At 3–5 weeks of age, the chicks were transferred to individual cages with hardware cloth floors where the efficacy experiments were conducted.

The *Eimeria tenella* cultures used in these experiments were serially propagated in our laboratory over a period of several years. These cultures were isolated by single oocyst inoculation of coccidiosis-free birds to ensure the purity of the cultures. Infection was accomplished by depositing a predetermined volume of calibrated oocyst suspension directly into the crop of each chick.

The compounds tested in these trials were incorporated into a standard ration and fed to the birds for 2 days prior to infection, and continued for the duration of the test.

The anticoccidial efficacy in these experiments was based on three factors: (1) mortality, (2) weight gain or loss, and (3) droppings scores. The primary criterion of efficacy was the mortality produced in the medicated–infected chicks as compared to the nonmedicated–infected chicks. Droppings scores and ratios of mean weight gains, medicated–infected *vs.* nonmedicated–noninfected, were used as indicators of morbidity.[3]

Acknowledgment.—The authors wish to thank Professor Joseph Cannon of the University of Iowa for helpful discussions of this work. They are also indebted to Mrs. Carol Barker and Mr. Marvin Carr for obtaining the analytical data and assisting with the experiments.

Chemotherapeutic Nitroheterocycles. Derivatives of 5-Nitrothiazole-2-carboxaldehyde and 5-Nitrothiazole-2-carboxylic Acid[1]

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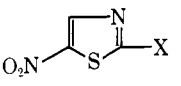
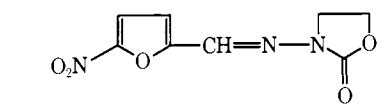
Received July 29, 1968
Revised Manuscript Received October 14, 1968

A series of new 5-nitrothiazoles bearing carbon substituents in the 2 position has been prepared. Treatment of 2-bromo-5-nitrothiazole with CuCN provided 5-nitrothiazole-2-carbonitrile, a key intermediate for subsequent conversion to other derivatives of 5-nitrothiazole-2-carboxylic acid. The corresponding aldehyde was obtained by condensing 2-methyl-5-nitrothiazole with benzaldehyde and oxidatively cleaving the resulting styryl intermediate. The compounds prepared in this study were evaluated *in vivo* for antimalarial and antischistosomal activity and *in vitro* for activity against bacteria, yeast, and a fungus. Little activity was noted in the malaria and schistosomiasis tests, but broad-spectrum inhibitory effects were widely evident in the *in vitro* assays. The most potent compound, 5-nitrothiazole-2-carboxaldehyde acethydrazone, was inhibitory at 1 μg/ml or less in all but one of the latter tests.

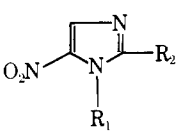
Among the several classes of nitroheterocyclic drugs possessing useful properties in clinical or veterinary medicine,[2] the 5-nitrothiazoles are of special recent interest. In addition to the well-established use of 2-amino-5-nitrothiazole, and simple derivatives thereof (**1a–c**), for the treatment of histomoniasis in turkeys,[3] another closely related nitrothiazole, niridazole (**1d**), has been found highly effective in human schistosomiasis[4–6] and amebiasis.[4,5,7] Favorable preliminary results against two other parasitic diseases, dracunculosis[8–10] and strongyloidiasis,[8,11] have also been reported for this drug. In a recent paper in which Avramoff, *et al.*,[12] revealed a group of bis-5-nitrothiazoles with marked *in vitro* antiprotozoal activity,



1a, X = NH_2
b, X = $NHCOCH_3$
c, X = NHCONHEt
d, X =



2



3a. $R_1 = CH_2CH_2OH$; $R_2 = CH_3$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = p\text{-}C_6H_4F$

they provided a brief survey of current developments in the nitrothiazole field.

A characteristic feature of essentially all reported chemotherapeutic nitrothiazoles is the presence of a free or substituted amino group in the 2 position. In contrast, the antiprotozoal nitrofurans[13,14] (*e.g.*, furazol-

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution Number 420 from the Army Research Program on Malaria.

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(7) (a) S. J. Powell, A. J. Wilmot, I. MacLeod, and R. Elsdon-Dew, *Am. J. Trop. Med. Hyg.*, **15**, 300 (1966); (b) T. Kradolfer and R. Jarumilinta, *Ann. Trop. Med. Parasitol.*, **59**, 210 (1965).

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(9) G. Raffier, *Acta Trop.*, **22**, 350 (1965).

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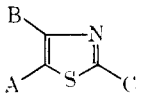
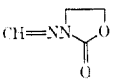
(14) K. Miura and K. Reckendrof, *Progr. Med. Chem.*, **5**, 320 (1967).

TABLE I

NITROTHIAZOLES



No.	A	B	C
4	NO_2	H	CN
5	NO_2	H	C(=NH)OEt
6	NO_2	H	$COOEt_6$
7	NO_2	H	
8	NO_2	H	CHO
9[a]	NO_2	H	CH_3
10	NO_2	COOEt	CH_3
11[b]	NO_2	CH_3	CH_3
12	NO_2	CH_3	$CH{=}CHC_6H_4Cl$-*p*
13	NO_2	$CH{=}CHC_6H_4Cl$-*p*	$CH{=}CHC_6H_4Cl$-*p*
14[c]	NO_2	CH_3	H
15	NO_2	H	$CH{=}CHC_6H_5$
16[d]	H	NO_2	CH_3
17[d]	NO_2	H	H
18	NO_2	H	$CH{=}NNHCONH_2$
19	NO_2	H	CH=NOH
20	NO_2	H	$CH{=}NNHCOCH_3$
21	NO_2	H	

[a] Reference 23. [b] Reference 25. [c] Reference 22. [d] C. Klein, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 1412 (1955).

idone, **2**), the 5-nitro-2-furyl nuclei of which are isosteric with the 5-nitro-2-thiazole nucleus, all bear carbon substituents in the 2 position, usually at the aldehyde or carboxyl oxidation level. The 5-nitroimidazoles (*e.g.*, **3**), which have also achieved prominence recently as antiprotozoal drugs[15-17] and are similarly isosteric with the 5-nitrothiazoles, are also characterized by a carbon substituent in the 2 position. As part of a program to devise novel antimalarial agents, it therefore seemed worthwhile to prepare 5-nitrothiazoles bearing carbon substituents in the 2 position. In effect, this would combine the carbon side-chain types from the well-established antiprotozoal furan and imidazole series with the nitrothiazole nucleus, also known to possess antiparasitic properties. Some support for this concept was provided by the report of Samuels and Stouder[18] that 2-methyl-4-nitrothiazole had some *in vitro* activity against *Trichomonas vaginalis*. Also, a low level of antimalarial activity in one of a series of nitrofurans was reported by Wiselogle.[19]

Chemistry.—The new compounds prepared in this study are listed in Table I, along with a few that were known previously. Preparative procedures are described in the Experimental Section and only a few general points need be discussed.

Derivatives of 5-nitrothiazole-2-carboxylic acid (**4**–**7**) were all quite sensitive to alkaline reagents. For example, black resinous products were formed immediately upon treating **6** with NH_3 or **4** with lithium aluminum tri-*t*-butoxyhydride.[20]

The synthesis of 5-nitrothiazole-2-carboxaldehyde (**8**) required 2-methyl-5-nitrothiazole (**9**) as precursor. At the time this study was undertaken this compound was unknown, although 2-methyl-4-nitrothiazole had twice been erroneously assigned the 5-nitro structure.[21,22] After this work was completed, Asato[23] described a nitration procedure for preparing **9** from 2-methylthiazole that was virtually identical with that developed for the present work. Asato established the structure of **9** by converting it to a derivative of **1a**. In the present work, conversion of ethyl 2-methylthiazole-4-carboxylate[24] to **9** *via* **10** served the same purpose.

During the exploratory phase of this work, 2,4-dimethyl-5-nitrothiazole[25] (**11**) was used in place of **9** as a model in condensation experiments. Condensation of **11** with *p*-chlorobenzaldehyde was found to favor reaction on the 2-methyl group (to give **12**) rather than the 4-methyl, although bis condensation to give **13** was predominant in all experiments. The structure of **12** was established by oxidation and decarboxylation to give **14**.[22] This result contrasts with that of Herrling and Mueckter[26] who assigned 4-styryl structures to monocondensation products obtained in a similar manner.

Biological Activity.—When tested against lethal *Plasmodium berghei* infections in mice,[27] compounds **4**, **5**, **7**, **9**, **11**, **13**, **16**, and **19**–**21** were without positive effect. Compounds **15** and **18** were marginally protective, prolonging survival times of treated mice by about 2 days at 640 mg/kg. As demonstrated in the malaria assay,[27] significant toxicity was present in the group; compounds **5**, **11**, **16**, **19**, and **21** caused toxicity deaths at 640 mg/kg. Compound **4** was lethal at doses of 40 mg/kg and above.

Five of the compounds (**5**, **11**, **18**, **20**, and **21**) were tested for antischistosomal activity in a mouse *Schistosoma mansoni* mortality assay,[28] but they did not prolong the survival time of treated mice at nontoxic doses.

In vitro assays against a series of four bacteria, two yeasts, and a fungus[29] indicated that distinct, broad-

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(16) (a) R. Atkinson, J. W. Bradley, J. R. Couch, and J. H. Quisenberry *Poultry Sci.*, **46**, 1003 (1967), and references cited therein; (b) J. H. Whitmore, T. W. Sullivan, and O. D. Grace, *ibid.*, **47**, 428 (1968).

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(19) F. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946, p 83.

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(22) K. Ganapathi and K. Kulkarni, *Proc. Indian Acad. Sci.*, **37A**, 758 (1953).

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(24) E. R. H. Jones, F. A. Robinson, and M. N. Strachan, *J. Chem. Soc.*, 87 (1946).

(25) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945); *Chem. Abstr.*, **40**, 4056 (1946).

(26) S. Herrling and H. Mueckter, German Patent 1,159,450 (1963).

(27) These tests were performed by Dr. Leo Rane of the University of Miami, Miami, Fla. The data were provided through the courtesy of Dr. David Jacobus of the Walter Reed Army Institute for Research. For a description of the test, see T. S. Osdene, P. B. Russell, and Leo Rane, *J. Med. Chem.*, **10**, 431 (1967).

(28) Col. William E. Rothe of the Walter Reed Army Institute of Research kindly provided test results and a description of the test procedure. Lt. Col. Myron G. Radke (406 Medical Laboratory, APO, San Francisco, Calif. 96343) directed the schistosomiasis assay work. For a description of the assay, see W. G. Downs and D. W. Henry, *J. Med. Chem.*, **12**, 25 (1969).

(29) A serial, twofold, tube-dilution procedure was employed. Reference 2 provides a description of the assay.

spectrum, growth-inhibitory properties are present in the type of nitrothiazole examined in this study. All of the compounds except **11**, **13**, and **15** blocked the growth of all test organisms in the 100–1000-μg/ml range and several (**19–21**) were uniformly active in the 0.1–10-μg/ml range. Furazolidone analog **21** was 0.1–0.01 times as active as the nitrofuran parent. Acethydrazone **20**, the most potent nitrothiazole in this test, was only slightly less active than furazolidone.

Experimental Section[30]

5-Nitrothiazole-2-carbonitrile (4).—A stirred mixture of 30 g (0.335 mole) of CuCN in 150 ml of DMF at 140° was treated with 30.0 g (0.144 mole) of 2-bromo-5-nitrothiazole.[21] After 1 or 2 min, the temperature of the mixture rose spontaneously to 154° without external heating and was then maintained at 150° by heating. Exactly 10 min after the bromo compound had been added, the mixture was cooled under the tap and poured slowly into 800 ml of vigorously stirred Et_2O. The yellow supernatant was decanted from the dark viscous oil that precipitated. The Et_2O phase was extracted four times with H_2O and dried (Na_2SO_4). Evaporation *in vacuo* left 13.3 g (59%) of an orange, readily crystalline product suitable for further reactions. A 3.1-g sample was recrystallized from aqueous MeOH to give 1.2 g of yellow crystals, mp 48.5–49.5°. *Anal.* ($C_4HN_3O_2S$) C, H, N.

Ethyl 5-Nitrothiazole-2-carboximidate (5).—A slightly warm, filtered, stirred solution of 6.0 g (39 mmoles) of crude **4** in 25 ml of absolute EtOH was placed in an ice bath and was treated quickly with a solution of 8 mmoles of NaOEt in 4 ml of absolute EtOH. The mixture, which instantly turned very dark, was seeded immediately and stirred for 3–4 min longer. Dilution with 50 ml of H_2O gave a dark, crystalline suspension of product (4.5 g). Recrystallization (charcoal) from 75 ml of 90% EtOH (diluted while warm with 150 ml of H_2O) gave 3.4 g (44%) of tan material, mp 87–88°. *Anal.* ($C_6H_7N_3O_3S$) C, H, N.

Ethyl 5-Nitrothiazole-2-carboxylate (6).—Hydrolysis of 189 mg (0.94 mmole) of **5** in dilute HCl (immediate reaction at 25°) provided 182 mg of crude product, mp 38–43°, analytical sample mp 48–49° (hexane). *Anal.* ($C_6H_6N_2O_4S$) C, H, N.

2-(5-Nitro-2-thiazolyl)-2-thiazoline (7).—A solution of 0.69 g (3.4 mmoles) of **5** and 0.39 g (3.4 mmoles) of 2-mercaptoethylamine hydrochloride in 6 ml of absolute EtOH was refluxed for 12 hr. The dark crystalline mass that formed was crushed *in situ*, and *ca.* 10–15 ml of H_2O was added. After cooling in ice, the dark brown, crude product (0.56 g) was filtered off and washed (H_2O). The crude material was extracted three times at 90–100° with a total of 50 ml of heptane. The combined extracts were concentrated on the steam bath under a stream of N_2 until the product began to precipitate. Chilling netted 266 mg (36%) of reddish, flaky crystals, mp 142–144.5°, analytical sample mp 145–146.5° (EtOH). *Anal.* ($C_6H_5N_3O_2S_2$) C, H, N.

2-Methyl-5-nitrothiazole (9) and 2-methyl-4-nitrothiazole (16) were prepared from 2-methylthiazole[31] by the method of Asato.[23]

2-(β-Styryl)-5-nitrothiazole (15).—A mixture of 28.8 g (0.20 mole) of **9**, 80 ml of benzaldehyde (*ca.* 0.8 mole), 20 ml of piperidine acetate catalyst solution, and 50 ml of absolute EtOH was heated at 70–80° for 10 hr. [The catalyst solution was prepared by mixing 5.7 ml (6.0 g, 0.10 mole) of AcOH and 9.9 ml (8.5 g, 0.10 mole) of piperidine in 50 ml of absolute EtOH.] A few crystals of previously obtained product were added at the beginning of the reaction. Cooling in ice caused precipitation of the dark brown, crystalline product. Purification was effected by washing thoroughly with EtOH and sublimation at 155–160° (0.1 mm); yield of yellow-orange crystals, 23.4 g (50%); mp 163–166°; analytical sample mp 164–166° (EtOH). *Anal.* ($C_{11}H_8N_2O_2S$) C, H, N.

5-Nitrothiazole-2-carboxaldehyde (8).—A mixture of 22.0 g (0.095 mole) of powdered **15**, 42.8 g (0.20 mole) of $NaIO_4$, 300 ml of ethylene glycol dimethyl ether (glyme), 100 ml of H_2O, and 1.0 g of OsO_4 (added last) was stirred mechanically for 12 hr at room temperature.[32] The reaction mixture was poured into *ca.* 1 l. of H_2O and extracted with $CHCl_3$ (three times). After drying ($NaSO_4$) solvents were largely removed *in vacuo* and the very dark residue was filtered through glass wool. The collected solids were washed with a little $CHCl_3$ and the combined filtrate and washings were distilled. Benzaldehyde was collected at 25–35° (1–3 mm), followed by the desired product (4.4 g, 29%) at 80–90° (1.0 mm). It crystallized upon cooling below room temperature and melted at about 20°. This compound, although nearly colorless, causes persistent dark brown to black stains on the skin.

A pure sample of the aldehyde was collected by glpc (conditions, 91.4 × 9.65 cm column packed with 7% SE 30 on Gas-pak F, 60–80 mesh, 147°, 100 ml of He/min); retention time 2.7 min. *Anal.* ($C_4H_2N_2O_3S$) C, H, N.

Derivatives of 5-nitrothiazole-2-carboxaldehyde formed rapidly in aqueous EtOH from equimolar amounts of reagents in the presence of a few drops of 3 *N* HCl. They precipitated spontaneously except for the oxime which required dilution with H_2O: **semicarbazone (18)**, mp 260–270° dec, 93%, yellow crystals (*Anal.* ($C_5H_5N_5O_3S$) C, H, N); **oxime (19)**, mp 153–163° dec, 83%, off-white crystals (*Anal.* ($C_4H_3N_3O_3S$) C, H, N); **acethydrazone (20)**, mp 238–244° dec, 67%, yellow crystals (*Anal.* ($C_6H_6N_4O_3S$) C, H, N); **3-(5-nitro-2-thiazolylmethylideneamino)-2-oxazolidinone (21)**, mp 220–225°, 89%, yellow crystals (*Anal.* ($C_7H_6N_4O_4S$) C, H, N).

Ethyl 2-Methyl-5-nitrothiazole-4-carboxylate (10).—Ethyl 2-methylthiazole-4-carboxylate[24] (1.0 g, 5.8 mmoles) was nitrated with N_2O_4–BF_3 in CH_3NO_2 by essentially the method used by Parent for 2-nitrothiazole.[33] Examination of the crude oily product (0.76 g, isolated by Et_2O extraction) by glpc showed it to consist of about 60% of **10**, 20% of starting material, and 20% of **9**; the latter compound was apparently formed from the product during work-up. Pure nitro ester was isolated by preparative glpc. It was an oil that crystallized upon chilling in the refrigerator. The ir spectrum was consistent with the assigned structure. *Anal.* ($C_7H_8N_2O_4S$) C, H, N.

2-Methyl-5-nitrothiazole (9) from Ethyl 2-Methyl-5-nitrothiazole-4-carboxylate (10).—A solution of 40 mg (0.18 mmole) of **10** in 0.5 ml of EtOH was heated overnight with 1 ml of 33% aqueous H_2SO_4. The mixture was diluted with 2.5 ml of H_2O and extracted with Et_2O. Removal of the Et_2O left 15 mg (56%) of crystalline product, mp 63–68°, whose ir spectrum was identical with that of **9**, lit.[23] mp 70–72°.

2,4-Di(*p*-chloro-β-styryl)-5-nitrothiazole (13).—A mixture of 2.0 g (12.7 mmoles) of 2,4-dimethyl-5-nitrothiazole,[25] 7.15 g of *p*-chlorobenzaldehyde (51 mmoles), 20 ml of absolute EtOH, and 1 ml of piperidine was heated at 75° for 1.5 hr. The product, which crystallized from the dark solution during the reaction, was filtered off and washed with EtOH and H_2O; crude weight 1.8 g. It was crystallized from Me_2CO to give 1.0 g of product melting at 221–227°, analytical specimen mp 225–227°. *Anal.* ($C_{19}H_{12}Cl_2N_2O_2S$) C, H, N.

2-(*p*-Chloro-β-styryl)-4-methyl-5-nitrothiazole (12).—A mixture of 0.40 g (2.5 mmoles) of 2,4-dimethyl-5-nitrothiazole,[25] 0.35 g (2.5 mmoles) of *p*-chlorobenzaldehyde, and 2 drops of piperidine was heated at 140° for 2 hr. The dark reaction mixture was cooled and triturated with 3.5 ml of absolute EtOH. The resulting crystalline suspension was chilled and filtered, and the crude product (416 mg) was washed with EtOH. Tlc (silica gel, Et_2O) showed that the bis condensation product (R_f 0.85) and the desired monocondensation product (R_f 0.75) were present in about equal quantities. Sublimation (150°, 0.1 mm) provided 196 mg (28%) of nearly pure **12** (by tlc). Recrystallized from Me_2CO and resublimed it melted at mp 170–172°. *Anal.* ($C_{12}H_9ClN_2O_2S$) C, H; N: calcd, 9.99; found, 10.45.

4-Methyl-5-nitrothiazole (14) from 2-(*p*-Chloro-β-styryl)-4-methyl-5-nitrothiazole (12).—A mixture of 0.28 g (1.0 mmole) of **12** in 10 ml of Me_2CO was stirred in an ice bath and treated over *ca.* 20 min with 0.42 g (2.67 mmoles) of $KMnO_4$. After

(30) Melting points were taken in a Mel-Temp apparatus and are corrected. Microanalyses were performed by Miss Betty McCarthy of the Stanford Research Institute Analytical Department. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(31) R. Handley, E. F. G. Herington, M. Azzaro, and J. Metzger, *Bull. Soc. Chim. France*, 1904 (1963).

(32) General procedure of R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(33) R. A. Parent, *ibid.*, **27**, 2282 (1962).

stirring 1 hr longer, 10–20 ml of H_2O was added and the MnO_2 was removed by filtration. The filtrate was made acidic by addition of 2–3 ml of 3 *N* HCl, and the resulting suspension was heated at 100° for 0.5 hr, cooled, and filtered. Extraction of the filtrate with Et_2O provided 48 mg of oil. Glpc indicated this to be about 80% *p*-chlorobenzaldehyde and 20% 4-methyl-5-nitrothiazole. The latter component was isolated by glpc in crystalline form, mp 48–50.5°. Its ir spectrum was identical with that of authentic 4-methyl-5-nitrothiazole (mp 52–53.5°), prepared by nitration of 4-methylthiazole,[22] and quite different from that of 2-methyl-5-nitrothiazole.

Acknowledgment. The author is grateful to Miss Debra Tinker for assistance during the early phases of this work.

Branched-Chain Sugar Nucleosides. V. Synthesis and Antiviral Properties of Several Branched-Chain Sugar Nucleosides

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Received September 16, 1968

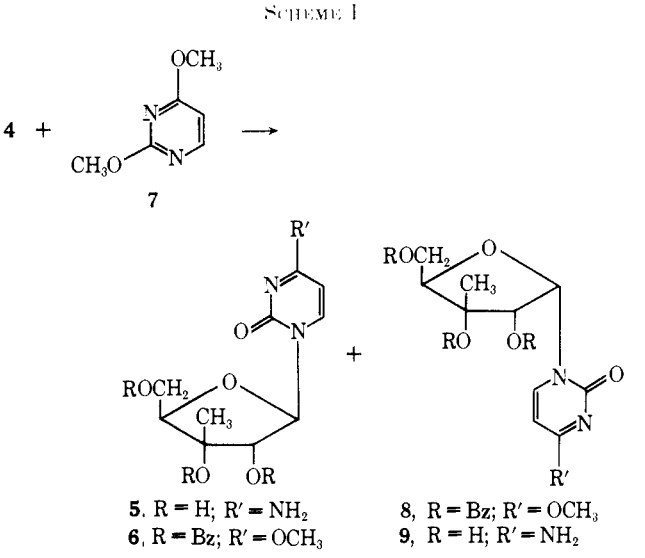
The synthesis of 3′-C-methylcytidine and its α-D anomer as well as 2′-C-methylcytidine, 2′-C-methyl-5-fluorocytidine, and 2′-C-methyl-5-fluorouridine *via* the Hilbert–Johnson reaction is described. In the synthesis of 2′-C-methylcytidine from N-acetylcytosinemercury a preponderance of the "O-glycoside" was formed. Biological testing indicates that 3′-C-methylcytidine as well as the previously synthesized 2′- and 3′-C-methyladenosines are effective antivaccinia agents in mice.

In earlier publications we described the synthesis of 2′-C-methyladenosine (**1**)[1a,b] and 3′-C-methyladenosine (**2**)[1c] from the novel branched-chain glycosyl halides 2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranosyl chloride (**3**) and 2,3,5-tri-O-benzoyl-3-C-methyl-α- (and β-) D-ribofuranosyl bromide (**4**), respectively. We have now used the halides **3** and **4** in the synthesis of several related pyrimidine 2′- and 3′-C-methyl nucleosides. This paper describes the syntheses of these compounds. The effective antiviral activity shown by 2′-C-methyladenosine (**1**), 3′-C-methyladenosine (**2**), and 3′-C-methylcytidine (**5**), as evidenced by the protection they afford mice infected with neurovaccinia, is also reported. These branched-chain sugar nucleosides are representatives of a new class of synthetic antiviral agents.

For the synthesis of 3′-C-methylcytidine (**5**), 2,3,5-tri-O-benzoyl-3-C-methyl-D-ribofuranosyl bromide (**4**) was converted to 1-(2,3,5-tri-O-benzoyl-3-C-methyl-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**6**) by a Hilbert–Johnson[2] reaction with 2,4-dimethoxypyrimidine (**7**) (Scheme I). In addition to **6**, the α-D anomer **8** was isolated from the reaction mixture in a yield about one-tenth that of the β-D anomer **6**. Reaction of the pyrimidinones **6** and **8** with methanolic ammonia produced 3′-C-methylcytidine **5** and its α-D anomer **9**, respectively.

In contrast, the Hilbert–Johnson reaction between 2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranosyl chloride (**3**) and 2,4-dimethoxypyrimidine (**7**) was very sluggish (Scheme II). Chromatography of the reaction products yielded the desired 1-(2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranosyl-4-methoxy-2(1H)-pyrimidinone (**10**), but failed to indicate that any of the α-D anomer of **10** had been produced.[3] When **10** was heated in methanolic NH_3, 2′-C-methylcytidine (**14**) was obtained.

SCHEME I



5, R = H; R′ = NH_2
6, R = Bz; R′ = OCH_3
8, R = Bz; R′ = OCH_3
9, R = H; R′ = NH_2

In a similar manner, reaction of the glycosyl chloride **3** with 2,4-dimethoxy-5-fluoropyrimidine (**15**)[4] produced 1-(2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranosyl)-5-fluoro-4-methoxy-2(1H)-pyrimidinone (**16**), which

(1) (a) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Amer. Chem. Soc.*, **88**, 4524 (1966); (b) S. R. Jenkins, B. Arison, and E. Walton, *J. Org. Chem.*, **33**, 1798 (1968); (c) R. F. Nutt, M. J. Dickinson, F. W. Holly, and E. Walton, *ibid.*, **33**, 2490 (1968).

(2) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930).

(3) T. J. Bardos, M. P. Kotick, and C. Czaniny, *Tetrahedron Lett.*, 1759 (1966), have shown that in reactions of silated pyrimidines with D-glycosyl halides, high temperatures favor the β-D configuration, whereas at low temperatures the α-D product predominates. The isolation of only β-D products in the reaction of **3** with alkoxypyrimidines may be a result of the high reaction temperatures required.

(4) M. Prystas and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 1900 (1965).