hypoxanthine (II), both the 9- and 7-isomers (III and IV) of (2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-2-acetamidohypoxanthine were formed in about equal amounts. They were separated readily by chromatography on alumina and were deactylated in methanolic sodium methoxide to the corresponding guanine 3′-deoxynucleosides V and VI.

The assignment of the position of attachment of the sugar moiety in the 7- and 9-(glucopyranosyl)guanines was made[4] primarily on the basis of a comparison of their ultraviolet absorption with that of authentic 7- and 9-methylated guanines.[5] Since then, absorption spectra of guanines substituted in other than the 7- and 9-positions have become available[6] and because they differ with the spectra for the 7- and 9-substituted products, they substantiate the earlier structural conclusions. Similarly, we have assigned the position of linkage of the 3-deoxyribofuranosyl moiety in V and VI as 9 and 7 on the basis of ultraviolet spectral comparisons.

These new 3-deoxyribofuranosylguanines have been tested[7] in several biological systems in order to compare their activities with those of other purine 3′-deoxynucleosides.

Experimental[8]

9-(2,5-Di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-2-acetamidohypoxanthine (III) and 7-(2,5-Di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-2-acetamidohypoxanthine (IV).—About 25 ml. of xylene was distilled from a suspension of 5.95 g. (14 mmoles) of chloromercuri-2-acetamidohypoxanthine (II)[4] in 175 ml. of xylene in order to remove last traces of water. The suspension was cooled to 25° and 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide [from 5 g. (12.3 mmoles) of methyl 2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranoside][1] in 25 ml. of dry xylene was added. The mixture was stirred and heated. At about 50 to 100°, the solid changed from a granular to flocculent form. After being refluxed for 1 hr., the hot mixture was filtered which removed 5.5 g. of solid. Leaching the solid with three 50-ml. portions of boiling chloroform removed 1.9 g. of soluble product and left 3.6 g. of starting chloromercuri derivative and inorganic salts.

The original filtrate was diluted with 2 vol. of petroleum ether (b.p. 30–60°) and the solid which separated was dissolved in the chloroform solution obtained above. The chloroform solution (plus an additional 100 ml.) was washed with two 75-ml. portions of 30% potassium iodide and one 75-ml. portion of water. The dried chloroform layer was concentrated and 3.5 g. of crude coupling product was obtained as a glass. T.l.c. on alumina in acetone–ethyl acetate (3:1) showed zones (made visible with iodine vapor) at R_f 0.0, 0.4, and 0.7.

The crude product was chromatographed on 50 g. of acid-washed alumina. Elution with 120 ml. of ethyl acetate removed 600 mg. of an impurity (R_f 0.7) derived from the bromo sugar. Further elution with about 700 ml. of acetone removed 1.17 g. of another component (R_f 0.4). This material was dissolved in 100 ml. of chloroform and washed with water. Concentration of the chloroform layer gave 1.05 g. (16.5%) of 7-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-2-acetamidohypoxanthine as an amorphous powder: $[\alpha]_D$ −19.3°; $[\alpha]_{578}$ −21° (*c* 1.0, $CHCl_3$); λ_{max}^{EtOH}, mμ (ε × 10^{-3}), 232 (27.9), 254 (16.5), 260 (15.0), 276 (12.1), 282 (11.9).

Anal. Calcd. for $C_{26}H_{23}N_5O_7$: C, 60.34; H, 4.48; N, 13.53. Found: C, 60.80; H, 4.48; N, 13.49.

Column elution was continued with methanol (750 ml.) which removed 900 mg. of product of R_f 0.0 on alumina t.l.c. in the acetone–ethyl acetate (3:1) system. This material was dissolved in 200 ml. of chloroform and washed with two 20-ml. portions of water. Concentration of the filtered chloroform solution under reduced pressure gave 740 mg. (12%) of 9-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-2-acetamidohypoxanthine as an amorphous solid: $[\alpha]_D$ −72°; $[\alpha]_{578}$ −76° (*c* 1.0, $CHCl_3$); λ_{max}^{EtOH}, mμ (ε × 10^{-3}), 225 (38.1), 267 (14.6), 280 (infl.) (12.1).

Anal. Found: C, 61.08; H, 4.75; N, 13.47.

9-(3-Deoxy-β-D-ribofuranosyl)guanine (3′-Deoxyguanosine, V).—A suspension of 800 mg. (1.5 mmoles) of 2-acetamido-9-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)hypoxanthine (III) in 8 ml. of dry methanol was treated with a solution prepared from 105 mg. (4.5 g.-atoms) of sodium and 8 ml. of dry methanol, and the mixture was refluxed for 2 hr. After 15 min. of refluxing, no further change in the ultraviolet absorption spectrum could be observed. The mixture was concentrated to dryness. The residue was dissolved in 35 ml. of water and the pH was adjusted to 7 by the addition of acetic acid. The clear solution was washed with three 8-ml. portions of chloroform, and the aqueous layer was concentrated to 10 ml. After being cooled for several hours, the precipitated product (260 mg.) was removed and washed with two 2.5-ml. portions of cold water. Recrystallization from 11 ml. of water gave 203 mg. of 9-(3-deoxy-β-D-ribofuranosyl)guanine. A second recrystallization gave 180 mg. (46%) of product, m.p. >300°, which was dried at 80° and reduced pressure for analysis: $[\alpha]_D$ −41.2°; $[\alpha]_{578}$ −44° (*c* 0.5, H_2O); $\lambda_{max}^{H_2O}$, mμ (ε × 10^{-3}), pH 1—255 (11.3), 275 (infl.) (7.6), pH 4—252 (11.9), 270 (infl.) (8.6), pH 6—252 (12.1), 272 (infl.) (8.8), pH 7—252 (11.8), 270 (infl.) (8.6), pH 11—253 (11.3), 270 (infl.) (8.95), pH 13—267 (9.9), 260 (infl.) (9.7).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.90; H, 4.97; N, 26.24.

7-(3-Deoxy-β-D-ribofuranosyl)guanine (VI).—A suspension of 900 mg. (1.74 mmoles) of 2-acetamido-7-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)guanine (IV) in 8 ml. of dry methanol was treated with a solution prepared from 132 mg. (5.7 g.-atoms) of sodium and 8 ml. of dry methanol, and the mixture was refluxed for 3.5 hr. Periodic examination of the ultraviolet absorption spectrum indicated that the reaction was complete after 2.5 hr. The mixture was concentrated and the residue was dissolved in 40 ml. of water. The solution was washed with 15 ml. of chloroform and the pH of the aqueous phase was adjusted to 7 with acetic acid. The precipitated product (356 mg.) was filtered and washed with 5 ml. of water, 10 ml. of alcohol–ether (1:9), two 10-ml. portions of boiling chloroform, and 10 ml. of ether. Two recrystallizations from water gave 247 mg. (53%) of 7-(3-deoxy-β-D-ribofuranosyl)guanine: m.p. >300°; $[\alpha]_D$ −10°; $[\alpha]_{578}$ −10° (*c* 0.25, 1 *N* NaOH); $\lambda_{max}^{H_2O}$, mμ (ε × 10^{-3}), pH 1—249 (8.6), 270 (infl.) (5.0), pH 4—240 (infl.) (4.6), 284 (5.1), pH 6—217 (17.7), 240 (infl.) (5.1), 285 (6.0), pH 7—217 (19.1), 242 (infl.) (5.6), 286 (6.3), pH 11—215 (19.6), 237 (infl.) (6.0), 285 (6.3), pH 13—238 (infl.) (7.0), 282 (5.6).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94, H, 4.90; N, 26.21. Found: C, 45.00; H, 4.85; N, 26.47.

(5) J. M. Gulland and L. F. Storey, *J. Chem. Soc.*, 692 (1938).

(6) (a) W. Pfleiderer, *Ann.*, **647**, 167 (1961); (b) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962); (c) R. Shapiro and C. N. Gordon, *Biochem. Biophys. Res. Commun.*, **17**, 160 (1964).

(7) C. O. Gitterman, R. W. Burg, G. E. Boxer, D. J. Meltz, and J. E. Hitt, *J. Med. Chem.*, in press.

(8) Microanalyses were performed by Mr. R. N. Boos and his associates, and the ultraviolet spectral measurements were done by Mr. E. A. MacMullin and his associates. Melting points were determined on a micro hot stage and are corrected.

Quaternary Ammonium Borodisalicylates and Borodihydroxynaphthoates

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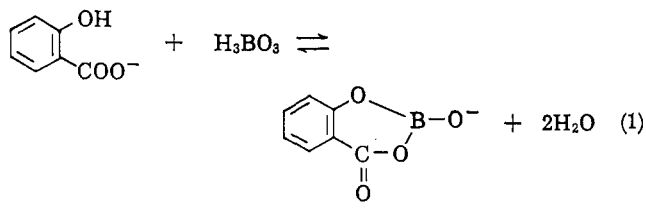
Although syntheses of borodisalicylic acid have been reported,[1] both the existence and properties of this substance are still subject to question. The metal and amine salts of this acid, however, are well known

(1) A. Foelsing, German Patent 288,388 (1914); J. Meulenhoff, *Rec. trav. chim.*, **44**, 161 (1925); O. Dimroth, R. Ruchti, K. Sagstetter, J. Hetzer, H. Bernzott, C. Bamberger, O. Rebmann, and R. Schweizer, *Ann.*, **446**, 97 (1925); C. E. Trautman, U. S. Patent 2,568,472 (1951); R. C. Mehrotra and G. Srivastava, *J. Indian Chem. Soc.*, **38**, 1 (1961).

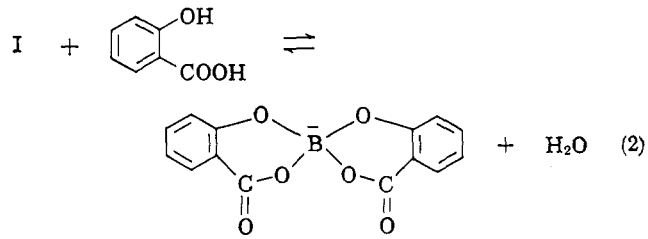
and have been copiously described.[2] There is also one reported preparation of the dimethylanilinium salts of two of the three possible borodihydroxynaphthoates.[3] The present report describes the hitherto unreported quaternary ammonium borodisalicylates and borodihydroxynaphthoates. These are all crystalline solids which are readily prepared and readily purified.

The equilibrium constants for reactions 1 and 2



(1)

I

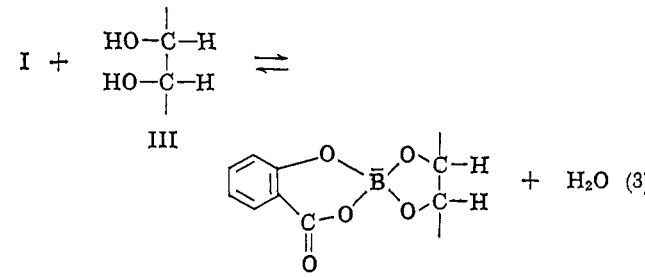


(2)

II

in water at 22 ± 0.2° have been reported by Schäfer[4] and have the values 23 and 133 l. mole^{-1}, respectively. Although I and II are very strongly favored at equilibrium, one would expect to be able to titrate a quaternary ammonium borodisalicylate in water as if it contained equimolar amounts of quaternary ammonium salicylate, salicylic acid, and boric acid, with salicylic acid being titrated first and then the boric acid being titrated in the presence of excess mannitol. Contrary to this expectation, a solution of either a quaternary ammonium borodisalicylate or borodihydroxynaphthoate in water at room temperature appears not to liberate a significant amount of acid during a normal pH titration. If the solution is heated to boiling and then titrated at room temperature, one titrates 93–96% of the salicylic acid in a 0.008 *M* solution of the salt. If mannitol is now added and the titration is continued, slightly more than 1 equiv. of additional base is consumed, but the total still falls short of the expected amount. An equimolar mixture of boric and salicylic acids or an equimolar mixture of boric acid, salicylic acid, and sodium salicylate behave much like the quaternary ammonium borodisalicylate in the first titration, but in these cases all of the salicylic and boric acids are titrated after mannitol is added.

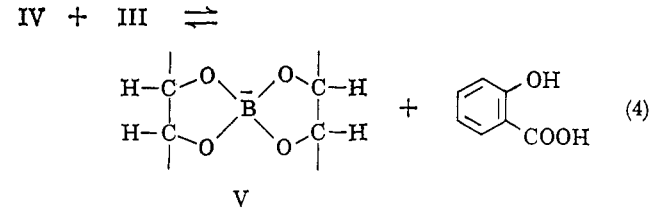
When mannitol (III) is added, the following two equilibria become involved. The titrations of the quaternary ammonium borodisalicylate indicate that some of the rates in the equilibria 1 and 2, and perhaps also 3, are slow and that some acid becomes trapped in an



III

(3)

IV



(4)

V

unavailable and unidentified species. It is possible that this species is I, which probably is present in solution in the protonated form and should not be an appreciably stronger acid than is boric acid itself.

Experimental[5]

Tetramethylammonium Borodisalicylate.—A mixture of salicyclic acid (27.6 g., 0.2 mole), boric acid (6.18 g., 0.1 mole), and tetramethylammonium hydroxide (9.1 g., 0.1 mole, as a 10% aqueous solution) was heated until the solution was homogeneous. The water was removed *in vacuo*, and the product was crystallized two times from 2-propanol: m.p. 164–167°, yield 30.4 g. (85%). Additional crystallization raised the melting point to 169–172°.

Anal. Calcd. for $C_{15}H_{20}BNO_6$: C, 60.53; H, 5.64; B, 3.03; N, 3.92. Found: C, 59.93; H, 5.70; B, 3.02; N, 3.63.

Tetraethylammonium Borodisalicylate.—The procedure was identical with that above. The product, crystallized two times from 2-propanol, had m.p. 121–123°, yield 99%.

Anal. Calcd. for $C_{22}H_{28}BNO_6$: C, 63.94; H, 6.83; B, 2.62; N, 3.39. Found: C, 63.38; H, 6.48; B, 2.65; N, 3.30.

Benzyltrimethylammonium Borodisalicylate.—Salicylic acid (82.9 g., 0.6 mole), boric acid (18.6 g., 0.3 mole), and benzyltrimethylammonium hydroxide (50.2 g., 0.3 mole, as a 40% solution in methanol) were mixed and warmed. Enough water was added to bring everything into solution. The solvents were removed *in vacuo*, and the crude product was crystallized from 2-propanol: m.p. 147–150°, yield 122.9 g. (94.5%). A sample twice recrystallized from 2-propanol had m.p. 150–151°.

Anal. Calcd. for $C_{24}H_{24}BNO_6$: N, 3.23. Found: N, 3.21.

Benzyltrimethylammonium Borodi(2-hydroxy-1-naphthoate).—To a hot, filtered solution of 2-hydroxy-1-naphthoic acid (18.8 g., 0.1 mole) in ethanol were added successively a solution of boric acid (3.1 g., 0.05 mole) in hot water and benzyltrimethylammonium hydroxide (42 g. of a 40% solution in methanol). Some ethanol was added, and the mixture was heated to solution. On cooling, addition of ether, and scratching, the product, 12 g. (45%) of an off-white solid, was obtained. Crystallization from 2-propanol–water and washing with acetone gave m.p. 185–187°.

Anal. Calcd. for $C_{32}H_{28}BNO_6$: N, 2.63. Found: N, 2.58.

Tetraethylammonium Borodi(3-hydroxy-2-naphthoate).—To a solution of 3-hydroxy-2-naphthoic acid (18.8 g., 0.1 mole, crystallized from ethanol, m.p. 222–224°) in hot ethanol were added successively a solution of boric acid (3.1 g., 0.05 mole) in the minimum amount of hot water and tetraethylammonium hydroxide (75 ml. of a 10% aqueous solution). After removal of the solvents with the water pump, the residue was dissolved in hot ethanol containing a small amount of water and filtered. An equal volume of ether was added, and the solution was cooled in the refrigerator until the product crystallized: yield 17.8 g. (70%), m.p. 224–225°, strong depression on mixture melting with 3-hydroxy-2-naphthoic acid.

Anal. Calcd. for $C_{30}H_{32}BNO_6$: N, 2.73. Found: N, 2.73.

(2) E. Jahns, *Arch. Pharm.*, **12**, 212 (1878); A. Foelsing, German Patent 230,725 (1909); British Patent 1616 (1910); J. Böeseken and J. Meulenhoff, *Koninkl. Ned. Akad. Wetenschap. Proc.*, **27**, 174 (1924); A. Rosenheim and H. Vermehren, *Ber.*, **57**, 1337 (1924); J. Meulenhoff, *Z. Anorg. Allgem. Chem.*, **142**, 373 (1925); *Rec. trav. chim.*, **44**, 161 (1925); J. Böeseken, H. D. Muller, and R. T. Japhongjouw, *ibid.*, **45**, 919 (1926); J. Böeseken and N. Vermaas, *J. Phys. Chem.*, **35**, 1477 (1931); C. E. Trautman, U. S. Patent 2,497, 521 (1950).

(3) J. Böeseken and A. Niks, *Rec. trav. chim.*, **59**, 1062 (1940).

(4) H. Schäfer, *Z. anorg. allg. Chem.*, **250**, 82 (1942).

(5) Microanalyses were by the Clark Microanalytical Laboratory, Urbana, Ill.

Tetraethylammonium Borodi(1-hydroxy-2-naphthoate).—A solution of 1-hydroxy-2-naphthoic acid, obtained from Matheson Coleman and Bell (18.8 g., 0.1 mole), in ethanol was shaken with charcoal and Celite and filtered. To the filtrate were added successively a solution of boric acid (3.1 g., 0.05 mole) in hot water and tetraethylammonium hydroxide (75 ml. of a 10% aqueous solution). The dark, sticky residue obtained by removal of the solvents was crystallized from ethanol–ether. Two crops of crude solid totaling 20.3 g. (79%) were obtained. Recrystallization from ethanol–ether followed by two crystallizations from 2-propanol–ether gave the analytical sample, m.p. 152–155°.

Anal. Calcd. for $C_{30}H_{32}BNO_6$: N, 2.73. Found: N, 2.70.

Tetraethylammonium Borodi(2-hydroxy-1-naphthoate).—A mixture of boric acid (6.2 g., 0.1 mole), 2-hydroxy-1-naphthoic acid (37.6 g., 0.2 mole), and tetraethylammonium hydroxide (147 ml. of a filtered 10% aqueous solution) was dissolved in a large volume of water and ethanol by boiling. Cooling and filtration gave 36.2 g. (71%) of white crystals, m.p. 179–183° after two crystallizations from ethanol.

Anal. Calcd. for $C_{30}H_{32}BNO_6$: N, 2.73. Found: N, 2.67.

An Alternative Synthesis of 2′,3′-Dideoxyadenosine[1]

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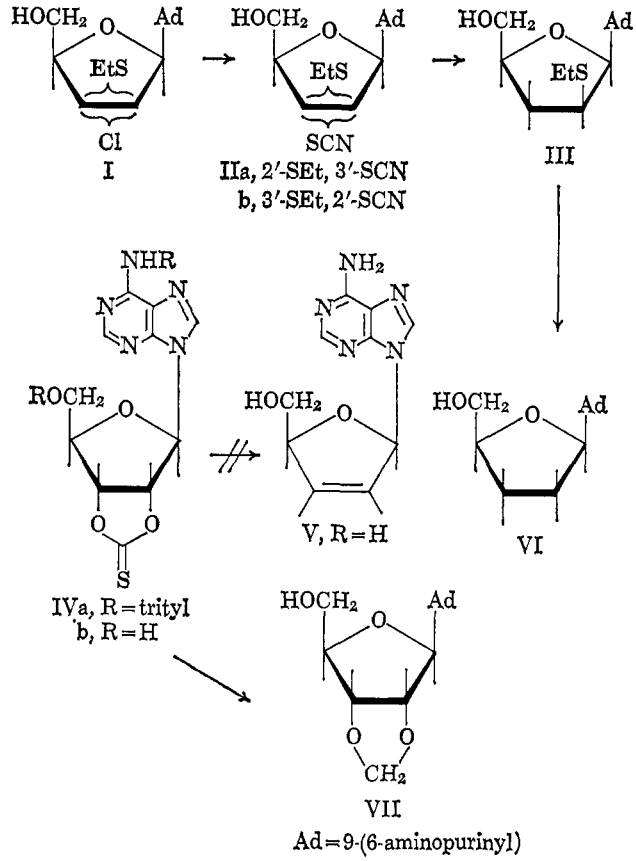
The reasons for interest in 2′,3′-dideoxyadenosine (VI) were discussed and the synthesis of VI was reported in a recent paper.[2] This report prompts us to describe our synthesis of 2′,3′-dideoxyadenosine by a different route and our attempts to prepare VI by a third route that would have been more direct (see Scheme I).

Reaction of the chloro ethylthio nucleoside I[3] with a sulfur nucleophile should give a nucleoside with 2′,3′-disulfur substitution that could undergo desulfurization to give VI. Preliminary experiments with the sodium salts of benzyl and ethyl mercaptan, potassium thiobenzoate, and potassium thiocyanate showed that only the last compound was a suitable reagent. The other compounds caused cleavage of the nucleoside to adenine. Heating the nucleoside I with potassium thiocyanate in methanol under nitrogen afforded the 3′-thiocyanate nucleoside IIa, presumably *via* an episulfonium ion intermediate,[3] as the only isolable product. Traces of the isomeric 2′-thiocyanate nucleoside IIb may have been present in the initial product, but were readily removed upon recrystallization. Desulfurization of IIa with commercial sponge-nickel[4] catalyst in N,N-dimethylformamide at 100° gave a mixture of the partially desulfurized nucleoside III and dideoxyadenosine (VI). The thiocyanate group was removed much more readily than the ethylthio group. Further desulfurization of the mixture afforded

SCHEME I



VI. The last desulfurization step was very sensitive to the quality of the sponge nickel.

The structure of III was assigned on the basis of n.m.r. spectroscopy experiments, using decoupling techniques. The C-1′ proton of III exhibited a doublet (τ 3.60) suggesting that it was coupled to only one proton on C-2′. A decoupling experiment confirmed this assignment and established the C-2′ proton signal at τ 6.08, an expected location if the 2′-carbon atom was bonded to a sulfur atom but not if it was bonded to only carbon and hydrogen. The structure of IIa followed from that of III. The infrared spectrum and analysis both showed that the thiocyanate group was lost in the conversion of IIa to III. The ethylthio group was not affected and must therefore be at C-2′ in IIa as well as in III. The thiocyanate group must be at C-3′.

The cyclic thionocarbonate derivatives of Corey and Winter[5] and of Horton and Turner[6] seemed promising for the conversion of adenosine (or other ribosyl nucleosides) to an olefin derivative and then to 2′,3′-dideoxyadenosine (or other dideoxy nucleosides). Using a blocked nucleoside model, it was found that N⁶,5′-O-ditrityladenosine[3b] and thiocarbonyldiimidazole[7] reacted readily by Horton and Turner's procedure[6] to give the 2′,3′-O-thionocarbonato nucleoside IVa. However, all attempts to carry IVa through the rest of the projected reaction sequence to 2′,3′-dideoxyadenosine were unsuccessful. Starting without blocking groups, it was possible to convert adenosine to the 2′,3′-O-thionocarbonate IVb, but attempts to convert

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 3585 (1964).

(3) (a) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **80**, 6453 (1958). (b) *Ibid.*, **81**, 3967 (1959). (c) The sharp melting point of I suggested that it may be one isomer; however, n.m.r. spectroscopy suggests it is a mixture with two C-1′ doublets centered at τ 3.48 and 3.96.

(4) Product of W. R. Grace Co., 50% solids in water.

(5) E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

(6) D. Horton and W. N. Turner, *Tetrahedron Letters*, 2531 (1964).

(7) H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).