Biological Studies.—The bases were tested as their water-soluble hydrochlorides. These compounds were screened by the Pharmacology Department.[12] The majority of the compounds are weak vasodepressor agents; doses of 4 mg./kg., i.v. in anesthetized dogs caused only fleeting depressions of the blood pressure. No effects were observed on the blood pressure responses to epinephrine, acetylcholine, carotid occlusion or peripheral vagus stimulation. Two of the compounds, 7 and 15, showed anti-serotonin activity in that they blocked the pressor effect of serotonin in dogs at the dose level of 4 mg./kg. None of the compounds inhibited the bronchoconstriction in cats induced by serotonin. None had significant ganglionic or neuromuscular blocking activity in cats.

NUTLEY, N. J.

(12) We are indebted to Dr. Lowell O. Randall and his associates for these results.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

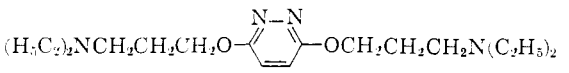
Pyridazine Derivatives. V.[1,2] Some Ethers and Thioethers Derived from 3,6-Dichloropyridazine

BY EDGAR A. STECK[3] AND R. PAULINE BRUNDAGE

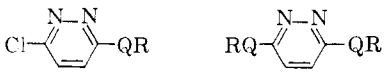
RECEIVED MAY 14, 1959

The greater number of pyridazine 3,6-bis-ethers, which were made for eventual pharmacological trials, contained basic groups. Certain other 3-chloro-6-pyridazyl ethers and thioethers were also prepared, as well as some of the bis-thioether types.

The detailed pharmacological evaluation of the bis-quaternary salts of 3,6-bis-(dialkylaminoalkoxy)-pyridazines, together with kindred thioethers,[1c] has established[4-6] that the series has novel patterns of neuromuscular blocking action. The greatest potency was found in the quaternary ammonium salts of I. Continuing interest was fostered by these results, and the present contribution relates to various ethers and thioethers which were prepared from 3,6-dichloropyridazine. In certain instances, it was readily possible to obtain the intermediate II, but the greater attention was devoted to the 3,6-bis-substituted pyridazines III. The basically-substituted derivatives of III were of especial interest, and variations in activity with modifications in character of the attachment and nature of quaternizing agents were fundamental aspects of the work.



I



II III

where Q is O or S and R is a group, alkyl, aralkyl or heteryl in nature

The nucleophilic displacement of one chlorine in 3,6-dichloropyridazine by reaction with alkoxides or phenoxides under mild conditions readily produced several representatives of II. These findings are in accord with recent reports.[7-9] Partial hydrolysis of the halide to 6-chloro-3-pyridazone[7] was achieved in acid medium (*cf.* ref. 10).

Symmetrical ethers (and thioethers, to a lesser extent) having the structure III were of particular interest as potential pharmacodynamic agents. In light of previous work,[1c,4-6] the ethers having basic centers formed the core of the program. The sodio (or potassio) derivatives of the hydroxy compounds were caused to act upon 3,6-dichloropyridazine in xylene for the preparation of the series summarized in Table I. The first few examples were synthesized as variants of 3,6-bis-(methoxy)-pyridazine, a compound reported since completion of this work.[7,8,11] All other compounds in the group of bis-ethers were made for the investigation of the interrelations existing between structure and activity of the salts of these pyridazines. In several instances, it was somewhat difficult to consider that there was maximal possible extension between the basic centers of the basic ethers in attempting a structure–activity relationship as neuromuscular blocking agents. We had previously[1c] remarked on the indications which have been gleaned in this regard on the distance between the two quaternary centers. As in our earlier work,[1c] we have here refrained from choosing a specific structure for the salts of the thioethers, but have tacitly considered that these are bis-quaternary salts involving the terminal chain nitrogens. The quaternizing agents employed were the customary ones. Certain additional salts were made from bases which we described previously[1c] to admit of further study (*cf.* refs. 4–6). As an example of another formation of the type III, the nucleophilic reagent sodium 2-diethylaminoethoxide acted upon 3-chloro-6-methoxypyridazine to produce the lower homolog of I by displacement of the methoxy group (*cf.*, *inter alia*, refs. 7, 9, 10, 12).

3,6-Dichloropyridazine was subjected to reaction with excess of thiourea, followed by dilute caustic, toward obtaining 3,6-dithiopyridazine. The product, however, was an excellent yield of a

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(2) E. A. Steck, *J. Org. Chem.*, in the press.

(3) McNeil Laboratories, Philadelphia 32, Penna.

(4) R. M. Gesler and J. O. Hoppe, *Federation Proc.*, **15**, 427 (1946).

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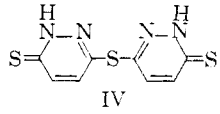
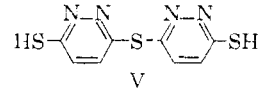
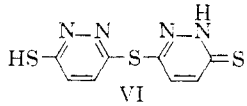
compound $C_8H_6N_4S_3$. This was the result of a two-stage transformation and, on the basis of color and solubility, the dithione-sulfide structure IV may well be preferred for the compound rather than the dithio-sulfide or thiol-thione-sulfide structures V or VI.



IV



V



VI

The anticipated (*cf.* refs. 7–9) compounds of type III resulted from the reaction of the sodium salts of methyl mercaptan, thiosalicylic acid, and 4 - chlorothiophenol with 3,6 - dichloropyridazine when used in a 2:1 ratio. A reaction of the thiophenol employing a 1:1 ratio of the compounds gave a 2:1 ratio of the bis- and monosubstituted products. In an extension of previous work,[1c] the bis-(4-nitrobenzobromide) was made from the sulfur analog of I.

Experimental[13]

A. Intermediates. 3-Dimethylamino-1-phenylpropanol was obtained from β-dimethylaminopropiophenone[14] by catalytic reduction.[15] It was a viscous oil, b.p. 70–72° (0.3 mm.), and gave a hydrochloride which melted 134.5–135.5° (lit.[15] m.p. 134–135°).

4-Dimethylamino-2-butanol, previously reported from these laboratories,[16] was prepared by a procedure used by Kyrides, *et al.*,[17] for related types. Methylvinylcarbinol[18] (64.5 g., 0.9 mole), liquefied dimethylamine (31.0 g., 0.69 mole), and tech. sodium hydroxide (31.8 g., *ca.* 0.7 mole) were shaken in an autoclave at 96–100° for 20 hours. The resulting, cooled mixture was quenched in ice-water and the layers separated. The aqueous layer was extracted well with ether, and the extracts united with the oil, then fractionated after drying. At *ca.* 200 mm., the excess methyl vinyl ketone passed over at *ca.* 48–58°, and the 4-dimethylamino-2-butanol was collected at 75–79° (50 mm.), $n^{25}D$ 1.4290. The yield was 47 g., or 58% of theory.

Anal. Calcd. for $C_6H_{15}NO$: N, 11.95. Found: N, 11.72.

2-(1-Methyl-2-piperidyl)-ethanol was prepared from 2-(2-pyridyl)-ethanol by reduction in acetic acid with platinum catalyst,[19] followed by methylation with formaldehyde and formic acid. The Leuckart methylation gave a 92% yield of pure product (previous preparation: ref. 20) which boiled at 63–66° (0.3 mm.), $n^{25}D$ 1.4833.

Anal. Calcd. for $C_8H_{17}NO$: N, 9.78. Found: N, 9.80.

3-(1-Piperidyl)-propanol was made by the method of Dunlop.[21]

1-(2-Hydroxyethyl)-4-methylpiperazine.—1-(2-Hydroxyethyl)-piperazine[22] was reductively methylated after the method of Wright, *et al.*[23]

1-(3-Hydroxypropyl)-4-methylpiperazine.—Piperazine was converted to the intermediate alkanol,[22] which was then alkylated reductively in ethanol with formalin present and using a 5% palladium–charcoal catalyst (*cf.* ref. 23). The desired compound was obtained in 83–85.5% yields in the form of an oil, b.p. 65–69° (0.3 mm.), $n^{25}D$ 1.4823. It solidified to a mass of white plates on standing.

Anal. Calcd. for $C_8H_{18}N_2O$: N, 17.71. Found: N, 17.56.

A dihydrochloride was obtained as fine needles from ethanol–ether, m.p. 245.5–246.5°, decomposition with intumescence.

Anal. Calcd. for $C_8H_{18}N_2O \cdot 2HCl$: O, 6.92; Cl, 30.67. Found: O, 6.85; Cl, 30.70.

B. 3-Chloro-6-pyridazyl Ethers. 3-Chloro-6-methoxypyridazine was made, by a method similar to that used by other workers,[7–9] by the addition of methanolic sodium methoxide solution to 3,6-dichloropyridazine in methanol. The vigorous exothermic reaction gave deposition of sodium chloride promptly, but refluxing was continued for an hour before the removal of the precipitate. Concentration of the filtrate gave a quantitative yield of crude 3-chloro-6-methoxypyridazine, m.p. 80–81.5°. White platelets melting at 88–88.5° (lit.[7] m.p. 90°) were obtained in 92% recovery by crystallization from hexane.

Anal. Calcd. for $C_5H_5ClN_2O$: Cl, 24.53; N, 19.38. Found: Cl, 24.53; N, 19.24.

The hydrochloride separated from ethanol–ether in the form of fluffy, white needles, m.p. 118–119° dec.

Anal. Calcd. for $C_5H_5ClN_2O \cdot HCl$: Cl (ionic), 19.59; N, 15.48. Found: Cl (ionic), 19.39; N, 15.48.

3-Chloro-6-(4-chlorophenoxy)-pyridazine.—3,6-Dichloropyridazine (14.9 g., 0.1 mole) was refluxed with a 10% excess of 4-chlorophenol (14.2 g.), dissolved in 10% sodium hydroxide, for a period of six hours. The white solid was collected after chilling and was dissolved in benzene extracts made of the filtrates, then washed with sodium chloride solution and dried. Removal of solvent left 23.0 g. (95.5%) of crude 3-chloro-6-(4-chlorophenoxy)-pyridazine, m.p. 100–101.5°. Two crystallizations from cyclohexane gave the pure compound as white prisms, m.p. 119.5–120° (immersed at 115°).

Anal. Calcd. for $C_{10}H_6Cl_2N_2O$: Cl, 29.32; N, 11.58. Found: Cl, 29.38; N, 11.39.

3-Chloro-6-(3,5-dimethylphenoxy)-pyridazine was prepared by the method described for the chlorophenoxy type. A 91% yield of crude product (m.p. 132–134°) resulted; after two crystallizations from cyclohexane, the prismatic needles melted at 135–135.5°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O$: Cl, 15.11; N, 11.96. Found: Cl, 15.17; N, 11.92.

3-Chloro-6-hydroxypyridazine, or the tautomeric 6-chloro-3-pyridazone, while not an ether is a simple representative of structure II, which describes the general type. It was made by acid-catalyzed, partial hydrolysis of the dichloro compound (*cf.* ref. 10).

A suspension of 14.9 g. (0.1 mole) of 3,6-dichloropyridazine in 2 l. of water, which contained 5 cc. of concentrated hydrochloric acid, was refluxed for three hours. Steam was passed through the mixture and 3 l. of distillate was collected; from the distillates, a 48% recovery of dichloropyridazine was obtained. The (concentrated) residues were chilled, and the tan solid collected. It was dissolved in boiling water and charcoaled, giving 4.31 g. of crude 6-hydroxy compound as a creamy solid, m.p. 134–136°. On the basis of the dichloro compound used, this represented a 32.8% yield, or a 67.5% yield on the basis of starting material consumed. The product was purified by extraction with heptane in a Soxhlet apparatus (to remove traces of the insoluble by-product, the dihydroxy compound, better known as maleic hydrazide), then it was crystallized from chloroform. The white rods melted at 141–142° (lit.[7,9] m.p. 138–140°).

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.80; H, 2.32; N, 21.47. Found: C, 37.14; H, 2.54; N, 21.63.

C. Pyridazine-3,6-bis Ether Types.—In general, the 3,6-bis-substituted pyridazines assembled in Table I were prepared by the procedure which we used previously.[1c] The

(13) The melting points reported are corrected values, whereas boiling points are not. Analyses were performed in the Analytical Section of this Institute, and under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer.

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(23) J. B. Wright, H. G. Kolloff and J. H. Hunter, *ibid.*, **70**, 3098 (1948).

TABLE I

3,6-BIS-(ALKOXY)-PYRIDAZINE TYPES

OR[a]	Base or salt[b]	Appearance	M.p., °C.[c] or b.p., °C. (mm.)	Solvent[d] (n^{25}D)	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
OCH_3	B	Felted needles	104.5–105[e]	Pe	83.5	51.42	5.75	19.99	51.83	6.19	20.02
$OCH_2C_6H_5$	B	Shimmering blades	136.5–137[e]	Hp	88	73.95	5.52	9.58	73.99	5.55	9.55
	2Mi	Microcryst.	202–204	Me		32.94[g]	5.33[f]	7.27	32.95[g]	5.33[f]	7.94
OCH_2CH_2 (Mp)	B	Yellow oil	*ca.* 180(0.02)	(1.5528)	87	66.26	9.45	11.60[f]	65.96	9.25	11.48[f]
	2Mh	Granules	240–242 d.	Me–D		47.83	7.30	28.94[g]	47.56	7.16	28.90[g]
OCH_2CH_2 (Pz)	B	Creamy plates	107–109	Pe	67.5			15.37[f]			15.28[f]
	4C	Microcryst.	192–193 d.	Me–E		27.79[g]		16.47	27.53[g]		16.40
$OCH_2CH_2CH_2N(C_2H_5)_2$	2Mh[i]	Microcryst.	162–164.5 d.	A–E	72	45.46	7.63	30.25	45.62[g]	7.61[g]	30.30[g]
	2Ei	Cryptocryst.	186–187.5 d.	D–Me	61	39.02[g]		8.61	38.80[g]		8.84
	Nb	Creamy microcryst.	181–182	*i*Pr–E	67.5	14.41[g]		12.63	14.70		12.99
$OCH_2CH_2CH_2$ (Pl)	B	Felted needles	73.5–75.5	Pe	71	66.26	9.45	15.46	66.13	9.45	15.26
	2Mi	Shiny needles	196.5–199	Me–D		39.27[g]		8.67	38.80[g]		8.43
$OCH(CH_3)CH_2CH_2N(CH_3)_2$	B	Straw col. oil	*ca.* 85(4μ)	(1.4889)	76	61.90	9.74	18.05	61.72	9.78	18.37
	2Mh	Prisms	*ca.* 210	A–D		31.95[g]	6.40[h]		31.85[g]	6.40[h]	
	20x	Cryptocryst.	157–159 int.	Me			32.62[h]	11.40		32.00[h]	11.29
$OCH(CH_3)CH_2CH_2N(C_2H_5)_2$	B	Golden oil	*ca.* 125(0.05)	(1.4858)	61	65.53	10.45	15.29	65.55	10.43	15.34
$OCH(C_6H_5)CH_2CH_2N(CH_3)_2$	B	Golden oil	*ca.* 160(1μ)	(1.5554)	73.5			6.45[f]			6.57[f]
	2Mi	Cryptocryst.	160–165 d.	Pr–*i*Pr		35.33[g]		7.80	35.30[g]		7.92
$OCH_2CH_2CH_3$ (Pz)	B	Blades	99.5–100	Pe–H	70.5	61.62	9.25	14.30[f]	61.40	8.92	15.25[f]
	4C	Microcryst.	222–224	Me–E		44.61	7.49	26.34[g]	44.33	7.26	26.50[g]

[a] Legend: Mp, 1-methyl-2-piperidyl; Pl, 1-piperidyl; Pz, 4-methyl-1-piperazinyl; [b] B, base; C, hydrochloride; Ei, ethiodide; Mb, methobromide; Mi, methiodide; Nb, 4-nitrobenzyl bromide; Ox, oxalate. [c] d. signifies decomposition, and int., intumescence. [d] A, ethanol; D, acetone; E, ether; H, hexane; Hp, heptane; Me, methanol; Pe, pentane; Pr, propanol; *i*Pr, propanol-2. [e] Halogen. [f] Basic nitrogen, by acetous perchloric acid titration method of G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938). [g] Sample re-dried immediately prior to analysis. [h] Oxygen. [i] *Cf.* refs. 7, 11. [j] Base reported previously.[1c,7,8]

non-basic ethers were made using sodium alkoxides with 10–14-hour reflux periods in xylene, and were isolated directly from the filtered liquors. All others were run under nitrogen for 15–20 hours, employing sodium only in instances where but two carbons separated the O and N functions; potassium was preferred. In most cases, the hydroxy compounds were refluxed with the metal for 4–6 hours before the second step.

Most of the quaternary salts were formed by refluxing in acetone or in methanol–acetone (0.5–2 hr.). Propanol-2 was useful; however, products frequently retained that solvent most tenaciously. Several new salts of I may be noted in the table.

3,6-Bis-(2-diethylaminoethoxy)-pyridazine has been prepared previously by us[1c] and other groups[7,8] by interaction of 3,6-dichloropyridazine and sodium 2-diethylaminoethoxide. The present mode of formation involves a nucleophilic displacement of the methoxy group as well as the chloride in 3-chloro-6-methoxypyridazine (*cf.* ref. 9).

Sodium 2-diethylaminoethoxide was prepared from the alcohol (9.4 g., 0.08 mole) in xylene (200 cc.). To this there was gradually added, while refluxing, a solution of 10.0 g. (0.07 mole) of 3-chloro-6-methoxypyridazine in 50 cc. of xylene, and then the reaction was continued for 14 hours. The usual isolation procedure[1c] gave 15.28 g. of light amber oil which contained halogen. This product was subjected to catalytic dehalogenation at 3 atmospheres, with 10% palladium–charcoal, in ethanol containing a slight excess of sodium hydroxide, and the base was distilled to yield 9.66 g. of golden oil, b.p. 85–90° (0.1 mm.), n^{25}D 1.4912. 3,6-Bis-(2-diethylaminoethoxy)-pyridazine has been described[1c] as a yellow oil, b.p. 132–137° (0.2 mm.), and having n^{25}D 1.4906. The identity was confirmed by formation of the bis-methiodide, which separated from methanol–ether as needles having a pinkish cast, m.p. 228–229° dec. (lit.[1c] m.p. 229–229.5° dec.). A mixed melting point of this sample of methiodide with an authentic sample[1c] of 3,6-bis-(2-diethylaminoethoxy)-pyridazine bis-methiodide was found to be 228–229° dec.

Anal. Calcd. for $C_{18}H_{36}I_2N_4O_2$: N, 9.43; I, 42.71. Found: N, 9.54; I, 42.3.

D. Pyridazyl Sulfide Types. Bis-(6-thiono-3-pyridazyl) Sulfide (IV).—A solution of 14.9 g. (0.1 mole) of 3,6-dichloropyridazine in 75 cc. of ethanol was added to a suspension of 23.5 g. (0.3 mole) of 97.4% pure thiourea in 150 cc. of ethanol, and the mixture was stirred under reflux for 6 hours. The mixture soon became free of solids and was brown in color. At the end of the reaction, the bulk of the solvent was removed, leaving a greenish-yellow paste which was then refluxed for 3 hours with 3.2 g. (0.08 mole) of 98% sodium hydroxide in 75 cc. of water. A greenish solid precipitated when the solution was acidified with acetic acid. Some green impurities were insoluble in ammonium hydroxide, and the clarified solution gave a bright yellow product upon acidification (hydrochloric acid). The crude sulfide (12.5 g., 98.5% yield) decomposed *ca.* 239–241°. It was thrice crystallized from aqueous pyridine and once from aqueous 2-methoxyethanol to obtain the pure compound (10.7 g., 84.5% yield) as bright yellow microcrystals which decomposed with intumescence at 266–267° (immersed at 260°).

Anal. Calcd. for $C_8H_6N_4S_3$: C, 37.78; H, 2.38; N, 22.03; S, 37.81. Found: C, 37.81; H, 2.31; N, 21.66, 20.92; S, 37.62, 38.05.

3,6-Bis-(methylmercapto)-pyridazine was prepared by the reaction of sodium methylmercaptide with 3,6-dichloropyridazine in boiling toluene during 18 hr. The crude product (m.p. 119–120.5°) was isolated by merely concentrating the filtered reaction mixture. It crystallized readily from heptane as blades, m.p. 124.5–125.5° (lit.[3] m.p. 126–127°). The yield was 73%.

Anal. Calcd. for $C_6H_8N_2S_2$: N, 16.27; S, 37.22. Found: N, 16.44; S, 36.83.

3,6-Bis-(2-carboxyphenylthio)-pyridazine.—A solution of 17.2 g. (0.112 mole) of thiosalicylic acid in aqueous sodium hydroxide (9.1 g., 0.224 mole, of caustic in 90 cc. of water) was made, and 7.5 g. (0.05 mole) of 3,6-dichloropyridazine added to it. The stirred mixture was refluxed for 7 hours, filtered, and excess of hydrochloric acid used to acidify it. A yellowish, gummy material separated and was transformed into a friable solid by trituration under water. It was then reprecipitated from ammoniacal solution and crystallized twice from 50% ethanol (charcoal). 3,6-Bis-(2-carboxyphenylthio)-pyridazine was thus obtained as a white, microcrystalline solid; the yield was 16.3 g. (85%). This compound decomposed (intumescence) *ca.* 170° when immersed in a bath at 160°, and the residue melted with darkening at *ca.* 203–205°.

Anal. Calcd. for $C_{18}H_{12}N_2O_4S_2$: N, 7.29; S, 16.68; neut. equiv., 192.2. Found[24]: N, 6.97; S, 16.49; neut. equiv., 195.0.

3-Chloro-6-(4-chlorophenylthio)-pyridazine and 3,6-Bis-(4-chlorophenylthio)-pyridazine.—Both of these compounds resulted from an attempt to make the former by use of a 1:1

(24) Dry basis; the sample retained 2.21% of moisture rather tenaciously.

ratio of dichloropyridazine and the sodium thiophenolate. The procedure was otherwise much as described in the case of thiosalicylic acid. A waxy, pale yellow solid was obtained as the crude product which separated during the reflux period. It was triturated well with ether and the creamy solid collected (A). The aqueous material and ether were retained (B). Solid A (9.4 g. from 7.5 g. of 3,6-dichloropyridazine; m.p. 138–140°) was crystallized from cyclohexane (800 cc.) to give feathery needles, m.p. 150–150.5° (5.6 g.). The liquors were retained for work-up. Analyses indicated that A was the bis compound (61% yield, based on 4-chlorothiophenol consumed, as evaluated).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2S_2$: Cl, 19.41; N, 7.67. Found: Cl, 19.51; N, 7.41.

The aqueous liquors (B) from the crude product were extracted well with ether, and these combined with the ether washings. Extraction of the ether (retained as C) with 10% caustic ultimately led to recovery of *ca.* 4% of 4-chlorothiophenol; C was washed with sodium chloride solution, dried and stripped of solvent, leaving a white solid which melted at 94–96° (6.0 g. from 7.5 g. of dichloropyridazine). Evaporation of the cyclohexane mother liquors from A left a white residue, m.p. 94.5–96° (3.6 g. from above run). The crude materials were combined and crystallized from pentane to yield fine white needles, m.p. 96.5–97.5°. This was 3-chloro-6-(4-chlorophenylthio)-pyridazine, a 38% yield being obtained.

Anal. Calcd. for $C_{10}H_6Cl_2N_2S$: N, 10.90; S, 12.47. Found: N, 10.73; S, 12.63.

When two equivalents of sodium 4-chlorothiophenolate were employed, the bis type was formed in 99% yield.

3,6-Bis-(3-diethylaminopropylthio)-pyridazine Bis-(4-nitrobenzobromide).—This quaternary salt was made by mixing the requisite base[1c] with 2.1 equivalents of 4-nitrobenzyl bromide and heating on the steam-bath (without solvent) for an hour. The crude product was pulverized, triturated with acetone, boiled in acetone–ethanol, and then crystallized twice from ethanol. A 62% yield of powder having an orange cast was obtained, m.p. 205–206.5° dec.

Anal. Calcd. for $C_{28}H_{46}Br_2N_6O_4S_2$: Br, 19.91; S, 7.99. Found: Br, 19.89; S, 8.20.

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Enzymatic Syntheses of C^{14}-Labeled Uridine Diphosphoglucose, Galactose 1-Phosphate, and Uridine Diphosphogalactose[1]

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Methods are described in detail for the enzymatic syntheses of C^{14}-labeled uridine diphosphoglucose from glucose-C^{14}, and of labeled galactose 1-phosphate and uridine diphosphogalactose from galactose-C^{14}. The syntheses are feasible on a preparative scale, and essentially pure samples of the labeled uridine diphosphoglycosyl compounds can be isolated in good yield. In the synthesis from galactose, the intermediate galactose 1-phosphate can be isolated as the barium salt, or, in a somewhat different procedure, the over-all synthesis of uridine diphosphogalactose from free galactose can be carried out in a single incubation. Methods are also defined for the enzymatic synthesis, on a preparative scale, of C^{14}-labeled uridine diphosphoglucuronic acid.

Uridine diphosphoglucose (UDPG[3]), first discovered by Leloir and co-workers[4] as a coenzyme for the transformation of Gal-1-P to G-1-P,[3] has been shown to act as a glucosyl donor in a variety of enzymatic reactions for the biosynthesis of di- and polysaccharides.[5–9] UDPG also undergoes enzymatic conversions to UDPGal[10,11] and to UDPGA,[12] both of which have likewise been implicated as glycosyl donors in biosynthetic reactions.[13–16]

Because of the interest in having radioisotope-labeled uridine diphosphoglycosyl compounds for use in the exploration of such pathways of glycosyl transfer and as tools to assay for interconversions of the nucleotide compounds themselves,[17] enzymatic syntheses were undertaken to label these compounds with C^{14} in the carbohydrate portion of the molecule. Such syntheses have been developed for UDPG and UDPGal, starting in each case with a readily available radioactive substrate, and achieving synthesis on a preparative scale in good yield and with a high degree of purity. In

(1) A preliminary report on part of this work has already appeared; E. P. Anderson and H. M. Kalckar, Absts. Am. Chem. Soc. 5C, Minneapolis, September, 1955.

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(3) The following abbreviations are used: UDPG, uridine diphosphoglucose; UDPGal, uridine diphosphogalactose; UDPGA, uridine diphosphoglucuronic acid; Gal-1-P, α-D-galactose 1-phosphate; G-1-P, α-D-glucose 1-phosphate; G-6-P, glucose 6-phosphate; 6-PG, 6-phosphogluconate; ATP, adenosine triphosphate; ADP, adenosine diphosphate; UTP, uridine triphosphate; CTP, cytidine triphosphate; PP, inorganic pyrophosphate; P_i, inorganic orthophosphate; DPN, diphosphopyridine nucleotide; TPN, triphosphopyridine nucleotide; *, C^{14}-labeled.

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