oxidation in 30 ml. of methanol was added 1.87 g. of periodic acid in 5 ml. of water, and the resulting solution stirred 15 hr. at room temperature. The solvent was removed at reduced pressure, the residue taken up in benzene and filtered through alumina to give 1.11 g. (83%) of 1-ketonordehydroabietane, the infrared spectrum of which was identical to that prepared by ozonization. The 2,4-dinitrophenylhydrazone had m.p. and mixed m.p. 90–91°.

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A Synthesis of 5-Chloro-6-ethoxypyrimidines[1]

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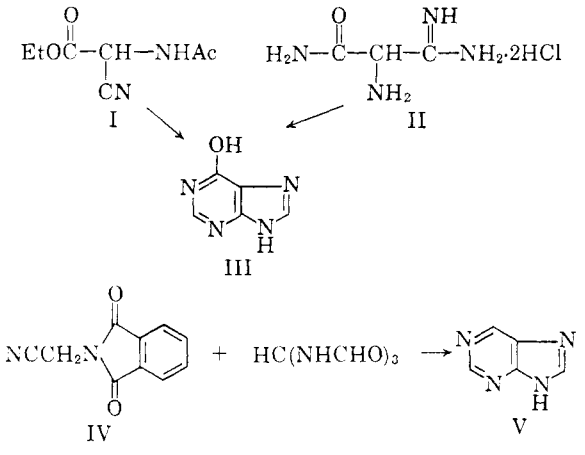
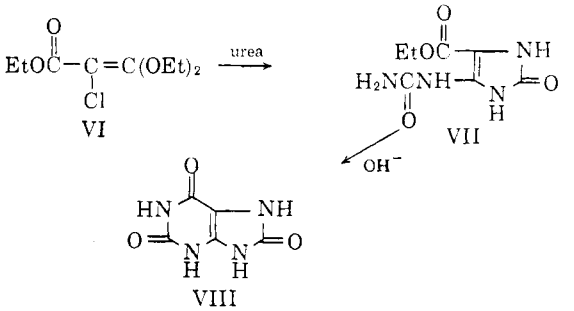
Condensation of ethyl α-chloro-β,β-diethoxyacrylate with amidines in the presence of sodium ethoxide has been found to give 2-substituted 4-hydroxy-5-chloro-6-ethoxypyrimidines in high yield. An intermediate conjugate addition compound, ethyl α-chloro-β,β-diethoxy-β-guanidinopropionate (IX), was isolated when guanidine was employed. An analogous series of 2-substituted 4-amino-5-chloro-6-ethoxypyrimidines was prepared by the condensation of α,β,β-trichloroacrylonitrile or the imino ether of α-chloro-β,β-diethoxyacrylonitrile with amidines. These 5-chloro-6-ethoxypyrimidines did not react further with amidines to give purines.

The bicyclic purine ring system is traditionally constructed from either a pyrimidine or imidazole precursor, with subsequent closure of the second ring (imidazole or pyrimidine, respectively), usually in the terminal step of the synthetic sequence.[2] The concept of employing a "skeletal backbone" intermediate which can serve as a building block for both rings is more recent. Examples of this approach to purine synthesis include the synthesis of hypoxanthine (III) in one step either from ethyl acetamidocyanoacetate (I), ammonia and ethyl orthoformate,[3] or from aminomalonamidamidine dihydrochloride (II) and ethyl orthoformate[4] (both reactions proceed *via* the intermediate formation of 4-aminoimidazole-5-carboxamide), and the synthesis of purine from phthalimidoacetonitrile and tris(formylamino)methane[5] (which proceeds *via* the intermediate formation of 4,5-diamino-pyrimidine).



In each of these examples, the 2 and 8 carbon atoms of the completed purine ring were supplied by a single one-carbon reagent.

A number of years ago Sweeting and co-workers[6] reported that the reaction of ethyl α-chloro-β,β-diethoxyacrylate (VI) with urea led first to the formation of 2-hydroxy-4-ureido-5-ethoxycarbonyl-imidazole (VII), which then underwent ring closure in alkali to give uric acid (VIII). This synthesis thus represented a further example of the utilization for purine synthesis of a "backbone" intermediate upon which both the pyrimidine and imidazole rings are constructed with a common second reagent. It appeared possible that the use of other polyfunctional three-carbon intermediates related to acrylic acid or acrylonitrile might extend the usefulness of this approach, and the present paper describes our investigations of this possibility.



By analogy with Sweeting's uric acid synthesis, the reaction of ethyl α-chloro-β,β-diethoxyacrylate with guanidine would be expected to give 2-amino-4-guanidino-5-ethoxycarbonylimidazole which, upon treatment with alkali, should cyclize to 2,8-diamino-6-hydroxypurine. To our surprise, the initial product formed from these two reagents was the conjugate addition compound IX, which cyclized quantitatively upon heating to give 2-amino-4-hydroxy-5-chloro-6-ethoxypyrimidine (X). Even prolonged, vigorous heating of this compound with excess guanidine failed to give a purine. This pyrimidine synthesis is thus analogous to the previously reported condensation of ethyl β,β-diethoxy-

(1) This investigation was supported by grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (grant no. CY-2551), and from the American Cancer Society.

(2) For recent reviews of synthetic routes to purines, see (a) A. Bendich in "The Nucleic Acids, Chemistry and Biology," E. Chargaff and J. N. Davidson, ed., Academic Press, Inc., New York, N. Y., 1955, p. 81. (b) G. A. Howard in "Chemistry of Carbon Compounds," E. H. Rodd, ed., Vol. IVc, Elsevier Publishing Company, Amsterdam, 1960, p. 1635. (c) J. H. Lister, *Rev. Pure Appl. Chem.*, **11**, 178 (1961).

(3) E. C. Taylor and C. C. Cheng, *Tetrahedron Letters*, **12**, 9 (1959).

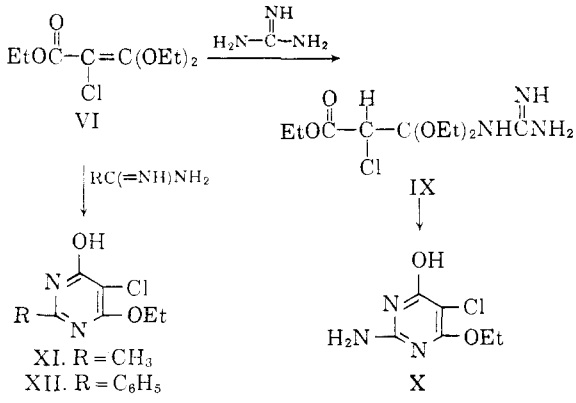
(4) E. Richter, J. E. Loeffler, and E. C. Taylor, *J. Am. Chem. Soc.*, **82**, 3144 (1960).

(5) H. Bredereck, F. Effenberger, and G. Rainer, *Angew. Chem.*, **73**, 63 (1961).

(6) S. E. Gebura, C. W. Bills, J. D. Park, and O. J. Sweeting, 124th National Meeting of the American Chemical Society, Chicago, Ill., 1953, Abstracts, p. 44-O.

acrylate to give 6-ethoxyuracil.[6] The different reaction course taken with urea in its reaction with ethyl α-chloro-β,β-diethoxyacrylate, as contrasted with the reaction observed with guanidine, may be a result of the inability of urea, as a much weaker base, to undergo the initial conjugate addition reaction.

The reaction of ethyl α-chloro-β,β-diethoxyacrylate with amidines to give 4-hydroxy-5-chloro-6-ethoxypyrimidines appears to be general. For example, acetamidine yielded 2-methyl-4-hydroxy-5-chloro-6-ethoxypyrimidine (XI) in 39% yield, and benzamidine gave the corresponding 2-phenyl derivative (XII), although in poor yield.

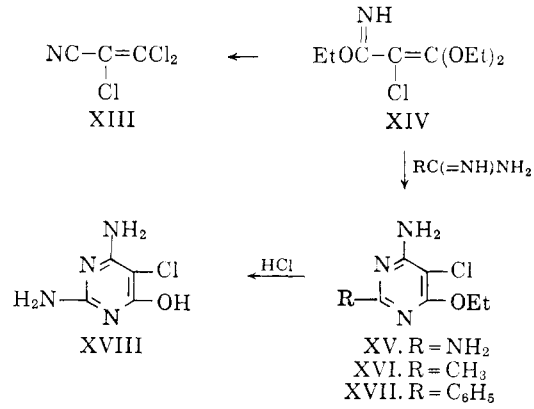


Attention was then turned to the reaction of analogously substituted acrylonitrile derivatives with amidines in the hope of realizing a useful synthesis of 2,8-disubstituted adenines. The requisite intermediate, α,β,β-trichloroacrylonitrile (XIII), was prepared from perchloropropylene as described previously.[7]

Treatment of XIII with guanidine in refluxing ethanol in the presence of excess sodium ethoxide gave 2,4-diamino-5-chloro-6-ethoxypyrimidine (XV) in 62% yield, but all attempts to convert this latter compound to 2,6,8-triaminopurine by further treatment with guanidine also failed. When α,β,β-trichloroacrylonitrile and guanidine were stirred in ethanol at room temperature instead of under reflux, the imino ether XIV was formed. This material gradually dissolved as stirring was continued, and XV then precipitated. The imino ether XIV thus appeared to be an intermediate in the conversion of XIII to XV, and this was readily confirmed by direct treatment of XIV [prepared from α,β,β-trichloroacrylonitrile (XIII) with three moles of sodium ethoxide] with guanidine to give 2,4-diamino-5-chloro-6-ethoxypyrimidine (XV) in 99% yield. Warming the 6-ethoxypyrimidine XV with dilute hydrochloric acid resulted in hydrolysis to 2,4-diamino-5-chloro-6-hydroxypyrimidine (XVIII).

Analogous results were obtained with other amidines. Thus, the condensation of XIV with acetamidine gave 2-methyl-4-amino-5-chloro-6-ethoxypyrimidine (XVI) in 96% yield, and condensation with benzamidine gave the corresponding 2-phenyl derivative in 94% yield. In no instance could further cyclization to a purine be achieved. (See col. 2.)

Numerous unsuccessful attempts were made to extend the possible usefulness of these acrylic acid intermediates to pyrimidine or purine synthesis. For example, attempted condensations of α,β,β-trichloroacrylonitrile (XIII) with hydrazine, methylhydrazine, phenylhydrazine, glycine, cyclopentadiene, butadiene, thiourea, and hydroxylamine were fruitless. Attempts to utilize the imino ether XIV further also proved unsuccessful. Attempted condensations with hydrazines, hydroxylamine, potassium thiocyanate, and thiourea, to cite but a few of the many reagents investigated, gave



either unchanged starting material or noncharacterizable products. It must be concluded that α,β,β-trichloroacrylonitrile (XIII) and ethyl α-chloro-β,β-diethoxyacrylate (VI) are of limited utility in the preparation of 5-chloro-6-ethoxypyrimidines as described above, but are not generally useful intermediates for purine synthesis. The preparation of uric acid from VI[6] remains the only successful purine synthesis from these polyfunctional acrylic acid derivatives.

Experimental

Imino Ether of α-Chloro β,β-diethoxyacrylonitrile (XIV).—A mixture of 10.0 g. of α,β,β-trichloroacrylonitrile[7] and 100 ml. of ethanol containing 4.5 g. of sodium was heated on a steam bath for 30 min. and then poured over ice. The crystalline precipitate which separated was collected by filtration, dried, and recrystallized from ether to give 12.3 g. (87%), m.p. 65°.

Anal. Calcd. for $C_9H_{16}NO_3Cl$: C, 48.76; H, 7.28; N, 6.32. Found: C, 48.96; H, 7.45; N, 6.37.

2-Amino-4-hydroxy-5-chloro-6-ethoxypyrimidine (X).—A mixture of 11.1 g. of ethyl α-chloro-β,β-diethoxyacrylate[8] and 4.9 g. of guanidine in 30 ml. of dimethylformamide was heated by means of an oil bath at 110° for 60 min., then evaporated to a small volume under reduced pressure and poured into 100 ml. of water. The oil which separated rapidly solidified and was collected by filtration and recrystallized from aqueous ethanol to give 7.3 g. of **ethyl α-chloro-β,β-diethoxy-β-guanidinopropionate (IX)** (52%) m.p. 145–146°, with resolidification and then remelting at 308–314°.

Anal. Calcd. for $C_{10}H_{20}N_3O_4Cl$: C, 42.63; H, 7.16; N, 14 92. Found: C, 42.67; H, 6.99; N, 15.36.

Heating this material for a few minutes above its melting point until the melt resolidified, followed by vacuum sublimation of the resulting solid, gave 2-amino-4-hydroxy-5-chloro-6-ethoxypyrimidine (X) in essentially quantitative yield, m.p. 316°.

Anal. Calcd. for $C_6H_8N_3O_2Cl$: C, 38.01; H, 4.25; N, 22.16. Found: C, 38.09; H, 4.30; N, 22.16.

2-Methyl-4-hydroxy-5-chloro-6-ethoxypyrimidine (XI).—A solution of 5.1 g. of ethyl α-chloro-β,β-diethoxyacrylate in ethanol was treated with a solution of acetamidine in ethanol (prepared from 12.0 g. of acetamidine hydrochloride and 100 ml. of ethanol with sodium ethoxide), and the mixture was evaporated to near dryness under reduced pressure. The residual material was maintained at 100° (oil bath temperature) for 90 min., cooled, and

(7) J. Boeseken and P. Dujardin, *Rev. trav. chim.*, **32**, 97 (1913).

(8) P. Fritsch, *Ann.*, **297**, 312 (1897).

triturated with ice–water. The suspended solid was collected by filtration and purified by vacuum sublimation to give 1.7 g. (39%) of colorless crystals, m.p. 216–218°.

Anal. Calcd. for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.80; H, 4.86; N, 14.99.

2-Phenyl-4-hydroxy-5-chloro-6-ethoxypyrimidine (XII).—An ethanolic solution of 5.5 g. of ethyl α-chloro-β,β-diethoxyacrylate and benzamidine (prepared by treatment of an ethanolic solution of 7.8 g. of benzamidine hydrochloride with the calculated amount of sodium ethoxide) was heated under reflux for 3 hr., evaporated to approximately 50 ml. under reduced pressure and poured into ice-cold diluted hydrochloric acid. The precipitate which separated was collected by filtration, dried, and purified by vacuum sublimation; yield, 1.0 g. (16%), m.p. 274°.

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: C, 57.49; H, 4.43; N, 11.17. Found: C, 57.26; H, 4.38, N, 10.99.

2,4-Diamino-5-chloro-6-ethoxypyrimidine (XV). Method A.—A mixture of 1.6 g. of α,β,β-trichloroacrylonitrile, 1.8 g. of guanidine carbonate, and 3.4 g. of sodium ethoxide in 75 ml. of ethanol was heated under reflux for 5 hr. and then poured into 50 ml. of ice water. The solid which separated was collected by filtration, dried. and sublimed *in vacuo* to give 1.2 g. (62%), m.p. 132°.

Anal. Calcd. for $C_6H_9N_4OCl$: C, 38.20; H, 4.81; N, 29.71; Cl, 18.80. Found: C, 38.29; H, 4.87; N, 29.82; Cl, 18.89.

Method B.—A mixture of 1.5 g. of guanidine and 2.6 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile in 20 ml. of dimethylformamide was heated at 100° for 45 min. and then evaporated to near dryness under reduced pressure. The residue was poured into water and the precipitated solid purified as described above to give 2.2 g. (99%), m.p. 132°.

2,4-Diamino-5-chloro-6-hydroxypyrimidine (XVIII).—A mixture of 2.0 g. of 2,4-diamino-5-chloro-6-ethoxypyrimidine and 25 ml. of concentrated hydrochloric acid was heated under reflux. A white solid started to precipitate from the reaction mixture after 5 min. After 30 min. of heating, the solid was collected by filtration, washed well with water, and recrystallized from water to give 1.2 g. (64%), m.p. 338–341°. A final purification for analysis was made by vacuum sublimation at 280°; m.p. 341–342°.

Anal. Calcd. for $C_4H_3N_4OCl$: C, 29.92; H, 3.14. Found: C, 30.36; H, 3.07.

2-Methyl-4-amino-5-chloro-6-ethoxypyrimidine (XVI). Method A.—A mixture of 5.2 g. of α,β,β-trichloroacrylonitrile and acetamidine (prepared from 12.6 g. of acetamidine hydrochloride and the calculated amount of sodium ethoxide) in 100 ml. of ethanol was stirred at room temperature for 30 min. and then poured into 150 ml. of water. The precipitated solid was collected by filtration, dried, sublimed *in vacuo*, and then recrystallized from methanol to give 2.5 g. (40%), m.p. 161°.

Anal. Calcd. for $C_7H_{10}N_3OCl$: C, 44.81; H, 5.37; N, 22.40. Found: C, 45.17; H, 5.44; N, 21.96.

Method B.—A mixture of 3.7 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile, 7.8 g. of acetamidine hydrochloride, 40 ml. of ethanol, and 40 ml. of 2 *N* sodium ethoxide in ethanol was evaporated under reduced pressure until all the ethanol had been removed, and the residue was then heated for 45 min. by means of an oil bath maintained at 100°. Addition of 20 ml. of ice–water to the residue precipitated a solid which was collected by filtration, washed thoroughly with water, dried, and sublimed *in vacuo* to give 3.0 g. (96%), m.p. 161°.

2-Phenyl-4-amino-5-chloro-6-ethoxypyrimidine (XVII).—A mixture of 3.3 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile and 2.4 g. of benzamidine in 15 ml. of ethanol was evaporated to dryness under reduced pressure and the residue heated in an oil bath maintained at 100°. After 20 min. the reaction mixture was triturated with 50 ml. of ice–water. The oil which initially separated soon solidified and was collected by filtration and recrystallized from aqueous methanol to give 3.5 g. (94%), m.p. 91.5–92°.

Anal. Calcd. for $C_{12}H_{12}N_3OCl$: C, 57.72; H, 4.85; N, 16.83. Found: C, 57.14; H, 4.70; N, 16.47.

N-Arylazetidines

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Two possible routes to N-arylazetidines have been examined. N-Phenylazetidine and N-*p*-tolylazetidine may be prepared by cyclization of the corresponding N-(3-bromopropyl)arylamines, a reaction which appears to be inhibited by electron-withdrawing substituents. N-Arylazetidines containing *ortho* or *para* nitro groups may readily be prepared by reaction of azetidine with the corresponding haloaromatic compound.

Azetidine is the least accessible of the lower alkylenimines, and many of its simpler derivatives are still unknown. Of the N-substituted azetidines, most of the known N-alkyl compounds are obtained in low yield, particularly when the alkyl group is small, and when this work began no N-aryl derivative had been prepared. An early claim to the preparation of N-phenylazetidine had been discounted[1] and, as a study consequent upon this work, we examined the possibility of preparing compounds of this series.

Of the possible preparative approaches to N-arylazetidines, we have examined two. The first involves the cyclization of intermediates of the type $ArNH(CH_2)_3X$. This particular method has been used in the synthesis of N-alkyl compounds, examples being the base-catalyzed cyclization of compounds in which X is a halogen atom[2,3] or a hydrogen sulfate group.[4] The second approach to N-arylazetidines involves nucleophilic substitution by azetidine on a suitably substituted benzene ring.

Cyclization.—N-(3-Bromopropyl)aniline was prepared through the corresponding alcohol. The action of hot (100°) 50% sodium hydroxide solution on the hydrobromide salt afforded small amounts of two products identified as 1,2,3,4-tetrahydroquinoline and julolidine (2,3,6,7-tetrahydro-1H,5H-benzo[*ij*]quinolizine). This result was in contrast to that obtained for the salt $MeNHCH_2CMe_2Br \cdot HBr$, which under similar conditions was known to yield the N-methylazetidine derivative.[3] The present result is apparently to be attributed to solubility difficulties; it is likely that the hydroxide had not, in fact, reacted with the bromopropylaniline, because on dry distillation of the base, the same products, tetrahydroquinoline and julolidine, could be obtained. When use was made of aqueous ethanolic sodium hydroxide, in which solubility troubles were absent, the major product was the substitution

(1) A. Fischer, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **25**, 463 (1960).

(2) (a) M. Kohn, *Ann.*, **351**, 134 (1907); (b) M. Kohn, *Monatsh.*, **28**, 423 (1907); (c) M. Kohn and J. Giaconi, *ibid.*, **28**, 461 (1907); (d) M. Kohn and D. Morgenstern, *ibid.*, **28**, 479, 529 (1907).

(3) C. Mannich and G. Baumgarten, *Ber.*, **70**, 210 (1937).

(4) (a) W. R. Vaughan, R. S. Klonowski, R. S. McFlhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961); (b) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, **78**, 4917 (1956); (c) A. T. Bottini and J. D. Roberts, *ibid.*, **80**, 5203 (1958); (d) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 623 (1949).