Table II—Elemental Analysis Data for III–XXIII

Compound	Formula	Calc./Found, % C	H	N
III	$C_{19}H_{18}N_4 \cdot HCl$	67.34/66.94	5.65/5.56	16.54/16.48
IV	$C_{19}H_{18}N_4O \cdot HCl$	64.31/64.12	5.40/5.23	15.79/15.80
V	$C_{29}H_{38}N_4 \cdot HCl \cdot 0.25\ H_2O$	72.02/72.05	8.23/8.32	11.59/11.70
VI	$C_{25}H_{18}N_4 \cdot 0.5\ H_2O$	78.30/78.53	4.99/4.71	14.61/14.73
VII	$C_{19}H_{17}N_5O \cdot HCl$	62.04/61.66	4.93/4.69	19.04/19.06
VIII	$C_{17}H_{15}N_5 \cdot HCl \cdot 0.5\ H_2O$	60.98/60.99	5.12/5.04	20.92/20.99
IX	$C_{20}H_{19}N_5O \cdot HCl \cdot 1.5\ H_2O$	58.75/58.97	5.67/5.32	17.13/17.33
X	$C_{18}H_{17}N_5 \cdot 2\ HCl \cdot H_2O$	54.83/55.17	5.37/5.25	17.76/17.71
XI	$C_{20}H_{21}N_5O \cdot HCl \cdot 0.5\ H_2O$	61.13/61.48	5.90/5.92	17.83/17.81
XII	$C_{21}H_{21}N_5 \cdot HCl$	66.39/65.99	5.84/5.85	18.44/18.17
XIII	$C_{21}H_{21}N_5O \cdot HCl$	63.71/63.59	5.60/5.70	17.69/17.43
XIV	$C_{21}H_{20}ClN_5O \cdot HCl \cdot 3\ H_2O$	52.07/52.19	5.62/5.39	14.46/14.42
XV	$C_{17}H_{13}ClN_4 \cdot HCl \cdot 1.25\ H_2O$	55.67/55.83	4.26/4.31	15.28/15.20
XVI	$C_{17}H_{13}ClN_4 \cdot HCl$	59.14/59.32	4.09/4.08	16.23/16.04
XVII	$C_{17}H_{13}FN_4 \cdot HCl$	62.10/62.50	4.29/4.32	17.04/17.15
XVIII	$C_{17}H_{14}N_4O \cdot HCl \cdot 0.5\ H_2O$	60.81/60.55	4.80/5.11	16.69/16.71
XIX	$C_{17}H_{14}N_4O \cdot HCl$	62.48/62.18	4.63/4.65	17.15/16.87
XX	$C_{17}H_{13}ClN_4O \cdot HCl$	56.52/56.25	3.91/3.91	15.51/15.29
XXI	$C_{20}H_{18}N_4O_2 \cdot HCl \cdot 0.5\ H_2O$	61.30/61.26	5.14/5.02	14.64/14.26
XXII	$C_{24}H_{18}N_4O \cdot HCl$	69.48/69.08	4.62/4.68	13.51/13.58
XXIII	$C_{20}H_{18}N_4O_2 \cdot HCl$	62.74/62.56	5.00/4.88	14.64/14.75

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New Compounds: Synthesis of D-Arabinofuranosylurea Derivatives

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Abstract □ Procedures are described for the preparation of a series of D-arabinofuranosylurea derivatives.

Keyphrases □ D-Arabinofuranosylurea derivatives—synthesis described □ Ureas, D-arabinofuranosyl—synthesis described

The structural resemblance of D-arabinofuranosylurea derivatives to nucleosides possessing cytotoxic activity such as cytarabine (1) suggested the synthesis of a series of these urea derivatives.

Oxidation of the pyrimidine base in 2′,3′,5′-tri-(*O*-acetyl)uridine or its N^3-methyl derivative (2) with permanganate, ozone, or osmium tetroxide gave, apart from unchanged starting material, urea or methylurea and poor yields of compounds whose structures were not established unambiguously.

Ureidoglycosides have been formed by an acid-catalyzed reaction between monosaccharides and urea (3). Normally, this reaction would result in the formation of ureidopyranosides. For the preparation of ureidofuranosides, protected furanose derivatives are required so that pyranosides are not formed under acidic reaction conditions. 2′,3′,5′-Tri-(*O*-benzyl)-D-arabinofuranose and a variety of ureas (Table I) were used. This particular derivative offered the advantage that the benzyl groups could be removed by catalytic hydrogenolysis (4) to give the required D-arabinofuranosylureas. The urea derivatives were obtained by heating the benzylated sugar, appropriate urea, and acetone (or acetone–water) with sulfuric acid or perchloric acid as a catalyst (5).

EXPERIMENTAL

Chemical-ionization mass spectra[1], with isobutane as the reagent gas, and NMR spectra were obtained[2]. Chemical shift data were measured relative to tetramethylsilane as an internal standard and are given in parts per million. Evaporations were conducted under diminished pressure at a bath temperature below 50°. Column chromatography was carried out on silica gel (60–200 mesh).

N^3-Methyl -2′,3′,5′-tri- (*O*-acetyl)uridine—2′,3′,5′-Tri-(*O*-ace-

[1] DuPont 21-490F mass spectrograph.

[2] Varian T-60 instrument.

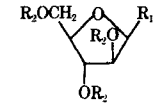

Table I—Urea Derivatives of β-D-Arabinofuranoside

Compound	R_1	R_2	Melting Point	Yield, %	Molecular Formula	Analysis, %		Molecular Weight[a]		NMR Data[b]		
						Calc.	Found	Calc.	Found	N—CH_3	N′—CH_3	NH_2
I (Procedure A)	$NHCONH_2$	$C_6H_5CH_2$	95–98°	12	$C_{27}H_{30}N_2O_5$	C 70.13 H 6.54 N 6.06	70.28 6.47 6.20	462	—	—	—	5.3 (br s)
I (Procedure B)	$NHCONH_2$	$C_6H_5CH_2$	Oil	25	$C_{27}H_{30}N_2O_5$							
I (Procedure C)	$NHCONH_2$	$C_6H_5CH_2$	95–98°	19	$C_{27}H_{30}N_2O_5$							
I (Procedure D)	$NHCONH_2$	$C_6H_5CH_2$	Oil	21	$C_{27}H_{30}N_2O_5$							
II	$NHCONHCH_3$	$C_6H_5CH_2$	83–85°	50	$C_{28}H_{32}N_2O_5$	C 70.59 H 6.72 N 5.88	70.62 6.68 5.90	476	—	—	2.6 (d)	—
III	$NCONHCH_3$ (N-CH_3)	$C_6H_5CH_2$	Oil	36	$C_{29}H_{34}N_2O_5$	C 71.02 H 6.93 N —	70.37 6.97 —	490	491 (M + 1)	2.8 (m)	2.8 (m)	—
IV	$NHCONHCONH_2$	$C_6H_5CH_2$	142–146°	14	$C_{28}H_{31}N_3O_6$	C 66.53 H 6.14 N 8.32	66.14 6.15 8.38	505	—	—	—	5.8 (br s)
V	$NHCSNH_2$	$C_6H_5CH_2$	200°[c]	51	$C_{27}H_{30}N_2O_4S$	C 67.78 H 6.33 N 5.86	67.90 6.28 5.61	478	—	—	—	5.4 (s)
VI	$NHCSNHCH_3$	$C_6H_5CH_2$	Oil	54	$C_{28}H_{32}N_2O_4S$	C 68.29 H 6.50 N 5.69	68.21 6.52 5.74	492	493 (M + 1)	—	3.0 (d)	—
VII	$NCSNHCH_3$ (N-CH_3)	$C_6H_5CH_2$	Oil	11	$C_{29}H_{34}N_2O_4S$	C 72.80 H 7.11 N —	72.21 7.19 —	506	—	2.4 (d) or 2.7 (d)	2.7 (d) or 2.4 (d)	—
VIII	$NHCONHCH_3$	H	150°	26	$C_7H_{14}N_2O_5$	C 40.78 H 6.80 N —	40.83 6.81 —	206	—	—	2.8 (d)	—
IX	$NCONHCH_3$ (N-CH_3)	H	Oil	96	$C_8H_{16}N_2O_5$	C 43.64 H 7.27 N 12.73	43.59 7.29 12.71	220	—	3.39 (s)	2.8 (s)	—

[a] By mass spectrometer. [b] Compounds VIII and IX in deuterium oxide; all others in deuterochloroform. [c] Compounds charred at the indicated temperature.

tyl)uridine (3.0 g) was dissolved in hot ethylene dichloride (10 ml). To the cooled solution was added a solution of diazomethane in ether (100 ml) prepared from nitrosomethylurea (10 g). The solution was allowed to stand at room temperature until no further nitrogen was evolved, and then the solution was evaporated to an oil (3.0 g). The oil was applied to a silica gel column with methanol–benzene (1:10) to give the title compound.

Anal.—Calc. for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.46. Found: C, 49.72; H, 5.31.

2′,3′,5′-Tri-(*O*-benzyl)-β-D-arabinofuranosylurea (I)—*Procedure A*—Urea (1.0 g, 0.017 mole), 2′,3′,5′-tri-(*O*-benzyl)-β-D-arabinofuranose (1.0 g, 0.0025 mole), acetone (30 ml), water (10 ml), and concentrated sulfuric acid (0.34 g, 0.9% w/w) were heated for 48 hr at 70° under reflux with stirring. The solution was cooled and neutralized with lead carbonate. The suspension was filtered, and the filtrate was evaporated. The residue was extracted with chloroform and water, and the chloroform extracts were evaporated to yield a syrup (1.2 g). Chromatography of the syrup on silica gel with benzene–ethyl acetate (7:3) yielded I as a syrup, which was crystallized from ether (0.13 g).

Procedure B—The steps were as described under *Procedure A*, except that no water was used in the reaction mixture. The yield of I was 0.28 g (oil).

Procedure C—The steps were as described under *Procedure A*, except that 0.9% (w/w) perchloric acid was used as a catalyst instead of sulfuric acid. The yield of I was 0.21 g (crystals from ether).

Procedure D—The steps were as described under *Procedure C*, except that no water was used in the reaction mixture. The yield of I was 0.15 g (oil). This procedure was used for the preparation of II–VII. The products from Procedures A–D showed identical NMR spectra.

***N*-β-D-Arabinofuranosyl-*N*′-methylurea (VIII)**—To a solution of II (1.94 g) in methanol (500 ml) was added 5% palladium-on-charcoal (100 mg). The reaction mixture was hydrogenated at 320 psi for 120 hr and then filtered through diatomaceous earth[3], and the filtrate was evaporated to an oil. The oil was crystallized from methanol to give VIII (0.24 g), mp 150°. Compound IX was prepared by the same procedure.

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New Compounds: Total Synthesis of *dl*-3a,4,6a-*cis*-4-(4-Carboxybutyl)-hexahydropyrrolo[3,4-*d*]imidazol-2-one Hydrochloride (*dl*-Azabiotin Hydrochloride)

HENRY C. WORMSER and HANLEY N. ABRAMSON [x]

Abstract □ The total synthesis of *dl*-3a,4,6a-*cis*-4-(4-carboxybutyl)-hexahydropyrrolo[3,4-*d*]imidazol-2-one hydrochloride (*dl*-azabiotin hydrochloride) was accomplished in a seven-step sequence from 2-ethoxycarbonylazepin-7-one.

Keyphrases □ Pyrroloimidazolone, substituted—synthesized in seven-step sequence □ Azabiotin—synthesized in seven-step sequence □ Biotin analog—substituted pyrroloimidazolone synthesized in seven-step sequence

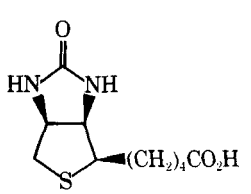
Biotin (I), a coenzyme, functions in several significant carbon dioxide fixation reactions in the cell. It is involved in carboxylation reactions catalyzed by propionyl coenzyme A carboxylase, acetyl coenzyme A carboxylase, pyruvate carboxylase, and β-methylcrotonyl coenzyme A carboxylase among others. Numerous aspects of the biochemical role of biotin were reviewed recently (1, 2).

BACKGROUND

Several analogs of biotin were synthesized, but few of these compounds substituted for biotin as a coenzyme. While biotin methyl ester and desthiobiotin show growth-promoting activity equivalent to that of biotin in many microorganisms, oxybiotin, biocytin, and biotin sulfoxide exhibit only limited activity. Many analogs possess substantial antibiotin activity.

The fact that carbobiotin (3) and oxybiotin have growth-promoting activity qualitatively, although not quantitatively, equivalent to that of biotin indicates that the sulfur atom of biotin is not essential for activity. The actual role of this sulfur atom has been a matter for debate. Glasel (4), on the basis of NMR data, postulated that the sulfur may act as a hydrogen acceptor in interactions with the protein component of biotin enzymes. This interpretation was challenged by Caplow (5), who pointed out that Glasel's observation could also be accounted for by assuming protonation of the ureide moiety.

However, Olah and White (6), employing conditions that hardly simulated biological media, presented unequivocal evidence that the sulfur is indeed protonated in magic acid (FSO_3H-SbF_5-SO_2). They suggested that the sulfur protonation occurs on the side *trans* to the carboxyl-



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