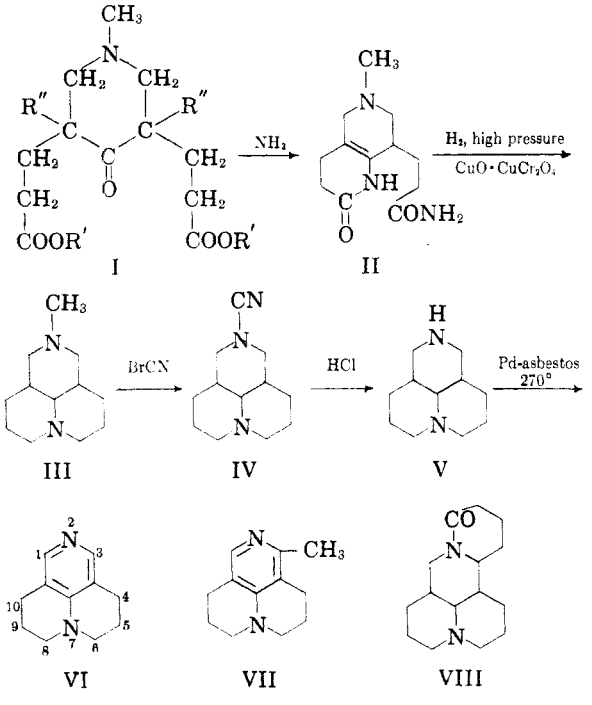
# Communications TO THE EDITOR

## The Total Synthesis of Nordehydro-α-matrinidine (4,5,6,8,9,10-Hexahydropyrido-[3,4,5-*i,j*] quinolizine)

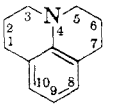
*Sir:*

We wish to report on the total synthesis of 4,5,6,8,9,10-hexahydropyrido [3,4,5-*i,j*]quinolizine[1] (VI). This ring compound, successfully synthesized for the first time, was found by direct comparison to be identical with nordehydro-α-matrinidine, obtained by Ochiai, *et al.*[2] by the demethylation of dehydro-α-matrinidine,[3] a soda-lime distillation product of matrine.[3] The present experimental result affords strong support to the structural formula (VIII) for matrine proposed by Tsuda[4] in 1936.




Refluxing of 1-methyl-3,5-dicarbethoxy-3,5-bis-(β-ethoxycarbonylethyl)-4-piperidone, (I, R′ = $C_2H_5$, R″ = $CO_2C_2H_5$) b.p.$_{0.1}$ 180° (obtained by the condensation of ethyl 4-oxo-1,3,5,7-heptanetetracarboxylate,[5] formaldehyde, and methylamine hydrochloride), with dilute hydrochloric acid afforded, in 90% yield, 1-methyl-3,5-bis-(β-carboxyethyl)-4-piperidone hydrochloride (I, R′ = H, R″ = H), m.p. 187–189°; Calc'd for $C_{12}H_{19}NO_5$·HCl: C, 49.06; H, 6.81; N, 4.70. Found: C, 48.66; H, 7.33; N, 4.91. This acid was converted into its ethyl ester (I, R′ = $C_2H_5$, R″ = H), m.p. 45–46°, b.p.$_{0.1}$ 150–153°: Calc'd for $C_{16}H_{27}NO_5$: C, 61.34; H, 8.62; N, 4.47. Found: C, 61.23; H, 8.62; N, 4.40, and allowed to stand in ammonia water. Ammonia was distilled off under reduced pressure, and the crude II[6] obtained by heating at 120–140° was submitted, without further purification, to hydrogenation in dioxane with a copper-chromium oxide catalyst, at 250° and 255 atmospheres pressure, from which 2-methylperhydropyrido[3,4,5-*ij*]-quinolizine[1] (III) was obtained. B.p.$_{0.01}$ 70°, m.p. 40–42°; Calc'd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.34; N, 14.42. Found: C, 73.9; H, 11.0; N, 14.59. *Monohydrate*, m.p. 74–75°. Treatment of III with cyanogen bromide afforded the N-cyano compound (IV), m.p. 51–53°: Calc'd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.42; H, 8.96; N, 20.43, which was heated with 20% hydrochloric acid to form the secondary amine (V), m.p. 46–50°, giving a *p-nitrobenzoate* of m.p. 116°. When V was heated with 40% palladium asbestos at 250–270°, it lost the theoretical amount of hydrogen to form VI, b.p.$_{0.05}$ 140–160° (bath temp.), m.p. 62–66°: Calc'd for $C_{11}H_{14}N_2$: C, 75.86; H, 8.05; N, 16.10. Found: C, 75.53; H, 7.80; N, 15.99. *Picrate*, m.p. 222–223°: Calc'd for $C_{11}H_{14}N_2 \cdot C_6H_3O_7N_3$: C, 50.62; H, 4.22. Found: C, 50.67; H, 4.10. Hydrobromide, m.p. 275°. $\nu_{max}$ (free base): 1588, 1516 cm.$^{-1}$ (pyridine ring); 1212, 1143 cm.$^{-1}$ (perhydroquinolizine-N). $\lambda_{max}^{H_2O}$ (hydrobromide): 292 mμ

(1) Ring Index name. A simpler, derived name for VI would be 9-azajulolidine, based on the long used trivial name "julolidine" for IX [*cf.* Reissert, *Ber.*, **24**, 841 (1891)]; Glass and Weissberger, *Org. Syntheses*, **Coll. Vol. 3**, 504 (1955); Braunholtz and Mann, *J. Chem. Soc.*, 393 (1955), combined with Ring Index numbering.

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(2) Ochiai and Okuda, *Pharm. Bull.* (*Japan*), **1**, 266 (1953); *Chem. Abstr.*, **49**, 8316 (1955).

(3) Manske and Holmes, *The Alkaloids*, Academic Press Inc., New York 1953, Vol. III, p. 178.

(4) Tsuda, *Ber.*, **69**, 429 (1936).

(5) Leonard and Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).

(6) Purification of II was very difficult but this structural formula was assigned since Δ²-6-piperidone-2-butyramide has been obtained in a pure state and in a good yield in this laboratory by the reaction of diethyl 5-oxoazelate and ammonia. A detailed report will be submitted as an original paper in the near future.

($\epsilon$ 16,500). By mixed fusion of VI and its picrate with nordehydro-$\alpha$-matrinidine and its picrate, no melting point depression was observed, and there was good agreement between their infrared spectra.

INSTITUTE OF APPLIED MICROBIOLOGY
UNIVERSITY OF TOKYO
HONGO, TOKYO, JAPAN
KYOSUKE TSUDA
SHIGENOBU OKUDA

PHARMACEUTICAL INSTITUTE
UNIVERSITY OF KYUSHU
FUKUOKA, JAPAN
SEITARO SAEKI
SHINICHI IMURA

TAKAMINE RESEARCH LABORATORY
SANKYO CO., LTD.
SHINAGAWA, TOKYO, JAPAN
YOSHINOBU SATO
HIROSHI MISHIMA

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## A New Synthesis of Purines

*Sir:*

Classical chemical purine syntheses, which involve the cyclization by pyrolysis of 4-amino-5-formamidopyrimidines[1] or modifications such as cyclization of 4,5-diaminopyrimidine sulfate salts by means of boiling formic acid or formamide,[2] have been shown to fail when applied to the conversion of chloropyrimidines to chloropurines.[2b,3,4] Rather, all chloropyrines described in the literature have been synthesized by chlorination of purinones,[3,5] a procedure which is often unsatisfactory.

Since chloropurines are important intermediates for the synthesis of natural and unnatural purine nucleosides[6] a new synthesis of purines was sought.

We have found that when 4,5-diaminopyrimidines are refluxed with mixtures of alkyl orthoformates and carboxylic acid anhydrides,[7,8,9] mixtures of purines and N-acylpurines are formed. Methyl, ethyl, and propyl orthoformates and acetic, propionic, and butyric anhydrides have been used successfully; evaporation of the excess reagents leaves a residual mixture of purine and N-acylpurine, the acyl group deriving from the anhydride. The acylpurine is hydrolyzed to the corresponding purine by action of dilute aqueous base (without heating and for limited time with chloropurines).

In this way 4,5-diaminopyrimidines bearing at the 2- and 6-positions amino, chloro, dimethylamino, hydrogen, hydroxyl, methyl, and methylthio substituents give the corresponding purines in good yield. This appears to be a general synthetic route to purines. It also allows for the ready isotopic labeling of purines by using esters of carbon-labeled orthoformate.

4,5-Diamino-6-dimethylamino-2-(methylthio)pyrimidine[10] (I), 0.500 g., 5 ml. of ethyl orthoformate, and 5 ml. of acetic anhydride, refluxed 2¼ hrs., the solution evaporated *in vacuo*, the residual 6-dimethylamino-2-(methylthio)purine[10] (II) and N-acetyl-6-dimethylamino-2-(methylthio)-purine heated 5 min., steam-bath, with 10 ml. of 1 *N* sodium hydroxide, and brought to *p*H 3.8 with acetic acid, yielded 0.428 g. (82%) of II, m.p. 278.5–281° (dec.), m.p. 285–286.5° (dec.) from sodium hydroxide followed by acetic acid. Calc'd for $C_8H_{11}N_5S$: C, 45.9; H, 5.30; N, 35.5; S, 15.3. (Found: C, 46.2; H, 5.55; N, 33.7; S, 15.4).

Similarly, I was cyclized to II by refluxing ethyl orthoformate-propionic anhydride (76% yield), ethyl orthoformate-butyric anhydride (23% yield), methyl orthoformate-acetic anhydride (80% yield), and propyl orthoformate-acetic anhydride (96% yield).

2,4,5-Triamino-6-pyrimidinol,[11] condensed with ethyl orthoformate and acetic anhydride, gave after hydrolysis 64% of guanine hemisulfate hydrate;[12] $\lambda_{max.}^{0.1\ N\ HCl}$ 248 m$\mu$ ($\epsilon$ 12,400); $\lambda_{max.}^{0.1\ N\ NaOH}$ 273 m$\mu$ ($\epsilon$ 9,760).

(1) cf. (a) Gabriel and Colman, *Ber.*, **34**, 1234 (1901). (b) Traube, *Ber.*, **37**, 4544 (1904). (c) Isay, *Ber.*, **39**, 250 (1906).

(2) (a) Bendich, Tinker, and Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948). (b) Robins, Dille, Willits, and Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(3) Bendich, Russell, and Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(4) Robins, Dille, and Christensen, *J. Org. Chem.*, **19**, 930 (1954).

(5) *Cf.* (a) Fisher, *Ber.*, **28**, 2480 (1895). (b) Fisher and Ach, *Ber.*, **30**, 2208 (1897). (c) Adams and Whitmore, *J. Am. Chem. Soc.*, **67**, 1271 (1945). (d) Davoll and Lowy, *J. Am. Chem. Soc.*, **73**, 2936 (1951). (e) Robins and Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).

(6) *Cf.* (a) Fisher and Helferich, *Ber.*, **47**, 210 (1914). (b) Davoll, Lythgoe, and Todd, *J. Chem. Soc.*, 967, 1685 (1948). (c) Davoll and Lowy, *J. Am. Chem. Soc.*, **74**, 1563 (1952). (d) Brown and Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(7) Albert, Brown, and Cheeseman, *J. Chem. Soc.*, 474 (1951), converted 2-aminopyrazine-3-carboxamide to 4-hydroxypteridine by refluxing ethyl orthoformate and acetic anhydride.

(8) After completion of this investigation Richter and Taylor, *Angew. Chem.*, **67**, 303 (1955), described the cyclization of aminomalonamidamidine dihydrochloride by ethyl orthoformate and acetic anhydride to produce hypoxanthine.

(9) Montgomery, *J. Am. Chem. Soc.*, in press, has independently found that chloro-4,5-diaminopyrimidines are cyclized to chloropurines by ethyl orthoformateacetic anhydride (private communication).

(10) Baker, Joseph, and Schaub, *J. Org. Chem.*, **19**, 631 (1954).

(11) Traube, *Ber.*, **33**, 1371 (1900).

(12) Cavalieri, Bendich, Tinker, and Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).