authentic 3-ethylacridine, m.p. 90–91°;[5] the respective infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.9; H, 6.32. Found: C, 87.1; H, 6.45.

Similarly, the *perchlorate* of the dehydrogenation product (m.p. 181–182°) was indistinguishable from that of synthetic 3-ethylacridine perchlorate of m.p. 184–185°.[5]

6-(2-Dimethylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIa). To an ice-cooled solution of 4 g. (*ca.* 6 moles) of dimethylamine in 125 ml. of dry ether (containing 3 ml. of 95% ethanol), 4 g. of powdered I was added and the system mechanically shaken for 15 hr. After removing dimethylamine hydrobromide (1.7 g. or 90%) the washed and dried ether solution afforded 3.5 g. of sirupy aminoketone. A solution of this in 15 ml. of acetone was acidified with 4 ml. of 2.2*N* ethanolic hydrogen chloride and strongly diluted with dry ether. Scratching induced the separation of the powdery hydrochloride. The salt was triturated twice with dry ether and the amino ketone regenerated (ammonium hydroxide-ether); yield 2.7 g. The latter, in 25 ml. of methanol with 0.15 g. of platinum oxide, absorbed 1.0 mole of hydrogen during 24 hr. and gave rise to 2.2 g. of sirupy aminoalcohol which, in 17 ml. of acetone, was acidified with 4 ml. of 2.2*N* ethanolic hydrogen chloride. Dropwise addition of dry ether (*ca.* 2 vols.) precipitated the crystalline hydrochloride; yield 1.5 g. Recrystallization from acetone gave 1.2 g. of colorless plates, m.p. 200–202°. Another recrystallization elevated the melting point to 204–206°.

Anal. Calcd. for $C_{19}H_{29}ClN_2O_2$: C, 64.7; H, 8.28. Found: C, 64.5; H, 8.17.

6-(2-Diethylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIb). Employing the above procedure, the condensation of 5 g. of powdered I with 2.3 g. (2.2 moles) of diethylamine in 75 ml. of U.S.P. ether gave in the order named: 5.4 g. of crude amino ketone base (sirup); 5.5 g. of amino ketone hydrochloride and 4.9 g. of regenerated base. Reduction of the latter in 25 ml. of methanol with 0.2 g. of platinum oxide (0.88 mole of hydrogen absorbed in 40 hr.) yielded 3.8 g. of a sirup which, in 20 ml. of acetone, was acidified with 2.5 ml. of 5.4*N* ethanolic hydrogen chloride. Dilution with dry ether yielded a yellow gum that crystallized when scratched. Recrystallization (acetone-ether) gave 2.9 g. of colorless plates, m.p. 194–196°. After a second recrystallization the m.p. 200–201° was noted.

Anal. Calcd. for $C_{21}H_{33}ClN_2O_2$: C, 66.2; H, 8.73. Found: C, 65.8; H, 9.07.

6-(2-Di-n-propylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIc). Five and one-half grams of powdered I was shaken with 3.45 g. (2.2 moles) of di-*n*-propylamine in 125 ml. of U.S.P. ether and, after the usual work-up, yielded in turn, 4.4 g. of crude amino ketone hydrochloride and 3.9 g. of regenerated amino ketone base which, in 25 ml. of methanol with 0.25 g. of platinum oxide, absorbed 0.9 mole of hydrogen (45 hr.) to give 3 g. of sirupy amino alcohol. The latter in acetone, gave an amorphous (gum) salt when treated with ethanolic hydrogen chloride and dry ether. Recrystallization (acetone-ether) yielded 2 g. of colorless prisms, m.p. 160–162°. Another recrystallization raised the m.p. to 166–168°.

Anal. Calcd. for $C_{23}H_{37}ClN_2O_2$: C, 67.5; H, 9.11. Found: C, 67.3; H, 9.08.

BETHESDA, MD.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

8-Selenapurines[1,2]

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Received February 7, 1958

Selenium-containing purine type compounds as possible antimetabolites for cancer therapy were prepared by reaction of 6-substituted 4,5-diaminopyrimidines with selenous acid. The compounds prepared were 6-amino-, 6-hydroxy-, and 6-morpholyl-8-selenapurine.

The carcinostatic activity resulting from the substitution of a nitrogen atom for the 8-carbon of guanine[5] made it of interest to introduce a more radical change in such compounds by substituting in this position an element less closely related to carbon and nitrogen. The element chosen was selenium.

The toxicity of selenium has been known for many years.[6] This was only of academic interest until it was realized that selenium is present in high concentrations in plants grown on soils rich in this element and that animals feeding on such plants become affected. The first report of the essential role of selenium in the animal body has recently been made.[7]

The approach used here has been the incorporation of the element selenium into heterocyclic systems which are related to known purine antimetabolites. These compounds are derivatives of 8-selenapurine, I. This ring system is shown as an ortho quinone since it is formed in a reaction analogous to the preparation of the known ortho quinone,2,1,3-benzoselenadiazole, II,[8-10] by the

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(2) Abstracted from part of a Dissertation submitted by Albert Carr in partial fulfillment of the requirements for the Doctor of Philosophy Degree at the University of Florida (*cf.* refs. 18 and 19).

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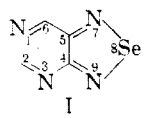
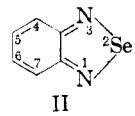
reaction of selenous acid with aromatic ortho diamines.

Confirmatory evidence was obtained from the infrared spectrum of 6-amino-8-selenapurine which shows a strong absorption peak at 1660cm.$^{-1}$ This peak is commonly ascribed to the quinone group[11] and it has been observed that ortho quinones have a somewhat higher carbonyl frequency than para quinones. The picture is less clear in the case of 6-hydroxy-8-selenapurine. Despite long drying and repeated runs only a broad shoulder from 1610 to 1710cm.$^{-1}$ was obtained.



I



II

Recently, Mautner[12] has reported several selenapurines. These, however, had the selenium atom placed outside the purine ring system and no report was made on any physiological activity. The only compound reported in the literature containing a selenium atom in a purine-type nucleus is 1,3-dimethyl-2,6-dioxy-8-selenapurine.[13]

6-Hydroxypurine, (hypoxanthine) is metabolized to xanthine and thence to uric acid by the enzyme xanthine oxidase. Bergmann and Dikstein[14] have proposed that xanthine oxidation to uric acid involves an initial addition of water to the double bond between carbon-8 and nitrogen-9 of the purine ring. Assuming that 8-selenahypoxanthine would be accepted by the enzyme system and hence oxidized to 8-selenaxanthine, it would be quite likely that the subsequent oxidative pathway would be blocked, since there would be no hydrolyzable double bond available in the selenium compound. The possibility of such a sequence of events is strengthened by the anomalous lack of substrate specificity of xanthine oxidase.[15] Since xanthine is known to function as an indirect guanine source,[16] the nucleic acid picture might be adversely affected.[17,18]

The method used in this investigation for the preparation of selenium heterocycles is an extension of earlier work.[19,20] This reaction of aromatic ortho diamines with selenium dioxide was first carried out by Hinsberg[21] in the preparation of 2,1,3-benzoselenadiazole. In the present investigation, selenous acid rather than selenium dioxide has been used as a selenium reagent.

4,5-Diamino-6-hydroxypyrimidine[22-24] was allowed to react with selenous acid in aqueous solution to give 6-hydroxy-8-selenapurine. 4,5,6-Triaminopyrimidine[25-27] was allowed to react with selenous acid to yield 6-amino-8-selenapurine.

Attempts were made to convert 6-hydroxy-8-selenapurine to 6-mercapto-8-selenapurine by reaction with phosphorus pentasulfide in tetralin. The selenodiazole ring system is evidently broken in such a reaction, since selenium metal can be seen in the reaction products. It was then decided to prepare the 6-chloro-8-selenapurine. The necessary pyrimidediamine, 6-chloro-4, 5-diaminopyrimidine,[28] upon reaction with selenous acid gave a mixture of products. Hydrolysis of the 6-chloro-group similar to that found in the purine series[28] is assumed to have been the difficulty.

A method for the introduction of amino-groups into the 6-position of purine molecules is found in the reaction of amines with 4-amino-6-chloro-5-nitropyrimidine,[29] followed by reduction and ring closure. Thus, 4,5-diamino-6-morpholylpyrimidine was prepared and found to react with selenous acid to give 6-morpholyl-8-selenapurine.

The compounds prepared have been submitted to the Sloan-Kettering Institute for Cancer Research for testing as cancer therapeutic agents: the results will be reported elsewhere.

EXPERIMENTAL

6-Hydroxy-8-selenapurine. To a solution of 4,5-diamino-6-hydroxypyrimidine[23] resulting from the dethiation of 2.5 g. (0.02 mole) of 4,5-diamino-6-hydroxy-2-mercaptopyrimidine was added a solution of 2.0 g. (0.02 mole) of selenous acid in 10 ml. of water. After standing 12 hr. at room temperature, 1.9 g. of long light-yellow needles were deposited. An analytical sample melting higher than 360° was prepared by two recrystallizations from water.

Anal. Calcd. for $C_4H_2N_4OSe$: C, 23.9; H, 1.0; N, 27.9; Se, 39.3. Found: C, 23.7; H, 1.06; N, 28.4; Se, 38.8.

6-Amino-8-selenapurine. To a solution of approximately

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0.05 mole of 4,5,6-triaminopyrimidine resulting from the reduction of 4,6-diamino-5-nitropyrimidine[26] was added 6.4 g. (0.05 mole) of selenous acid in 20 ml. of water. After standing 24 hr., 4.0 g. of product was collected. An analytical sample was recrystallized twice from water yielding red-brown platelets melting above 360°.

Anal. Calcd. for $C_4H_3N_5Se$: C, 24.0; H, 1.5; N, 35.0; Se, 39.5. Found: C, 23.7; H, 1.11; N, 35.3; Se, 38.3.

Spectra. The ultraviolet-visible absorption spectra of 6-hydroxy-8-selenapurine and 6-amino-8-selenapurine are listed in Table I.

6-Morpholyl-8-selenapurine. To the methanol solution of 4,5-diamino-6-morpholylpyrimidine resulting from the catalytic reduction of 0.004 mole of 4-amino-6-morpholyl-5-nitropyrimidine[29] was added 0.5 g. (0.004 mole) of selenous acid in 10 ml. of methanol. After standing 3 days, large yellow crystals of product were deposited, weighing 0.7 g. The compound melted at 205.5–206°.

Anal. Calcd. for $C_8H_9N_5OSe$: N, 25.9. Found: N, 25.5.

TABLE I

ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA OF TWO 8-SELENAPURINE COMPOUNDS IN WATER

Compound	Values[a] Given as λ_{max} in mμ (Log ε)
6-Amino-8-selenapurine	233 (3.86)
	339 (3.93)
	302 (3.56)
	388 (3.19)
6-Hydroxy-8-selenapurine	236 (3.89)
	276 (3.32)
	337 (4.00)

[a] Underlined wavelengths denote shoulders.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE HEYDEN NEWPORT CHEMICAL CORP.]

Synthesis of Anhydro Analogs of Chloramphenicol

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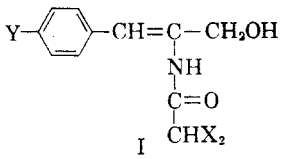
Four anhydro analogs of chloramphenicol have been prepared by the selective lithium aluminum hydride reduction of α-acylamidocinnamates derived from the alcoholysis of the corresponding azlactones. Bacteriostatic and fungistatic tests demonstrated that none of the four dehydro analogs possessed any significant degree of biological activity.

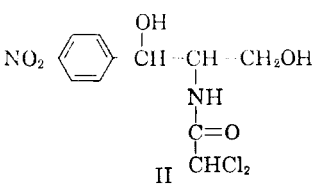
One phase of an antibiotics program conducted at these laboratories several years ago consisted of a search for analogs of chloramphenicol which would retain a high level of antibiotic activity and yet show a low order of toxicity. There resulted from this program four derivatives of cinnamyl alcohol with the general formula I.



I

X = H or Cl
Y = H or NO_2

The structural relationship of these compounds to chloramphenicol (II) is obvious.



II

C. F. Huebner and C. R. Scholz[2] describe the preparation of α-acetamido-*p*-nitrocinnamic acid, α-dichloroacetamido-*p*-nitrocinnamic acid, and ethyl α-dichloroacetamido-*p*-nitrocinnamate. The work described in this report is therefore a logical extension of their work, in view of the fact that the corresponding cinnamyl alcohols or the true anhydro analogs of chloramphenicol were prepared. In addition the cinnamyl alcohol structure was varied with respect to substitution in the ring and in the side chain.

α-Acetamidocinnamyl alcohol (III) was prepared by converting D,L-*threo*-phenylserine (IV) to 2-methyl-4-benzal-5-oxazalone (V) which was alcoholyzed to ethyl α-acetamidocinnamate (VI). The ester group was selectively reduced with lithium aluminum hydride to the desired alcohol.

α-Dichloroacetamidocinnamyl alcohol (VII) was prepared from D,L-*threo*-*N*-(dichloroacetyl)phenylserine (VIII), which was converted through the oxazalone (IX) and ester (X) as described in the conversion of (V) to (III).

α-Acetamido-*p*-nitrocinnamyl alcohol (XI) was synthesized by condensing *p*-nitrobenzaldehyde with aceturic acid in the presence of acetic anhydride to form 2-methyl-4-(*p*-nitrobenzal)-5-oxazalone (XII), which was converted as before to (XI) through the ester (XIII).

α-Dichloroacetamido-*p*-nitrocinnamyl alcohol, anhydrochloramphenicol (XIV), was synthesized by the nitration of α-dichloroacetamidocinnamyl alcohol (VII) with copper nitrate in an acetic anhydride–glacial acetic acid medium. Anhydrochloramphenicol was also synthesized by

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