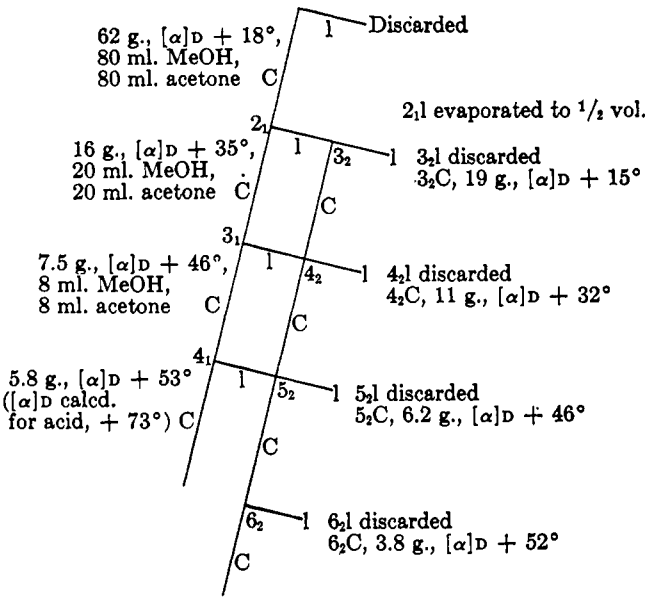
CHART I

Starting material: 200 g. of gum rosin + 600 ml. of acetone + 68 g. of 2,6-dimethylpiperidine



Palustric acid is an intermediate and a product of the thermal and acid isomerization of levopimaric[4,5] and neoabietic[6,7] acids. On thermal isomerization palustric acid yields an equilibrium mixture of abietic, neoabietic, and palustric acids.[8]

The only method available for the isolation of palustric acid has been by partition chromatography.[2] The method described in this paper is based on the precipitation of the 2,6-dimethylpiperidine salt of the resin acids from an acetone solution of pine oleoresin or rosin followed by selective crystallization of the salt from a methanol–acetone (1:1) solution. The yield of pure palustric acid from slash gum rosin was 4%. Gum rosin is preferable as a starting material since, as shown in Table I, abietic acid is coprecipitated along with palustric acid and gum rosin has a more favorable palustric acid to abietic acid ratio than either S.D. wood rosin or tall oil rosin.

TABLE I

COMPOSITION OF METHYL ESTER SAMPLES

	%[a] of each peak off g.l.c.				
Peak[b]	Gum rosin	Crude salt	Salt 2₁C	Salt 3₁C	Salt 4₁C
Me pimarate	6	2.0	..	..	..
Unidentified	2.8	..	..	..	..
Me elliotinoate	3.2	..	..	..	..
Me palustrate	20.4	47.3	76.9	83.7	96.7
Me isopimarate	21.2	5.4	..	..	..
Me abietate	33.6	37.2	22.0	16.3	3.3
Me neoabietate	12.8	8.1	1.4	..	..

[a] Per cent of the material that comes off the column at 225°, 5% Craig Polyester. [b] Each peak except 2 was identified by comparison with an authentic sample of the resin acid methyl ester.

(4) V. M. Loeblich, D. E. Baldwin, R. T. O'Connor, and R. V. Lawrence *J. Am. Chem. Soc.*, **77**, 2823 (1955).

(5) D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *ibid.*, **78**, 2015 (1956).

(6) V. M. Loeblich and R. V. Lawrence, *ibid.*, **79**, 1497 (1957).

(7) D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *J. Chem. Eng. Data*, **3**, 342 (1958).

(8) N. M. Joye, Jr., and R. V. Lawrence, *J. Org. Chem.*, **26**, 1024 (1961).

The composition of the starting rosin, the crude salt, and the salt at each step in the purification was determined by gas chromatography of the methyl esters. Table I shows the progress of the purification.

Experimental

Isolation of the 2,6-Dimethylpiperidine Salt of Palustric Acid from Gum Rosin.—WW gum rosin (200 g., acid no. 168) was dissolved in 600 ml. of acetone. To the rosin solution was added with stirring 68 g. of 2,6-dimethylpiperidine. The solution was allowed to stand at room temperature overnight and the precipitated salt was removed by filtration. The salt was removed from the filter and washed twice by slurrying with 200-ml. portions of warm acetone. The resulting white, crystalline amine salt was dissolved in an equal weight of hot methanol, filtered, and an equal volume of acetone was added. A modified scheme of triangular recrystallization diagrammed in Chart I was used.

Combination of fractions 4_1C and 6_2C gave 9.6 g. of salt with $[\alpha]^{25}D$ +52° (*c* 1.0, alcohol), λ_{max}^{alc} 265 mμ (ε 8300), and m.p. 156–162° (sealed evacuated tube). This weight of amine salt represents a 4% yield of palustric acid based on the acid number of the rosin.

Conversion of Amine Salt to the Acid.—A 10-g. portion of the amine salt was converted to the free acid by dissolving it in 350 ml. of 95% ethanol and adding, with stirring, 100 ml. of cold 3 *N* H_3PO_4. Ice–water was added to the cold acidified solution until no further cloud appeared. The precipitated acid was washed with water to remove excess mineral acid and recrystallized once from a minimum amount of hot 95% ethanol. Since palustric acid is isomerized to abietic acid by strong acids it should be separated from the acidified solution as rapidly as possible. The specific rotation of the final product was +69°,[9] while α at 265–266 mμ was 28.2, and m.p. 162–167°. Further recrystallizations showed no improvement in purity.

(9) The difference in the specific rotation of the free acid and that calculated for the acid from the salt is assumed to be caused by some resolution of the amine during recrystallization.

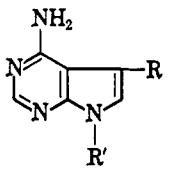
New Syntheses of Pyrrolo[2,3-*d*]- and Pyrrolo[3,2-*d*]pyrimidines[1]

EDWARD C. TAYLOR AND EDWARD E. GARCIA

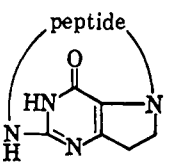
Department of Chemistry, Princeton University, Princeton, New Jersey

Received October 7, 1964

Interest in pyrrolopyrimidines has been greatly heightened as a result of the recent discovery that both the [2,3-*d*]- and [3,2-*d*-] systems occur as heterocyclic bases in a number of antibiotics. Tubercidin (**1a**) and Toyocamycin (**1b**) have been shown to be derivatives of 4-aminopyrrolo[2,3-*d*]pyrimidine,[2] and Viomycin (**2**) has recently been shown to possess a dihydropyrrolo-



1a, R = H; R' = β-D-ribose
b, R = CN; R' = D-ribose



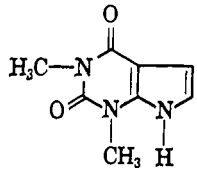
2

(1) This work was supported in part by a research grant (CY-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

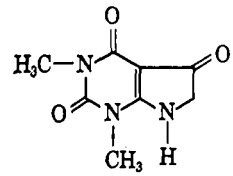
(2) For a recent discussion and literature references, see E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **86**, 951 (1964).

[3,2-*d*]pyrimidine moiety.[3] We wish to describe several new synthetic methods for the preparation of derivatives of both ring systems.

Synthetic approaches to pyrrolo[2,3-*d*]pyrimidines (7-deazapurines) have recently been reviewed, and a new approach to this system *via* pyrrole intermediates has been discussed.[2] Not included in this survey was a recently described approach to derivatives of this system by reaction of 1,3-dimethyl-6-aminouracil with chloroacetaldehyde or chloroacetyl chloride to give **3** and **4**, respectively.[4] We have found an additional synthetic approach to this ring system from 6-aminopyrimidine derivatives based upon a reaction first

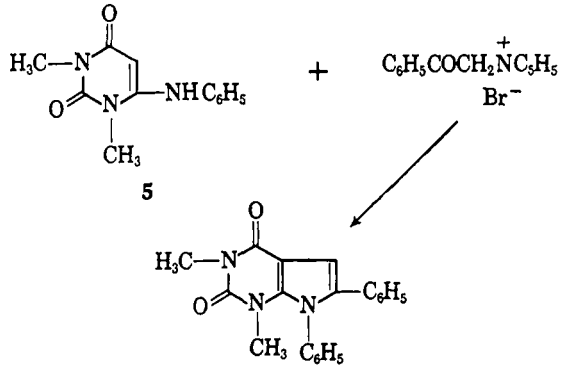


3



4

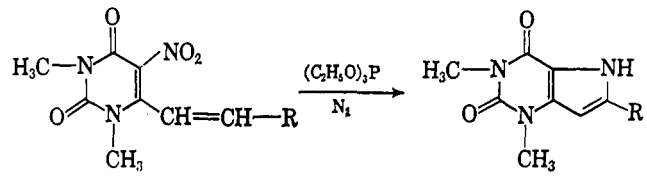
described by Hirose, Takagi, and Uno[5] and by Osterheld,[6] in which the reaction of phenacylpyridinium bromide with aromatic primary amines was shown to give substituted indoles. We have found that the condensation of 1,3-dimethyl-6-anilinouracil (**5**), prepared from the corresponding 6-amino compound *via* the exchange amination procedure of Whitehead and Traverso,[7] with phenacylpyridinium bromide yields 1,3-dimethyl-6,7-diphenyl-7H-2,4(1H,3H)pyrrolo[2,3-*d*]pyrimidinedione (**6**). This condensation would appear to be of potential interest for the preparation of further 6,7-disubstituted derivatives.



5

6

Previously available synthetic routes to isomeric pyrrolo[3,2-*d*]pyrimidines involved the cyclization of a malonic ester, pyruvate ester, acetic ester, or methyl 6-substituent with an amino or acetylated amino group or a Schiff base in the 5-position of the pyrimidine ring.[8-12] A potentially attractive synthetic alternative appeared to be available by adaptation of the nitrene-insertion reaction described by Cadogan and Cameron-Wood,[13] who showed that treatment of *o*-nitrostilbene with triethylphosphite gave 2-phenylindole. Requisite starting materials for the preparation of pyrrolo[3,2-*d*]-pyrimidines by this route would be 5-nitro-6-styryl derivatives. Two representatives of this class of compounds have been prepared by the condensation of 1,3,6-trimethyl-5-nitrouracil with *p*-methoxybenzaldehyde and *p*-dimethylaminobenzaldehyde to give **7a** and **7b**, respectively. When these compounds were heated



7 **8**

a, R = $-C_6H_4-OCH_3(p)$
b, R = $-C_6H_4-N(CH_3)_2(p)$

at reflux under nitrogen with triethylphosphite, they were converted in moderate yield to the pyrrolo[3,2-*d*]-pyrimidines **8a** and **8b**. Since the reaction of trialkylphosphites with oxygen (to give trialkylphosphates) has been shown to be photoinitiated,[14] it appeared reasonable that a photoinitiated oxidation of triethylphosphite by a nitro group might take place, provided that atmospheric oxygen were excluded. Irradiation of a dilute solution of **7a** in triethylphosphite under nitrogen for 114 hr. did indeed result in the formation of the pyrrolo[3,2-*d*]pyrimidine **8a** in small yield. The very low solubility of the starting pyrimidine in triethylphosphite may well have been the limiting factor in this conversion.

Although the nitrene insertion reactions do not proceed so satisfactorily as in previously reported, non-heterocyclic cases, they may offer some synthetic advantage for the preparation of condensed pyrrole derivatives which might otherwise be difficultly accessible.

Experimental[15]

1,3-Dimethyl-6-anilinouracil (5).—A mixture of 1.55 g. (0.01 mole) of 1,3-dimethyl-6-aminouracil, 0.9 g. of aniline hydrochloride, and 1.5 ml. of aniline was heated at 150° for 3 hr. Water and *ca.* 50 ml. of chloroform were added to the cooled sirup and, after thorough mixing, the chloroform was separated and washed twice with water. Evaporation of the chloroform gave a white solid which was recrystallized from chloroform–ethyl acetate to give 1.15 g. (50%) of white crystals, m.p. 185° (lit.[16] m.p. 181–182°).

(3) J. H. Bowie, A. W. Johnson, and G. Thomas, *Tetrahedron Letters*, **No. 15**, 863 (1964); J. H. Bowie, D. A. Cox, A. W. Johnson, and G. Thomas, *ibid.*, **No. 45**, 3305 (1964).

(4) C. W. Noell and R. K. Robins, *J. Heterocyclic Chem.*, **1**, 34 (1964).

(5) S. Hirose, S. Takagi, and T. Uno, *Yakugaku Zasshi*, **81**, 1353 (1961); *Chem. Abstr.*, **56**, 7255e (1962).

(6) K. Osterheld, Diploma Thesis, University of Giessen, 1961; cited by F. Kröhnke, *Angew. Chem., Intern. Ed. Engl.*, **2**, 225 (1963).

(7) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3973 (1960).

(8) K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, and Y. Ando, *Yakugaku Zasshi*, **75**, 770 (1955); *Chem. Abstr.*, **49**, 14001 (1955).

(9) F. L. Rose, *J. Chem. Soc.*, 4116 (1954).

(10) K. Tanaka, *et al.*, Japan Patent 223 (Jan. 21, 1955); *Chem. Abstr.*, **50**, P16879 (1956).

(11) K. Tanaka, T. Sugawa, Y. Sanno, and Y. Ando, Japan Patent 1375 (Feb. 27, 1958); *Chem. Abstr.*, **53**, P1389*b* (1959).

(12) W. Pfleiderer and H. Mosthaf, *Ber.*, **90**, 738 (1957).

(13) J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.* (London), 361 (1962).

(14) J. B. Plumb and C. E. Griffin, *J. Org. Chem.*, **28**, 2908 (1963).

(15) Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined on a Thomas-Hoover silicon bath apparatus.

(16) W. Pfleiderer and H. Ferch, *Ann.*, **615**, 52 (1958).