polymer, indicated by both the periodate and formic acid data at both 72 and 92 hr. If we compare polymers prepared by different methods (but consider our above reservations) we may conclude that the 155° "solution melt" product has about the same degree of branching as the 150° "two-stage" polymer, but the 175° "solution melt" polymer has a higher degree of branching than the 170° "two-stage" polymer. This would be in line with the lower intrinsic viscosity of the "solution melt" polymers, and can be explained by the more free mobility of the monomers and the lower *n*-mers in the polymerizing mixture, leading to more frequent additions of these species through their A* groups to the B* groups of the same monomeric unit in the polymer.

Figures 5 and 6 indicate the same correlations in relative degrees of branching in "solution melt" polyglucose fractions, showing the periodate oxidation as a time process, except in this experiment the formic acid figures in the lower temperature product are not sufficiently different to illustrate fractionation by branching.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XIII. Ribosides of 6-Substituted Purines

BY JAMES A. JOHNSON, JR.,[2] H. JEANETTE THOMAS AND HOWARD J. SCHAEFFER

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The syntheses of six 6-substituted-9-β-D-ribofuranosylpurines from 6-chloro-9-β-D-ribofuranosylpurine have been accomplished.

Since it is known that certain unnatural purines are converted into nucleosides by enzymes[3] or into nucleotides by enzymes[4] and biological systems,[5] there is a distinct possibility that purine antagonists, such as 6-mercaptopurine, are ribosidated[6] or ribotidated[4] before they become active biological agents. In order to test this hypothesis, we have prepared several 6-substituted purine ribosides so that a comparison of their anticancer activity with the free purines can be made. An ideal starting material for our synthetic program was 6-chloro-9-β-D-ribofuranosylpurine (I) which was first prepared by Brown and Weliky[7] by the condensation of chloromercuri-6-chloropurine with 2,3,5-tri-O-acetylribofuranosyl chloride. The structure and stereochemistry of I were established by its conversion into adenosine with methanolic ammonia at 100°. We have prepared I by the recently published[8] improved procedure in which 2,3,5-tri-O-benzoylribofuranosyl chloride was condensed with chloromercuri-6-chloropurine.

The usefulness of 6-chloropurine riboside (I) in the synthesis of 6-substituted purine ribosides has already been demonstrated by the preliminary report[9] from this Laboratory of the synthesis of 6-mercapto-9-β-D-ribofuranosylpurine (II) from I. A modification of the method which we employed has been described recently by Kissman and Weiss,[10] who prepared several 6-substituted aminopurine ribosides from 6-chloro-9-β-D-(2′,3′,5′-tri-O-benzoylribofuranosyl)-purine. The present paper gives complete details of the synthesis of II (see the Experimental section) and describes further transformation products of 6-chloropurine riboside (I).

Treatment of 6-chloropurine riboside (I) with two equivalents of sodium methoxide for 30 minutes at 65° gave a good yield of 6-methoxy-9-β-D-ribofuranosylpurine (III). The course of the reaction was followed by examining the ultraviolet spectra of aliquots removed from the reaction mixture at increasing time intervals and observing the shift in the peak from 263 mμ (6-chloro) to 248 mμ (6-methoxy).

The synthesis of 6-methylaminopurine riboside (IV) was accomplished by heating a solution of I with aqueous methylamine at 80° for 16 hours. The replacement of the chloro group[11] proceeded smoothly, and the desired product was isolated in good yield. No attempt has been made to determine whether a shorter reaction time would be sufficient since little decomposition occurred even with these reaction conditions.

Recently, it was demonstrated[12] that 6-benzylmercaptopurine is as effective as 6-mercaptopurine against Adenocarcinoma 755. In order to determine if the corresponding riboside would possess or have enhanced anticancer activity, we undertook the synthesis of 6-benzylmercapto-9-β-D-ribofuranosylpurine (V). The reaction of I with two equivalents of sodium benzylmercaptide at 65°

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Grant Number CY2942. Part XII, J. A. Montgomery and C. Temple, Jr., THIS JOURNAL, **80**, 409 (1958).

(2) Esso Research Laboratory, Baton Rouge, La.

(3) M. Friedkin, *Federation Proc.*, **11**, 216 (1952).

(4) L. N. Lukens and K. A. Herrington, *Biochim. et Biophys. Acta*, **24**, 432 (1957).

(5) R. W. Brockman, M. C. Sparks and M. S. Simpson, to be published.

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(7) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(8) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

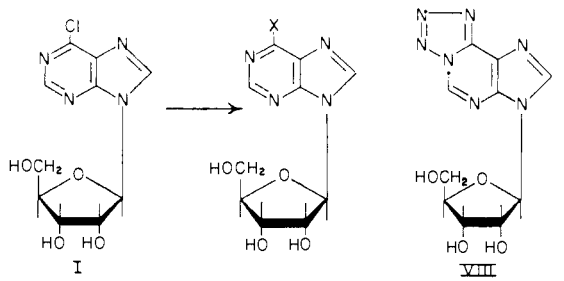
(9) J. A. Johnson, Jr., and H. J. Thomas, THIS JOURNAL, **78**, 3863 (1956).

(10) H. M. Kissman and M. J. Weiss, *J. Org. Chem.*, **21**, 1053 (1956).

(11) Dr. Alexander Hampton of the Sloan-Kettering Division of Cornell University Medical College informed us that he has prepared 6-methylaminopurine riboside (IV) in a 64% yield by the reaction of 6-methylmercaptopurine riboside with methylamine for six hours at 125°. The physical properties of the compounds prepared by the different procedures are in good agreement.

(12) H. E. Skipper and J. R. Thomson, unpublished results.

was shown by ultraviolet analysis to be complete in one hour. The crude reaction product was obtained as a tan glass; considerable difficulty was experienced in the purification of crude V since we were unable to obtain the crystalline riboside V from the solvents commonly used to purify nucleosides or by partition chromatography. However, the pure compound was obtained when we found that V would crystallize from ethyl ether and could be recrystallized from di-*n*-butyl ether.

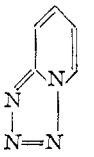


I VIII

II, X = HS- V, X = $C_6H_5CH_2S$-
III, X = CH_3O- VI, X = H_2NNH-
IV, X = CH_3NH- VII, X = N_3-

The preparation of 6-hydrazinopurine riboside (VI) was accomplished by the method that Montgomery and Holum[13] used for the synthesis of 6-hydrazinopurine: *i.e.*, treatment of the chloro compound with anhydrous hydrazine at room temperature. In the case of I, the replacement was complete within 30 minutes. Since this compound is unstable in aqueous solution, considerable care must be employed in order to obtain the analytical sample.

For the preparation of 6-azidopurine riboside (VII), two well-known reactions could be employed: (1) direct replacement of the chloro group with the azide ion,[14] and (2) treatment of the hydrazino group with nitrous acid.[14,15] Treatment of I with sodium azide proceeded with decomposition, and the desired product could not be isolated. Therefore, 6-hydrazinopurine riboside (VI) was treated with nitrous acid at 0°; from the reaction mixture there was obtained a high yield of product which, after purification, exhibited only one spot in paper chromatography in two solvent systems and analyzed well for VII. However, an examination of its infrared spectrum revealed the absence of absorption in the region of 2130 cm.$^{-1}$, whereas absorption in this region is characteristic of the azido group.[16,17] A more likely structure for the compound in question is that of the tetrazolopurine riboside (VIII), a compound that has the same empirical formula as the azido compound VII. Formation of a tetrazole from a hydrazino compound previously has been observed by Fargher and Furness,[18] who found that 2-hydrazinopyridine, upon treatment with nitrous acid, gave the tetrazolopyridine (IX). Other examples of this type of reaction are known,[19] as are cases of the facile conversions of azides into tetrazolo derivatives.[20,21]



IX

With respect to the infrared absorption of tetrazoles, it has been suggested[17] that the only characteristic absorption bands associated with this ring system lie in the 1110–1000 cm.$^{-1}$ region. However, this region in the infrared spectrum is not useful in distinguishing between VII and VIII since this is the region in which the C–O stretching absorption from the sugar moiety occurs.

In order to determine if the product in question has the azido (VII) or the tetrazolo (VIII) structure, we studied the infrared spectra of azides and tetrazoles joined to heterocyclic nuclei. The infrared spectrum of a compound presumed to be 6-azidopurine[22] did not exhibit azido absorption in the region of 2130 cm.$^{-1}$ but did exhibit tetrazolo absorption at 1045 cm.$^{-1}$, whereas several other purines did not exhibit strong absorption in the 1110–1000 cm.$^{-1}$ region. Furthermore, 5,7-dimethyltetrazolo[a]pyrimidine,[23–25] a compound related to the tetrazolopurine riboside (VIII), did not, of course, exhibit absorption in the 2130 cm.$^{-1}$ region but did possess a band at 1035 cm.$^{-1}$. However, 2-azidopurine, prepared by the reaction of 2-hydrazinopurine[10] with nitrous acid, did exhibit strong absorption at 2135 cm.$^{-1}$. The infrared spectrum of 2,4-diazidopyrimidine,[11] having two azido groups, gave double peaks in the azido region, one at 2160 cm.$^{-1}$ and one at 2130 cm.$^{-1}$.

Further insight into the structure of the product from the reaction of 6-hydrazinopurine riboside (VI) and nitrous acid was obtained by a comparison of the infrared spectra in the 1650–1500 cm.$^{-1}$ region of certain purines and their ribosides. Thus, 6-chloropurine, 6-chloropurine riboside and 2-chloropurine all exhibit typical purine absorption in this region (see Table I). Since the azido group is a pseudohalogen, it would not be anticipated that such a group would have appreciable influence on the pattern of absorption in the 1650–1500 cm.$^{-1}$ region. This is established by the fact that 2-azidopurine exhibits an absorption pattern in the 1650–1500 cm.$^{-1}$ region almost identical to the various chloro-substituted purines (see Table I). On the other hand, the infrared spectrum of the product from the reaction of 6-hydra-

(13) J. A. Montgomery and L. B. Holum, THIS JOURNAL, **79**, 2185 (1957).

(14) F. R. Benson, T. W. Hartzel and E. A. Otten, *ibid.*, **76**, 1858 (1954).

(15) J. H. Boyer and F. C. Carter, *Chem. Revs.*, **54**, 1 (1954).

(16) J. H. Boyer, THIS JOURNAL, **73**, 5248 (1951).

(17) E. Lieber, D. R. Levering and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(18) R. G. Fargher and R. Furness, *J. Chem. Soc.*, **107**, 688 (1915).

(19) F. R. Benson, *Chem. Revs.*, **41**, 1 (1947).

(20) R. Stolle and F. Helwerth, *Ber.*, **47**, 1132 (1914).

(21) J. v. Braun and W. Rudolph, *ibid.*, **74**, 264 (1941).

(22) This material was furnished by Dr. Aaron Bendich of the Sloan-Kettering Institute, who has stated that this compound can be prepared by the reaction of 6-hydrazinopurine with nitrous acid or by the reaction of 6-chloropurine with sodium azide. See A. Bendich, A. Giner-Sorolla and J. J. Fox, in G. E. W. Wolstenholme and C. M. O'Connor, Editors, "Ciba Foundation Symposium on the Chemistry and Biology of Purines," J. and A. Churchill, Ltd., London, 1957, p. 3.

(23) This compound was supplied by Dr. F. R. Benson of the Chemical Research Division of Remington Rand, Inc., for testing in animal tumors.

(24) C. Bulow, *Ber.*, **42**, 4429 (1909).

(25) F. C. Nachod and E. A. Steck, THIS JOURNAL, **70**, 2819 (1948).

zinopurine riboside with nitrous acid exhibits a widely different pattern of absorption in this region (see Table I) which might be expected if the aromatic purine nucleus was modified by the formation of a tetrazolo compound (VIII).

TABLE I

INFRARED SPECTRA OF SOME PURINES IN THE 1650–1500 CM.$^{-1}$ REGION

Compound	Maximum absorption[c] I	II	III	IV
6-Chloropurine[a,b]	..	1605	1570	1490
6-Chloropurine riboside[8]	..	1590	1555	1490
2-Chloropurine[b]	..	1610	1570	1485
2-Azidopurine	..	1605	1565	1490
Prod. from reacn. of VI and nitrous acid	1645	..	..	1500

[a] A. Bendich, P. J. Russell and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954). [b] J. A. Montgomery, *ibid.*, **78**, 1928 (1956). [c] In general, the intensities of the absorption bands are: column I and II, strong; column III, medium; column IV, weak or medium.

A comparison of the ultraviolet spectra of several substituted purines offers further evidence on the structure of the product obtained from the reaction of 6-hydrazinopurine riboside (VI) and nitrous acid. An examination of Table II reveals that the ultraviolet spectra of purines which are substituted with groups such as chloro, amino, azido or hydrazino exhibit one peak of maximum absorption, and this peak is located in the 260–280 mμ region. However, the ultraviolet spectrum of the product from the reaction of VI and nitrous acid exhibits three peaks in approximately the same region. It is not likely that this unusual spectrum is caused by an azido group since 2-azidopurine exhibits the expected[14] absorption spectrum. Therefore, it is probable that this atypical ultraviolet spectrum is caused by modification of the aromatic purine nucleus through the formation of the tetrazolo compound VIII.

TABLE II

ULTRAVIOLET SPECTRA OF SOME SUBSTITUTED PURINES

Compound	Maximum absorption, mμ[a] I	II	III
2-Azidopurine[b]	..	280	..
6-Chloropurine riboside[7]	..	264	..
6-Aminopurine riboside[c]	..	260	..
6-Hydrazinopurine riboside (VI)	..	261	..
Prod. from reacn. of VI with nitrous acid	252	260	287

[a] The ultraviolet spectra were, in general, determined in aqueous solution at *p*H 1 since most of the compounds were stable in this media. [b] Determined at *p*H 7 since this compound is unstable at *p*H 1 and at *p*H 13. [c] Nutritional Biochemicals Corporation, Cleveland, Ohio.

The preceding discussion on the infrared and ultraviolet spectra of several purines offers strong, although not conclusive, evidence that the structure of the reaction product of 6-hydrazinopurine riboside (VI) and nitrous acid is the tetrazolo derivative VIII.

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for the microanalytical results reported, to Mr. D. L. Norton and Mr. W. A. Rose for the ultraviolet and infrared spectral determinations, and to Dr. J. A. Montgomery and Dr. B. R. Baker for their helpful discussions on this research. Some of the analyses reported were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Experimental[26]

6-Chloro-9-β-D-ribofuranosylpurine (I) was prepared as previously described.[8] From 6.0 g. of chloromercuri-6-chloropurine and 7.8 g. of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose was obtained 1.9 g. (43%) of pure product, m.p. 178–179° dec.

6-Mercapto-9-β-D-ribofuranosylpurine (II).[9]—To a refluxing suspension of 2.0 g. (7.0 mmoles) of 6-chloro-9-β-D-ribofuranosylpurine in 40 ml. of absolute methanol was added 14 ml. of 1 *N* methanolic sodium hydrogen sulfide.[28] The mixture was refluxed for 10 minutes, solution being complete in 7 minutes. The reaction mixture was evaporated to dryness; the residue was dissolved in 15 ml. of hot water and then acidified with acetic acid. The cooled solution deposited 2.1 g. of nearly pure 6-mercapto-9-β-D-ribofuranosylpurine, m.p. 217–220° dec. One recrystallization from 25 ml. of water gave 1.7 g. (87%) of pure product, m.p. 222–224° dec., $[\alpha]^{26}D$ −73 ± 1° (2.0% in 0.1 *N* NaOH). Spectral data: λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 322 (22.5); *p*H 6.7, 320 (21.5); *p*H 13, 310 (22.1); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3370 (broad, OH), 2800–2300 (acidic hydrogen), 1595 and 1530 (C=C and C=N), 1105 and 1040 (C–O–).

Anal. Calcd. for $C_{10}H_{12}N_4O_4S$: C, 42.2; H, 4.26; N, 19.7. Found: C, 42.2; H, 4.49; N, 19.8.

6-Methoxy-9-β-D-ribofuranosylpurine (III).—To a suspension of 0.50 g. (1.7 mmoles) of 6-chloro-9-β-D-ribofuranosylpurine in 7 ml. of absolute methanol was added 3.4 ml. of 1 *N* sodium methoxide. The mixture was heated under reflux for 30 minutes; the cooled solution was adjusted to *p*H 6 with concentrated hydrochloric acid and evaporated *in vacuo*. The product was dissolved in hot ethyl acetate, and the mixture was filtered to remove the insoluble sodium chloride. From the filtrate there was obtained 0.42 g. (87%) of crude product, m.p. 139–142°. Two recrystallizations from ethyl acetate produced the pure product, m.p. 144–146°, $[\alpha]^{32}D$ −44 ± 2° (0.82% in water). Spectral data: λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 250 (11.2); *p*H 7, 248 (11.7); *p*H 13,250 (11.7); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3500–3200 (broad, OH), 1600 and 1580 (shoulder) (C=C and C=N), 1090 and 1060 (C–O–).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.74; H, 5.13; N, 19.78.

6-Methylamino-9-β-D-ribofuranosylpurine (IV).—A solution of 500 mg. (1.74 mmoles) of 6-chloro-9-β-D-ribofuranosylpurine in 25 ml. of a 40% solution of methylamine in water was heated in a Parr bomb at 80° overnight. The solution was concentrated to dryness *in vacuo*, and the residue was crystallized from methanol; yield 361 mg. (74%), m.p. 132°, resolidified at approximately 160° and remelted at 198° dec. Two recrystallizations from methanol produced the pure material; yield 132 mg. (36.6%), m.p. 135–140°, resolidified at 160° and remelted at 208° dec. This material was very hygroscopic, but after drying for 72 hours at 110° (0.8 mm.), the anhydrous material was obtained; $[\alpha]^{26}D$ −54 ± 2° (0.63% in water). The ultraviolet spectrum of the analytical sample indicated that the first crop was 91% pure. Spectral data: λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 262 (16.6); *p*H 7, 266 (15.9); *p*H 13, 267 (15.9); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3360 (broad, OH and NH); 1635, 1600 and 1510 (C=C and C=N); 1110, 1090 and 1065 (C–O–).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.63; H, 5.56; N, 24.67.

(26) The ultraviolet spectra were determined with a Beckman model DK-2 spectrophotometer in aqueous solution except where a specific solvent is indicated, the infrared spectra with a Perkin–Elmer model 21 spectrophotometer, and the optical rotations with a standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[27] Melting points were determined on a Kofler hot-plate.

(27) A. Keston, Abst. 127th Meeting, Am. Chem. Soc., p. 18c (1955).

(28) C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

6-Benzylmercapto-9-β-D-ribofuranosylpurine (V).—To a suspension of 500 mg. (1.74 mmoles) of 6-chloro-9-β-D-ribofuranosylpurine in 80 ml. of methanol was added 3.48 mmoles of sodium benzylmercaptide (prepared by adding benzylmercaptan to 1 *N* sodium methoxide). The mixture was heated under reflux for one hour; solution occurred after the first few minutes of heating. The reaction solution was neutralized with 1 *N* hydrochloric acid and evaporated *in vacuo*. The residue was extracted with ethyl ether or di-*n*-butyl ether; concentration of the extract gave the crystalline product. One recrystallization from di-*n*-butyl ether gave the pure material; yield 265 mg. (41.0%), m.p. 156–158°, $[\alpha]^{32}D$ −49 ± 2° (0.65% in methanol). Spectral data: λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 293 (19.1); *p*H 7, 292 (20.4); *p*H 13, 292 (20.5); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3400 (broad, OH); 1570 and 1500 (C=C and C=N); 1120, 1080 and 1050 (C-O-).

Anal. Calcd. for $C_{17}H_{18}N_4O_4S \cdot {}^1/_2H_2O$: C, 53.30; H, 5.00; N, 14.63. Found: C, 53.66; H, 4.93; N, 14.83.

6-Hydrazino-9-β-D-ribofuranosylpurine (VI).—6-Chloro-9-β-D-ribofuranosylpurine (200 mg.) was added in three portions over a period of ten minutes to 1.0 ml. of anhydrous hydrazine which was kept in a water-bath at 25°. The reaction solution was allowed to stand at room temperature for 30 minutes, then 5 ml. of isopropyl alcohol was added. The oil which separated crystallized, and the solid was collected by filtration; yield 189 mg. (95.0%), m.p. 176–181° dec. One recrystallization from absolute ethanol gave the pure compound; yield 123 mg. (61.8%), m.p. 214–216° dec. Spectral data: λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 261 (15.0); *p*H 7 and *p*H 13, unstable; $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3250 (broad, OH and NH); 1635 (shoulder), 1610 and 1580 (C=C and C=N); 1095, 1075 and 1055 (C-O-).

Anal. Calcd. for $C_{10}H_{14}N_6O_4$: C, 42.54; H, 5.00; N, 29.79. Found: C, 43.04; H, 5.21; N, 29.86.

Treatment of 6-Hydrazino-9-β-D-ribofuranosylpurine (VI) with Nitrous Acid.—To a solution of 0.50 g. (1.8 mmoles) of 6-hydrazinopurine riboside (VI) in 10 ml. of 5% acetic acid, cooled in an ice-bath, was added a solution of 0.14 g. (2.0 mmoles) of sodium nitrite in 25 ml. of water. Crystals began to separate after 10 minutes; the reaction mixture was kept cold for one hour, and the solid was collected by filtration; yield 0.48 g. (92%), m.p. 218° dec. Recrystallization from water gave the pure product; yield 0.36 g. (69%), m.p. 222° dec., $[\alpha]^{32}D$ −12 ± 3° (0.51% in 0.1 *N* HCl). Spectral data: λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 252 (4.78), 260 (4.82), 287 (8.29); *p*H 7, 251 (4.97), 260 (4.90), 287 (7.93); *p*H 13, unstable; $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3420–3250 (broad, OH); 1640 (unassigned); 1500 (C=C or C=N); 1105, 1080 and 1045 (C-O-).

Anal. Calcd. for $C_{10}H_{11}N_7O_4$: C, 40.96; H, 3.78; N, 33.44. Found: C, 41.05; H, 3.65; N, 33.28.

2-Azidopurine.—To a solution of 300 mg. (2.00 mmoles) of 2-hydrazinopurine[13] in 12 ml. of 10% acetic acid, which was cooled in an ice-bath, was added a cold solution of 165 mg. (2.40 mmoles) of sodium nitrite in 15 ml. of water. The reaction mixture immediately began to deposit a solid; the mixture was kept cold for one hour, and the solid was collected by filtration, washed with cold water and dried; yield 301 mg. (93.0%), m.p. 245° dec. One recrystallization from water gave 250 mg. (78.0%) of pure product, m.p. 240–250° dec. Spectral data: λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 7,280 (5.06); *p*H 1 and *p*H 13, unstable; $\bar{\nu}$ in cm.$^{-1}$ (KBr): 2135 (azido group), 1610 and 1565 (C=C and C=N).

Anal. Calcd. for $C_5H_3N_7$: C, 37.27; H, 1.87; N, 60.75. Found: C, 37.40; H, 2.12; N, 60.81.

2,4-Diazidopyrimidine.—This compound was prepared by the method described in the literature.[14] From 300 mg. of 2,4-dihydrazinopyrimidine, there was obtained 64 mg. of pure product, m.p. 88–90.5°. Spectral data: λ_{max} in mμ ($\epsilon \times 10^{-3}$): ethanol, 239 (21.5), 284 (7.93); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 2160 and 2130 (azido group), 1620 and 1530 (C=C and C=N).

BIRMINGHAM 5, ALABAMA

[COMMUNICATION NO. 1919 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Preparation of Thiazolidines and Related Compounds: Lactams and Lactamidines

BY G. L. OLIVER, J. R. DANN AND J. W. GATES, JR.

RECEIVED AUGUST 8, 1957

The reaction of cysteine and analogous aminothiols with *o*-cyanobenzaldehyde has been shown to produce cyclic amidine or "γ-lactamidine" structures. This cyclization reaction is similar to the lactam formation encountered in the reaction of these aminothiol-type compounds with phthalaldehydic acid and levulinic acid. The structures of these lactamidine compounds have been confirmed by potentiometric titration and by infrared absorption spectra studies.

The preparation of the γ-lactam of benzylhomopenicilloic acid (I) and of many related compounds having the γ-lactam configuration has been presented in detail.[1] The γ-lactam of benzylhomopenicilloic acid (I) has been prepared by ring closure of either the ethyl ester or free acid of α-phenylacetamido - 4 - carboxy - 5,5 - dimethyl - 2 -thiazolidinepropionic acid (II). In a similar manner, α - benzamido - 4 - carboxy - 2 - thiazolidinepropionic acid (III) produced the γ-lactam IV by ring closure.

In the continuation of an investigation presented in previous publications[2,3] involving the isolation and preparation of related thiazolidine structures, examples of γ-lactams and γ-lactamidines have been prepared. In this present work, the reaction of cysteine (V) with phthalaldehydic acid (VI) and with levulinic acid (VII) produced the free acids VIII and IX which readily lost water and produced the γ-lactams X and XI by ring closure. The free acids lost water to form the lactams, even on drying the samples for analysis.

Additional examples of this type of structure were prepared by reaction of *o*-aminobenzenethiol (XII), of β-mercaptoethylamine (XIII) and of homocysteine (XIV) with these reactive carbonyl reagents, as illustrated in Chart I. The free acids were not isolated in the reactions of phthalaldehydic acid or levulinic acid with β-mercaptoethylamine or homocysteine; only the lactams were obtained. The lactam structure is confirmed by the titration curve which resembles that of the N-acetylthiazolidine-4-carboxylic acid (XXIV), rather than that of 2-methylthiazolidine-2,4-dicarboxylic acid[2] (Fig. 1).

In the course of examination of thiazolidine-4-carboxylic acid derivatives, the reaction of cysteine with *o*-cyanobenzaldehyde was carried out as indicated here.

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(3) J. R. Dann and J. W. Gates, Jr., *ibid.*, **79**, 1650 (1957).