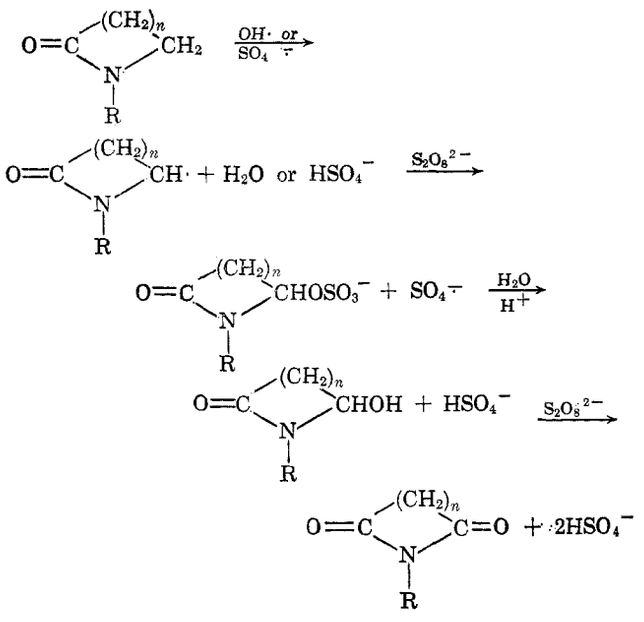
Free-radical attack of the methylene adjacent to the amide nitrogen has been observed before.[2-6] The exothermicity, high reaction rate, oxygen inhibition, and reaction products of these oxidations are consistent with a chain process similar to that proposed[3] for the dealkylation of amides. In the five- and six-membered lactams oxidation to the imide is apparently favored over ring opening.



It is of interest to note that N-methyl was not attacked in the N-methyl lactams studied and that only attack of methylene α to the amide nitrogen was observed. Limited demethylation of 1,4-dimethyl-2,5-piperazinedione was observed, however.

Carbon dioxide and ammonia from oxidation of the 2,5-piperazinediones probably results from initial cleavage of the ring followed by further oxidation of the ring scission products. Methylene groups in the diketopiperazines are apparently less susceptible to attack owing to the presence of a carbonyl adjacent to the methylene.

Experimental Section[7]

Infrared spectra were determined on a Perkin-Elmer Infracord 137 spectrophotometer. Gas–liquid partition chromatograms were obtained on an Aerograph Hy-Fl chromatograph, Model A-600-B, using a 6-ft. column packed with 10% neopentyl glycol succinate on firebrick at 200°. Analyses for ammonia nitrogen were performed by H. M. Wright of this laboratory.

Reactions with Potassium Persulfate.—The procedure was similar to that for the dealkylation of amides[3] with the following modifications. Since 2 moles of persulfate/mole of lactam was necessary for complete reaction, 0.05 mole of lactam was used rather than 0.10 mole. In the oxidation of 2-piperidone, 400 ml. of water was used. Each imide was characterized by comparing its boiling point or melting point and infrared spectrum with those of an authentic sample.[8] Glutarimide was purified by recrystallization from water.

Each reaction was performed two or more times, and the results were reproducible within a few per cent. In control experiments recoveries of known quantities of imides were 70% or greater by the methods of isolation used. To determine the effect of persulfate on imide, 0.05 mole of imide was treated under the above conditions. In each case the reaction formed water-soluble, intractable tars and yielded less imide than did control mixtures without persulfate. The product yields based on starting material are listed in Table I.

(4) W. Walter, M. Steffen, and K. Heyns, *Chem. Ber.*, **94**, 2462 (1961).

(5) C. H. Bamford and E. F. T. White, *J. Chem. Soc.*, 1860 (1959); 4490 (1960).

(6) K. Schwetlick, *Angew. Chem.*, **72**, 208 (1960).

(7) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

(8) Imides were prepared by the method of S. S. G. Sircar, *J. Chem. Soc.*, 600 (1927).

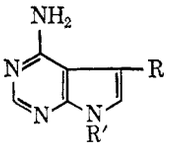
3-Cyano-4-aminopyrazolo[3,4-*d*]pyrimidine. An Azalog of the Aglycone of Toyocamycin[1]

EDWARD C. TAYLOR AND AHMAD ABUL-HUSN

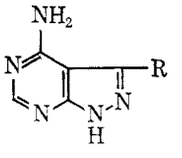
Department of Chemistry, Princeton University, Princeton, New Jersey

Received May 10, 1965

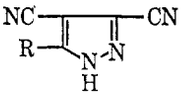
We recently described[2] the synthesis of 3-cyano-4-aminopyrrolo[2,3-*d*]pyrimidine (**1**) and 4-aminopyrrolo-[2,3-*d*]pyrimidine (**2**), the aglycones of the antibiotics Toyocamycin (**3**) and Tubercidin (**4**), starting from tetracyanoethylene as the aliphatic precursor. In view of the observation[3] that the unusual toxicity of **4** (and thus presumably of **3** also) is related to its action as a nucleic acid antagonist, the preparation of a Toyocamycin analog derived from 4-aminopyrazolo-[3,4-*d*]pyrimidine[4] appeared particularly worthwhile. We wish to describe in this Note the preparation of 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (**5**), the desired "azalog" of the aglycone **1**.



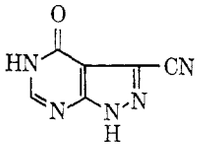
1, R = CN; R′ = H
2, R = R′ = H
3, R = CN; R′ = *d*-ribose
4, R = H; R′ = β-*d*-ribose



5, R = CN
6, R = COOH
7, R = H



8, R = NH_2
9, R = N=$CHOC_2H_5$
10, R = NHCHO



11

Condensation of tetracyanoethylene with semicarbazide hydrochloride, followed by hydrolysis, has been shown to give 5-aminopyrazole-3,4-dicarbonitrile (**8**) in good yield.[5] Since this intermediate contains the *o*-aminonitrile grouping requisite for conversion to a condensed 4-aminopyrimidine system,[6] it appeared to

(1) This work was supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **87**, 1995 (1965).

(3) G. Acs, E. Reich, and M. Mori, *Proc. Natl. Acad. Sci. U. S.*, **52**, 493 (1964).

(4) For a discussion of the biological activity of this purine antagonist, see E. Y. Sutcliffe, K. Y. Zee-Cheng, C. C. Cheng, and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 588 (1962).

(5) C. L. Dickinson, J. K. Williams, and B. C. McCusick, *J. Org. Chem.*, **29**, 1915 (1964).

(6) For a discussion and leading references, see ref. 2.

be an ideal intermediate for the preparation of **5**. Indeed, reaction of **8** with triethyl orthoformate gave 5-(ethoxymethylenamino)pyrazole-3,4-dicarbonitrile (**9**), which upon treatment with alcoholic ammonia was converted to the desired aglycone analog, 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (**5**). An attempt to purify **9** by crystallization led to rapid and complete hydrolysis to 5-formamidopyrazole-3,4-dicarbonitrile (**10**); in fact, **9** reverted slowly to **10** even upon standing in the presence of air.

The structure of **5** was confirmed by alkaline hydrolysis to the carboxylic acid **6**, which upon decarboxylation (effected by vacuum sublimation) gave 4-aminopyrazolo[3,4-*d*]pyrimidine (**7**), identical (ultraviolet and infrared) with an authentic sample. The ease of decarboxylation of **6** contrasts with the difficulty experienced in attempts to decarboxylate the corresponding acid in the naturally occurring pyrrolo[2,3-*d*]pyrimidine series.[2] Nitrous acid readily converted **5** to 3-cyano-4(5H)-pyrazolo[3,4-*d*]pyrimidinone (**11**).

Attempts to convert the aglycone **1** and its azalog **5** to their respective ribosides are in progress.

Experimental Section

3-Cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (5).—A mixture of 6.45 g. (0.05 mole) of 5-aminopyrazole-3,4-dicarbonitrile[5] and 70 ml. of triethyl orthoformate was heated under reflux for 7 hr., with precautions to protect the reaction mixture against atmospheric moisture. Excess triethyl orthoformate was removed by evaporation under reduced pressure and the residual, crude ethoxymethylenamino derivative **9** dissolved in 100 ml. of absolute ethanol and added to 50 ml. of ethanolic ammonia (saturated at 0°). After 24 hr. at room temperature, the solid which had separated was collected by filtration; a second crop of product was obtained by concentration of the filtrate; the total yield was 6.40 g. (83%). The analytical sample was prepared by crystallization from water. The product slowly decomposed upon heating above 200°. It showed bands at $\lambda_{max}^{C_2H_5OH}$ 233 and 282 mμ (ε 9630 and 10,010).

Anal. Calcd. for $C_6H_4N_6$: C, 45.04; H, 2.52; N, 52.53. Found: C, 44.86; H, 2.44; N, 52.44.

5-Formamidopyrazole-3,4-dicarbonitrile (10).—Crude 5-(ethoxymethylenamino)pyrazole-3,4-dicarbonitrile (**9**), prepared by evaporation of the triethyl orthoformate reaction mixture as described above, was recrystallized from pyridine–petroleum ether (30–60°), with no special precautions to use scrupulously dry solvents. The product so obtained decomposed slowly upon heating above 200°; it exhibited a strong amide carbonyl band at 1700 cm.$^{-1}$ (infrared) and $\lambda_{max}^{C_2H_5OH}$ 216 and 245 mμ (ε 14,300 and 11,500).

Anal. Calcd. for $C_6H_3N_5O$: C, 44.76; H, 1.88; N, 43.52. Found: C, 44.73; H, 1.88; N, 43.46.

Conversion of 3-Cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (5) to 4-Aminopyrazolo[3,4-*d*]pyrimidine (7).—A mixture of 2.0 g. of 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine and 50 ml. of 10% aqueous sodium hydroxide was heated under reflux for 24 hr., cooled and acidified with 9% aqueous hydrochloric acid. Filtration gave 1.60 g. (72%) of a product whose infrared spectrum indicated the presence of bands characteristic of a carboxylic acid and the loss of the nitrile band (2235 cm.$^{-1}$) characteristic of the starting material. Vacuum sublimation of this crude carboxylic acid resulted in smooth decarboxylation to give 4-aminopyrazolo[3,4-*d*]pyrimidine, identical in every respect (ultraviolet and infrared) with an authentic sample.[7]

3-Cyano-4(5H)-pyrazolo[3,4-*d*]pyrimidinone (11).—A suspension of 1.25 g. of 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine in 40 ml. of 8% aqueous hydrochloric acid was stirred at 0° while a solution of 5 g. of sodium nitrite in 10 ml. of water was added slowly over the course of 1 hr. An additional 1 g. of sodium nitrite was then added and the reaction mixture was brought to boiling. Cooling resulted in the separation of 0.75 g. (60%) of a white, crystalline solid which was recrystallized from water: m.p. 348° dec.; $\lambda_{max}^{C_2H_5OH}$ 225, 232, and 261 mμ (ε 9660, 12,268, and 14,000).

Anal. Calcd. for $C_6H_3N_5O$: C, 44.76; H, 1.88; N, 43.52. Found: C, 44.56; H, 1.92; N, 43.42.

(7) We are indebted to Dr. Harry B. Wood, Jr., Cancer Chemotherapy National Service Center, National Institutes of Health, for supplying us with this material.

Indolothiopyrylium Compounds. II. 1,2,3,4-Tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]-thiopyran and -thiopyrylium Salts[1,2]

THOMAS E. YOUNG AND PETER H. SCOTT[3]

William H. Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania

Received August 17, 1965

In a recent article[2] we described the preparation of benz[*b*]indolo[2,3-*d*]thiopyrylium perchlorate, as well as a number of substituted derivatives, and presented n.m.r. spectral data which favored the electronic distribution of the thiopyrylium formulation of this new aromatic ring system. We now wish to report the synthesis of 1,2,3,4-tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyrylium perchlorate (**6a**) and the corresponding chloride **6b** (see Scheme I), which, except for the location of the positive charge, are analogous to and essentially iso-π-electronic with salts of the indole alkaloid sempervirine.[4] The free base, 1,2,3,4-tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyran (**7**), is also of interest as a new pseudoazulene,[5] formally derived from cyclopenta[*c*]thiopyran (**8**)[6,7] by aza replacement of the 5-methine group and fusion of additional carbocyclic rings at the c and g (3,4 and 6,7) bonds.

The 6,7,8,9-tetrahydrobenzo[*g*]thiochroman-4-one (**2**) required as starting material was prepared by ring closure of 3-(tetralyl-*ar*-2-thio)propionic acid (**1**) with concentrated sulfuric acid, and separated from the isomeric ketone **3** *via* fractional crystallization and subsequent hydrolysis of the semicarbazones as already described.[8] The structure of ketone **2**, although assigned but not unambiguously established by the original authors,[8] was corroborated by its n.m.r. spectrum (in deuteriochloroform), which, in addition to a series of three multiplets centered at[9] δ 3.04, 2.71, and 1.75, representing the 12 aliphatic protons, exhibited two singlets (integration for one proton each) at δ 7.80 and 6.94, corresponding to the two aromatic protons. The δ value of the low-field singlet

(1) Abstracted from the Ph.D. Dissertation of P. H. Scott, Lehigh University, 1965.

(2) Part I: T. E. Young and P. H. Scott, *J. Org. Chem.*, **30**, 3613 (1965).

(3) Warner-Lambert Research Fellow, 1963–1965.

(4) R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949); R. B. Woodward and B. Witkop, *ibid.*, **71**, 379 (1949).

(5) R. Mayer, *Angew. Chem.*, **69**, 481 (1957); *Naturwiss.*, **13**, 312 (1958).

(6) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Am. Chem. Soc.*, **85**, 3448 (1963); A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson, and A. G. Osborne, *ibid.*, **81**, 1255 (1959).

(7) A. G. Anderson, Jr., and W. F. Harrison, *ibid.*, **86**, 708 (1964); *Tetrahedron Letters*, **No. 2**, 11 (1960).

(8) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1819 (1923).

(9) Values of δ in parts per million are taken as positive downfield from tetramethylsilane used as internal standard.