This material was converted into its 2,4-dinitrophenylhydrazone which was recrystallized from aqueous ethanol to give fine needles, m.p. 135–136° (lit.[12] 135–137°). This derivative was subjected to eight successive recrystallizations, and the crystals, assayed at the fifth and eighth stages of purification, were found to possess constant activity. Specific activity of the initially obtained geronic acid 2,4-dinitrophenylhydrazone: 146.3 mμc./mg. C; specific activity after fifth recrystallization: 146.1 mμc./mg. C; specific activity after eighth recrystallization; 147.9 mμc./mg. C.

The ether solution remaining after the extraction with aqueous sodium bicarbonate was dried over anhydrous magnesium sulfate and evaporated to give 0.310 g. (23%) of crude lactone III. This lactonic fraction resisted attempts at crystallization, and was therefore subjected to vacuum sublimation. A 20.6-mg. sample of the sublimate (recognized as III by its infrared spectrum) was dissolved in a small volume of ether containing 122.8 mg. of authentic, non-radioactive lactone III. The ether solution was evaporated to dryness under a stream of nitrogen, and the solid residue was recrystallized twice from petroleum ether (30–60°) to give plate-like crystals, m.p. 50–51°. An assay of this product gave a specific activity of 0.923 mμc./mg. C.

Treatment of Geronic Acid with Labeled Carbon Monoxide.—Concentrated sulfuric acid (20 ml.) was shaken with labeled carbon monoxide (5.7 mg., 0.20 mmole, 3 mc.) for one hour, using the technique described in the previous experiment. Geronic acid (0.53 g., 3.1 mmoles) was then mixed with this solution. After shaking overnight, the reaction mixture was poured into *ca.* 150 ml. of ice and water. The resultant solution was subjected to continuous extraction with ether. The ether solution was washed twice with water, dried over anhydrous magnesium sulfate, and evaporated. The recovered geronic acid was converted into its 2,4-dinitrophenylhydrazone, which was recrystallized from aqueous ethanol to give fine needles, m.p. 135–136°, showing a specific activity of 2.75 mμc./mg. C; specific activity after fourth crystallization, 2.30 mμc./mg. C; after seventh recrystallization, 1.98 mμc./mg. C.

(12) H. H. Strain, THIS JOURNAL, **57**, 758 (1935).

ITHACA, N. Y.

[CONTRIBUTION FROM THE DIVISION OF NUCLEOPROTEIN CHEMISTRY SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH AND THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Pyrimidine Nucleosides. V. 2-Oxo-hexahydropyrimidines and Their Nucleosides[1]

BY JACK J. FOX AND DINA VAN PRAAG

RECEIVED JUNE 22, 1959

Treatment of 4-thiothymidine and 4-thiouridine with activated Raney nickel led to the complete reduction of the heterocyclic nucleus. This unexpected nuclear reduction was shown to be characteristic of 4-thiouracils and of 2-hydroxypyrimidines. 2-Thiouracil and 4-hydroxypyrimidines, by contrast, do not undergo ring reduction with this catalyst. Rhodium-on-alumina catalyst will also reduce 2-hydroxypyrimidines to their corresponding N,N′-trimethyleneureas. Raney nickel or rhodium-on-alumina will reduce uracil and its 1-methyl homolog to their corresponding 5,6-dihydro derivatives. Syntheses of 4-thiouracil and 1-methyl-2-oxopyrimidine are described.

Previous papers in another series[2,3] dealt with the synthesis of 4-thiothymidine and 4-thiouridine by direct thiation of suitably blocked thymidine and uridine with phosphorus pentasulfide in pyridine. It was desired to prepare the desulfurized derivatives of these 4-thionucleosides by the use of activated Raney nickel catalyst. Bougault and associates[4] have shown that Raney nickel in neutral or in alkaline solutions removes sulfur from aliphatic sulfhydryl compounds and disulfides. Mozingo and co-workers[5] demonstrated that dibenzyl or di-*p*-tolyl disulfides may be desulfurized to benzene and toluene, respectively, under mild conditions by this catalyst without reduction of the benzenoid nucleus. On the other hand, examples in which nuclear reduction accompanied desulfurization have been noted. Alderton and Fevold[6] have observed that cyclohexylformyl-alanine may be prepared easily by refluxing benzoyl-*dl*-alanine with Raney nickel (prepared according to Mozingo[5]) in 80% alcohol.

Since the demonstration by Roblin and associates[7] that 2-mercapto-4,5-diamino-6-hydroxypyrimidine may be desulfurized by Raney nickel[5] to 4,5-diamino-6-hydroxypyrimidine, a host of 2-mercaptopyrimidines have been de-thiated in this fashion.[8] It was generally accepted, therefore, that mercapto groups of pyrimidines, having served their purpose in synthetic procedures, may be removed easily by this catalyst to yield the desulfurized pyrimidines. In the present paper, examples are reported in which nuclear reduction of certain mercaptopyrimidines accompanied desulfurization when activated Raney nickel[9] was employed.

Treatment of the 3′,5′-di-*O*-benzoate of I (R = H, R′ = CH_3) or the tri-*O*-benzoate (I, R = OBz, R′ = H) with Raney nickel[9] in refluxing ethanol for 15 minutes afforded crystalline, desulfurized derivatives (II). After removal of the protecting benzoyl groups with ethanolic ammonia in a sealed tube, a glass was obtained which was devoid of selective ultraviolet absorption. It is to be noted that 5,6-dihydropyrimidine derivatives (*i.e.*, of uracil or thymine) do exhibit selective absorp-

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-3190) and from the Ann Dickler League.

(2) J. J. Fox, I. Wempen, A. Hampton and I. L. Doerr, THIS JOURNAL, **80**, 1669 (1958).

(3) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich and G. B. Brown, *ibid.*, **81**, 178 (1959).

(4) J. Bougault, E. Cattelain and P. Chabrier, *Bull. soc. chim.*, [5] **7**, 781 (1940).

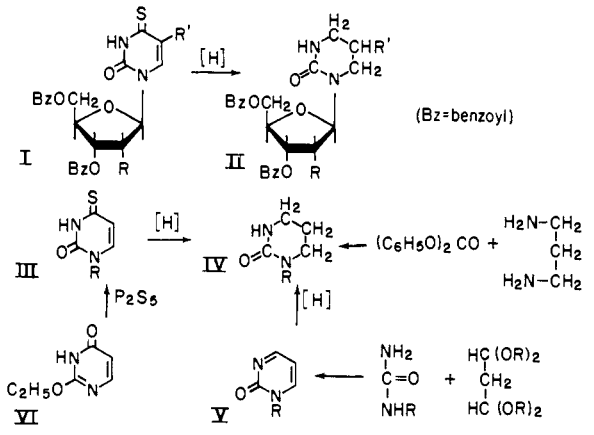
(5) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

(6) G. Alderton and H. L. Fevold, *ibid.*, **73**, 463 (1951).

(7) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, *ibid.*, **67**, 290 (1945).

(8) See D. J. Brown, *Rev. Pure and Applied Chem.*, **3**, 115 (1953), for a review of desulfurization reactions on pyrimidines.

(9) The activated Raney nickel used in these studies was prepared by the procedure of D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950). Similar results were obtained from commercially-available preparations of activated Raney nickel purchased from the Raney Catalyst Co., Chattanooga, Tenn., as well as from the Davidson Chemical Co., Cincinnati, Ohio.



tion in the 220–240 mμ region.[10] A series of experiments were therefore undertaken with 4-thiouracil (III, R = H) and its 1-methyl homolog.

Though the preparation of 4-thiouracil had been reported,[11] the method is laborious. It was found, however, that thiation of 2-ethoxy-4-hydroxypyrimidine[12] (VI) with phosphorus pentasulfide in pyridine (followed by acidification of the reaction mixture) gave a 50% yield of 4-thiouracil (III, R = H). 1-Methyl-4-thiouracil was prepared by thiation of 1-methyluracil as previously described.[3] Reaction of 4-thiouracil with Raney nickel in refluxing ethanol afforded a crystalline substance (IV, R = H) which possessed no selective ultraviolet absorption. The properties of this derivative were similar to those reported by Fischer and Koch[13] for "trimethylenecarbamid" (2-oxo-hexahydropyrimidine or N,N′-trimethyleneurea) which they obtained by condensation of 1,3-diaminopropane with diethyl carbonate. A sample of N,N′-trimethyleneurea (prepared by the use of diphenyl carbonate instead of diethyl carbonate) was identical with that obtained by reduction of III (R = H) with Raney nickel. Analogous results were obtained from 1-methyl-4-thiouracil (III, R = CH_3) which gave the N-methyl homolog of IV. It is obvious, therefore, that complete reduction of the heterocyclic nucleus had occurred during the desulfurization reaction with Raney nickel. It is concluded, therefore, that the products obtained by the treatment of I(R′ = H, R = OBz) or I(R′ = CH_3, R = H) with this catalyst are II, namely, the N-(2,3,5-tri-*O*-benzoyl-β-D-ribosyl) and the N-(3,5-di-*O*-benzoyl-2-deoxy-β-D-ribosyl) derivatives of N,N′-trimethyleneurea and 2-oxo-5-methylhexahydropyrimidine, respectively. Crystalline N-(2-deoxy-β-D-ribofuranosyl)-2-oxo-5-methylhexahydropyrimidine was obtained by reduction of 4-thiothymidine[3] with Raney nickel under conditions similar to those used for the synthesis of II.

It may be postulated that the first step in these rather unexpected reductions involved removal of the sulfur atom leading to 2-hydroxypyrimidines which, in the presence of the activated Raney nickel, were reduced further to the 2-oxo-hexahydropyrimidine derivatives. Indeed, spectral analysis of the course of the reductive desulfurization of 1-methyl-4-thiouracil showed initially the loss of the maximum at 335 mμ with the appearance of a new peak at 312 mμ[14] followed, eventually, by the total loss of ultraviolet absorption. In accord with this view, 2-hydroxypyrimidine[15,16] (V, R = H) was treated with Raney nickel in refluxing ethanol for 15 minutes. Trimethyleneurea was obtained in good yields from the reaction. The same hexahydropyrimidine (IV, R = H) was obtained by hydrogenation of V with rhodium-on-alumina[17] catalyst. 1,2-Dihydro-1-methyl-2-pyrimidinone (V, R = CH_3) was prepared in good yield by modifications of the procedure of Hunt, *et al.*,[16] by condensation of 1,1,3,3,-tetraethoxypropane with N-methylurea. When treated with Raney nickel or with rhodium-on-alumina, this pyrimidine was also converted smoothly to the N-methyl derivative of IV.

Brown[18] demonstrated that an 82% yield of 4-hydroxypyrimidine may be obtained by refluxing 2-thiouracil for two hours with activated Raney nickel in aqueous ammonia without any evidence of nuclear reduction. It is significant, in this regard, that 4-hydroxypyrimidine is also resistant to reduction by rhodium-on-alumina. Thus, 2-hydroxy- and 2-hydroxy-4-thiopyrimidine, in contrast to 4-hydroxy- and 4-hydroxy-2-thiopyrimidine, are susceptible to ring reduction. These findings may have pertinence to some of the previously-reported reductions of pyrimidine derivatives with Raney nickel. Boarland and co-workers[19] obtained a 42% yield of pyrimidine by reduction of 2-mercaptopyrimidine with Raney nickel. The possibility of nuclear reduction products having formed as side reactions was raised by these authors.[19] Hunt, *et al.*,[16] suggested on the basis of indirect evidence that some di- or tetrahydro-4,6-dimethylpyrimidine may have been formed as by-products in the Raney nickel desulfurization of 2-mercapto-4,6-dimethylpyrimidine. Whittaker[20] was unable to isolate any 5-aminopyrimidine by treatment of 2,4-dimercapto-5-aminopyrimidine with Raney nickel.[5] Vanderhaeghe[21] obtained only trace amounts of 4-methylpyrimidine by similar treatment of 2,4-dimercapto-6-methylpyrimidine. In none of these cases were ring-reduced compounds isolated or characterized. In light of the aforementioned studies in our laboratory, it is indeed plausible that such products were formed.

Activated Raney nickel will also reduce the dioxypyrimidines (uracil and 1-methyluracil) to their

(10) R. D. Batt, J. K. Martin, J. M. Ploeser and J. Murray, THIS JOURNAL, **76**, 3663 (1954).

(11) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908).

(12) G. E. Hilbert and E. F. Jansen, THIS JOURNAL, **57**, 552 (1935).

(13) E. Fischer and H. Koch, *Ann. Chem.*, **232**, 222 (1886).

(14) A maximum at 302 mμ at *p*H 6.0 has been reported for 1-methyl-2-pyrimidone by D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, 211 (1955).

(15) D. J. Brown, *Nature*, **165**, 1010 (1950).

(16) R. R. Hunt, J. F. W. McOmie and E. R. Sayer, *J. Chem. Soc.*, 525 (1959).

(17) W. E. Cohn and D. G. Doherty, THIS JOURNAL, **78**, 2863 (1956). A 5% rhodium-on-alumina catalyst was obtained from Baker & Co., Inc., Newark, N. J.

(18) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

(19) M. P. V. Boarland, J. F. W. McOmie and R. N. Timms, *J. Chem. Soc.*, 4691 (1952).

(20) N. Whittaker, *ibid.*, 1565 (1951).

(21) H. Vanderhaeghe and M. Claesen, *Bull. soc. chim. Belg.*, **66**, 276 (1957)

respective 5,6-dihydro derivatives[22] through the time of reduction required is much longer than that needed for the total ring saturation of 2-hydroxypyrimidines (V) previously mentioned.

Acknowledgments.—The authors are indebted to George B. Brown for helpful discussions and continued interest. The authors thank the Kay-Fries Chemicals, Inc., for a sample of 1,1,3,3-tetraethoxypropane.

Experimental[23]

4-Thiouracil.—2-Ethoxy-4(3H)-pyrimidinone[12,24] (7.0 g., 0.05 mole) and 33 g. of phosphorus pentasulfide were refluxed for 2 hours in reagent grade pyridine to which 1.0 ml. of water[25] had been added slowly. After removal of approximately one-half of the pyridine *in vacuo*, the solution was poured into vigorously-stirred water and filtered from a small residue. After concentration of the filtrate to near dryness, the residue was dissolved in dilute ammonia, treated with charcoal, filtered and the filtrate acidified with acetic acid. Upon cooling, product precipitated (3.2 g., 50%), m.p. 270–280°. After recrystallization from hot water, yellow prisms were obtained, m.p. 289–290 dec. (Wheeler and Liddle[11] report m.p. 328° (eff.)). The ultraviolet absorption spectrum of this product was identical with that reported by Elion, *et al.*[26]

Anal. Calcd. for $C_4H_4N_2OS$: N, 21.87; S, 25.00. Found: N, 21.99; S, 25.10.

1,2-Dihydro-1-methyl-2-pyrimidinone (V, R = CH_3).—N-Methylurea (3.7 g., 0.05 mole), in 20 ml. of ethanol and 10 ml. of concentrated hydrochloric acid was treated with 11.0 g. of tetraethoxypropane. The mixture was stirred and warmed to 60°. After 1 hr., the brown reaction mixture was cooled and filtered and the precipitate washed with ether. The crude hydrochloride salt (m.p. 235°) was dissolved in aqueous sodium carbonate and the solution brought to *p*H 5 with dilute sulfuric acid. After concentration to dryness, the residue was extracted in a soxhlet with 250 ml. of acetone; 4.0 g. (72%), m.p. 125–126° (Brown, *et al.*,[14] report 127–128°). The product formed a picrate salt, m.p. 162° (reported[14] 162–164°). Light absorption properties were also similar to those reported (*p*H 6, maxima at 215 and 302 mμ).[14]

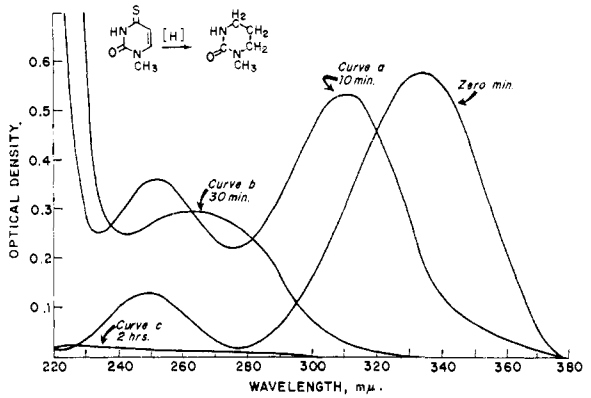


Fig. 1.

Reduction of 4-Thiouracil with Raney Nickel. Synthesis of N,N′-Trimethyleneurea.—4-Thiouracil (1.28 g., 0.01 mole) in 400 ml. of ethanol was treated under reflux and stirring with 6 g. of activated Raney nickel[9] (wet weight) for 15 minutes. The course of the reaction was followed spectrally. After loss of the "sulfur peak" at 327 mμ, a new peak appeared at 246 mμ (indicative of the formation of a 5,6-dihydropyrimidine derivative). At the end of the 15-minute period, all selective absorption (220–380 mμ range) was lost. After filtration from catalyst and concentration of the filtrate to dryness *in vacuo*, a residue was obtained which was crystallized from hot ethanol; 0.6 g. (60%), m.p. 259–260°. A mixed-melting point with N,N′-trimethyleneurea prepared (*vide infra*) by modifications of the procedure of Fischer and Koch[13] showed no depression.

N,N′-Trimethyleneurea by Reduction of 2-Hydroxypyrimidine. (A) With Raney Nickel.—2-Hydroxypyrimidine[15,16] (0.48 g., 0.005 mole) in 200 ml. of ethanol was refluxed with 4 g. of activated Raney nickel[9] for 15 minutes. The reaction mixture was processed in a manner similar to that used for the preparation of trimethyleneurea from 4-thiouracil (*vide supra*); 450 mg. (90%), m.p. 258–259°.

(B) With Rhodium-on-Alumina.—2-Hydroxypyrimidine (0.96 g., 0.01 mole) in 400 ml. of water and 0.9 g. of rhodium-on-alumina catalyst[17] was shaken at room temperature under one atmosphere of hydrogen. A theoretical uptake of hydrogen (2 moles per mole) occurred within 30 minutes. After filtration from catalyst, the solution was processed in the usual manner (*vide supra*), yielding 0.8 g. (80%) of N,N′-trimethyleneurea, m.p. 258–259°.

N,N′-Trimethyleneurea (modification of the procedure of Fischer and Koch[13]).—1,3-Diaminopropane (7.4 g., 0.1 mole) and 21.4 g. of diphenyl carbonate were heated in a sealed tube at 180° for 3 hours. Upon cooling and adding 150 ml. of ethanol a crystalline precipitate was obtained; 4.8 g. (50% yield), m.p. 259–260°, mixed melting points with samples obtained from the three methods of preparation listed above were undepressed. The product gave solubility properties similar to those reported[13] and formed a picrate salt as described by Tafel and Weinschenk.[27]

N-Methyl-N,N′-trimethyleneurea (IV, R = CH_3) **(N-Methyl-2-oxo-hexahydropyrimidine). A. From 1-Methyl-4-thiouracil.**—1-Methyl-4-thiouracil[3] (1.42 g., 0.01 mole) was refluxed for 15 minutes with 6 g. of activated Raney nickel.[9] The catalyst was removed and the filtrate concentrated to dryness. The residue was sublimed (130° at 1 mm.) to afford 0.8 g. of product, m.p. 86–89°, 70% yield.

Anal. Calcd. for $C_5H_{10}N_2O$: C, 52.60; H, 8.83; N, 24.55. Found: C, 52.66; H, 8.84; N, 24.55.

Picrate Salt.—Treatment of the above compound in ethanol with an ethanolic solution of picric acid afforded the picrate salt, m.p. 134–135° (recrystallized from ethanol).

Anal. Calcd. for $C_{11}H_{13}N_5O_8$: C, 38.49; H, 3.81; N, 20.40. Found: C, 38.66; H, 3.90; N, 19.96.

By gradual addition of the Raney nickel over a two-hour period, the course of the reductive desulfurization may be followed spectrally (see Fig. 1). The desulfurization is shown by curve *a* by loss of the peak at 335 mμ, and the new peak at 312 mμ. Curve *b* indicates the first step in the reduction of the heterocyclic nucleus (presumably by reduction of the 5,6-double bond) with selective absorption at 260 mμ. Finally, the formation of the hexahydropyrimidine derivative is indicated by curve *c* in which ultraviolet absorption is essentially lost. It is to be noted that completely reduced 2-oxypyrimidines can be distinguished from their partially-saturated derivatives by the absence of selective absorption in the former (IV).

B. By Reduction of 1-Methyl-2-pyrimidinone (V, R = CH_3) **with Raney Nickel.**—Treatment of 220 mg. (0.002 mole) of 1-methyl-2-oxypyrimidone with 2 g. of activated Raney nickel in ethanol under reflux for 15 minutes yielded, after filtration from catalyst and concentration to dryness, 500 mg. of the picrate salt, m.p. 134–135° (72%).

C. By Reduction of 1-Methyl-2-pyrimidinone with rhodium.—Treatment of 1-methyl-2-pyrimidone with rhodium-on-alumina catalyst and processing the reaction mixture in a manner similar to that employed for the synthesis of N,N′-trimethyleneurea (see above) afforded a residue which was sublimed (see method A), m.p. 86–89° (80%); picrate salt, m.p. 134–135°.

N-(3,5-Di-*O*-benzoyl-2-deoxy-β-D-ribofuranosyl)-2-oxo-5-methylhexahydropyrimidine (II, R = H, R′ = CH_3). —1-(3,5-Di-*O*-benzoyl-2-deoxy-β-D-ribosyl)-4-thiothymine[3]

(22) During the course of these investigations, the reduction of 1-methyluracil with Raney nickel to its 5,6-dihydro derivative was reported (D. M. Brown, D. B. Parihar, A. R. Todd and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958)), but no experimental details were given.

(23) All melting points are uncorrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(24) Cyclo Chemical Corporation, Los Angeles, Calif.

(25) See ref. 2, footnote 35.

(26) G. B. Elion, W. S. Ide and G. H. Hitchings, THIS JOURNAL, **68**, 2137 (1946).

(27) J. Tafel and A. Weinschenk, *Ber.*, **33**, 3383 (1900).

(4.66 g., 0.01 mole) in 500 ml. of ethanol was refluxed with stirring with 16 g. of activated Raney nickel.[9] After 15 minutes, the mixture was filtered and concentrated to dryness *in vacuo*. The residue was dissolved in ethanol, treated with charcoal, filtered and cooled whereupon large needle-like crystals were formed, 2.8 g. (64%), m.p. 135–136°; light absorption properties: (in ethanol), maxima at 230 and 274 mμ, shoulder at 280 mμ. Essentially similar ultraviolet absorption properties were exhibited by 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-D-ribose[28] (maxima at 230 and 272 mμ, shoulder at 280 mμ.

Anal. Calcd. for $C_{24}H_{25}N_2O_6$: C, 65.92; H, 5.76; N, 6.39. Found: C, 65.75; H, 5.94; N, 6.13.

N-(2-Deoxy-β-D-ribofuranosyl)-2-oxo-5-methylhexahydropyrimidine.—4-Thiothymidine[3] (770 mg.) in 200 ml. of absolute ethanol was refluxed with 5 g. (wet weight) of activated Raney nickel for 15 minutes. After filtration from catalyst, the filtrate was concentrated to dryness and the residue dissolved in a small amount of ethanol. After several weeks in the refrigerator, white, crystalline needles formed (0.2 g.) which were recrystallized from ethanol, m.p. 186–187°. This product was devoid of light absorption in the ultraviolet.

Anal. Calcd. for $C_{10}H_{18}O_4N_2$: C, 52.17; H, 7.83; N, 12.17. Found: C, 52.23; H, 7.87; N, 12.31.

N-(2,3,5-Tri-*O*-benzoyl-β-D-ribosyl)-2-oxo-hexahydropyrimidine (II, R = OBz, R′ = H).—1-(2,3,5-Tri-*O*-benzoyl-β-D-ribosyl)-4-thiouracil[3] (5.72 g., 0.01 mole) was treated with Raney nickel[9] as in the case of the thymidine analog (*vide supra*). The residue obtained by removal of solvent was dissolved in ethanol, treated with charcoal, filtered and cooled. Small needle-like crystals were obtained; 3.0 g. (55%), m.p. 143–145°; light absorption properties (in ethanol): maximum at 230 mμ, shoulders at 273 and 280 mμ.

Anal. Calcd. for $C_{30}H_{28}N_2O_8$: C, 66.17; H, 5.18; N, 5.15. Found: C, 66.22; H, 5.22; N, 5.41.

Debenzoylation of II (R = H, R′ = CH_3 or R = OBz, R′ = H) with alcoholic ammonia or with sodium ethoxide yielded a glass. Spectral analysis (in ethanol) showed no selective absorption in the ultraviolet region. They were not investigated further.

Reduction of Uracil with Raney Nickel. Synthesis of 5,6-Dihydrouracil.—Uracil (1.12 g., 0.01 mole) in 500 ml. of water was refluxed with 15 g. of activated Raney nickel. After two hours (the absorption spectrum of the solution indicated the presence of some uracil) the catalyst was removed by filtration and the filtrate concentrated to dryness. The residue was dissolved in ethanol and cooled, 560 mg. (53%), m.p. 269–270 (Batt, *et al.*,[10] report 272–275°).

Reduction of 1-Methyluracil. Synthesis of 1-Methyl-5,6-dihydrouracil.—1-Methyluracil (1.26 g.) in 400 ml. of ethanol was stirred under reflux with 20 g. of activated Raney nickel for 6 hr. Spectral analysis of the reaction mixture indicated the presence of some unchanged starting material. After filtration and concentration of the filtrate to dryness, the residue was dissolved in hot ethyl acetate from which 1-methyl-5,6-dihydrouracil crystallized; 0.47 g. (34%), m.p. 169–170° (reported[14] m.p. 170–172°).

A similar product in 86% yield may be obtained by reduction of 1-methyluracil in water with rhodium-on-alumina catalyst at atmospheric pressure. A theoretical uptake (1 mole in 30 min.) was noted, m.p. 169–170° (mixed-melting point with material obtained by Raney nickel reduction (*vide supra*) was undepressed.

NEW YORK 21, N. Y.

(28) J. J. Fox and I. Wempen, unpublished synthesis.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

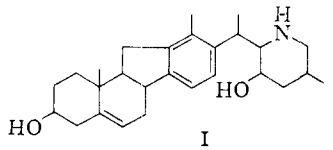
N-Alkyl Derivatives of Veratramine

BY FREDERICK C. UHLE, JAMES E. KRUEGER AND F. SALLMANN

RECEIVED JUNE 22, 1959

A description of the preparation of a series of N-alkyl derivatives of veratramine is given. Statements are made concerning the nature and significance of the pharmacological properties of the compounds.

Veratramine (I) has been shown to possess powerful cardiodecelerator properties which are manifested on the normal resting rate as well as on the elevated rate arising from accelerans stimulation or from the administration of sympathomimetic amines.[1] The pharmacodynamic effect, which appears to be mediated directly at the sino-atrial node of the mammalian heart, is neither annulled by the presence of atropine nor accompanied by a negative inotropic action (impairment of contractility) on the myocardium.



I

Following the original observations with the naturally occurring alkaloid, related compounds were found to harbor similar properties, although no other substance approached veratramine itself in absolute potency. Since the active alkanolamines of the early studies all were piperidine or pyrrolidine derivatives, it was considered for a time that the secondary degree of substitution of the nitrogen atom might be of prominence in those drug–receptor interactions which lead to evocation of the biological response. However, such a view became untenable when occasion arose to prepare, and to examine, N-methylveratramine, for the tertiary base was found to display a definite, although much attenuated, effect of the type characteristic of the parent compound.

On several counts, this finding was regarded of sufficient importance for further pursuit. Obviously, N-alkylation provides the opportunity of systematic modification of only a single variable in an extensible series of compounds suitable for comparative study. Moreover, the availability of highly active tertiary amines would permit greater ease of masking of the 3β- and 23-hydroxyl groups in less polar functions, a manner of alteration frequently of profound consequence for pharmacological behavior. In fact, considerable encouragement was offered by the very next compound to be synthesized, N-*n*-butylveratramine, which proved to be nearly as active as veratramine itself.

Additional N-alkylation products of the alkaloid

(1) O. Krayer, *J. Pharmacol. Expetl. Therap.*, **96**, 422 (1949); **97**, 427 (1950).