20,21-Dihydroxybisnorchol-4-en-3-one (20-isomeric mixture) (XVIII) *from* XIV. The isopropylidene derivative XIV was oxidized by Oppenauer oxidation in the usual manner and the oxidation product chromatographed. The ether-benzene (1:20) eluates gave, after recrystallization from ether, XVIII in 75% yield, m.p. 168–169°; $[\alpha]_D^{23}$ +55° (c, 0.55 in chloroform); infrared: ν_{max}. 3600, 1675, 1620 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{34}O_3$ (346.49): C, 76.26; H, 9.89. Found: C, 76.43; H, 9.67.

20,21-Dihydroxy-bisnorchol-4-en-3-one (20-isomeric mixture) (XVIII) *from* XVI. The oxydation of XVI to XVII followed by the hydrolysis to XVIII was carried out as described for the conversion of X to III. From 100 mg. of XVI there was obtained 77 mg. XVIII, m.p. 167–169°, having an infrared absorption identical with that of XVIII obtained from XIV.

Progesterone (XX) *from XVII.* A solution of 100 mg. of XVIII in 100 ml. 80% acetic acid was shaken overnight with 5 gm. of sodium bismuthate. The mixture was worked up exactly as described for IV from III. The crude product was chromatographed and the fractions, obtained with ethyl acetate–benzene (1:10) gave, after recrystallization from ethyl acetate–hexane, progesterone, m.p. 125–128°, in quantitative yield.

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WORCESTER, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY]

Synthesis of Some 5-Alkyl-6-azauracils[1]

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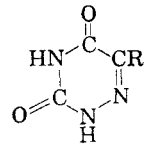
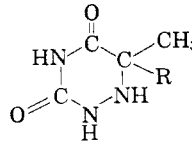
A number of 5-alkyl-6-azauracils (6-alkyl-*asym*-triazine-3,5-diones) have been synthesized by ring closure of the appropriate α-keto acid semicarbazones in non-aqueous media in the presence of sodium ethoxide. As compared to 6-azauracil, these compounds show increased narcotic activity in mice, and were designed to aid in studies dissociating the narcotic from the anti-tumor activities of 6-azauracil. Their acid dissociation constants, ultraviolet spectra, and infrared spectra were measured.

Recent work on the anti-tumor activity of 6-azauracil (*asym*-triazine-3,5-dione, I)[2–4] disclosed that this compound also possesses narcotic activity in mice[5] and induces a variety of disturbances of the central nervous system in man.[6] The 5-methyl homolog of 6-azauracil, 6-azathymine (6-methyl-*asym*-triazine-3,5-dione, II) exhibits even greater narcotic activity in mice than does 6-azauracil.[5,7] On the other hand, 5,6-dihydro-6-azathymine (6-methyl-1,6-dihydro-*asym*-triazine-3,5-dione, IX)[8] and 5,5 - dimethyl - 5,6 - dihydro - 6 - azauracil (6,6-dimethyl-1,6-dihydro-*asym*-triazine-3,5-dione, X)[9] failed to show any narcotic activity in mice.[10] These observations indicate that the 6-alkyl substitution on the *asym*-triazine ring may be closely related to the increase in narcotic potency and that unsaturation of the triazine structure is essential for this activity. In order to clarify and substantiate the above correlation and thus possibly to contribute to studies of the relation of the narcotic and the anti-tumor activities of 6-azauracil, as well as to search for a new structural type of hypnotics related to the barbiturates, several higher homologs of the 6-alkylated *asym*-triazine-3,5-diones have been synthesized.[11]



I, R = H
II, R = CH_3
III, R = C_2H_5
IV, R = n-C_3H_7



V, R = $CH(CH_3)_2$
VI, R = n-C_5H_{11}
VII, R = n-C_7H_{15}
VIII, R = $CH_2C_6H_5$
IX, R = H
X, R = CH_3

(1) This work was supported by grants CY-2789 and CY-2817 from the National Cancer Institute, Public Health Service. Presented before the Division of Medicinal Chemistry, 134th Meeting of the American Chemical Society, September 1958, Chicago.

(2) For a discussion of the nomenclature of this compound see P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).

(3) M. T. Hakala, L. W. Law, and A. D. Welch, *Proc. Amer. Assoc. Cancer Research*, **2**, 113 (1956).

(4) J. J. Jaffe, R. E. Handschumacher, and A. D. Welch, *Yale J. Biol. & Med.*, **30**, 168 (1957).

(5) A. D. Welch, R. E. Handschumacher, and J. J. Jaffe, *Proc. Am. Assoc. Cancer Research*, **2**, 249 (1957).

(6) C. E. Wells, C. A. Ajmone-Marsan, E. Frei, J. N. Tuohy, and B. I. Schnider, *EEG Clin. Neurophysiol.*, **9**, 325 (1957).

(7) P. Mantegazza, R. Tommasini, R. Fusco, and S. Rossi, *Arch. int. pharmacodyn.*, **95**, 123 (1953).

(8) J. Thiele and J. Bailey, *Ann.*, **303**, 82 (1898).

(9) J. Bailey, *Am. Chem. J.*, **28**, 386 (1902).

(10) A. D. Welch, R. E. Handschumacher, and J. J. Jaffe, unpublished data.

(11) A number of 6-arylalkyl-*asym*-triazine-3,5-diones and 6-*t*-butyl-*asym*-triazine-3,5-dione were synthesized by Bougault (*J. pharm. chim.*, **11**, 5 (1915), and ref. 12), but most of them did not fit in the testing scheme in which a regular lengthening of the 6-alkyl chain was desired.

TABLE I

Compound	Relative[10] Hypnotic Activity	pK_a	Ultraviolet absorption spectra Max., mμ (0.1N HCl)	ϵ_{max}	Max., mμ (0.1N NaOH)	ϵ_{max}
I	1.0	6.9	258	5,590	286	3,770
II	2.7	7.6	261	5,200	246	4,770
III	5.0	7.47	260	5,580	246	4,900
IV	8.2	7.5	261	5,850	250	5,220
V	8.2	7.45	261	5,920	246	5,150
VI	13.7	7.42	262	4,090	251	5,000
5-(1-Methyl)butyl-6-azauracil[a]	13.7					
5-(1-Ethyl)propyl-6-azauracil[a]	13.7					
VII	22.4	7.8[b]	263	4,280	247	6,070
VIII	13.0	7.43	260	5,830		

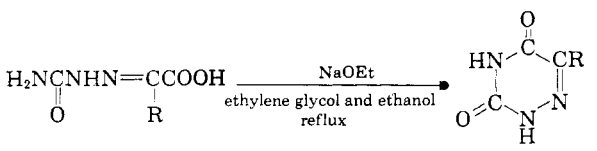
[a] Prepared by workers of the Squibb Institute for Medical Research. [b] Determined by titrating the sodium salt.

TABLE II

Semicarbazone	Yield, %	M.P.	M.P. (Reported)	Analyses, %	C	H	N	Recrystal'n Solvent
Pyruvic acid	94	201° (dec.)	200° (dec.)[a]					
α-Ketobutyric acid	91	188–189° (dec.)	190° (dec.)[b]					
α-Keto-*n*-valeric acid	96	175–176° (dec.)	220° (dec.)[c]					
Dimethylpyruvic acid	63	158–159° (dec.)		Calcd.	41.61	6.40	24.26	Ethyl acetate
				Found	41.62	6.33	22.80	
α-Keto-*n*-heptylic acid	82	148–149° (dec.)		Calcd.	47.74	7.51	20.88	Acetonitrile
				Found	48.04	7.72	20.86	
α-Keto-*n*-nonanoic acid	Quant.	156–158° (dec.)		Calcd.	52.38	8.35	18.33	Acetonitrile
				Found	52.67	8.60	18.61	
Phenylpyruvic acid	92	174° (dec.)	180° (dec.)[d]					

[a] H. J. Backer, *Rec. trav. chim.*, **31**, 27 (1912). [b] R. Barré, *Compt. rend.*, **184**, 826 (1927). [c] E. E. Blaise, *Compt. rend.*, **157**, 1443 (1913). [d] See ref. 12.

6-Azathymine was first prepared by Thiele and Bailey by the oxidation of 5,6-dihydro-6-azathymine (IX), a compound obtainable in low yields by a complex reaction sequence.[8,9] Both Bailey, and later, Bougault observed that the semicarbazone of pyruvic acid or its ethyl ester could not be cyclized under various conditions attempted,[9,12] and the latter finally prepared 6-azathymine by the cyclization of the thiosemicarbazone of pyruvic acid, followed by replacement of the sulfur atom with oxygen.[13] However, it has now been found that the semicarbazone of pyruvic acid can be cyclized to give 6-azathymine in one step in a mixture of ethylene glycol and absolute ethanol containing sodium. This method was originally developed for the synthesis of 6-azauracil-2-C^{14} from glyoxylic acid semicarbazone[2] and is found to be applicable to the synthesis of 5-alkyl-6-azauracils (II to VIII), from the semicarbazone of the appropriate α-keto acids, in yields of 50% to 94%:



When α-semicarbazidoisobutyric acid was subjected to the same condition, it failed to cyclize to form X, although its ethyl ester, and the esters of α-semicarbazidopropionic acid, were found to cyclize slowly to give X and IX, respectively, at room temperature in the presence of alcoholic potassium hydroxide.[9]

The narcotic activity of these compounds was tested preliminarily in mice and was found to increase with the lengthening of the alkyl chain; in those cases tested, branching of the chain does not seem to have any effect.[10] (Table I).

The infrared spectra of the 5-alkyl-6-azauracils all show broad peaks in the 3.0–3.5 μ region and very sharp doublets in the 5.75–5.95 μ region due to the —C—NH— groups. They also show weak peaks at 6.25 μ due to the substituted imine bond, which is absent in the spectra of IX, X, and uracil as expected. The medium peak at 13.42–13.6 μ region may be ascribed to the *asym*-triazine ring, since uracil, *sym*-triazine-2,4-dione and the α-keto acid semicarbazones do not show the peak. The acid dissociation constants and ultraviolet absorption spectra are shown in Table I.

(12) J. Bougault, *Ann. chim.* (9) **5**, 317 (1916).
(13) J. Bougault and L. Daniel, *Compt. rend.*, **186**, 1216 (1928).

TABLE III

Compound	Yield, %	Recrystal'n Solvent	M.P.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
II	51	Water	210–212°[a]						
III ($C_5H_7N_3O_2$)	56	Benzene	145–147°	42.55	42.84	4.99	4.87	29.77	29.56
IV ($C_6H_9N_3O_2$)	63	Benzene	132–134°	46.44	46.14	5.84	5.84	27.09	27.23
V ($C_6H_9N_3O_2$)	71	Water	195–196°	46.44	46.57	5.84	5.92	27.09	27.01
VI ($C_8H_{13}N_3O_2$)	53	Benzene	126–128°	52.44	52.47	7.15	7.14	22.40	22.67
VII ($C_{10}H_{17}N_3O_2$)	73	Water	117–119°	56.85	56.59	8.11	8.08	19.89	20.05
VIII ($C_{10}H_9N_3O_2$)	94	Water	204–206°[b]	59.10	58.78	4.46	4.50	20.68	21.07

[a] Mixture m.p. with an authentic sample. [b] See ref. 12, m.p. 208°.

EXPERIMENTAL[14]

Preparation of the semicarbazones of α-keto acids. To a solution of semicarbazide hydrochloride (2.23 g., 0.02 mole) in water (10 ml.) was added the α-keto acid[15] (0.02 mole) in small portions with stirring at room temperature; a colorless precipitate of the semicarbazone separated shortly afterwards. In some cases, addition of a little ethanol was required to produce a homogeneous mixture prior to the precipitation. The semicarbazones were dried and used in the cyclization step without further purification.

5-Alkyl-6-azauracils. A solution of the α-keto acid semicarbazone (0.01 mole) in ethylene glycol (40 ml.) was added rapidly to sodium (0.69 g., 0.03 mole) dissolved in absolute ethanol (20 ml.) and the clear solution was refluxed gently for 15 hr. After reducing the solution to dryness on a water aspirator at 120°, the residue was dissolved in hot water (15 ml. to 100 ml. depending on the individual homolog) and the hot solution adjusted to *p*H 2 with conc. hydrochloric acid. The 5-alkyl-6-azauracil crystallized on cooling.

Attempted cyclization of α-semicarbazidoisobutyric acid. A solution of the acid (1.61 g., 0.01 mole) in ethylene glycol (40 ml.) was added to sodium (0.72 g., 0.031 mole) in absolute ethanol (25 ml.) and the clear solution refluxed gently for 24 hr. After reducing the solution to dryness on a water aspirator at 120°, the residue was dissolved in hot water (10 ml.) and the solution acidified to *p*H 2. Upon further concentration of the acidified solution, α-semicarbazidoisobutyric acid crystallized out unchanged (0.5 g.). After one recrystallization from water, it melted at 174–176°, mixed m.p. with an authentic sample, 174–176°.

Infrared Spectra. The spectra were measured in pressed potassium bromide disks on a Perkin-Elmer double-beam instrument, model 21.

Ultraviolet spectra. The spectra were measured on a Beckman spectrophotometer, model DU. Solutions were made up in volumetric flasks from weighed quantities of the compounds.

Dissociation constants. The pK_a's were determined potentiometrically in duplicate using a Photovolt *p*H meter, model 110. A solution of 0.0005 mole of the compound in 100 ml. of carbon dioxide-free water was titrated with 0.066*N* sodium hydroxide. In the case of 5-*n*-heptyl-6-azauracil, which is difficultly soluble in water, equimolar quantities of sodium hydroxide were added and the solution back-titrated with 0.046*N* hydrochloric acid.

Acknowledgment. The author wishes to express her thanks to Professor A. D. Welch for his suggestion of this problem and encouragement during the progress of this work.

NEW HAVEN, CONN.

(14) Melting points are uncorrected. Analyses by Huffman Microanalytical Labs., Wheatridge, Col., and by Schwarzkopf Microanalytical Labs., Woodside, N. Y.

(15) With the exception of pyruvic acid and sodium phenylpyruvate, all the α-keto acids employed in this work were purchased from Aldrich Chemical Co., Milwaukee, Wis.