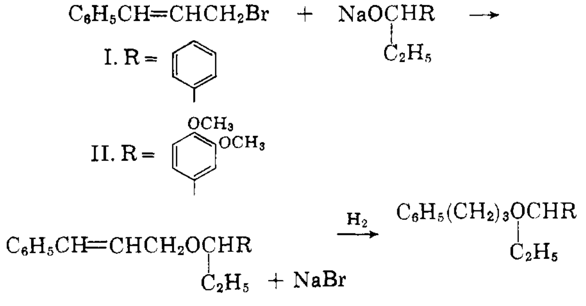
I



II



The synthesis of 3-phenyl-1-propyl α-ethylbenzyl ether (I) was accomplished by the intermediate



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[1] For the previous paper in this series, see M. F. Browne and R. L. Shriner, *J. Org. Chem.*, **22**, 1320 (1957).

[2] From the Ph.D. thesis submitted to the Graduate College of the State University of Iowa. Allied Chemical Corporation Fellow, 1953–1954. Present address: Phillips Petroleum Co., Bartlesville, Okla.

[3] F. E. Brauns, "The Chemistry of Lignin," Academic Press, Inc., New York, 1952. F. E. Brauns and D. A. Brauns, "The Chemistry of Lignin, Supplement Volume Covering the Literature for the Years 1949–1958," Academic Press, Inc., New York, 1960.

[4] M. Beets, *Rec. trav. chim.*, **70**, 20 (1951).

[5] M. Beets and R. Van Essen, *Rec. trav. chim.*, **70**, 25 (1951); E. Drukker and M. Beets, *Rec. trav. chim.*, **70**, 29 (1951).