[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J.]

The Rearrangement of 5-Nitroso-6-aminopyrimidines to *s*-Triazines[1a,b,2]

BY EDWARD C. TAYLOR AND CHARLES W. JEFFORD[3]

RECEIVED MARCH 21, 1962

The novel rearrangement of a number of 5-nitroso-6-aminopyrimidines to cyano-*s*-triazines is described. Beckmann conditions result in cleavage of the pyrimidine ring at the C_4–C_5 bond to give open-chain intermediates which recyclize to cyano-*s*-triazines.

5-Nitroso-6-aminopyrimidines are well-known intermediates for the synthesis of a variety of condensed pyrimidine heterocycles,[4] where the C_5- and C_6-nitrogen atoms become part of the new second ring. 5-Nitroso-pyrimidines can be readily prepared either by the nitrosation of suitably substituted 4-aminopyrimidines or by the thermal isomerization of the amidine salts of isonitrosomalononitrile.[4]

We now report a new reaction of 5-nitroso-6-aminopyrimidines whereby they can be converted into cyano-*s*-triazines. There seem to be no previous instances recorded in the literature for the one-step conversion of a pyrimidine into an *s*-triazine, although the reverse process is known.[5]

When 2 - phenyl - 4,6 - diamino- 5 - nitrosopyrimidine (I) was heated for one hour with 1.1 equivalents of benzenesulfonyl chloride in excess pyridine, the 2-cyano-4-phenyl-6-amino-*s*-triazine (II) was obtained in 30% yield. The structure of this compound was confirmed by the following reaction sequence. Partial hydrolysis by means of polyphosphoric acid or sulfuric acid afforded 2-carboxamido-4-phenyl-6-amino-*s*-triazine, which on treatment with sodium hypobromite was converted to 2-phenyl-4,6-diamino-*s*-triazine (benzoguanamine), identical with an authentic sample.[6] Reduction by means of hydrogen and Adams catalyst gave 2-aminomethyl-4-phenyl-6-amino-*s*-triazine. The action of acetic anhydride in the cold on 2-phenyl-4,6-diamino-5-nitrosopyrimidine (I) resulted in diacetylation of the pyrimidine without rearrangement. The product, m.p. 220°, was recovered unchanged after subsequent heating in pyridine. The action of phosphorus oxychloride on I resulted in the formation of 2-phenyl-4,6-diamino-5-chloropyrimidine. Its structure was confirmed by reductive dehalogenation to the known 2-phenyl-4,6-diaminopyrimidine.[7] Although electrophilic chlorination of the unhindered C_5-position in pyrimidines is well known,[8,9] chlorination with group replacement is not, and perhaps this reaction represents an interesting precedent. The effluent gases from the reaction mixture were cooled with the intention of isolating nitrosyl chloride, but none was obtained.

Other reagents usually employed in Beckmann rearrangements were used in the hope of improving yields; however, boron trifluoride etherate, dicyclohexylcarbodiimide and polyphosphoric acid all were without effect on 2-phenyl-4,6-diamino-5-nitrosopyrimidine. However, this rearrangement was shown to occur with ease in other 5-nitroso-6-aminopyrimidines through the agency of milder reagents. Hot acetic anhydride caused the rearrangement, in good yield, of 2-methylthio-4,6-diamino - 5 - nitrosopyrimidine (III) and 2 - (3-pyridyl) - 4,6 - diamino - 5 - nitrosopyrimidine (IV) to 2 - cyano - 4 - methylthio - 6 - acetylamino-*s* - triazine (V) and 2 - cyano - 4 - (3 - pyridyl)-6-acetylamino-*s*-triazine (VI), respectively. Heating for short periods of time (5–30 minutes) sufficed to bring about these rearrangements in high yield. 2 - *p* - Anisyl - 4,6 - diamino - 5 - nitrosopyrimidine (VII) and 2 - dimethylamino - 4,6-diamino-5-nitrosopyrimidine (VIII) were converted by hot acetic anhydride to 2-cyano-4-*p*-anisyl-6-diacetylamino-*s*-triazine (IX) and 2-cyano-4-dimethylamino-6-diacetylamino-*s*-triazine (X), respectively, together with their monoacetylated derivatives XI and XII.

Similarly, heating 2-dimethylamino-4-hydroxy-5-nitroso-6-aminopyrimidine (XIII) with acetic anhydride for a short time gave 2-cyano-4-dimethylamino-6-hydroxy-*s*-triazine (XIV). The action of phosphorus oxychloride on XIII, then treatment with aqueous ammonia, gave 2-carboxamidino-4-dimethylamino-6-chloro-*s*-triazine (XV), identical with the product obtained by the action of the same reagents on XIV.

2,6-Diamino-5-nitroso-4-hydroxypyrimidine (XVI), which was insoluble in acetic anhydride, was rearranged successfully to 2-cyano-4-amino-6-hydroxy-*s*-triazine (XVII) upon heating with trifluoroacetic anhydride. The action of acetic anhydride on 2 - phenyl - 4 - hydroxy - 5 - nitroso-6-aminopyrimidine gave only non-characterizable material, whereas phosphorus oxychloride resulted in the smooth formation of 2-cyano-4-phenyl-6-chloro-*s*-triazine (XVIII). The identity of XVIII was confirmed by its conversion to the known 2-phenyl-4,6-diethoxy-*s*-triazine.[10]

(1) (a) A preliminary note describing some of the results of this present investigation has been published (E. C. Taylor, C. W. Jefford and C. C. Cheng, *J. Am. Chem. Soc.*, **83**, 1261 (1961)). (b) Presented before the Division of Organic Chemistry at the 140th Meeting of the American Chemical Society, Sept. 3–8, 1961, in Chicago, Ill.

(2) This investigation was supported in part by research 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 (Grant No. T-122C).

(3) Parke, Davis and Co. Fellow in Chemistry, 1959–1960.

(4) E. C. Taylor, O. Vogl and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(5) T. L. Cairns, A. W. Larchar and B. C. McKusick, *ibid.*, **74**, 5633 (1952).

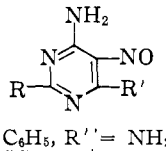
(6) We are grateful to the American Cyanamid Co. for the generous provision of authentic 2-phenyl-4,6-diamino-*s*-triazine.

(7) G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 476 (1944).

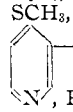
(8) E. C. Taylor and P. Drenchko, *J. Am. Chem. Soc.*, **74**, 1101 (1952).

(9) J. P. English, J. H. Clark, J. W. Clapp, D. Seeger and R. H. Ebel, *ibid.*, **68**, 453 (1946).

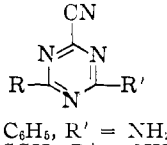
(10) C. Grundmann, H. Ulrich and A. Kreutzberger, *Ber.*, **86**, 181 (1953).



I, R = C_6H_5, R' = NH_2
III, R = SCH_3, R' = NH_2

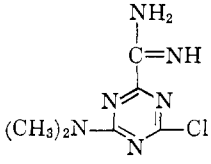


IV, R = N, R' = NH_2
VII, R = *p*-$CH_3OC_6H_4$, R' = NH_2
VIII, R = $N(CH_3)_2$, R' = NH_2
XIII, R = $N(CH_3)_2$, R' = OH
XVI, R = NH_2, R' = OH

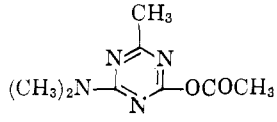


II, R = C_6H_5, R' = NH_2
V, R = SCH_3, R' = $NHCOCH_3$

VI, R = N, R' = $NHCOCH_3$
IX, R = *p*-$CH_3OC_6H_4$, R' = $N(COCH_3)_2$
X, R = $N(CH_3)_2$, R' = $N(COCH_3)_2$
XI, R = *p*-$CH_3OC_6H_4$, R' = $NHCOCH_3$
XII, R = $N(CH_3)_2$, R' = $NHCOCH_3$
XIV, R = $N(CH_3)_2$, R' = OH
XVII, R = NH_2, R' = OH
XVIII, R = C_6H_5, R' = Cl



XV

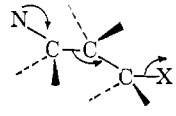


XIX

The infrared spectra of these 2-cyano-*s*-triazines in Nujol mull are noteworthy in that no nitrile absorption band is evident. The only exceptions were 2-cyano-4-methylthio-6-acetylamino-*s*-triazine (V) and 2-cyano-4-phenyl-6-chloro-*s*-triazine (XVIII), the spectra of which display a weak band at 2250 cm.$^{-1}$. As Bellamy[11] indicates, this behavior is not without precedent; however, quenching is generally exhibited when an oxygen-containing group is attached to the same carbon atom as the nitrile. It should also be noted that Sensi and Gallo[12] have found that electron-withdrawing groups *ortho* or *para* to an aromatic nitrile group diminish the nitrile intensity. In the cyano-*s*-triazines, the three nitrogen atoms concertedly succeed in quenching the nitrile intensity entirely.

2-Cyano-4-dimethylamino-6-hydroxy-*s*-triazine (XIV) was converted into its carboxamide in good yield by alkaline hydrogen peroxide and sulfuric acid giving poor yields. Three of the cyano-*s*-triazines were catalytically reduced by Ferris' method,[13] which employs Raney nickel in the presence of sodium acetate and acetic anhydride as solvent at moderate hydrogen pressure and temperature. Whereas the reduction of 2-cyano-4-dimethylamino-6-acetylamino-*s*-triazine (XII) and 2-cyano-4-methylthio-6-acetylamino-*s*-triazine (V) gave the corresponding 2-aminomethyl derivatives, similar reduction of 2-cyano-4-dimethylamino-6-hydroxy-*s*-triazine (XIV) gave 2-methyl-4-dimethylamino-6-acetoxy-*s*-triazine, (XIX) resulting from hydrogenolysis of the initially formed aminomethyl compound.

These transformations of 5-nitroso-6-aminopyrimidines to cyano-*s*-triazines may be considered as examples of the abnormal Beckmann reaction. Ajello[14] had made use of the normal Beckmann rearrangement to obtain pyrimidines from nitrosopyrroles, but this merely represents a simple case of ring expansion. In the case of the 2-substituted-4,6-diamino-5-nitrosopyrimidines, it seems reasonable to suggest that the nitrosopyrimidine is initially esterified in its oxime form XX to give XXI. 1,4-*cis*-Elimination of the acid, HOZ, then occurs with cleavage of the C_4–C_5 bond to give the open chain intermediate XXII. This elimination is similar to the scission of the tosylates and benzoates of α-aminoketoximes to give nitriles and carbimonium salts.[15] Recyclization of XXII then gives the cyano-*s*-triazine. Until recently it has been reasonably assumed that the α-N-atom and the bonding electrons of the incipient leaving group must have the transoid configuration XXIII as a prerequisite for a concerted mechanism with consequent rate enhancement. However, Grob[16] has shown recently that solvolysis of the *syn*-oximes of α-aminoacetophenones occurs with



XXIII

concerted elimination. The stereoelectronically unfavorable transition state for cisoid elimination necessarily raises the free energy of activation and accordingly the cisoid oximes rearrange much more slowly than the *trans*-oximes. With the 5-nitroso-6-aminopyrimidines, there is an unfavorable *cis* relationship between the 6-imino group and the 5-oxime ester group, which means that, although a concerted mechanism is not impossible, elimination will undoubtedly be slow.[17] However, when an electron-releasing substituent is in the 2-position (*e.g.*, $N(CH_3)_2$, SCH_3, *p*-$MeOC_6H_4$) of the pyrimidine ring, involvement of the 6-imino group is no longer necessary in the cleavage step, as an electronically better situation can develop between the

(11) L. J. Bellamy in "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 265.

(12) P. Sensi and G. G. Gallo, *Gazz. chim. ital.*, **85**, 224 (1955).

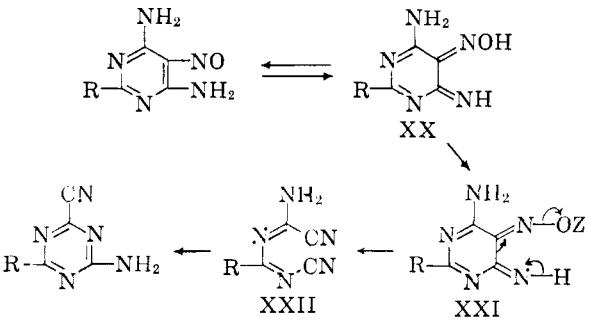
(13) F. E. Gould, G. S. Johnson and A. F. Ferris, *J. Org. Chem.*, **25**, 1658 (1960).

(14) T. Ajello, *Gazz. chim. ital.*, **69**, 460 (1939); **72**, 325 (1942).

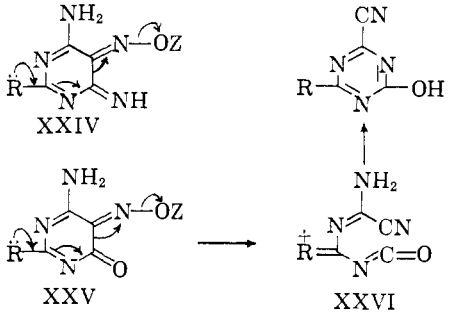
(15) H. Fischer, C. A. Grob and E. Renk, *Helv. Chim. Acta*, **42**, 872 (1959).

(16) H. Fischer and C. A. Grob, *Tetrahedron Letters*, No. **26**, 22 (1960).

(17) The stability of the ground state of the imino oxime ester should not be neglected. F. Greer and D. E. Pearson (*J. Am. Chem. Soc.*, **77**, 6649 (1955)) report that 2,6-dimethyl-acetophenoneketoxime undergoes immediate, normal rearrangement, the facility of which is due, no doubt, to the lack of planarity of the molecule in the ground state.



2-substituent and the 5-oxime ester group (XXIV).



Facile elimination then results. Our findings appear to be generally consonant with this interpretation, although the easy rearrangement of 2-(3-pyridyl)-4,6-diamino-5-nitrosopyrimidine cannot be rationalized in this way.

In the case of the 2-substituted 4-hydroxy-5-nitroso-6-aminopyrimidines, tautomerism to the oxime form can involve proton transfer from the amino or the hydroxyl group, with the latter being more likely. Only with the oxime ester in the keto (XXV) rather than the imino form can participation of the 2-substituent occur in the transition state. The result is cleavage to the isocyanate nitrile intermediate XXVI which then cyclizes to the observed product.

It is probably unlikely that the oxime ester cleaves in a two-step process, as the electron-deficient nitrogen atom so formed could then react in diverse ways.[18] Raphael[19] has found that benzenesulfonyl chloride and pyridine convert *p*-nitrosophenol into *p,p'*-dihydroxyazoxybenzene; although the mechanism is obscure in that it is hard to explain the reduction, nonetheless the intermediacy of an electron-deficient nitrogen atom is possible.

Experimental[20]

Substituted 4,6-Diamino-5-nitrosopyrimidines.—The 2-phenyl, 2-methylthio, 2-(3-pyridyl) and 2-*p*-anisyl derivatives of 4,6-diamino-5-nitrosopyrimidine were prepared by the procedure of Taylor, Vogl and Cheng.[4]

N,N-Dimethylguanidinium Salt of Isonitrosomalononitrile.—To a stirred solution of 37 g. of N,N-dimethylguanidine hydrochloride[21] in 300 ml. of methanol at room temperature was added, in small portions, 67 g. of the finely powdered silver salt of isonitrosomalononitrile.[4] Stirring was continued for one hour after addition was complete. The silver chloride was removed by filtration and the yellow colored filtrate was evaporated to dryness on the water-bath. Recrystallization of the soft yellow product from ethyl acetate gave pale yellow crystals, m.p. 123°, in almost quantitative yield.

Anal. Calcd. for $C_6H_{10}N_6O$: C, 39.6; H, 5.5; N, 46.2. Found: C, 39.8; H, 5.8; H, 45.9.

2-Dimethylamino-4,6-diamino-5-nitrosopyrimidine (VIII).—A mixture of 13 g. of the N,N-dimethylguanidine salt of isonitrosomalononitrile and 60 ml. of α-picoline was heated under reflux for 6 hours. On cooling, a red solid deposited, which after being washed with a little ether and dried, weighed 3.8 g. (29%). Recrystallization from ethyl acetate yielded magenta-colored crystals, m.p. 282°, identical with a sample prepared by Todd's method.[22]

2-Phenyl-4,6-diamino-5-chloropyrimidine.—A mixture of 10 g. of 2-phenyl-4,6-diamino-5-nitrosopyrimidine and 100 ml. of phosphorus oxychloride was heated under reflux for 1 hour. The cooled solution was poured over crushed ice, stirred, and left for 5 hours. A yellow precipitate formed which was removed by filtration. The filtrate was then neutralized with aqueous ammonia (sp. gr. 0.88) and left overnight. The yellow solid was collected by filtration, washed with water, and dried; yield 2.5 g. Sublimation of this yellow solid at 183° and 0.65 mm. gave 1.5 g. (15%) of lustrous colorless crystals, m.p. 205–208°. Recrystallization from benzene yielded colorless needles, m.p. 218°.

Anal. Calcd. for $C_{10}H_9N_4Cl$: C, 54.5; H, 4.1; N, 25.4; Cl, 16.1. Found: C, 54.8; H, 4.2; N, 25.85; Cl, 16.1.

Reductive Dehalogenation of 2-Phenyl-4,6-diamino-5-chloropyrimidine.—To a solution of 0.51 g. of 2-phenyl-4,6-diamino-5-chloropyrimidine in 30 ml. of methanol, 2 ml. of 1% aqueous sodium hydroxide and 0.1 g. of palladium-on-charcoal (5%) was added. The mixture was hydrogenated with shaking at room temperature at 16 p.s.i. for 24 hours. The catalyst was removed by filtration and the methanolic filtrate was concentrated to about 10 ml. The addition of ether to the methanol solution with subsequent cooling yielded a colorless solid, which after recrystallization from methanol–ether gave colorless crystals, m.p. 197°. This compound was identical (m.p., mixed m.p., infrared) with authentic 2-phenyl-4,6-diaminopyrimidine.[7]

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.0. Found: C, 64.2; H, 5.3; N, 29.7.

2-Cyano-4-phenyl-6-amino-*s*-triazine (II).—A mixture of 15 g. of 2-phenyl-4,6-diamino-5-nitrosopyrimidine and 12 ml. of benzenesulfonyl chloride in excess pyridine was heated under reflux for 1 hour. The green color of the solution changed to brown during the first 15 minutes of heating. The cooled solution was poured over crushed ice. A yellow solid was deposited, which, after having been washed with water and dried, weighed 10 g. This solid on sublimation at 165° and 0.02 mm. for 24 hours yielded 4.1 g. (30%) of green-tinted crystals. Recrystallization from methanol–water gave colorless crystals, m.p. 207°.

Anal. Calcd. for $C_{10}H_7N_5$: C, 61.0; H, 3.55; N, 35.5. Found: C, 61.1; H, 3.6; N, 35.4.

2-Aminomethyl-4-phenyl-6-amino-*s*-triazine.—To a solution of 0.5 g. of 2-cyano-4-phenyl-6-amino-*s*-triazine in methanol, 0.2 g. of Adams catalyst was added. The mixture was hydrogenated at room temperature and at 26 p.s.i. with shaking for 10 hours. The catalyst was removed by filtration and the methanol evaporated on the water-bath. The yield of the colorless residue was nearly quantitative. Recrystallization of the residue from methanol–ether yielded a colorless solid which was sublimed to give colorless crystals, m.p. 168°.

Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.7; H, 5.5; N, 34.8. Found: C, 59.7; H, 5.7; N, 34.4.

2-Carboxamido-4-phenyl-6-amino-*s*-triazine.—Two grams of 2-cyano-4-phenyl-6-amino-*s*-triazine was dissolved in 50 ml. of sulfuric acid (sp. gr. 1.84) and allowed to stand overnight. The solution was poured over crushed ice and aqueous ammonia (sp. gr. 0.88) added to *p*H 7. The white gelatinous precipitate was collected by filtration and dried; yield 2.25 g. (100%). Recrystallization from pyridine gave colorless crystals, m.p. 324°.

(18) E. Wenkert and B. F. Barnett, *J. Am. Chem. Soc.*, **82**, 4671 (1960).

(19) R. A. Raphael and E. Vogel, *J. Chem. Soc.*, 1958 (1952).

(20) All melting points are uncorrected. The microanalyses were performed by Dr. G. Robertson, Florham Park, N. J., and the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(21) E. A. Werner and J. Bell, *J. Chem. Soc.*, **121**, 1790 (1922).

(22) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *ibid.*, 2490 (1949).

Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.9; H, 4.2; N, 32.5. Found: C, 55.95; H, 4.35; N, 32.8.

Conversion of 2-Carboxamido-4-phenyl-6-amino-*s*-triazine to 2-Phenyl-4,6-diamino-*s*-triazine.—Four hundred milligrams of finely powdered 2-carboxamido-4-phenyl-6-amino-*s*-triazine was dissolved in 5 ml. of sodium hypobromite solution (prepared by dissolving 0.6 ml. of bromine in a solution of 2.4 g. of sodium hydroxide in 20 ml. of water). The solution was then warmed at 80° for 15 minutes, neutralized with dilute hydrochloric acid and left overnight. The colorless precipitate was collected and dried; yield 0.30 g. (40%). Recrystallization from ethyl acetate gave 2-phenyl-4,6-diamino-*s*-triazine, identical (m.p., mixed m.p., infrared) with an authentic sample.[6]

Acetylation of 2-Phenyl-4,6-diamino-5-nitrosopyrimidine (I).—Using gentle heating, 7.5 g. of 2-phenyl-4,6-diamino-5-nitrosopyrimidine was dissolved in excess acetic anhydride. The resulting solution was left at room temperature overnight. Yellow-green needles deposited, which were collected and dried; yield 8.2 g. (92%). Recrystallization from benzene yielded yellow-green needles, m.p. 220°.

Anal. Calcd. for $C_{14}H_{13}N_5O$: C, 56.2; H, 4.4; N, 23.4. Found: C, 56.3; H, 4.5; N, 23.0.

2-Cyano-4-methylthio-6-acetylamino-*s*-triazine (V).—A solution of 4.5 g. of 2-methylthio-4,6-diamino-5-nitrosopyrimidine in excess acetic anhydride was heated under reflux for 3 hours. The bulk of the acetic anhydride was removed on the water-bath *in vacuo* and ether was added to the residual solution to precipitate 3.7 g. of a yellowish-brown solid. Vacuum sublimation yielded 1.9 g. (38%) of a pale yellow solid which was recrystallized from ethanol to give colorless crystals, m.p. 213°.

Anal. Calcd. for $C_7H_7N_5OS$: C, 40.2; H, 3.4; N, 33.5; S, 15.3. Found: C, 40.1; H, 3.6; N, 33.3; S, 14.8.

2-Cyano-4-dimethylamino-6-acetylamino-*s*-triazine (XII).—A solution of 5.0 g. of 2-dimethylamino-4,6-diamino-5-nitrosopyrimidine in excess acetic anhydride was heated under reflux for 30 minutes. The solution went dark green in color initially, then brown. Excess acetic anhydride was removed *in vacuo* on the water-bath. The viscous residue on treatment with ether gave 4.1 g. (72%) of a light brown solid. Sublimation *in vacuo* and recrystallization from methanol gave colorless needles, m.p. 200°.

Anal. Calcd. for $C_8H_{10}N_6O$: C, 46.6; H, 4.9; N, 40.8. Found: C, 46.5; H, 4.9; N, 40.6.

2-Cyano-4-dimethylamino-6-diacetylamino-*s*-triazine (X).—A solution of 5.6 g. of 2-dimethylamino-4,6-diamino-5-nitrosopyrimidine in excess acetic anhydride was heated under reflux for 10 minutes. The solution became first dark green and then brown. Excess acetic anhydride was removed by evaporation under reduced pressure, leaving a brown residue. Trituration with ether gave 2.2 g. of a yellow solid which was recrystallized from methanol–ether to give 1.3 g. (21%) of 2-cyano-4-dimethylamino-6-acetylamino-*s*-triazine (XII), m.p. 200°. The ethereal filtrate from the trituration was evaporated to a small volume and cooled to give 3.8 g. (50%) of a yellow solid, m.p. 100°. Recrystallization from ethanol gave pale yellow rhombs, m.p. 100°.

Anal. Calcd. for $C_{10}H_{12}N_6O_2$: C, 48.4; H, 4.9; N, 33.9. Found: C, 48.5; H, 4.95; N, 33.85.

2-Cyano-4-(3-pyridyl)-6-acetylamino-*s*-triazine (VI).—A solution of 5.7 g. of 2-(3-pyridyl)-4,6-diamino-5-nitrosopyrimidine in excess acetic anhydride was heated under reflux for 35 minutes. On cooling, light brown crystals were obtained, which were collected and washed with ether; yield 5.2 g. Vacuum sublimation gave 3.3 g. (51%) of nearly colorless material, m.p. 249°. Recrystallization from ethanol gave the pure product, m.p. 250°.

Anal. Calcd. for $C_{11}H_8N_6O$: C, 55.0; H, 3.4; N, 35.0. Found: C, 54.9; H, 3.5; N, 34.85.

2-Cyano-4-(*p*-anisyl)-6-acetylamino-*s*-triazine (XI).—A solution of 3.1 g. of 2-*p*-anisyl-4,6-diamino-5-nitrosopyrimidine in excess acetic anhydride was heated under reflux for 1 hour. On cooling, a tan-colored solid deposited which was removed by filtration. Subsequent work-up showed this tan solid to be amorphous material. The acetic anhydride filtrate was then evaporated to a small volume. Addition of a small amount of ether to the filtrate caused deposition of 0.30 g. (9%) of a yellow solid. Sublimation *in vacuo* afforded a yellow material, m.p. 177°.

Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 58.0; H, 4.1. Found: C, 58.4; H, 4.4.

2-Cyano-4-(*p*-anisyl)-6-diacetylamino-*s*-triazine (IX).—The acetic anhydride–ether filtrate from the above experiment was allowed to stand overnight. A yellow solid (0.65 g. (16%), m.p. 140°) deposited. Recrystallization from ethanol gave 2-cyano-4-(*p*-anisyl)-6-diacetylamino-*s*-triazine as colorless clustered needles, m.p. 132°.

Anal. Calcd. for $C_{15}H_{13}N_5O_3$: C, 57.9; H, 4.2; N, 22.5. Found: C, 57.7; H, 4.4; N, 22.6.

2-Cyano-4-dimethylamino-6-hydroxy-*s*-triazine (XIV).—A solution of 16.9 g. of 2-dimethylamino-4-hydroxy-5-nitroso-6-aminopyrimidine[23] in 150 ml. of acetic anhydride was heated under reflux for 30 minutes. Refrigeration overnight resulted in the separation of 11.5 g. of pale yellow feathery needles. The mother liquor yielded a further 3.0 g. on partial concentration (total yield 14.5 g., 95%). Recrystallization from acetone gave very pale yellow needles, m.p. 262° dec.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.2; N, 42.4. Found: C, 43.7; H, 4.4; N, 42.7.

2-Cyano-4-amino-6-hydroxy-*s*-triazine (XVII).—A solution of 5.0 g. of 2,6-diamino-5-nitroso-4-hydroxypyrimidine in 125 ml. of trifluoroacetic anhydride was heated under reflux for 1 hour. The solvent was removed by distillation. Addition of ether to the brown residue and cooling precipitated a nearly colorless solid (4.3 g., 98%). Recrystallization from methanol afforded colorless crystals, m.p. > 350°.

Anal. Calcd. for $C_4H_3N_5O$: C, 35.0; H, 2.2. Found: C, 35.4; H, 2.8.

2-Carboxamidino-4-chloro-6-dimethylamino-*s*-triazine (XV). Method A.—A solution of 10.0 g. of 2-dimethylamino-4-hydroxy-5-nitroso-6-aminopyrimidine in 100 ml. of phosphorus oxychloride was heated under reflux for 2 hours. The cooled solution was poured into a stirred mixture of crushed ice and ammonia and the mixture extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate. Removal of the chloroform left 2.1 g. (19%) of a pale yellow solid, m.p. 196°. Recrystallization from benzene followed by vacuum sublimation gave colorless crystals, m.p. 208°.

Method B.—A solution of 5.0 g. of 2-cyano-4-dimethylamino-6-hydroxy-*s*-triazine in excess phosphorus oxychloride was heated under reflux for 1 hour. The cooled solution was poured into a stirred mixture of crushed ice and ammonia. The tan-colored precipitate was collected and dried; yield 1.4 g. (23%), m.p. 185°. Vacuum sublimation followed by recrystallization from benzene gave colorless crystals, m.p. 208°, identical with the product obtained by method A.

Anal. Calcd. for $C_6H_9N_6Cl$: C, 35.9; H, 4.5. Found: C, 36.4; H, 4.7.

2-Cyano-4-phenyl-6-chloro-*s*-triazine.—A solution of 12.7 g. of 2-phenyl-4-hydroxy-5-nitroso-6-aminopyrimidine in excess, freshly-distilled phosphorus oxychloride was heated under reflux for 1 hour, and the cooled solution was poured over crushed ice, stirred and filtered. The brown-orange solid so obtained was washed four times with cold water and then extracted several times with boiling ether. Evaporation of the ether extracts to dryness gave 6.4 g. of a yellow-orange solid, m.p. 105°. This material was dissolved in hot benzene, petroleum ether (b.p. 60–70°) added, and a small amount (0.64 g.) of brown solid separated by filtration and discarded. Evaporation of the filtrate to dryness afforded 5.4 g. (42%) of a yellow solid, m.p. 109–110°. Sublimation *in vacuo* gave colorless crystals, m.p. 110°.

Anal. Calcd. for $C_{10}H_5N_4Cl$: C, 55.4; H, 2.3; N, 25.8; Cl, 16.4. Found: C, 55.6; H, 2.5; N, 25.8; Cl, 16.6.

2-Phenyl-4,6-diethoxy-*s*-triazine.—A solution of 1.00 g. of 2-cyano-4-phenyl-6-chloro-*s*-triazine in 100 ml. of ethanol and 2 ml. of 10% aqueous sodium hydroxide solution was left at room temperature for 3 hours. The solution was then evaporated to dryness and water added to the residue. Filtration gave 0.92 g. (90%) of pale yellow crystals. Recrystallization from aqueous ethanol gave white flocculent crystals, m.p. 73°. This compound is reported[10] to melt at 76–76.5°.

(23) B. Roth, J. M. Smith and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2864 (1951).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.7; H, 6.2; N, 17.1. Found: C, 63.8; H, 6.25; N, 17.5.

2-Carboxamido-4-dimethylamino-6-hydroxy-*s*-triazine.—To a stirred mixture of 25 ml. of 1 *N* sodium hydroxide solution and 100 ml. of 3% hydrogen peroxide at 75–80°, 3.85 g. of finely powdered 2-cyano-4-dimethylamino-6-hydroxy-*s*-triazine was slowly added. After the addition, the mixture was stirred for 2.5 hours, cooled and neutralized with dilute acetic acid. A pale yellow precipitate formed which was collected and dried; yield 2.72 g. (64%), m.p. 272°. Recrystallization from ethanol gave colorless crystals, m.p. 287°.

Anal. Calcd. for $C_6H_9N_5O_2$: C, 39.3; H, 4.95; N, 38.2. Found: C, 39.0; H, 5.2; N, 38.0.

2-Methyl-4-dimethylamino-6-acetoxy-*s*-triazine (XIX).—A mixture of 11.7 g. of 2-cyano-4-dimethylamino-6-hydroxy-*s*-triazine, excess acetic anhydride, 0.9 g. of anhydrous sodium acetate and 0.2 g. of W-7 Raney nickel[24] was hydrogenated at 40 p.s.i. for 1 hour at 50°. The mixture was filtered, excess acetic anhydride was removed *in vacuo* and the residual liquid allowed to stand overnight. The colorless crystals which deposited (1.3 g., 66%) were recrystallized from benzene; m.p. 200°.

(24) These reaction conditions have been claimed (ref. 13) to effect a mild reduction of nitriles in good yield without secondary amine formation.

Anal. Calcd. for $C_5H_{12}N_4O$: C, 49.0; H, 6.2; N, 28.6. Found: C, 48.3; H, 6.0; N, 28.75.

2-Aminomethyl-4-methylthio-6-acetylamino-*s*-triazine.—A mixture of 1.00 g. of 2-cyano-4-methylthio-6-acetylamino-*s*-triazine, excess acetic anhydride, 0.6 g. of anhydrous sodium acetate and about 0.2 g. of W-7 Raney nickel was hydrogenated at 45 p.s.i. for 2 hours at 50°. The solution was filtered while warm, the acetic anhydride was removed by distillation, and the residue was dissolved in ethanol. Ether was added to the ethanol solution, causing the deposition of 0.91 g. (89%) of pale yellow solid. Recrystallization from ethanol–ether gave light tan-colored crystals, m.p. 211°.

Anal. Calcd. for $C_7H_{11}N_5OS$: C, 39.4; H, 5.2. Found: C, 39.4; H, 5.3.

2-Aminomethyl-4-dimethylamino-6-acetylamino-*s*-triazine.—A mixture of 1.00 g. of 2-cyano-4-dimethylamino-6-acetylamino-*s*-triazine, excess acetic anhydride, 0.6 g. of anhydrous sodium acetate and about 0.2 g. of W-7 Raney nickel was hydrogenated at 43 p.s.i. for 1 hour at 50°. The catalyst was removed by filtration and the acetic anhydride solution was evaporated to dryness, leaving 0.80 g. (78%) of colorless solid. Recrystallization from ethanol–ether gave white crystals, m.p. 159°.

Anal. Calcd. for $C_8H_{14}N_6O$: C, 45.7; H, 6.7. Found: C, 45.3; H, 6.7.

CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

1-(Hydroxycyclopentyl)-thymines and Anhydro Derivatives. Evidence for Zwitterionic Structures for Anhydronucleoside Derivatives of Thymine and Uracil[1a]

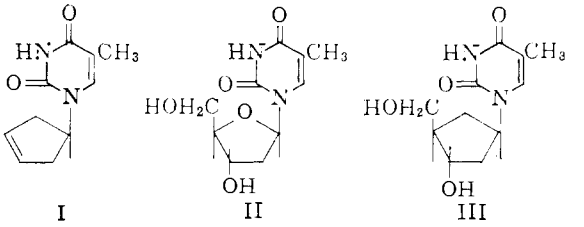
BY K. C. MURDOCK AND ROBERT B. ANGIER

RECEIVED APRIL 4, 1962

1-(3-Cyclopenten-1-yl)-thymine (I) in strong sulfuric acid unexpectedly isomerized to give a cyclic ether closely related to the anhydronucleosides. Dipole moments and other data strongly suggest that such anhydro compounds are zwitterions such as IVa. Alkaline hydrolysis cleaved the ether linkage of IVa without Walden inversion to give the hydroxycyclopentylthymine XI, while cleavages with trifluoroacetic acid and hydrogen chloride led to hydroxy- and chlorocyclopentylthymines with inverted configurations. The cleavage product with methyl iodide was an iodinated, N-3-methyl derivative VI. In accord with this methylation and other data it is postulated that the inversions of configuration in the acidic cleavages result from the attack of an anion on N-3-protonated intermediates which may be viewed as oxonium ions (*i.e.*, Vb). The olefin I and perbenzoic acid gave a pair of isomeric oxides XIV and XV. Cleavages of the oxide functions with alkali, trifluoroacetic acid, hydrogen, pyridine, hydrogen bromide, methanol, ammonia and hydrogen cyanide led to a variety of hydroxycyclopentylthymines. The respective configurations of the oxides XIV and XV were revealed when it was established that only one of them (XV) could be cyclized to form an anhydro derivative XII. Related cyclizations occurred with halogenated compounds (VII and XVII) in the presence of a hindered amine, and with the olefin I and N-bromoacetamide.

Preceding papers describe syntheses leading to 1-(3-cyclopenten-1-yl)-thymine (I).[1b] This report describes the conversion of I to a variety of hydroxycyclopentylthymines, cyclopentane counterparts of thymidine (II) desired as potential anticancer or mutagenic agents. A stereospecific synthesis of 1-(*trans*-3-hydroxy-*cis*-4-hydroxymethylcyclopentyl)-thymine (III) is reported separately.[2]

The synthesis of III involved a Prins condensation of the olefin I with formaldehyde in acetic acid. Part of the present report deals with the product of an unexpected reaction which occurred in an early attempt to accomplish this condensation in 83% sulfuric acid. In this case the product was not III, but an isomer of the starting olefin.



I II III

It was found that the isomerization also proceeded rapidly and smoothly at room temperature in the absence of the formaldehyde (79% yield). The product showed an altered ultraviolet absorption pattern in which the maximum of the thyminyl group at 272 mμ was gone and a *pair* of new maxima were present at 230 and 258 mμ. The infrared absorption spectrum was also strikingly different, with new, strong, sharp peaks at 6.02, 6.16 and 6.55 μ, and without the 3.16 and 14.3 μ peaks characteristic of the –NH and olefinic groups of the starting material. These spectral properties and

(1) (a) Preliminary communication: K. C. Murdock and R. B. Angier, *Tetrahedron Letters*, 415 (1962); (b) K. C. Murdock and R. B. Angier, *J. Org. Chem.*, papers in press.

(2) K. C. Murdock and R. B. Angier, "Abstracts, 141st Meeting, American Chemical Society, Washington, D. C., March, 1962," p. 22-N; *J. Am. Chem. Soc.*, **84**, 3758 (1962).