Registry No.—*d*-1, 27259-78-5; *d*-3, 27259-79-6; *d*-4, 27317-55-1; *d*-5, 27317-56-2; *dl*-6, 27259-80-9; *l*-6, 27259-81-0; *l*-7, 27259-82-1; *d*-8, 27259-83-2; *d*-9, 27259-84-3; *dl*-10, 27259-85-4; *l*-10, 27259-86-5; *dl*-11, 27259-88-7; *dl*-12, 27259-87-6; *l*-12, 27259-89-8; *d*-13, 27259-90-1; *l*-13, 27259-91-2; *dl*-14, 27259-92-3; *l*-14, 27259-93-4; *l*-15, 27259-94-5; *l*-16, 27259-95-6; *dl*-17, 27259-96-7; *d*-17, 27259-97-8.

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Notes

Preparation of Guanine Pentofuranosyl Nucleosides Using a Friedel–Crafts Catalyst[1]

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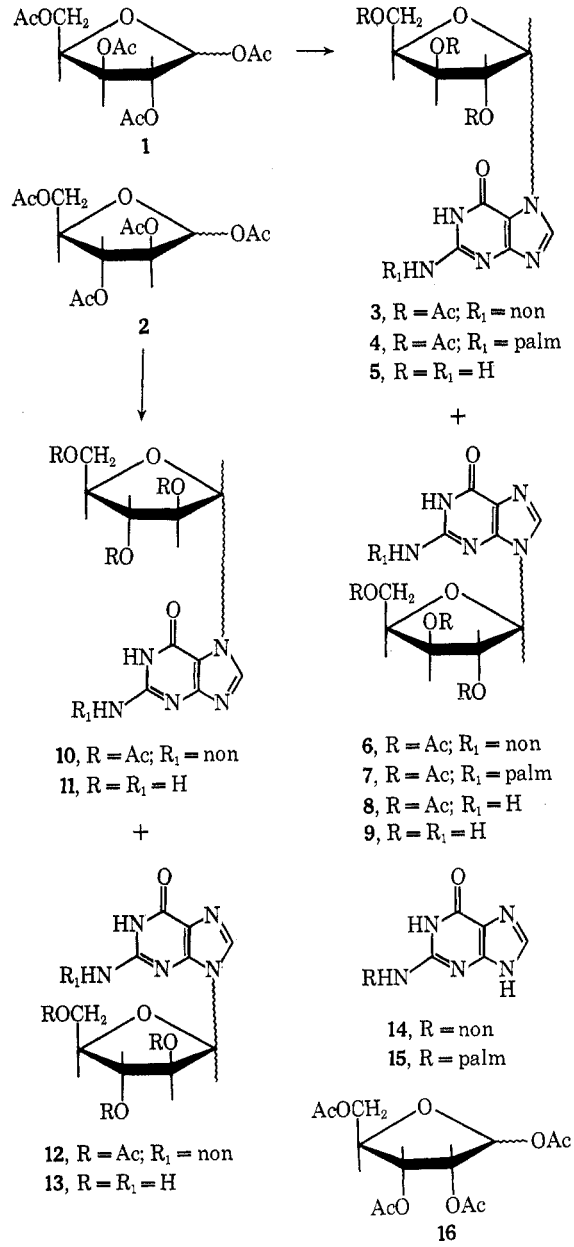
Furukawa and Honjo[2] described recently a novel and simple method of purine ribonucleoside preparation which employs Friedel–Crafts catalysts as condensing agents for the appropriate *N*-acylpurines and 2,3,5-tri-*O*-acyl-1-*O*-acetyl-D-ribofuranoses. The method gave only β-nucleosides and provided an especially useful method for the synthesis of guanosine. Because guanine nucleosides are less directly accessible by other routes[2,3] and because of our needs for considerable quantities of the guanine nucleoside (β-**9**),[4] we have applied this technique using 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**1**) as the sugar. The results were of sufficient interest to warrant some experiments with 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose (**2**). Our findings are reported in this manuscript.

The reaction was carried out as described by Furukawa and Honjo[2] with **1** and either N^2-nonanoylguanine (**14**) or N^2-palmitoylguanine[2] (**15**) using chlorobenzene and aluminum chloride (see Table I). N^2-Nonanoylguanine (**14**) reacted faster; thus, after 2 hr at reflux, the reaction of **1** with **14** was complete, while that with **15** had progressed only to a small extent, according to tlc data. N^2-Nonanoylguanine also gave a higher ratio of 7- to 9-substituted nucleoside than **15**. Surprisingly, the α anomer was formed in large amounts with the



[non = $CH_3(CH_2)_7CO$–; palm = $CH_3(CH_2)_{14}CO$–]

α:β anomer ratio being about 1:1 for both acylguanines and for both 7 and 9 isomers. A substantial improve-

(1) This work is carried out under the auspices of Chemotherapy, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the sponsoring agency.

(2) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968). These authors noted a trace amount of 7-ribofuranosylguanine in their preparation of guanosine.

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

(4) (a) S. Susaki, A. Yamazaki, A. Kamimura, K. Mitsugi, and I. Kumashiro, *Chem. Pharm. Bull.*, **18**, 176 (1970); (b) A. P. Martinez, *et al.*, manuscript in preparation describing the synthesis of β-**9** *via* the mercury derivative[4c] of 2-acetamido-6-chloropurine; (c) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

TABLE I

PREPARATION OF GUANINE NUCLEOSIDES USING ALUMINUM CHLORIDE CATALYST

Expt no.	N^2-Acylguanine, mmol	Sugar, mmol	$AlCl_3$, mmol	Reflux time, hr	Yield of product, % 9 isomer (α:β)	7 isomer (α:β)
1	**14**, 17.2	**1**, 20.8	17.2	2	58 (1:1)	10.5 (1:1)
2	**14**, 8.6	**1**, 9.4	9.0	18[a]	19 total[a]	
3	**14**, 33.4	**1**, 35.6	34.6	2[b]	51 (1:4)	13 (1:1)
4	**15**, 2.6	**1**, 3.9	4.5	18[c]	49 (1:1)	1.5 (1:1)
5	**15**, 10.0	**1**, 13.0	10.0	15	44 (1:1)	2.3 (1:1)
6	**14**, 4.1	**2**, 5.0	4.5	2	40 (4:1)	13.3 (5:1)[d]
7	**14**, 3.4	**2**, 3.7	3.4	3[b]	34 (4:1)	15.5 (5:1)[d]
8	**14**, 8.6	**16**, 10.4	11.6	2	35[e] (1:6)	11 (1:2)

[a] Considerable darkening and decomposition toward latter stages of 18-hr reaction. Because of the low yields, no effort was made to separate the isomers. [b] In expt 3 and 7, the base **14** and $AlCl_3$ were combined first in chlorobenzene and then sugar was added. See Experimental Section. [c] This reaction was initially kept at 90° for 18 hr. There was no reaction; so the mixture was brought to reflux temperature and maintained there for 18 hr. [d] Predominant anomer assumed to be α. [e] This yield is in excellent agreement with the 35% y obtained from N^2-octanoyl guanine in ref 2.

ment in the amount of β anomer (α:β, 1:4) of the 9 isomer was realized by the slow addition of the sugar **1** to the preformed complex of N^2-nonanoylguanine (**14**) and aluminum chloride; however, the α:β ratio of the 7 isomer remained unchanged. The anomer ratios were determined from the nmr spectra in which the H-8 protons of the two anomers could be distinguished.

Column chromatography using Florisil[5] readily separated the 7 isomer from the 9 isomer, but neither the anomers of **6** nor **7** were resolved. Attempts to separate the anomers by various techniques were unsuccessful with **9** and its 3′,5′-isopropylidene derivative. However, fractional crystallization of the triacetate **8** afforded the pure α and β anomers. Deacylation of β-**8** afforded β-**9** whose properties agree with (known) literature values.[4] Likewise α-**8** and the 7 isomers, **3** and **4**, were deacylated. Thin layer chromatography was used to separate the anomers of the blocked 7 isomers, α-**3** and β-**3**. Their uv maxima occurred at identical wavelengths to each other and to the original mixture. Hence they were both 7 isomers and must be anomers.

Since the xylose **1** afforded so much α-nucleoside by the aluminum chloride process, the method was applied to 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose (**2**). Should a 1:1 mixture of nucleoside anomers be formed, this might be a useful route to β-nucleosides of arabinofuranose. Generally, such β-nucleosides have been obtained by using arabinose derivatives blocked with nonparticipating groups for the nucleoside condensations[6] or by interconversion of the corresponding xyloside.[7] Using the procedure of Furukawa and Honjo,[2] the reaction of **2** and **14** (see expt 6, Table I) afforded some of the 7-nucleoside **10**, together with the major product, the 9-nucleoside **12**; these 7 and 9 isomers were separable by Florisil chromatography. One anomer predominated for both **10** and **12**; this was shown to be the α anomer for **12** by deacylation and comparison with authentic β-**13**[8a] and α-**13**.[8b] The reaction of **2** with the preformed complex of N^2-nonanoylguanine and aluminum chloride (expt 7) did not change the anomer ratio of **12**.

The reaction of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (**16**) with N^2-nonanoylguanine (**14**) was examined (expt 8) and found to give, after Florisil chromatography, about 11% of the 7-substituted nucleoside **17** and 35% of the 9-substituted nucleoside **18**, the corresponding ribose derivatives of **3** and **6**, respectively. The α- to β-anomer ratios were about 1:2 for **17** and 1:6 for **18**. That **17** was indeed a mixture of anomers and not a mixture of isomers was established in the same way as for **3**.

As applied to the synthesis of guanine pentofuranosides, the above results corroborate those of Furukawa and Honjo.[2] The reaction of suitable N^2-acylguanines with suitable peracylated pentofuranoses using a Friedel–Crafts catalyst like aluminum chloride is indeed a simple and direct route that affords good yields of the guanine nucleosides. With N^2-palmitoylguanine, formation of the 9-substituted nucleoside in preference to the 7 isomer is favored more than with N^2-nonanoylguanine (and perhaps N^2-octanoylguanine[2]). The anomeric nature of the 9-substituted guanine nucleoside is dependent on the pentose. One anomer of the 9-nucleoside is formed predominantly with ribose and arabinose; these are the β anomer and α anomer, respectively. This would be expected on the basis of participation by the 2-acyl group of the pentose as suggested by Furukawa and Honjo.[2] With xylose the α:β ratio of the 9-nucleoside is 1:1, but this can be altered to favor the β anomer by changing the reaction conditions. This propensity of xylose to give more of an anomeric mixture is also seen in other techniques for nucleoside condensation by the fusion method[9] and the mercury salt method.[10]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Optical rotations were obtained with a Perkin-Elmer Model 141 automatic polarimeter; nmr, with a Varian A-60 or HA 100; CD, with a Jasco Model ORD/UV-5, Sproule Scientific SS 107 CD modification. Evaporations were carried out *in vacuo* at or below 50° initially with a water aspirator and finishing at <0.1 mm. Anhydrous magnesium sulfate was used as drying agent. Type 3A, 1/16-in. pellets of Linde Molecular Sieves (an alkali metal aluminosilicate with 3-Å pore size) were used in the condensation reactions. Celite is a diatomaceous earth product of Johns-Manville. Tlc was run on silica gel HF (E. Merck AG Darmstadt) in these solvent system: TA, ether–

(5) Trade name for the magnesium silicate product of the Floridin Co.

(6) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

(7) (a) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2648 (1960); (b) E. J. Reist, A. Benitez; L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(8) (a) E. J. Reist and L. Goodman, *Biochem.*, **3**, 15 (1964). (b) Properties agreed with those found for α-**13** previously prepared by another route: R. W. Blackford and E. J. Reist, unpublished results.

(9) W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

(10) O. P. Crews, Jr., and L. Goodman in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 139.

ethyl acetate (2:8); TB, methanol–ethyl acetate (2:8); TC, same 4:6 ratio. The spots were detected under uv light and reported as R_f in relation to solvent front.

General Method of Condensation.—To a stirred mixture of N^2-nonanoylguanine (**14**) (see expt 1, Table I, for amounts of reactants), 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**1**), and 5 g of molecular sieves in 200 ml of chlorobenzene was added anhydrous aluminum chloride. The reaction mixture was brought to reflux in an oil bath, 20 ml of solvent was distilled off, and the reaction mixture was heated and stirred at reflux for the required length of time. The reaction mixture was evaporated to dryness and worked up as described below.

Method with Preformed Complex of N^2-Acylguanine and Aluminum Chloride.—A stirred mixture of N^2-nonanoylguanine (**14**) (see expt 3 for amounts of reactants) and molecular sieves in 300 ml of chlorobenzene was distilled to remove about 20 ml of solvent. To the hot mixture was added the aluminum chloride carefully during 2–3 min. The mixture was then heated at reflux while the sugar **1** in 90 ml of chlorobenzene was added dropwise over 3 hr. After the addition, the reaction was heated at reflux for the required length of time and evaporated to dryness. The residue was dissolved in 500 ml of ethyl acetate, diluted with 225 ml of ether, and filtered through Celite. The Celite residue was washed with 250 ml of ether–ethyl acetate (1:1). The combined filtrate and wash was evaporated to leave 19.0 g of a solid tan foam. This was thoroughly stirred in 500 ml of ether for 30 min and filtered to remove the soluble sugar and some nonanoic acid. The crude, ether-insoluble product was dissolved in 75 ml of chloroform and charged on a column (30 mm diam) of 330 g of Florisil. The initial eluents of 500 ml each of chloroform and chloroform–ethyl acetate (1:1) and the next 700 ml of methanol–ethyl acetate (1:10) were discarded. Further elution with methanol–ethyl acetate (1:10) gave a 230-ml fraction containing 2.39 g (13%, see expt 3) of the 7 isomer **3**; a 145-ml fraction contained 0.63 g (3.4%) of the 7 and 9 isomers. The next 860-ml fraction and finally 800 ml of methanol–ethyl acetate (1:4 to 2:3) afforded 9.05 g (51%) of 9 isomer **6**.

9-(2,3,5-*O*-Triacetyl-D-xylofuranosyl)-N^2-nonanoylguanine (6).—The 9 isomer **6** from the Florisil column was a solid foam: uv max (pH 1) 262 mμ (ε 17,200), 275 (sh) (14,200); uv max (pH 7) 258 (16,600), 275 (sh) (12,300); uv max (pH 13) 264 (12,800);[11] nmr ($DCCl_3$) δ 7.92 (s, H-8 of β-**6**), 7.72 (s, H-8 of α-**6**), 6.40 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of α-**6**), 5.93 (d, $J_{1',2'}$ = 2.5 Hz, H-1′ of β-**6**) with the relative areas of the peaks for α:β being 1:4; nmr (DMSO-d_6) δ 8.05 and 8.00 (both s, H-8 of β-**6**) and α-**6**, respectively), 6.35 (d, $J_{1',2'}$ = 5 Hz, H-1′ of α-**6**), 5.88 (d, $J_{1',2'}$ = 3 Hz, H-1′ of α-**6**); R_f 0.25 in TA. No satisfactory chromatographic system was found that would resolve the α and β anomers of **6**.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: 54.6; H, 6.42; N, 12.7. Found: C, 54.4; H, 6.59; N, 13.0.

7-(2,3,5-*O*-Triacetyl-D-xylofuranosyl)-N^2-nonanoylguanine (3).—The 7 isomer **3** from the Florisil column was a solid foam: uv max (pH 1) 218 mμ (ε 15,700), 264 (16,100); uv max (pH 7) 223 mμ (ε 21,800), 264 (14,300); uv max (pH 13) 269 mμ (ε 10,700);[14] nmr ($CDCl_3$) δ 8.17 and 8.02 (both singlets, H-8 of anomers), 6.95 (d, $J_{1',2}$ = 3.5 Hz, H-1′) and 6.54 (d, $J_{1',2'}$ = 1.8 Hz, H-1′) with the relative areas of the peaks for the α:β anomers being about 1:1; R_f 0.50 in solvent TA. Repeated development (3–4 times) in ether resolved the anomer of **3** with approximate R_f 0.57 and 0.67.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.7; H, 6.43; N, 12.8.

For uv analysis, some **3** was separated by thin layer chromatography using multiple development (5 times) with ether–ethyl acetate (6:4) as solvent to afford the anomers with R_f 0.53 and 0.67. These spots were eluted and their uv measured. The maxima of both were found to occur at wavelengths identical with that reported above for the original mixture. Hence both are 7 isomers and must be anomers.

7-(D-Xylofuranosyl)guanine (5).—A solution of 1.00 g (1.82 mmol) of **3** and 2.0 ml of 1 *N* sodium methoxide in 50 ml of absolute methanol was heated at reflux for 3 hr, neutralized with 2 *N* hydrochloric acid, and evaporated. The residue was triturated with a mixture of 75 ml of chloroform and 75 ml of water, and then collected on a filter and washed with water and ether to afford 0.32 g (62%) of **5**. Recrystallization from water afforded 0.30 g (55%) of white crystalline **5**: mp above 290°; $[\alpha]^{20}D$ −70 (*c* 0.5, DMF); uv max (pH 1), 249 mμ (ε 10,300); uv max (pH 7) 217 mμ (ε 21,800), 240 (sh) (6200), 285 (7600); uv max (pH 13) 240 (sh) (7700), 282 (6800).[15]

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot {}^2/_3H_2O$: C, 40.6; H, 4.89; N, 23.7. Found: C, 40.8; H, 4.58; N, 23.7.

9-(D-Xylofuranosyl)guanine (9).—Deacylation of 5.0 g of the anomeric mixture of **6** by the procedure used for **3** afforded 1.64 g (64%) of the anomeric mixture **9**, $[\alpha]^{21}D$ −28 (*c* 0.25, H_2O). This crystallized readily from water to give a 70% recovery of **9**, mp 228–230°, $[\alpha]^{20}D$ −29 (*c* 0.25 H_2O). The anomers could not be separated by column chromatography on Dowex 1 (Cl^-) nor by crystallization of the 2′,3′-*O*-isopropylidene derivative.

A mixture of 1.51 g of **9**, $[\alpha]^{21}D$ −28 (*c* 0.25, H_2O), was treated with 2.5 ml of acetic anhydride in 50 ml of pyridine for 2 hr at 65° to afford the tri-*O*-acetyl derivative **8**, R_f 0.29 (β-**8**) and 0.24 (α-**8**) in TB. Crystallization from methanol afforded 0.55 g (26%) of **9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)guanine (β-8)**:[4b] mp 236–237°; $[\alpha]^{20}D$ −16 (*c* 0.50, DMF); nmr (D_6MSO) δ 7.74 (s, H-8), 5.83 (d, $J_{1',2'}$ = 3 Hz, H-1′) with no signals for α anomer observed (probably 5% detectable); R_f 0.29 in TB; R_f 0.71 in TC. The mother liquors were evaporated and the residue was crystallized from acetone twice to give 0.25 g (12%) of **9-(2,3,5-tri-*O*-acetyl-α-D-xylofuranosyl)guanine** (α-**8**): mp 218–219°; $[\alpha]^{20}D$ +33 (*c* 0.50, DMF); uv max (pH 1) 258 mμ (ε 11,800), 280 (sh) (7900); uv max (pH 7) 253 mμ (ε 13,000), 270 (sh) (9000); uv max (pH 13), 258–266 mμ (ε 11,000); nmr (DMSO-d_6) δ 7.65 (s, H-8), 6.22 (d, $J_{1',2'}$ = 5 Hz, H-1′) with no signals of β-**8** (probably 5% detectable); R_f 0.24 in solvent TB.

Anal. Calcd for $C_{16}H_{19}N_5O_8$: C 46.9; H, 4.68; N, 17.1. Found: C, 46.9; H, 4.78; N, 16.7.

Deacylation of β-**8**, as done for **3**, afforded β-**9**, $[\alpha]^{20}D$ −55 (*c* 0.50, DMF) and $[\alpha]^{20}D$ −35 (*c* 0.25, H_2O). Two recrystallizations from water did not change the rotation: $[\alpha]^{20}D$ −36.1 ± 1.6 (*c* 0.25, H_2O); other properties agreed with known values.[4] Similarly, deacylation of α-**8** afforded 54% of α-**9**: mp 260–261°; $[\alpha]^{20}D$ −15.3 (*c* 0.5, H_2O); uv max like that of β-**9**; R_f 0.21 in TC.

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.9; H, 5.02. Found: C, 39.5; H, 4.74.

7-(2,3,5-Tri-*O*-acetyl)-D-arabinofuranosyl)-N^2-nonanoylguanine (10).—The 7 isomer **10** from the Florisil column was a solid foam: uv max like that of **3**;[14] R_f 0.28–0.38 dumbbell shaped; α and β anomers?) in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.1; H, 6.57; N, 12.2.

9-(2,3,5-Tri-*O*-acetyl)-D-arabinofuranosyl)-N^2-nonanoylguanine (12).—The 9 isomer **12** from the Florisil column was a solid foam: uv max like that of **6**;[11] R_f 0.10 in TA; nmr ($DCCl_3$) δ 7.83 (s, H-8 of α-**12**), 7.78 (s, H-8 of β-**12**), 6.05 (d, $J_{1',2''}$ = 2.5 Hz, H-1′ of α-**12**) with the H-1′ of β-**12** not being definitely located. The relative areas of the H-8 peaks for α:β were 4.3:1.2. CD results confirm that major product is α anomer.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. found: C, 54.1; H, 6.57; N, 12.9.

A portion of **12** was deacylated to **13**, whose CD indicated it to be mainly α anomer and whose properties were like those of an authentic sample of α-**13**[8b] and not β-**13**.[8a]

7-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)-N^2-nonanoylguanine (17).—The 7 isomer **17** from the Florisil column was a solid foam: $[\alpha]^{23}D$ +20 (*c* 0.50, $CHCl_3$); nmr (DMSO-d_6) δ 8.32 (s, H-8 of β-**17**), 8.18 (s, H-8 of α-**17**), 6.66 (d, $J_{1',2'}$ = 5 Hz, H-1′ of α-**17**), 6.18 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of β-**17**) with the respective peak areas for the α:β anomers being 1:2; uv max was like that of **3**; R_f 0.31–0.39 in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.3; H, 6.38; N, 12.5.

For uv analysis, some **17** was separated by thin layer chromatography using multiple development (5 times) with ether–ethyl acetate (6:4) as solvent to afford two spots with R_f 0.33 and 0.46. These were eluted and their uv measured. The maxima of both occurred at wavelengths identical with that reported above for the original mixture. Hence both are 7 isomers and must be anomers.

(11) The uv is similar to N^2-acetyl-9-benzylguanine[12] and N^2-acyl-9-alkylguanines.[13]

(12) B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.*, **15**, 1066 (1967).

(13) K. Nagasawa and Y. Kato, *ibid.*, **16**, 1674 (1968).

(14) The uv is similar to N^2-acetyl-7-benzylguanine.[12]

(15) The uv is similar to 7-benzylguanine.[12]

9-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)-N^2-nonanoylguanine (18).—The 9 isomer **18** from the Florisil column was a solid foam: $[\alpha]^{22}D$ −43 (*c* 0.50, $CHCl_3$); nmr (DMSO-d_6) δ 8.10 (s, H-8 of β-**18**), 7.94 (s, H-8 of α-**18**), 5.95 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of β-**18**) with H-1′ of α-**18** not discernible above noise level, but perhaps at 6.3; the peak areas for H-8 of α:β are 1:6; uv max was like that of **6**; R_f 0.11 in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.3; H, 6.38; N, 12.5.

Registry No.—**3** (α isomer), 27460-34-0; **3** (β isomer), 27460-35-1; **5**, 27460-36-2; **6** (α isomer), 27460-37-3; **6** (β isomer), 27460-38-4; **8** (α isomer), 27460-39-5; **8** (β isomer), 27460-40-8; **9** (α isomer), 27462-38-0; **9** (β isomer), 27462-39-1; **10**, 27462-40-4; **12** (α isomer), 27462-41-5; **12** (β isomer), 27462-42-6; **17** (α isomer), 27617-86-3; **17** (β isomer), 27462-43-7; **18** (α isomer), 27570-86-1; **18** (β isomer), 27462-43-7.

Furano Compounds. XII. Synthesis of Furano[2,3-*b*]xanthones

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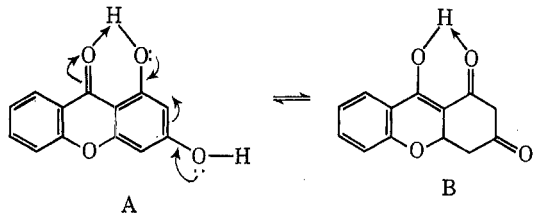
Syntheses of furano[2,3-*b*]xanthones from 3-hydroxyxanthone have been recorded earlier.[1b] Since many naturally occurring xanthones possess a phloroglucinol unit, attempts have now been made to add a furan ring to 1,3-dihydroxyxanthone.

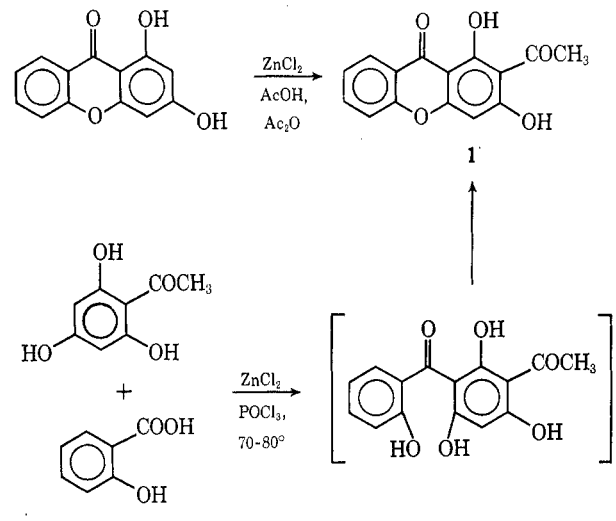
For the addition of a [2,3-*b*]-fused furan ring, the essential step is to introduce a 2-formyl or 2-acetyl group into the 1,3-dihydroxyxanthone molecule. 1,3-Dihydroxyxanthone undergoes formylation to yield 1,3-dihydroxy-4-formylxanthone.[2] However, acetylation of 1,3-dihydroxyxanthone under normal Friedel–Crafts or Fries conditions results in a mixture of products. Using freshly fused $ZnCl_2$, HOAc, and Ac_2O, Badawi, *et al.*,[3] acetylated 2-methyl-5,7-dihydroxychromone to get 2-methyl-5,7-dihydroxy-6-acetylchromone. When 1,3-dihydroxyxanthone was submitted to acetylation under these conditions, a single crystalline product could be obtained. This was identified as 1,3-dihydroxy-2-acetylxanthone (**1**).

The reactivity of the 2 position of 1,3-dihydroxyxanthone may be attributed to the presence of its 2,4-dihydroxybenzoyl moiety A which may undergo tautomeric change to a β-diketonic structure B containing a reactive methylene group in the 2 position.



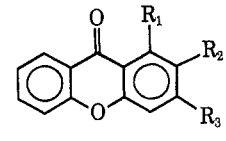
A B

The identity of **1** has been proved by another synthesis involving condensation of phloroacetophenone with salicylic acid in the presence of freshly fused $ZnCl_2$ and $POCl_3$. This reaction probably entails the nonchelated *p*-hydroxyl group in the formation of the γ-pyrone ring.

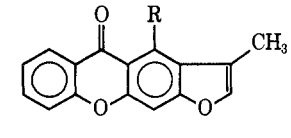


Location of the acetyl group at the 2 position is confirmed by the fact that **1** affords a new 1,2,3-trihydroxyxanthone upon Dakin oxidation. The trimethyl ether of this is different from 1,3,4-trimethoxyxanthone.[2] On acetylation using $B(OAc)_3$ and Ac_2O, 1,2,3-diacetoxyxanthone gave 1-hydroxy-2,3-diacetoxyxanthone, since the chelated hydroxyl forms a boracetate complex while the nonchelated hydroxyls undergo normal acetylation. Acetylation using Ac_2O and a drop of pyridine yielded 1,2,3-triacetoxyxanthone. Methylation of 1-hydroxy-2,3-diacetoxyxanthone using methyl iodide and silver oxide in acetone yielded 1-methoxy-2,3-diacetoxyxanthone which on hydrolysis with alkali gave 1-methoxy-2,3-dihydroxyxanthone.

Condensation of ethyl bromoacetate with **1** using acetone/K_2CO_3 yielded exclusively ethyl 1-hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetate (**2g**) since the 1-hydroxyl group is strongly chelated by both the xanthone and acetyl carbonyls. Hydrolysis of **2g** with 5% Na_2CO_3 in acetone gave 1-hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetic acid (**2h**). When heated with sodium acetate/acetic anhydride, **2h** underwent cyclization with decarboxylation and acetylation yielding 1-acetoxy-3-methylfurano[4,5-*b*]xanthone (**3a**). Hydrolysis with 5% alcoholic potash smoothly converted it into the required 1-hydroxy-3-methylfurano[2,3-*b*]xanthone **3b**.



2a, R_1, R_2, R_3 = OH
b, R_1, R_2, R_3 = OCH_3
c, R_1 = OH; R_2, R_3 = $OCOCH_3$
d, R_1, R_2, R_3 = $OCOCH_3$
e, R_1 = OCH_3; R_2, R_3 = $OCOCH_3$
f, R_1 = OCH_3; R_2, R_3 = OH
g, R_1 = OH; R_2 = $COCH_3$; R_3 = $-OCH_2COOEt$
h, R_1 = OH; R_2 = $COCH_3$; R_3 = $-OCH_2COOH$



3a, R = $OCOCH_3$
b, R = OH

(1) (a) Regional Engineering College, Warangal-4 (AP), India. (b) Y. S. Agasimundi and S. Rajagopal, *J. Org. Chem.*, **30**, 2084 (1965); *Monatsh. Chem.*, **97**, 423 (1966); *Chem. Ber.*, **100**, 383 (1967).

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(3) M. M. Badawi and M. B. E. Fayez, *Tetrahedron*, **21**, 2965 (1965).