Acknowledgment.—We wish to express our thanks to the staff of the Section on Microanalytical Services and Instrumentation of this Institute for spectra and elemental analyses.

Synthesis of Some 3′-O-Methyl Purine Ribonucleosides[1]

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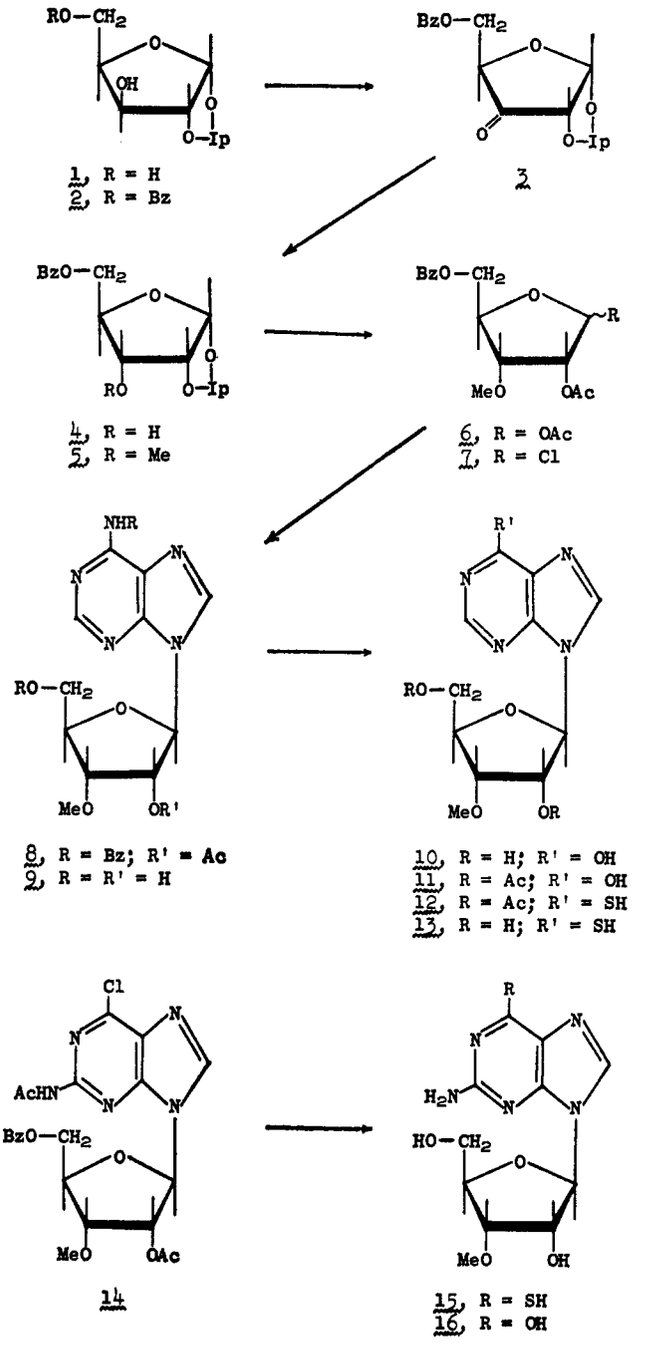
Received November 22, 1966

A wide variety of methylated nucleosides have been isolated by degradation of ribonucleic acids.[2] Some of the methylated derivatives have been 2′-O-methyl ribonucleosides, and, recently, Robins and co-workers[3] have described elegant methods for synthesizing these interesting compounds. We have been interested in the isomeric 3′-O-methyl ribonucleosides, both because one can imagine these as occurring in certain of the nucleic acids and as compounds where the alteration in the sugar moiety could result in unique biological properties. Certainly the change from a β-D-riboside to β-D-arabinoside and β-D-xyloside in adenine nucleosides has had profound biological effects.[4,5] Other changes in the sugar moiety may be equally useful. The synthesis of 3′-O-methyluridine has recently been reported by Furukawa, *et al.*,[6] using a method that seems restricted to the pyrimidine nucleosides. We report in this manuscript a preparation of 3′-O-methyl-D-ribose that permits a general synthesis of 3′-O-methylribofuranoside nucleosides and its application to the synthesis of some new purine 3′-O-methylribosides.

The key intermediate in the synthesis of the 3′-O-methyl nucleosides was 5-O-benzoyl-1,2-O-isopropylidene-3-O-methyl-α-D-ribofuranose (**5**) (see Scheme I). Although its precursor, **4**, is known,[7] the literature preparation required considerable modification before **4** could be conveniently prepared. In the conversion of 1,2-O-isopropylidenexylose **1** into the 5-O-benzoyl derivative **2**,[8] it was not necessary to attempt the difficult isolation of crystalline **2**. The syrupy **2**, obtained in high yield, was equally suitable for oxidation to the crystalline ketone **3** where purification was easy. Oxidation of **2** with acetic anhydride and dimethyl sulfoxide[9] was more convenient than the original chromium trioxide procedure[7] or the use of ruthenium tetraoxide.[10,11] Catalytic hydrogenation of **3** at 4 atm proceeded as satisfactorily to afford **4** as the hydrogenation at 60 atm.[7]

SCHEME I



Reaction of **4** with methyl iodide and silver oxide in N,N-dimethylformamide[12] afforded **5**. Examination of the crude methylation product by nmr indicated the presence of a small amount of a second methyl ether that was removed during recrystallization. The high yield of crystalline **5** suggested that acyl migration was an insignificant factor in this methylation.[13]

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract No. PH 43-64-500. The opinions expressed are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

(2) See references given by R. H. Hall, *Biochemistry*, **3**, 876 (1964).

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(4) (a) J. J. Brink and G. A. LePage, *Cancer Res.*, **24**, 312 (1964); (b) J. J. Brink and G. A. LePage, *Can. J. Biochem.*, **43**, 1 (1965).

(5) D. B. Ellis and G. A. LePage, *ibid.*, **43**, 617 (1965).

(6) Y. Furukawa, K. Kobayashi, Y. Kanai, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **13**, 1273 (1965).

(7) K. Oka and H. Wada, *Yakugaku Zasshi*, **83**, 890 (1963); *Chem. Abstr.*, **60**, 1825 (1964).

(8) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

(9) (a) We are indebted to Kenneth J. Ryan of these laboratories for demonstrating the utility of the acetic anhydride–dimethyl sulfoxide oxidation[9b] for converting **2** into **3**. (b) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).

(10) V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965).

(11) R. F. Nutt, B. Arison, F. W. Holly, and E. Walton, *J. Am. Chem. Soc.*, **87**, 3273 (1965).

(12) N. F. Taylor and G. M. Riggs, *J. Chem. Soc.*, 5600 (1963).

(13) See W. A. Bonner, *J. Org. Chem.*, **24**, 1388 (1959), for a discussion of acyl migration during methylation of carbohydrates. See E. G. Gros and S. M. Flematti, *Chem. Ind.* (London), 1556 (1966), for the suggested use of diazomethane and boron trifluoride–etherate to avoid acyl migration during methylation.

Acetolysis of **5** by the usual procedure[14] yielded the 1,2-di-O-acetate **6** as a syrup in high yield and good purity as indicated by nmr and infrared spectra. Refluxing the diacetate **6** with chloromercuri-6-benzamidopurine in 1,2-dichloroethane with titanium tetrachloride as catalyst[15] afforded the blocked nucleoside **8** as a foam. Deacylation with methanolic ammonia gave 3′-O-methyladenosine **9** in 47% yield from the diacetate **6**. This was the preferred method. Alternately, the diacetate **6** was converted into the chloro sugar **7** and condensed with chloromercuri-6-benzamidopurine. Upon deacylation 3′-O-methyladenosine was obtained in 14% yield from the diacetate **6**. Nitrous acid treatment converted 3′-O-methyladenosine into the 3′-O-methylinosine **10** rather slowly, but in high yields. Because of its tendency to gel, **10** was not characterized, but converted into its crystalline diacetate **11**. Thiation of **11** with phosphorus pentasulfide gave **12** which was deacylated to 3′-O-methylthioinosine **13**.

Unlike chloromercuri-6-benzamidopurine, the mercury derivative[16] of 2-acetamido-6-chloropurine reacted more satisfactorily with the chloro sugar **7** than with the diacetate **6** and titanium tetrachloride. By the first method, the nucleoside **14** was obtained as a foam. This was contaminated with mercury that could not be removed completely by the usual potassium iodide wash,[17a] but required treatment with methanolic hydrogen sulfide.[17b] Subsequent treatment of purified **14** with sodium hydrogen sulfide and deacylation yielded 3′-O-methylthioguanosine (**15**). Treatment of **14** with sodium 2-hydroxyethylmercaptide led to 3′-O-methylguanosine (**16**) directly. This is another example of the new guanine nucleoside synthesis.[18]

Experimental Section[19]

5-O-Benzoyl-1,2-O-isopropylidene-α-D-*erythro*-3-pentosulofuranose (3).—By the literature procedure,[8] 20.0 g (0.105 mole) of 1,2-O-isopropylidene-α-D-xylofuranose (**1**) was treated with 13.0 ml (0.111 mole) of benzoyl chloride in pyridine. In the work-up, benzene was used instead of chloroform, and toluene was used as a chaser in the evaporation that left 28.9 g (86% yield of **2** plus toluene) of syrup suitable for the next step.

Following a known method,[9b] a solution of 5.49 g (18.6 mmoles) of the above syrupy **2**, 60 ml of dimethyl sulfoxide, and 40 ml of acetic anhyride afforded 1.66 g (31% from **2**; 27% from **1**) of the ketone **3**, mp 97–98.5° (lit.[7] mp 93–94.5°) from ether, R_f 0.30 in solvent TA. When the ratio of reagents to **2** was reduced by 50%, the yield of crystalline **3** dropped to 10%.

5-O-Benzoyl-1,2-O-isopropylidene-3-O-methyl-α-D-ribofuranose (5).—Catalytic hydrogenation of 8.44 g (28.9 mmoles) of **3** in 150 ml of ethanol containing 0.20 g of 82.11% platinum dioxide at 60 psi (initial pressure) in a Parr apparatus at room temperature for 24 hr afforded 6.87 g (81%) of the ribose **4**, mp 80.5–81.5° (lit.[7] mp 78–79°) from cyclohexane.

By a literature procedure,[12] 1.49 g (5.04 mmoles) of **4**, 1.6 ml (25.7 mmoles) of methyl iodide, and 3.0 g (13 mmoles) of silver oxide in 10 ml of N,N-dimethylformamide were allowed to react for 24 hr at room temperature, worked up, and recrystallized from 15 ml of *n*-hexane to afford 1.12 g (72%) of the methyl ether **5**, mp 75.5–76.5°, and a second crop, mp 74.5–76° (total 1.25 g, 80%). For analysis, a sample from an earlier run was recrystallized from *n*-hexane to afford **5** as long, colorless needles: mp 76–77°; no OH absorption at 3 μ in the infrared spectrum; $[\alpha]^{24}D$ +75° (*c* 1.99, chloroform); nmr, singlet at τ 6.53 (OCH_3); homogeneous in solvent TA with R_f 0.45.

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54. Found: C, 62.7; H, 6.68.

The nmr spectrum of crude **5**, before recrystallization, exhibited the main singlet at τ 6.53 (OCH_3) and a very minor singlet at 6.63 which we attributed to the presence of a second methyl ether.

1,2-Di-O-acetyl-5-O-benzoyl-3-O-methyl-D-ribofuranose (6).—In the usual way,[14] 2.94 g (9.5 mmoles) of **5** in 5 ml of acetic anhydride and 45 ml of acetic acid was treated at 10–15° with 2.8 ml of sulfuric acid. After 24 hr at room temperature, the reaction was worked up to afford 3.47 g (103%) of **6** as a pale yellow syrup: λ_{max}^{film} 5.70 and 5.78 μ (C=O of acetate and benzoate); nmr, singlet at τ 3.90 (C 1 proton, β anomer) and a barely detectable doublet at 3.62 which we attributed to the C 1 proton of the α anomer. Compound **6** moved as two spots in solvent TA with R_f 0.40, main spot (**5** has R_f 0.45) and R_f 0.28, trace (probably α anomer).

9-(3′-O-Methyl-β-D-ribofuranosyl)adenine (9). Method A.—A suspension of 1.84 g (5.2 mmoles) of the diacetate **6**, 3.10 g (6.5 mmoles) of chloromercuri-6-benzamidopurine (from 4.84 g of a 36% Celite mixture) and 0.72 ml (6.5 mmoles) of titanium tetrachloride[15] was heated at reflux for 24 hr. The mixture was worked up to afford 2.31 g (83%) of the blocked nucleoside **8** as a yellow foam; in solvent TB it showed a main spot with R_f 0.35 and trace evidence for unreacted purine and sugar. A filtered solution of 2.27 g (4.3 mmoles) of **8** was deacylated with methanolic ammonia at 100° for 15 hr. The crude product was crystallized from 6 ml of absolute ethanol to afford 0.63 g of **9**, mp 177–178°, and a second crop, mp 176.5–178° (total 0.68 g, 47% from **6**). Two recrystallizations from absolute ethanol afforded the analytical sample of **9**: mp 177–178°; λ_{max}^{pH1} 206 mμ (ε 21,000) and 257 mμ (ε 14,600), λ_{max}^{pH7} 206 mμ (ε 20,800) and 260 mμ (ε 14,800), λ_{max}^{pH13} 215 mμ (ε 9300) and 260 mμ (ε 14,800); $[\alpha]_{589}^{25}$ −57° (*c* 0.8, water); homogeneous in solvents A, B, and C with R_{Ad} 1.0, 1.56, and 1.15, respectively.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.38; N, 24.9. Found: C, 47.2; H, 5.45; N, 24.9.

Method B.—A solution of 1.36 g (3.9 mmoles) of the diacetate **6** in dry ether was saturated with hydrogen chloride at 0°, kept for 3 days at 0°, and evaporated to afford 1.24 g (98%) of the chloro sugar **7** as a yellow syrup. A portion (1.23 g, 3.7 mmoles) of **7** and 1.90 g (4.0 mmoles) of chloromercuri-6-benzamidopurine (2.97 g of a 36% Celite mixture) were refluxed in xylene for 3 hr and worked up to afford 1.51 g (76%) of the blocked nucleoside **8**. A portion (1.47 g, 2.7 mmoles) of **8** was treated with methanolic ammonia, as above, and crystallized from absolute ethanol to afford 0.15 g (14% from **6**) of 3′-O-methyladenosine (**9**), in two crops, mp 176.5–178° and 175–176°, that were identical with **9** prepared by method A.

9-(2,5-Di-O-acetyl-3-O-methyl-β-D-ribofuranosyl)-6-hydroxypurine (11).—A solution of 4.44 g (15.8 mmoles) of 3′-O-methyladenosine (**9**), 4.35 g (63 mmoles) of sodium nitrite, 80 ml of water, and 16 ml of acetic acid was kept at room temperature for 48 hr and then evaporated *in vacuo*. The residue was dried by the addition and removal *in vacuo* of three 50-ml portions of absolute ethanol–toluene (1:1). The residue of **10** was suspended in 150 ml of dry pyridine, treated with 10 ml of acetic anhydride, stirred at room temperature for 24 hr, then diluted with 10 ml of methanol, and stirred an additional 30 min. The mixture was

(14) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1753 (1958).

(15) D. H. Murray and J. Prokop, *J. Pharm. Sci.*, **54**, 1468 (1965).

(16) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

(17) (a) Other investigators have noted that removal of mercury salts from nucleoside products may vary in difficulty. See footnote 12 in E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965). (b) Prolonged treatment of **14** with methanolic hydrogen sulfide gave a small amount of by-product which was difficult to remove.

(18) G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **32**, 859 (1967).

(19) Melting points were taken on a Fisher-Johns apparatus and are corrected. Anhydrous magnesium sulfate was used as the drying agent. All evaporations were performed under reduced pressure with the bath temperature generally below 60°. Paper chromatography was done by the descending technique on Whatman No. 1 paper; and the spots were detected under ultraviolet light. Where adenine was used as a standard, the spots were located relative to R_{ad} 1.00. Solvent systems were A, 1-butanol saturated with water; B, water; C, benzene–methanol–water (2:6:1); D, 5% aqueous disodium hydrogen phosphate, pH 8.9; and E, 1-butanol–acetic acid–water (5:2:3). Thin layer chromatography (tlc) was done on silica gel HF plates with these solvent systems: TA, chloroform–ethyl acetate (19:1); TB, ethyl acetate. The tlc spots were located relative to the front, R_f 1.00, and were detected under ultraviolet light. The nmr spectra were run as solutions in deuteriochloroform using tetramethylsilane as an internal standard on either the Varian A-60 or HA-100 spectrometer. Rotations were determined with a Rudolph photoelectric polarimeter.

evaporated *in vacuo* and two 75-ml portions of toluene were added and removed *in vacuo*. Trituration of the residue with 50 ml of water gave 5.38 g (93%) of **11** as a white crystalline powder, mp 264.5–265.5°, homogeneous and suitable for use in the next step. Two recrystallizations from water afforded the analytical sample of **11**: mp 267–268°; $\lambda_{max}^{pH\ 1}$ 248 mμ (ε 11,900), $\lambda_{max}^{pH\ 7}$ 248 mμ (ε 12,300), $\lambda_{max}^{pH\ 13}$ 253 mμ (ε 13,200); $[\alpha]_{589}^{22}$ −20° (*c* 0.5, pyridine); it moved as one spot in solvent systems A, B, and C with R_{Ad} 1.34, 2.16, and 1.43, respectively.

Anal. Calcd for $C_{15}H_{18}N_4O_7$: C, 49.2; H, 4.95; N, 15.3. Found: C, 49.2; H, 5.03; N, 15.5.

9-(2,5-Di-O-acetyl-3-O-methyl-β-D-ribofuranosyl)-6-mercaptopurine (12).—A suspension of 1.83 g (5.0 mmoles) of **11**, 75 ml of dry pyridine, and 4.44 g (20 mmoles) of phosphorus pentasulfide was heated at reflux and stirred under a nitrogen atmosphere for 4 hr. During this time, complete solution was attained. The solution was evaporated. The residue was triturated with 100 ml of 5% sodium bicarbonate solution for 20 hr, collected, and washed thoroughly with water and absolute ethanol to afford 1.71 g (89%) of **12** as a pink, crystalline powder, mp 218.5–221.5° dec, free of starting material and suitable for the next step. A portion was recrystallized three times from water to afford the analytical sample of **12**: mp 245.5–248° dec; $\lambda_{max}^{pH\ 1}$ 223 mμ (ε 9600) and 321 mμ (ε 24,400), $\lambda_{max}^{pH\ 13}$ 232 mμ (ε 15,500) and 310 mμ (ε 23,800); $[\alpha]_{589}^{25}$ −41° (*c* 0.5, pyridine); it moved as one spot in solvents C and D with R_{Ad} 1.52 and 1.87, respectively.

Anal. Calcd for $C_{15}H_{18}N_4O_6S$: C, 47.1; H, 4.74; N, 14.7; S, 8.39. Found: C, 46.8; H, 5.00; N, 14.7; S, 8.71.

9-(3-O-Methyl-β-D-ribofuranosyl)-6-mercaptopurine (13).—A suspension of 5.56 g (14.5 mmoles) of unrecrystallized **12**, 200 ml of methanol, and 22 ml of 1 *M* sodium methoxide in methanol was stirred and heated at reflux for 2 hr and then evaporated *in vacuo*. The residue was dissolved in 100 ml of water, treated with charcoal, and neutralized to afford 3.07 g (71%) of **13** as a tan powder, mp 196.5–198.5° dec, with a second crop, mp 197.5–199° dec (total 3.49 g, 80%). Two recrystallizations from water afforded the analytical sample of **13** as white, fibrous crystals: mp 200–201° dec; $\lambda_{max}^{pH\ 1}$ 224 mμ (ε 9200) and 322 mμ (ε 23,700), $\lambda_{max}^{pH\ 7}$ 226 mμ (ε 10,100) and 318 mμ (ε 23,200), $\lambda_{max}^{pH\ 13}$ 232 mμ (ε 14,100) and 311 mμ (ε 22,800); $[\alpha]_{589}^{23}$ −77° (*c* 1.0, 0.1 *N* sodium hydroxide); it moved as one spot in solvents B, C, and D with R_{Ad} 2.08, 1.32, and 1.75, respectively.

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.3; H, 4.73; N, 18.8; S, 10.8. Found: C, 44.2; H, 5.08; N, 18.7; S, 10.9.

2-Amino-6-mercapto-9-(3-O-methyl-β-D-ribofuranosyl)purine (15).—A suspension of 18.3 g (41 mmoles) of the mercury derivative[16] of 2-acetamido-6-chloropurine (in admixture with 8.5 g of Celite), in 1300 ml of xylene, was dried by distillation of 200 ml of solvent. To this was added 12.3 g (37.4 mmoles) of the chloro sugar **7** in 75 ml of xylene and 13 g of molecular sieves (Linde Type 4A), and the mixture was refluxed for 4 hr. The reaction was worked up[16] to afford the blocked nucleoside **14** as a yellow gum. This still contained some mercury salts. The gum was dissolved in 400 ml of methanol, treated with a stream of hydrogen sulfide for 30 min,[17b] and filtered. The solvent was evaporated; 100 ml of benzene was added and evaporated to afford 15.1 g (80%) of the blocked nucleoside **14** as a yellow gum that contained small amounts of purine and sugar material according to thin layer chromatography in solvent TB.

To a solution of 4.28 g (8.5 mmoles) of the blocked nucleoside **14** in 100 ml of methanolic hydrogen sulfide was added 26 ml of 1 *M* sodium hydrogen sulfide in methanol, and the solution was maintained at reflux temperature while hydrogen sulfide was bubbled through it for 2 hr. The hydrogen sulfide was replaced by nitrogen, which was bubbled through for 15 min, and finally 13 ml of 1 *M* methanolic sodium methoxide was added. After refluxing for 2 hr more, the solution was evaporated. The residue was dissolved in 40 ml of water, washed with three 15-ml portions of benzene, treated with charcoal, and neutralized with acetic acid to afford 1.07 g (40%) of **15**, mp 226–229° dec. Crystallization from 90 ml of water afforded 0.774 g (29%) of **15**, mp 232–235° dec. Two more crystallizations from water afforded the analytical sample of **15**, as an off-white powder: mp 232.5–235° dec; $\lambda_{max}^{pH\ 1}$ 207 mμ (ε 23,800), 264 (8000), and 344 (22,000); $\lambda_{max}^{pH\ 7}$ 209 mμ (ε 22,600), 225 sh (~13,600), 257 (8150), and 342 (24,300); $\lambda_{max}^{pH\ 13}$ 251 mμ (ε 13,600), 271 (7000), and 319 (20,400); $[\alpha]_{589}^{25}$ −70° (*c* 1, 0.1 *N* sodium hydroxide); homogeneous in solvents B, C, and E with R_{Ad} 2.19, 1.04, and 0.96, respectively.

Anal. Calcd for $C_{11}H_{15}N_5O_4S$: C, 42.2; H, 4.83; N, 22.4; S, 10.2. Found: C, 41.8; H, 4.80; N, 22.1; S, 10.6.

2-Amino-6-hydroxy-9-(3-O-methyl-β-D-ribofuranosyl)purine (16).—To a solution of 4.28 g (8.5 mmoles) of the blocked nucleoside **14** (see procedure for **15** above) in 100 ml of methanol was added a solution of 2.1 ml (30 mmoles) of 2-mercaptoethanol in 25 ml of 1 *M* methanolic sodium methoxide. The solution was refluxed under a nitrogen atmosphere for 3 hr and evaporated. The residue was dissolved in 40 ml of water, washed with three 15-ml portions of benzene, allowed to stand for 1.5 hr, and neutralized with acetic acid, and the resultant gel was kept at 5° overnight. The crystalline product was collected to afford 0.733 g (29%) of **16**, which decomposed at 258–300° without melting. Three recrystallizations afforded the analytical sample of **16** as white fibrous needles, which decomposed at 263–300° without melting: $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 12,300) and 267 mμ sh (ε ~8500), $\lambda_{max}^{pH\ 7}$ 252 mμ (ε 13,200) and 270 mμ sh (ε ~9400), $\lambda_{max}^{pH\ 13}$ 258 mμ sh (ε ~11,300) and 264 mμ (ε 11,400); $[\alpha]_{589}^{25}$ −69° (*c* 1, 0.1 *N* sodium hydroxide); homogeneous in solvents C with R_{Ad} 1.04 (guanosine, R_{Ad} 0.86) and E with R_{Ad} 0.89 (guanosine, R_{Ad} 0.68).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.4; H, 5.09; N, 23.6. Found: C, 44.1; H, 5.10; N, 23.9.

Registry No.—**3**, 6698-46-0; **5**, 10300-20-6; **6**, 10300-21-7; **9**, 10300-22-8; **11**, 10300-23-9; **12**, 10300-24-0; **13**, 10300-25-1; **15**, 10300-26-2; **16**, 10300-27-3.

Acknowledgments.—We thank Dr. Peter Lim and his staff for the infrared and ultraviolet spectra and paper chromatography and Mr. O. P. Crews, Jr., and his staff for large-scale preparations of some intermediates.

A Novel Synthesis of 1,1-Dimethyl-3,3-diphenylindan[1]

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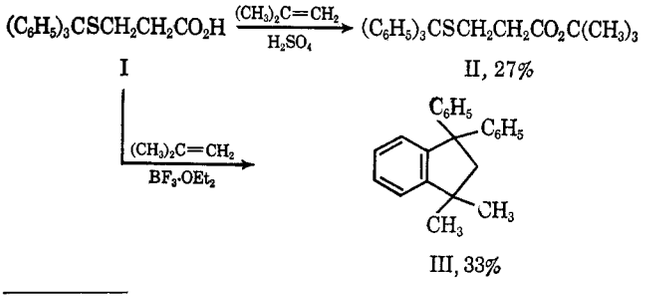
Received November 4, 1966

During recent investigations concerning the preparation of esters from acids containing acid-labile sulfur-protecting groups, 5,5,5-triphenyl-4-thiapentanoic acid (I) was converted to *t*-butyl 5,5,5-triphenyl-4-thiapentanoate (II) in 27% yield *via* the classical method involving isobutylene and sulfuric acid in chloroform. In an attempt to improve the yield, the reaction was repeated using an equivalent amount of boron trifluoride etherate and otherwise identical reaction conditions. The only isolable product from this reaction was a crystalline hydrocarbon obtained in 33% yield;



(1) Supported by Research Grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service.

(2) National Science Foundation Cooperative Fellow, 1964–1966.