reaction of cytidine 5′-monophosphoric acid, or of cytidine and orthophosphoric acid under the same conditions. On the other hand, cytidine 2′(3′)-monophosphoric acid was extensively cyclized to **7**. Therefore, we conclude that the predominant pathway in the conversion **6** → **7** proceeds *via* a direct ring opening of the anhydro link by orthophosphate to yield cytidine 2′-monophosphoric acid (**6c**) which then undergoes cyclization to **7**.

Discussion

The synthetic methods described in this paper provide easy routes to a variety of pyrimidine anhydronucleosides, many of which have not been previously described[10] or have been accessible only with difficulty. Because our method utilizes free sugars as starting materials, it is equally applicable, for example, to the synthesis of L nucleosides from the readily available L-arabinose.[11,12] A great variety of nucleosides could be generated by varying the sugars and electrophiles used in the standard synthesis.

(10) M. Ikehara, M. Kaneko, and Y. Nakahara, *Tetrahedron Lett.*, 4707 (1968).

Registry No.—**2**, 36994-58-8; **4a**, 10212-28-9; **4b**, 36963-54-9; **6a**, 36963-55-0; **6b**, 10212-20-1; **9**, 36963-57-2; **11**, 36963-58-3; **12**, 33886-19-0; **14**, 27963-97-9; **16**, 36963-61-8; **18**, 27964-04-1; **20**, 36959-85-0; **21**, 36959-86-1.

Acknowledgments.—We gratefully acknowledge Dr. Leslie E. Orgel for his support of this work and for many helpful discussions. We also wish to thank Dr. Sheldon S. Hendler for his continued encouragement, and Mr. William D. Fuller for technical assistance. Financial support from the National Science Foundation (Grant GB 24837) and from the National Institutes of Health (Grant CA 12960) is gratefully acknowledged.

(11) D. T. Gish, G. L. Neil, and W. J. Wechter, *J. Med. Chem.*, **14**, 882 (1971); R. L. Tolman and R. K. Robins, *ibid.*, **14**, 1112 (1971).
(12) A. Holy, *Tetrahedron Lett.*, 189 (1971).

Elimination Reactions on the Di- and Trimesylated Derivatives of N^3-Benzyluridine

TADASHI SASAKI,* KATSUMARO MINAMOTO, AND HIDEAKI SUZUKI

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Received February 8, 1972

To investigate the base-catalyzed elimination reactions on multiply mesylated pyrimidine ribonucleosides, N^3-protected uridine derivatives, 3-benzyl-2′,3′-di-*O*-mesyluridine (**7**) and 3-benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**), were synthesized as model compounds, which would be less likely to undergo cyclonucleoside formation. Sodium benzoate catalyzed elimination reaction on **7** and **8** gave the 2′-uridinenes, **9** and **17**, with a mesyloxy group at $C_{2'}$, which were converted to the crystalline 2′-uridinenes, **10** and **11**. Treatment of **10** with potassium carbonate gave a new class of compound, *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**). **8** with sodium acetate and sodium iodide gave 5′-substituted compounds, **18** and **19**, respectively. **8** with potassium carbonate gave 2′,3′-epoxy nucleoside (**20**) and **13**. This suggests the intervention of two synchronous reaction paths.

Although didehydronucleosides are potentially useful intermediates for the transformations of the sugar moieties of nucleosides, examples of their use in synthesis are limited.[1,2] This reflects the fact that this class of compounds are less accessible than the cyclonucleosides. In the pyrimidine series, 2′,3′-[3-6] and 3′,4′-unsaturated[7] nucleosides have been obtained by base-catalyzed elimination reactions. An elegant synthesis of 4′,5′-unsaturated uridine was also reported.[8] However, similar investigations on the introduction of 2′,3′-unsaturated bonds into the ribonucleosides are quite few.[4,9] This spurred us to examine the direction of base-catalyzed elimination reactions on N^3-protected uridine derivatives, where cyclonucleoside formation was considered less probable.

This paper deals with a simple revised method for selective N^3-benzylation of uridine and its derivatives, and the results of some elimination studies on their di- and tri-O-mesylated derivatives.

Preparation of the Starting Materials for the Elimination Reactions.—Benzylation of uridine and its derivatives was studied previously for the purpose of working out selective 2′-*O*-benzylation required for ribooligonucleotide synthesis.[10-12] In these cases, concomitant N^3-benzylation was also noted. For the present purpose, it was necessary to find better reaction conditions for the selective N^3-benzylation. Combination of benzyl chloride and potassium carbonate in a mixture of acetone and *N*,*N*-dimethylformamide (DMF) as a medium eventually proved to be satisfactory. Thus, 5′-*O*-trityluridine (**1**) (Scheme I) with a slight excess of benzyl chloride and potassium carbonate gave exclusively 3-benzyl-5′-*O*-trityluridine (**2**) after 3-hr reflux in a mixture containing equal amounts of acetone and DMF. The use of benzyl bromide revealed at least one more product in a lesser amount. Detritylation of **2** gave 3-benzyluridine (**3**)[11,12] in good yield. To establish structure **3**, 2′,3′-*O*-isopropylideneuridine (**4**) was benzylated to give 3-benzyl-2′,3′-*O*-isopropylideneuridine (**5**) as a homogeneous foam whose nmr spec-

(1) J. R. McCarthy, Jr, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968).
(2) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffat, *ibid.*, **93**, 4323 (1971).
(3) J. P. Horwitz, J. Chua, M. Noel, and J. T. Donnatti, *J. Org. Chem.*, **32**, 817 (1967).
(4) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *ibid.*, **31**, 205 (1966).
(5) J. P. Horwitz, J. Chua, M. A. Da Rooge, and M. Noel, *Tetrahedron Lett.*, 2725 (1964).
(6) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, 1343 (1966).
(7) J. Zemlicka, R. Gasser, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **92**, 4744 (1970).
(8) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, **88**, 5684 (1966).
(9) W. H. Ruyle, T. Y. Shen, and A. A. Pachett, *J. Org. Chem.*, **30**, 4353 (1965).
(10) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 3459 (1956).
(11) N. Imura, T. Tsuruo, and T. Ukita, *Chem. Pharm. Bull.*, **16**, 1105 (1968).
(12) H.-U. Blank and W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **742**, 1 (1970).

trum was compatible with structure **5**. Treatment of **5** with 80% acetic acid yielded **3**. The reaction sequences **1** → **2** → **3** and **4** → **5** → **3** firmly established the position of benzylation in **2** and also in **5**. Uridine itself was analogously benzylated at N^3 in 72% yield. Imura and coworkers[11] also carried out the direct benzylation on uridine using benzyl bromide and sodium hydride in dimethyl sulfoxide, and obtained **3** in 30.5% and N^3,2′-*O*-dibenzyluridine in 33% yield. The 5′-*O*-trityl group in **2** is so labile to acid that attempted purification of **2** on silica gel resulted in complete conversion to **3**. Mesylation of **3** smoothly gave the 2′,3′,5′-tri-*O*-mesyl derivative **8**, thus giving further support to the assigned structures, since we have ample experience that the position N^3 of uridine cannot be mesylated at room temperature even with a large excess of mesyl chloride, if the work-up involves treatment with water. **2** was mesylated quantitatively to the 2′,3′-di-*O*-mesyl derivative **6**, which was converted to **7** in good yields.

The nmr spectra of these compounds showed neither NH signals nor the known characteristic splittings of H^5 signals due to the long-range interaction with the N^3 proton.[13]

Elimination Reactions on 3-Benzyl-2′,3′-di-*O*-mesyluridine (7) and 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8).—Reaction of **7** with excess sodium benzoate in DMF gave the starting material **7** (23.6%) and 1-(3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**9**) as a foam (37%) as shown in Scheme II. Its nmr spectrum exhibited a doublet of doublets at δ 6.7 with equal splittings (1.6 Hz) and a triplet at δ 5.95 (J = 1.6 Hz). The signal of $H_{4'}$ appeared at δ 5.25 (broad doublet, J = 3.3 Hz). The formation of another product in much smaller amount was indicated by thin layer chromatography, but repeated attempts to isolate it were unsuccessful. Mesylation of **9** gave crystalline 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**), which was easily substituted with sodium iodide to yield 1-(3′,5′-dideoxy-5′-iodo-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**11**). This series of compounds, **9**–**11**, showed characteristic similarities in their nmr spectra,[14] as an example of which the 100-MHz spectrum of compound **10** is given in Figure 1. The structure assigned to **10** (and therefore that of **9**, **11**, and **17**) is based upon the following considerations and its conversion to compound **13**. The introduction of one olefinic bond suggested as possible structures A–D. The latter two, which might arise by a cis elimination of methanesulfonic acid, were ruled out because the presence of $H_{1'}$ and $H_{4'}$ is indicated in the nmr spectrum. The resonance of $H_{4'}$ and $H_{1'}$ of N^3-benzylated uridine derivatives usually lie in the range of 4.25–4.50 and 5.6–6.1 ppm, respectively, and are more or less comparable with those of uridine.[17] If a double bond is inserted between these protons, the observed signal centered at δ 5.12 can be reasonably assigned to $H_{4'}$. A chemical shift, δ 5.0, was reported for $H_{4'}$ in 2′,3′-dideoxycytidinene.[3] In the 60-MHz spectrum of **11** (see Experimental Section), the resonance of $H_{4'}$ appeared at δ 4.8–5.1 as a complex multiplet. Irradiation at δ 4.98 resulted in the collapse of the $C_{5'}$ protons (a pair of doublets at δ 3.28 and 3.38) into a singlet and of the other two protons (the doublet of doublets and the triplet at δ 6.76 and 6.22) into a similar doublet (J = 1.6 Hz). The final choice for structure A was given by a close inspection of the nmr spectra of **10** and its derivative **13** mentioned below. The quartet-like resonance of $H_{4'}$ at δ 5.12 is actually

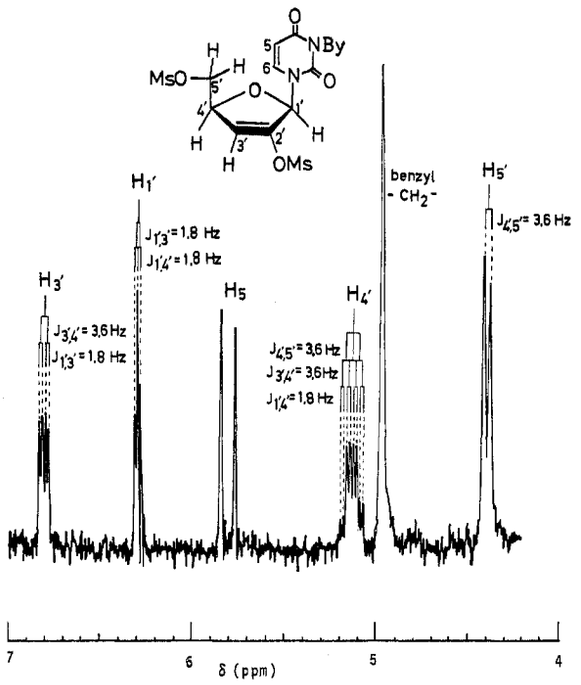
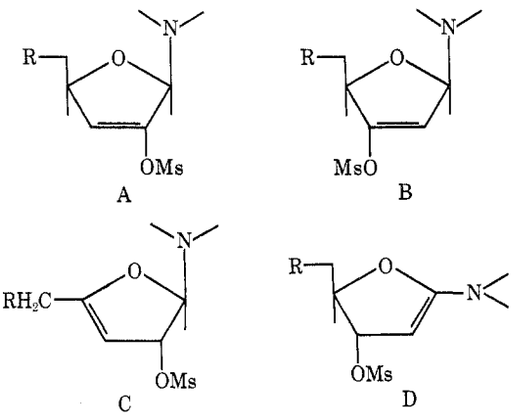


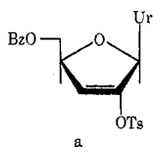
Figure 1.—Nuclear magnetic resonance spectrum of 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**) in DMSO-d_6 at 100 MHz.



R = OMs, I, OH, and $PhCO_2$

(13) A. F. Cook and J. G. Moffat, *J. Amer. Chem. Soc.*, **89**, 2697 (1967).

(14) Recently we synthesized 1-(5′-*O*-benzoyl-3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (a) *via* an unambiguous route. It



a

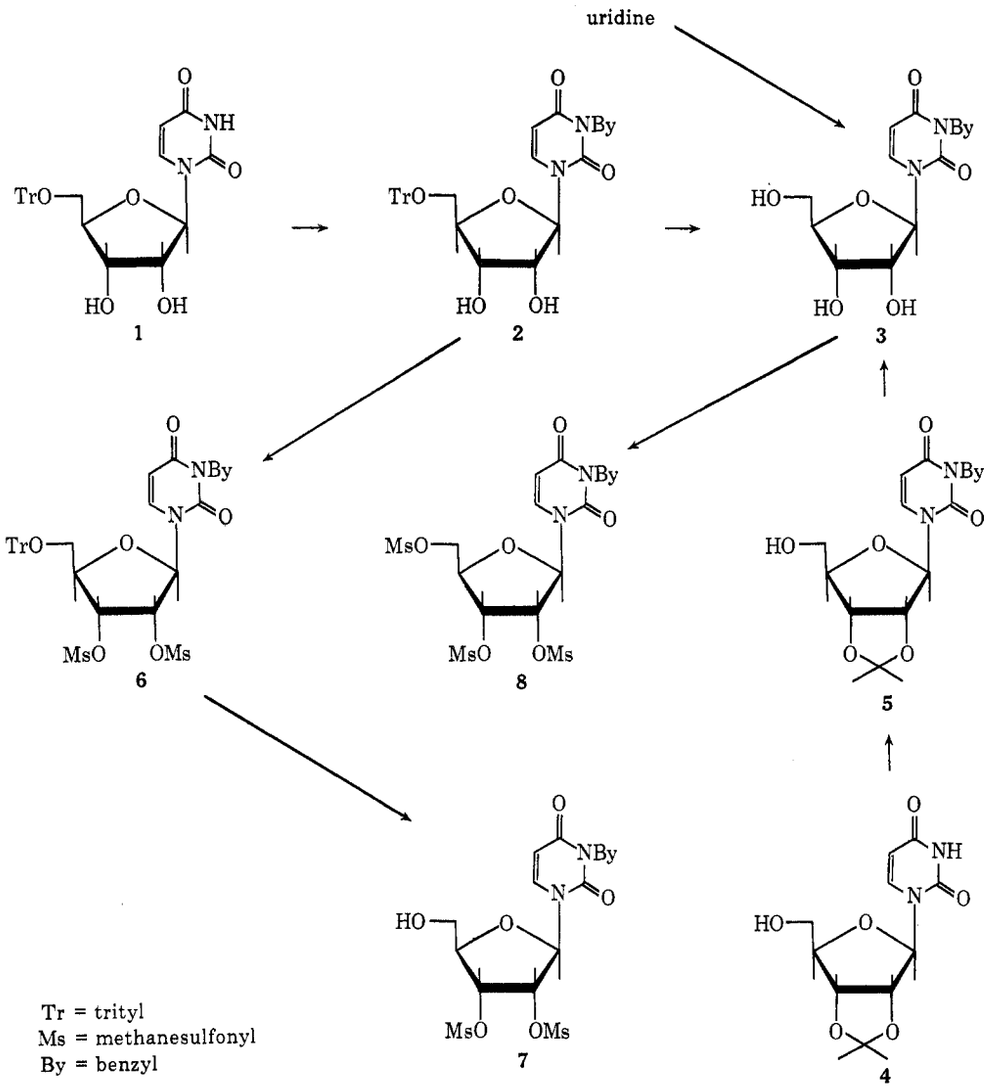
might be noted that the low field resonances (of $H_{1'}$ and $H_{3'}$) of compound a, 5-*O*-benzoyl-2-*O*-tosyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranoside,[15] and 1-(2′,3′-dideoxy-2′-bromo-β-D-*glycero*-pent-2′-enofuranosyl)uracil[16] are strikingly similar in their splitting patterns; *i.e.*, a triplet and a doublet of doublets, in this order downward, were observed for the two low field furanose–ene protons. $H_{4'}$ in compound a gave a distinct octet with equal splittings of 1.6 Hz (to be described in a succeding paper).

(15) J. Hildesheim, A. Gaudemer, and S. D. Gero, *Chem. Ind. (London)*, 94 (1970).

(16) Y. Furukawa, Y. Yoshiko, K. Imai, and M. Honjo, *Chem. Pharm. Bull.*, **18**, 554 (1970).

(17) F. E. Hruska, *J. Amer. Chem. Soc.*, **93**, 1795 (1971).

SCHEME I



an octet with a relative intensity[14] of 1:1:3:3:3:3:1:1, and with equal splittings of 1.8 Hz, which, along with the triplet at δ 6.29 and the doublet of doublets at δ 6.8, can be theoretically expected, if we suppose structure A to be actual, in which the assignments of $H_{1'}$ and $H_{3'}$ and the coupling constants of the whole sugar protons are as shown in Figure 1. It is important to note that the signal of $H_{4'}$ contains two similar coupling constants of 3.6 Hz, one of which is due to the $H_{4'},H_{5'}$ interaction. The other should be assigned to a proton–proton interaction other than the 1′,4′ or allylic coupling on the basis of its magnitude. Hence, this splitting of 3.6 Hz must be assigned to a vicinal coupling with $H_{3'}$, which has a reasonable dihedral angle of ~60° with $H_{4'}$ as indicated by a molecular model. Thus, the assignments of $H_{1'}$ and $H_{3'}$ as shown are a logical result from the above arguments.[18,19] Attempts to convert **10** to **12** by partial hydrogenation were unsuccessful. When **10** was treated with potassium carbonate in hot DMF, a new crystalline compound, *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**), was obtained as the major product. The structural assignment is based on its analysis, uv (λ_{max} 256 nm), ir (ν C=O 1733, 1709, and 1668 cm^{-1}), nmr, and mass spectrum. In the ir spectra of 2′- and 3′-ketouridine and their derivatives, characteristic absorptions of the furanose ketones were observed between 1750 and 1800 cm^{-1}.[13,20] The absorption of **13** at 1733 cm^{-1} suggested the presence of a conjugated carbonyl on the furanose ring. Interestingly, as Moffatt and coworkers experienced also,[13] this compound had a tendency for covalent hydration, which rendered its purification troublesome. Its nmr spectrum exhibited four one-proton multiplets at δ 1.35, 1.57, 2.20, and 4.75 as shown in Figure 2. The anomeric proton appeared at δ 5.55 as a sharp singlet, revealing its insulation from the other sugar protons.[21] The two-proton singlet at δ 4.9 is due to the benzyl methylene. In this case, a chemical shift at as high as 1.35 or 1.57

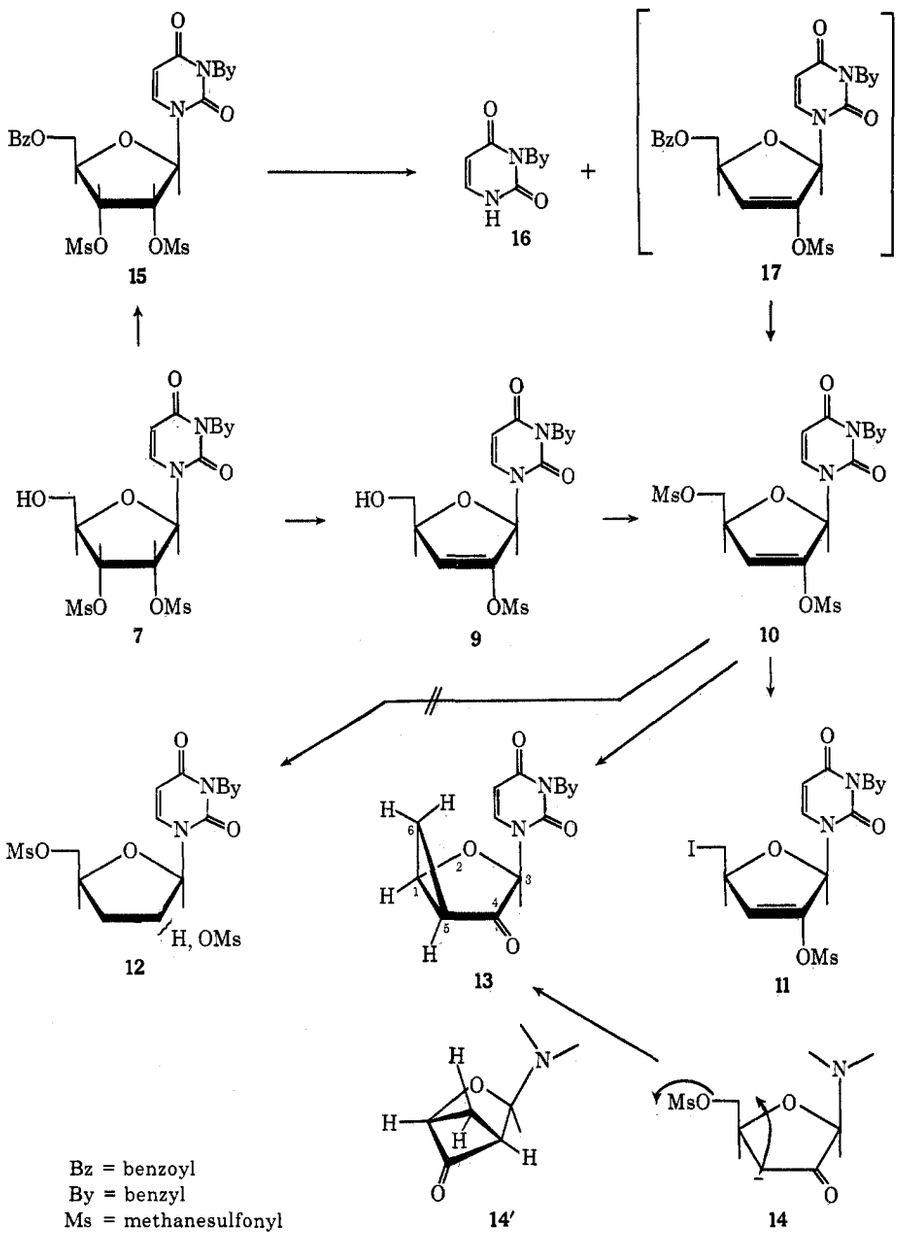
(18) The anomeric protons of some didehydronucleosides resonate at lower fields than the olefinic protons (see ref 1, 3, and 7). In our case, however, the strong deshielding effect by the mesyl group must be considered. For a deshielding effect by a mesyl in a saturated system, compare compounds **7**, **8**, and **5** in the Experimental Section.

(19) If structure B is to be assigned to **10**, the $H_{4'}$ signal should give a septet with a relative intensity of 1:1:3:3:3:1:1 and with equal splittings of 1.8 Hz, while the other protons, $H_{1'}$ and $H_{2'}$, should appear as the same doublet of doublets with a relative intensity 1:1:1:1 and equal splittings of 1.8 Hz.

(20) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

(21) The anomeric proton of 2′-ketouridine[13] and 2′-ketocytidine[20] resonates, respectively, at δ 5.42 and 5.48, each as a sharp singlet.

SCHEME II



ppm should be ascribed to a cyclopropane proton. The cyclopropane proton adjacent to the carbonyl in cyclopropyl methyl ketone resonates at δ 1.86[22] and that in methyl 2-bromocyclopropanecarboxylate at δ 2.07.[23] Hence, the sextet at δ 2.20 can be reasonably assigned to H_5. Thus, complete analyses for these complicated signals were achieved as shown, taking $J_{1,6A} = J_{1,5} = J_{5,6B} = 4.4$ Hz as a key coupling constant. Compound **13** is a new type of nucleoside derivative for which there is no literature analog to permit direct spectral comparison, and its material shortage impeded further chemical modification. The formation of **13** from **10** is also mechanistically justified by the intermediacy of the β-keto anion **14** formed after demesylation of **10**.[24] A ring expansion reaction *via* a similar intramolecular cyclopropane formation has been recorded.[25] A fused cyclobutanone structure **14'** can be excluded, since the β protons of cyclobutanone itself resonate at δ 1.96[26] and the anomeric proton should give a doublet ($J \cong 3$ Hz) as predicted by a molecular model study, on the basis of which the dihedral angle between the anomeric and its adjacent proton is expected to be approximately 60° in this rigid system. Furthermore, cyclobutanone absorbs at 1775 cm^{-1} in its ir spectrum.[27]

Some principal fragmentation patterns in the mass spectra of **10**, **11**, and **13** are given in Schemes III and IV. Molecular ions for **10** and **11** could not be measured because of their too high molecular weights.

(22) F. A. Bovey, "NMR Data Tables for Organic Compounds," Vol. 1, Interscience, New York, N. Y., 1967, p 97.

(23) See ref 22, p 93.

(24) We have demonstrated sodium benzoate catalyzed detosylation rather than desulfonyloxylation of compound a (to be described in a succeeding paper).

(25) H. W. Whitlock, Jr., and P. F. Schatz, *J. Amer. Chem. Soc.*, **93**, 3837 (1971).

(26) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 198.

(27) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 149.

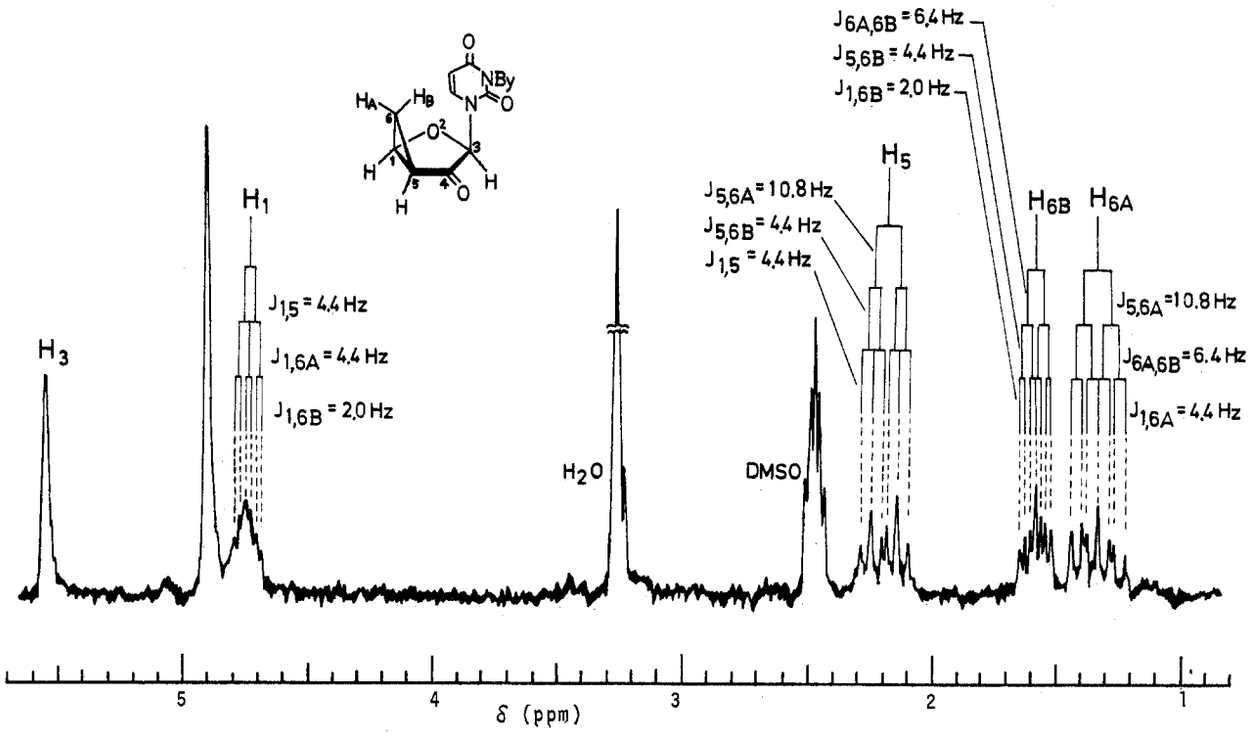
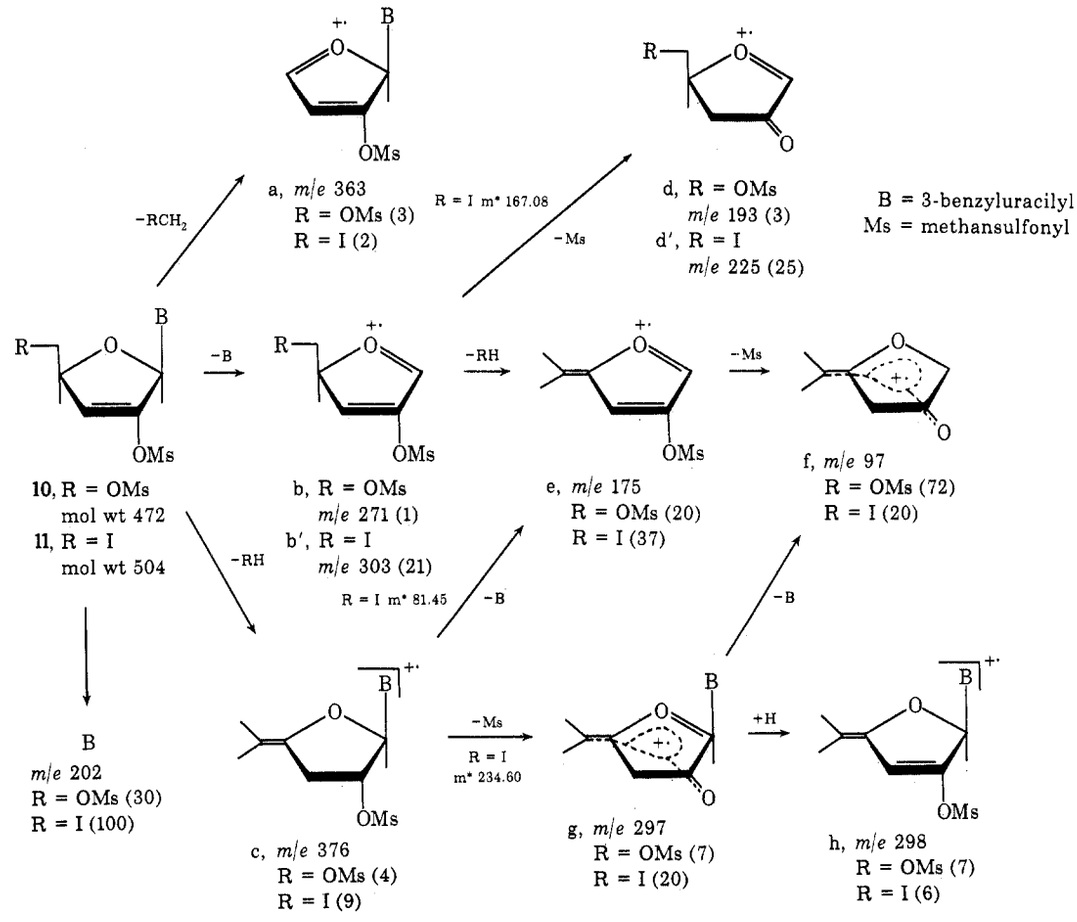


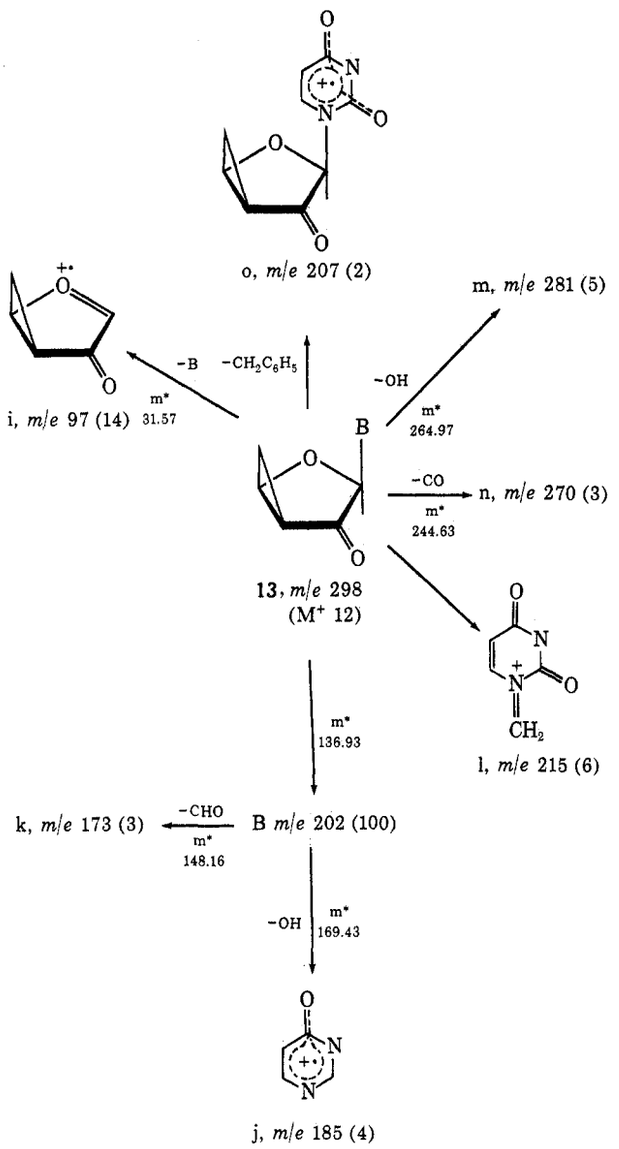
Figure 2.—Nuclear magnetic resonance of *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**) in DMSO-d_6 at 100 MHz.

SCHEME III[a]



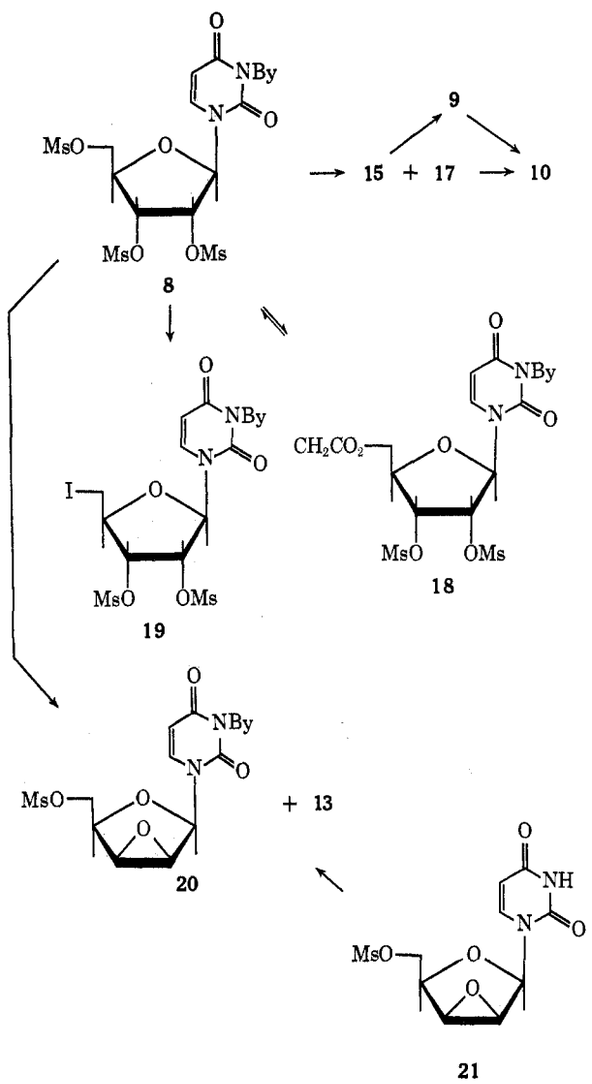
[a] Base peak for **10**: *m/e* 91 (benzyl or tropylium cation). Values in parentheses are relative intensities.

SCHEME IV



[a] Values in parentheses are relative intensities.

SCHEME V



Oxonium radicals like a, b, b′ (Scheme III) and i (Scheme IV) have enough precedents in the mass spectra of carbohydrates and nucleosides.[28,29] The 4′,5′-dehydro types of ions, c, e, f, g, and h, have also literature analogs.[30] Although metastable peaks appeared quite rarely in the case of **10** and **11**, the fragmentation sequences shown are reasonable. It seems interesting to note possible identity of ion f with ion i. The dehydronucleosides **10** and **11** seem to have a striking tendency of aromatization, thus limiting chances to cleave the bond between $C_{2'}$ and $C_{3'}$. Hence, as far as our qualitative analyses are concerned, decisive data were not obtained for a choice between A and B.

Since we noted that 3-benzyl-2′,3′-di-*O*-mesyl-5′-*O*-trityluridine (**6**) did not react with sodium benzoate under analogous conditions, presumably for steric reasons, a similar elimination reaction was carried out on 3-benzyl-5′-*O*-benzoyl-2′,3′-di-*O*-mesyluridine (**15**). Thin layer chromatography indicated that the reaction proceeded more or less similarly as in the case of **7**. The action of excess potassium carbonate or potassium *tert*-butoxide on **15** gave 3-benzyluracil (**16**) and 1-(3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**17**) as major product, which was directly converted to **10** *via* debenzoylation and mesylation.

Similarly, 3-benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) gave compounds **15** and **17** in 35 and 48% yield, respectively (Scheme V). The facile nucleophilic displacement of 5′-*O*-mesyl or tosyl groups is well documented,[31-33] and in this case **17** must have formed *via* **15**. With a view to converting **15** to highly crystalline **8**, **15** was treated with excess ammonia to give, unexpectedly, the noncrystalline compound **9** as major product, which was mesylated again to give **10**. Sim-

(28) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

(29) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, San Francisco, Calif., 1964, Chapter 27.

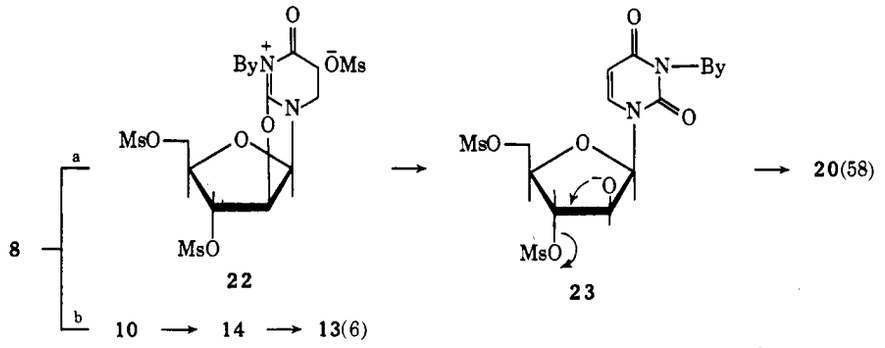
(30) A. M. Lawson, R. N. Stillwell, M. M. Tacker, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **93**, 1014 (1971).

(31) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **82**, 2794 (1960).

(32) N. C. Yong and J. J. Fox, *ibid.*, **83**, 3060 (1961).

(33) E. Benz, N. F. Elmore, and L. Goldman, *J. Org. Chem.*, **30**, 3067 (1965).

SCHEME VI



ilar treatment of **17** also gave **10**. The action of sodium acetate on **8** yielded 3-benzyl-5′-*O*-acetyl-2′,3′-di-*O*-mesyluridine (**18**) as the sole product, which was reconverted to **8**. Substitution of **8** with sodium iodide also proceeded smoothly to give 3-benzyl-5′-deoxy-5′-iodo-2′,3′-di-*O*-mesyluridine (**19**) in good yield. Treatment of **8** with potassium carbonate gave no olefinic compounds. Instead, 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil (**20**) was obtained as major product with a small amount of **13** (Scheme VI). Characterization of **20** was difficult but was eventually carried out by simple benzylation of 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil.[34] As far as this particular experiment is concerned, two synchronous reaction paths are now obvious[35] (Scheme VI).

Discussion

The synthetic use of 2′,3′-unsaturated nucleosides has been limited to their use as precursors for 2′,3′-dideoxynucleosides.[3,6,16] The principal reason for this is probably the lack of factors for selective attack by chemical reagents at the double bond, whereas the 4′,5′ double bond would offer at least *regiospecificity* as exemplified by the specific introduction of a fluorine atom into the 4′ position of adenosine.[2] From this point of view, our experimental data described above are interesting since (1) the base-induced β elimination generally occurred specifically to leave a mesyl group at $C_{2'}$; (2) the strong electron-withdrawing mesyl group might regulate the attack, *e.g.*, of a dipolar addition reagent,[36] and (3) the mesyl group might be chemically modified without difficulty. Although we initially expected that the bulky aglycon moiety would exert a strong steric influence, it was rather surprising that the 2′ hydrogen was invariably more open to the attack of the basic reagents regardless of the size of the 5′-O substituent. Apparently, the same thing is true regardless of the kind and size of basic catalyst, since even ammonia must have attacked the 2′ hydrogen. This observation seems to suggest that the sugar moieties in the nucleoside derivatives exert a specific effect on the orientation of β elimination, an effect which might be clarified by accumulation of further data. A central problem in this work was the necessity for discriminating between two possible products of type A and B, which was solved in this particular case by the close analyses of the nmr spectra of **10** and **13**. Compound **13** offers a new possibility for the chemical modification of nucleosides. Although the N^3-benzyl group on the uracil skeleton is known to resist the usual catalytic hydrogenolysis,[11,37] the results obtained by us may be of some help after introduction of an appropriate protecting reagent.

(34) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).

(35) The possible formation of the cyclonucleoside **22** was once suggested by a referee.

(36) As one referee suggested, a resonance effect stemming from electron-donating contribution of oxygen would be expected in $CH_3SO_2CH{=}CH{-}$. A steric effect might also be considered.

Experimental Section

All melting points are uncorrected. The electronic spectra were measured on a JASCO Model ORD/UV-5 spectrophotometer. The nmr spectra were recorded with a JNM C-60 HL ($CDCl_3$) and Varian HA-100 spectrometer (DMSO-d_6), TMS being used as an internal standard. In the case of the hydroxyl-containing compounds, measurements after D_2O exchanges were also carried out. The mass spectra were measured by a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 75–80 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 200–250°. Wakogel B-5 silica gel, supplied by the Wako Pure Chemical Industries, was used for thin layer chromatography, while column chromatography was carried out using Mallinkrodt silicic acid (100 mesh) after washing with ethyl acetate.

3-Benzyl-5′-*O*-trityluridine (2).—To a solution of 5′-*O*-trityluridine (1) (2.12 g, 4 mmol) in a mixture of DMF (4 ml) and acetone (4 ml) were added benzyl chloride (0.58 ml, 5 mmol) and anhydrous potassium carbonate (0.78 g, 5.6 mmol). The mixture was gently refluxed for 3 hr, cooled to room temperature, and poured into ice–water (300 ml). The precipitating solid was filtered and dried (2.48 g). Thin layer chromatography at this stage showed one main product with trace amounts of the starting material and trityl carbinol. Preparative thin layer chromatography with the use of silica gel and a mixed solvent, chloroform–ethyl acetate (3:1, v/v), gave 1.96 g (86%) of **2** as a foam.

Anal. Calcd for $C_{35}H_{32}N_2O_6$: C, 72.90; H, 5.59; N, 4.86. Found: C, 73.13; H, 5.56; N, 4.72.

3-Benzyluridine (3). A.—The crude solid product **2** obtained by the same procedure as above was treated with 80% acetic acid at 90° for 1 hr. After the solvent was evaporated off, the residual paste was dissolved in benzene and again evaporated. The same procedure was followed a couple of times to give a pale yellow semisolid, which was triturated with ether (30 ml), and the ethereal solution was removed by decantation. This procedure was repeated five times. After standing overnight, the combined ethereal solutions gave a second crop, which was filtered, combined with the above obtained solid, and recrystallized from methanol to give **3** as colorless needles (1 g, 75%), mp 182° (lit.[11] mp 175.5–176.5°).

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.55; H, 5.54; N, 8.19.

B.—Uridine (977 mg, 4 mmol), benzyl chloride (0.7 ml, 6 mmol), and potassium carbonate (0.95 g, 6.8 mmol) were combined in a mixture of DMF (4 ml) and acetone (4 ml), and the mixture was heated to reflux for 4 hr. After acetone was evaporated off, the mixture was poured into ice–water (30 ml), and

(37) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3478 (1971).

the pasty precipitate was extracted with ethyl acetate (250 ml). The extract was recrystallized from methanol to give 0.96 g (72%) of colorless crystals, mp 181–182°. The identity of the product with a specimen prepared by the procedure a was confirmed by infrared spectroscopy and the mixture melting point determination.

C.—2′,3′-*O*-Isopropylideneuridine (4) (284.4 mg, 1 mmol), benzyl chloride (0.17 ml, 1.5 mmol), and potassium carbonate (240 mg, 1.7 mmol) were combined in a mixture of DMF (1 ml) and acetone (2 ml), and the mixture was heated to reflux for 2 hr. After the solvent was evaporated, the residual oil was triturated with water (5 ml) and the water was decanted off. The residue was taken into chloroform (100 ml), dried over sodium sulfate, evaporated to a paste, and applied on a silica gel column (30 × 1.5 cm). Elution with a mixed solvent, chloroform–ethyl acetate (3:1), gave **5** as a colorless, pure foam (0.28 g, 75%): nmr ($CDCl_3$) δ 1.35 (3 H, s, Me), 1.56 (3 H, s, Me), 2.86 (1 H, broad singlet, OH), 3.76 (2 H, m, 5′ CH_2), 4.25 (1 H, m, $H_{4'}$), 4.87 (2 H, broad singlet, $H_{2'}$ and $H_{3'}$), 5.03 (2 H, s, benzyl methylene), 5.59 (1 H, s, $H_{1'}$), 5.68 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 7.1–7.4 (5 H, m, Ph), 7.36 (1 H, d, $J_{5,6}$ = 8 Hz, H_6, partially merged with the phenyl signal). This sample was directly treated with 80% acetic acid at 95° for 2 hr. The reaction mixture was completely evaporated to a paste, which was recrystallized from methanol to give **3** (0.2 g).

3-Benzyl-2′,3′-di-*O*-mesyl-5′-*O*-trityluridine (6).—Compound **2** (1.835 g, 3.18 mmol) in dry pyridine (15 ml) was added with mesyl chloride (0.7 ml, 9 mmol), left at 0° for 8 hr, and then poured into ice–water (300 ml) to give a solid precipitate, which was filtered. The wet solid was dissolved in chloroform and dried with sodium sulfate. Evaporation of the solvent gave 2.24 g of a foam, which was purified by thin layer chromatography, using silica gel and a mixture, chloroform–ethyl acetate (3:1), to give a homogeneous foam (1.76 g, 85%). It is to be noted that the 5′-trityl group in the 3-benzyl compounds (**2** and **6**) is easily cleaved in attempts to separate by silica gel column using mixtures of chloroform and ethyl acetate as eluents.

Anal. Calcd for $C_{37}H_{36}O_{10}S_2N_2$: C, 60.65; H, 4.95; N, 3.82. Found: C, 60.68; H, 5.18; N, 3.75.

3-Benzyl-2′,3′-di-*O*-mesyluridine (7).—To an ice-cold stirred solution of **6** (1.5 g, 2.3 mmol) in chloroform (20 ml) was added HCl-saturated chloroform (5 ml) and the mixture was allowed to warm up to room temperature. After 1 hr of stirring at room temperature, the mixture was evaporated to a paste, which was taken into benzene and again evaporated. This procedure was followed several times. The paste was then digested with ether (10 ml) many times, until the ether washing gave no trityl-positive spot on tlc. Recrystallization of the semisolid residue from methanol gave **7** as colorless needles, mp 151–153° (0.72 g). A second crop (0.24 g) was obtained from the ether washings: total yield 85%; λ_{max}^{EtOH} 257 nm (ε 10,200); nmr (DMSO-d_6) δ 3.24 (3 H, s, Me), 3.28 (3 H, s, Me), 3.73 (2 H, broad singlet, 5′-CH_2), 4.28 (1 H, d, J = 3.4 Hz, $H_{4'}$), 4.98 (2 H, s, benzyl methylene), 5.38 (2 H, m, $H_{2'}$, $H_{3'}$), 5.85 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.10 (1 H, d, J = 4.6 Hz, $H_{1'}$), 7.24 (5H, s, Ph), 7.97 (1H, d, $J_{5,6}$ = 8 Hz, H_6).

3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8).—To an ice-cold solution of **3** (1.03 g, 3.1 mmol) in anhydrous pyridine (15 ml) was added mesyl chloride (1.15 g, 10 mmol) and the mixture was left at 0° overnight. Then the reaction mixture was left at room temperature for 1 hr and poured into ice–water (300 ml). The solid precipitate was filtered, dissolved in chloroform, dried over sodium sulfate, and evaporated to a paste. Crystallization from a mixture of ethanol and ethyl acetate gave **8** as colorless, fine needles (1.58 g, 90%): mp 181–183°; λ_{max}^{EtOH} 257 nm (ε 9900): nmr (DMSO-d_6) δ 3.15 (3 H, s, Me), 3.25 (3 H, s, Me), 3.30 (3 H, d, Me), 4.50 (3 H, broad singlet, an overlap of the signals of $H_{4'}$ and 5′-CH_2), 4.99 (2 H, s, benzyl methylene), 5.35 (1 H, t, $J_{2',3'}$ = 6, $J_{3',4'}$ = 4.0 Hz, $H_{3'}$), 5.63 (1 H, q, $J_{2',3'}$ = 6, $J_{1',2'}$ = 4.5 Hz, $H_{2'}$), 5.83 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.06 (1 H, d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$), 7.24 (5 H, s, Ph), 7.75 (1 H, d, $J_{5,6}$ = 8 Hz, H_6).

1-(3′-Deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (9).—3-Benzyl-2′,3′-di-*O*-mesyluridine (7) (0.68 g, 1.38 mmol) and sodium benzoate (600 mg, 4.15 mmol) were combined in DMF (8 ml), and the mixture was heated at 110–120° for 1 hr. After cooling, the mixture was filtered *in vacuo* and the solid was washed with a small amount of ethanol. The filtrate was concentrated to half volume and poured into ice–water (100 ml). The pasty precipitate was filtered and the filtrate was extracted with ethyl acetate (2 × 50 ml). The ethyl acetate extracts were combined with the above obtained paste, dried over sodium sulfate, and evaporated to a paste. Tlc with the use of silica gel and 20% ethanol in benzene indicated a major product with a small amount of by-product, which ran on the tlc plate slightly faster than the former. The mixture was applied on a silica gel column (35 × 2 cm) and eluted with chloroform–ethyl acetate (2:1) to give the starting material (160 mg, 23.6%). Preparative thin layer chromatography was repeatedly carried out on the recovered product mixture, using silica gel plates and a solvent mixture, chloroform–ethyl acetate (3:1), to give **9** as a homogeneous foam (0.2 g, 37%): nmr ($CDCl_3$) δ 3.03 (3 H, s, Me), 3.78 (2 H, br t, 5′-CH_2), 5.04 (2 H, s, benzyl methylene), 5.25 (1 H, br d, $J_{3',4'}$ = 3.3 Hz, $H_{4'}$), 5.7 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 5.95 (1 H, t, J = 1.6 Hz, $H_{1'}$), 6.7 (1 H, dd, $J_{1',3'}$ = 1.6, $J_{3',4'}$ = 3.3 Hz, $H_{3'}$), 7.1–7.4 (5 H, m, Ph), 7.7 (1 H, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.74; H, 4.84; N, 7.32.

1-(3′-Deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (10).—To an ice-cold stirred solution of **9** (0.16 g, 0.4 mmol) in anhydrous pyridine (2 ml) was added mesyl chloride (0.1 ml), and the mixture was left at 0° overnight. The reaction mixture was then poured into ice–water (100 ml) and the separating oil was extracted with chloroform (3 × 50 ml). The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to a paste, which gradually crystallized on standing at room temperature under the presence of ethanol. Repeated crystallization from a mixture of ethanol and acetone gave **10** as colorless, fluffy crystals: mp 167–169° (80 mg, 42.5%); λ_{max}^{EtOH} 257 nm (ε 8800); nmr (DMSO-d_6) δ 3.12 (3 H, s, 2′-mesyl) and 3.43 (3 H, s, 5′-mesyl). For the signals of the other sugar protons see Figure 1. Additional signals lie at 7.23 (5 H, s, Ph) and 7.56 ppm (1 H, d, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{18}H_{20}N_2O_9S_2$: C, 45.77; H, 4.23; N, 5.93. Found: C, 45.85; H, 4.32; N, 5.76.

1-(3′,5′-Dideoxy-5′-iodo-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (11).—A mixture of **10** (0.15 g) and sodium iodide (0.3 g) in dry acetone (5 ml) was refluxed for 4 hr. After the solvent was evaporated, the residue was taken into ethyl acetate (50 ml) and the brown solution was washed with water (5 ml). This was then decolorized by shaking with 5% sodium thiosulfate solution, washed once with water (5 ml), and dried with sodium sulfate. Evaporation of the solvent gave a paste, which was chromatographed on a silica gel column using chloroform–ethyl acetate (3:1) as eluent. The main fraction gradually crystallized on standing at room temperature. Recrystallization from a mixture of ethanol and acetone gave **11** as colorless granules: mp 157° (75 mg, 68%); nmr ($CDCl_3$) δ 3.28 (1 H, d, J = 3.38 Hz, $H_{5'a}$), 3.38 (1 H, d, J = 2.0 Hz, $H_{5'b}$), 5.1 (2 H, s, benzyl methylene), 4.8–5.1 (1 H, complex multiplet, $H_{4'}$), 5.26 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.22 (1 H, t, J = 1.6 Hz, $H_{1'}$), 6.76 (1 H, dd, J = 3.2 and 1.6 Hz, $H_{3'}$), 7.1–7.6 (6 H, m, Ph and H_6).

Anal. Calcd for $C_{17}H_{17}O_6N_2SI$: C, 40.49; H, 3.40; N, 5.56. Found: C, 40.78; H, 3.43; N, 5.64.

***endo*-3-(3-Benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane** (13).—1-(3′-Deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (10) (0.11 g, 0.233 mmol) and anhydrous potassium carbonate (0.1 g, 0.73 mmol) were combined in a mixture of DMF (1 ml) and acetonitrile (1 ml), and the mixture was gently refluxed for 3.5 hr. After cooling, the inorganic solid was filtered and washed with a small amount of acetone. The combined filtrate and washings were concentrated *in vacuo*, dissolved in ethyl acetate (50 ml), washed with water (10 ml), and dried with sodium sulfate. The ethyl acetate solution was concentrated to a gum and chromatographed on a silica gel column using chloroform–ethyl acetate (3:1) as eluent, to give a crystalline compound, which was recrystallized from a mixture of acetone and ether to afford **13** as colorless needles of mp 163–166° (after drying under high vacuum at 90° for 5 days), yield 28 mg (40%).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.62; H, 4.73; N, 9.39. Found: C, 64.95; H, 4.82; N, 9.18.

Reaction of Potassium Carbonate with 3-Benzyl-5′-*O*-benzoyl-2′,3′-di-*O*-mesyluridine (15).—To a stirred cold solution of **7** (0.8 g, 1.62 mmol) in anhydrous pyridine (5 ml) was added benzoyl chloride (280 mg). After standing at room temperature overnight, the reaction mixture was poured into ice–water (30 ml) and the sticky precipitate was filtered, dissolved in chloro-

form (100 ml), and washed with 5% sodium bicarbonate (10 ml) and water (10 ml). The chloroform solution was dried over sodium sulfate and evaporated *in vacuo* to a paste, which weighed 0.96 g (100%) after drying in a desiccator under high vacuum for 20 hr. Thin layer chromatography with an aliquot of the product evidenced the reaction to be complete. The whole product was dissolved in DMF (7 ml), added with anhydrous potassium carbonate (555 mg, 4 mmol), and the mixture was heated at 110° for 20 min under stirring. The brown reaction mixture was evaporated *in vacuo* to a gum, which was dissolved in ethyl acetate (100 ml), washed with water (30 ml), dried over sodium sulfate, and again evaporated to a gum. Thin layer chromatography with the use of silica gel plates and a mixture of chloroform and ethyl acetate (3:1) revealed a major product running the half length of the plates with a slightly slower moving minor product. Preparative thin layer chromatography gave colorless crystals (**16**) of mp 183–184° (from ethyl acetate) from the slower moving band (20 mg); λ_{max}^{EtOH} 257 nm (ϵ 7200); nmr (DMSO-d_6) δ 5.12 (2 H, s, benzyl methylene), 5.84 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 7.42 (5 H, s, Ph), 7.55 (1 H, d, $J_{5,6}$ = 8 Hz, H_6), 11.14 (1 H, br, s, NH).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.49; H, 4.75; N, 13.68.

The faster moving impure material was combined with the mother liquor separated from **16**, and again submitted to preparative thin layer chromatography with the use of a mixture of chloroform and ethyl acetate (3:1). Complete purification was unsuccessful. The recovered total material (0.34 g of paste) was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and left at room temperature overnight. The mixture was evaporated to a paste, which was taken into ethyl acetate (50 ml) and washed with 5% sodium bicarbonate (10 ml) and water (10 ml). After drying over sodium sulfate, the ethyl acetate solution was evaporated *in vacuo* to a foam, which was treated with mesyl chloride (0.1 ml) in pyridine (3 ml) at 0° overnight. The reaction mixture was added with methanol (1 ml), left at room temperature for 30 min, and then evaporated *in vacuo* at a temperature below 45°. The residual paste was taken into ethyl acetate (50 ml), washed with water (10 ml), dried, and again evaporated to a gum, which gave 0.18 g of colorless crystals of mp 168° from a mixture of ethanol and ethyl acetate. Its identity with **10** was confirmed by infrared and ultraviolet spectral comparison.

Reaction of 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8) with Sodium Benzoate.—3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) (0.7 g, 1.22 mmol) and sodium benzoate (0.7 g, 4.88 mmol) were combined in DMF (10 ml) and the mixture was heated at 100–110° for 1 hr under stirring. After cooling, the mixture was poured into ice–water (300 ml) and the solid precipitate was filtered by suction. The semidry material was dissolved in chloroform (200 ml) and dried over sodium sulfate. Evaporation of the solvent gave a paste, an aliquot of which was examined by tlc to show two major spots of approximately equal intensities and two faster moving traces. The absence of the starting material was also indicated. The total paste was chromatographed on a silica gel column with the use of a mixed solvent, chloroform–ethyl acetate (5:1), to effect the separation of the major products as a slightly faster moving material A, foam, 0.23 g, and a slower running material B, foam, 0.255 g. Comparative thin layer chromatography suggested the identity of A with compound **17**. The total product A was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and the mixture was left at room temperature overnight. The reaction mixture was concentrated to a gum, which was taken into ethyl acetate (50 ml) and washed with 5% sodium bicarbonate (5 ml) and water (5 ml). The ethyl acetate solution was dried and evaporated to a paste, which was completely dried under high vacuum and treated with mesyl chloride (0.07 ml) in dry pyridine (1.5 ml) overnight. After the usual work-up, the crude mixture was applied on a silica gel column (30 × 1 cm) and eluted with chloroform–ethyl acetate (3:1) to give a colorless foam (30 mg) of unknown structure and then the major product as a paste. The latter was crystallized from a mixture of ethanol and acetone to give a wool of mp 169–170° (70 mg). Its identity with **10** was fully confirmed by infrared spectral comparison. The yield of material A (**17**), based on the constitution of **17**, was 48%. On the other hand, the product B was suggested to be identical with compound **15** by its nmr spectrum, which contained signals assignable to two phenyl groups and two mesyl groups (δ 3.05, 6 H, d). The yield of the practically pure product B (**15**) conformed to 35%. This was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and the mixture was left at room temperature for two days. After the usual work-up as described above, the obtained pasty material was treated with mesyl chloride (0.07 ml) in dry pyridine (1.5 ml) overnight. The reaction mixture was worked up essentially in a similar way to above. Thin layer chromatography indicated one main product with two other trace amounts of by-products. Crystallization from a mixture of ethanol and acetone gave **10** (80 mg).

3-Benzyl-5′-*O*-acetyl-2′,3′-di-*O*-mesyluridine (18).—Compound **8** (0.57 g, 1 mmol) and sodium acetate (0.41 g, 5 mmol) were combined in DMF (10 ml), and the mixture was heated at 100° for 1 hr under stirring. The brown reaction mixture was poured into ice–water (100 ml) and the precipitate was filtered, dissolved in chloroform (150 ml), washed with water (30 ml), and dried with sodium sulfate. After the solvent was evaporated, the residual paste was submitted to preparative thin layer chromatography with the use of silica gel and a mixture of chloroform and ethyl acetate (3:1). The major portion was again chromatographed on a silica gel plate using chloroform–ethyl acetate (4:1) to give 240 mg of **18** as a homogeneous foam: nmr ($CDCl_3$) δ 2.05 (3 H, s, acetyl), 3.10 (3 H, s, mesyl), 3.15 (3 H, s, mesyl), 4.40 (3 H, br s, an overlap of $H_{4'}$ and 5′-methylene signals), 5.05 (2 H, s, benzyl methylene), 5.32 (2 H, br d, $H_{2'}$ and $H_{3'}$), 5.73 (1 H, s, $H_{1'}$), 5.79 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), and 7.2–7.5 (6 H, m, Ph and H_6). This sample was dissolved in a mixture of pyridine (1 ml) and concentrated ammonia (1 ml) and warmed at 50° for 3 hr. The mixture was concentrated and worked up as above to give 120 mg of an impure foam, which was dissolved in pyridine (2 ml) and treated with mesyl chloride (0.04 ml) at room temperature for 10 hr. After the usual work-up, 80 mg of crystals (**8**) were obtained.

3-Benzyl-5′-deoxy-5′-iodo-2′,3′-di-*O*-mesyluridine (19).—A mixture of **8** (0.2 g) and sodium iodide (0.4 g) in acetone (8 ml) was heated to reflux for 5 hr. The reaction mixture was evaporated to a gum, which was taken into chloroform (100 ml) and washed with dilute sodium thiosulfate solution and water. The separated organic layer was dried with sodium sulfate and evaporated to a paste, which was crystallized from a small amount of ethyl acetate or acetone to afford colorless granules, mp 143–146° (0.15 g, 70.5%).

Anal. Calcd for $C_{18}H_{21}O_9S_2N_2I$: C, 36.01; H, 3.53; N, 4.67. Found: C, 35.71; H, 3.46; N, 4.67.

Reaction of 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8) with Potassium Carbonate.—3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) (0.5 g, 0.89 mmol) and anhydrous potassium carbonate (400 mg, 2.9 mmol) were combined in DMF (4 ml) and the mixture was stirred at 115–120° for 20 min. The solvent was evaporated off and the tarry residue was extracted with chloroform (4 × 50 ml) under the presence of water (15 ml), when the tar remained undissolved between both layers. The separated organic layer was dried with sodium sulfate and again concentrated to a paste. Preparative thin layer chromatography with the use of silica gel and a mixed solvent, chloroform–ethyl acetate (3:1), gave colorless needles, mp 162–164°, from the slightly faster moving band, which was identified with **13** in all respects, yield 15 mg (6%). The pasty material recovered from the slower moving band was again submitted to preparative tlc to give 0.25 g of **20** as a homogeneous foam (0.25 g, 58%): λ_{max}^{EtOH} 258 nm (ϵ 9500); nmr ($CDCl_3$) δ 3.9 (2 H, q, J = 3.0 and 6.7 Hz, 5′-methylene), 4.35 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.1 (2 H, s, benzyl methylene), 5.8 (1 H, $J_{5,6}$ = 8 Hz, H_5), 6.2 (1 H, s, $H_{1'}$), 7.3 (5 H, br m, Ph), and 7.55 (1 H, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{17}H_{16}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.64; H, 4.71; N, 6.85.

This was characterized as 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil by spectral comparison with a specimen prepared below.

Synthesis of 1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil (20) from 1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil.—1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil (0.38 g, 1.24 mmol), benzyl chloride (0.17 ml, 1.44 mmol), and potassium carbonate (220 mg, 1.6 mmol) were combined in a mixture of DMF (1.2 ml) and acetone (1.2 ml), and the mixture was refluxed for 2 hr. Thin layer chromatography indicated the formation of only one product and the presence of the starting material. The solvent was removed by evaporation and the residue was extracted with ethyl acetate (2 × 30 ml) under the presence of water (10 ml). After the usual work-up, the pasty extract was applied on a silica gel column and eluted with a mixture, chloroform–ethyl acetate

(2:1), to give 0.35 g (72%) of a homogeneous foam. This was identified with compound **20** obtained above by nmr and uv spectroscopy.

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.77; H, 4.71; N, 6.78.

Registry No.—**1**, 6554-10-5; **2**, 37440-10-1; **3**, 14985-34-3; **4**, 362-43-6; **5**, 32464-90-7; **6**, 37440-11-2; **7**, 37440-12-3; **8**, 37440-13-4; **9**, 37440-14-5; **10**, 37445-38-8; **11**, 37567-14-9; **13**, 37445-39-9; **15**, 37445-43-5; **16**, 28734-85-2; **17**, 37445-44-6; **18**, 37445-40-2; **19**, 37445-41-3; **20**, 37445-42-4; **21**, 37445-45-7; uridine, 58-96-8.

Stobbe Condensations of Dimethyl 3,5-Bis(benzyloxy)homophthalate[1a]

RICHARD N. HURD*[1b] AND DINUBHAI H. SHAH

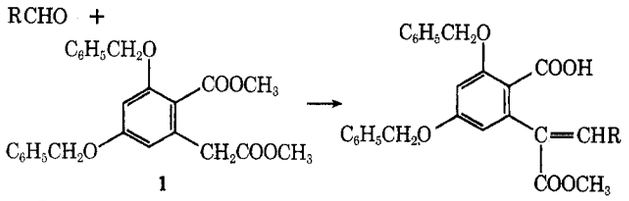
Research Department, Commercial Solvents Corporation, Terre Haute, Indiana 47808

Received April 20, 1972

Dimethyl 3,5-bis(benzyloxy)homophthalate (**1**) reacts with aliphatic aldehydes under conditions of the Stobbe condensation to give preparative yields of Stobbe acid esters analogous to the Stobbe products of succinic esters. From butyraldehyde (**2**) and 4-benzyloxybutyraldehyde (**4**), respectively, are obtained 2,4-bis(benzyloxy)-6-(1-carbomethoxy-1-penten-1-yl)benzoic acid (**5**) and 6-(5-benzyloxy-1-carbomethoxy-1-penten-1-yl)-2,4-bis(benzyloxy)benzoic acid (**7**). In the case of 4-chlorobutyraldehyde (**3**), the Stobbe product (**6**) forms a cation (**9**) in the presence of base that undergoes intramolecular displacement of chlorine to give the cyclopropane derivative (**8**). In the condensation of **1** and **4** to give **7**, a second product (**12**) is concurrently formed that is analogous to the paraconic esters formed in the Stobbe condensations of succinic esters. 3,4-Dihydroisocourmarins such as **12** have not been observed previously in Stobbe condensations of homophthalic esters. Ester acid (**7**) was readily saponified to diacid **13** and reduced to the β-resorcyclic acid derivative **14**.

In the course of development of a synthetic route for (*R,S*)-zearalanone,[2] we have studied the reaction of dimethyl 3,5-bis(benzyloxy)homophthalate (**1**) with several aliphatic aldehydes under conditions of the Stobbe condensation.[3]

The original concept of the Stobbe reaction as a basic condensation of esters of succinic acid with aldehydes and ketones has been extended to homophthalic esters with a variety of aromatic aldehydes and ketones.[4] We find that this condensation proceeds smoothly with aliphatic aldehydes using sodium hydride as base,[5] to give preparative yields of the Stobbe half-esters. With butyraldehyde (**2**), for example, a quantitative yield of the Stobbe half-ester **5** was readily obtained.

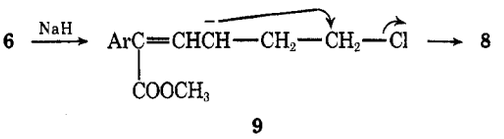


1

2, R = C_3H_7
3, R = $ClCH_2CH_2CH_2-$
4, R = $C_6H_5CH_2OCH_2CH_2CH_2-$

5, R = C_3H_7
6, R = $ClCH_2CH_2CH_2-$
7, R = $C_6H_5CH_2OCH_2CH_2CH_2-$
8, R = 

With 4-chlorobutyraldehyde (**3**), a secondary reaction also took place. In addition to normal Stobbe condensation (which would have given the half-ester **6**), cyclization occurred so that the only product isolated (in 63% yield) was the cyclopropane-containing half-ester **8**. The mechanism of formation of **8** probably involves the reaction of base with the first-formed Stobbe product **6** to give carbanion **9**, which



9

then cyclizes to **8** by intramolecular displacement of chlorine. Similar intermediates have been proposed before in the formation of cyclopropane derivatives, such as in the reaction of 4-chlorobutyronitrile and sodamide to give cyclopropanenitrile.[6] We believe that the formation of **8** represents the first observation of cyclization of a derivative of 6-halo-2-hexenoic acid to a cyclopropane.

The familiar, accepted mechanism for the Stobbe reaction proposed an intermediate paraconic ester.[3] In the use of succinic esters in the Stobbe reaction, paraconic esters have been identified and isolated on several occasions. A similar mechanism for the reaction of an aldehyde with methyl homophthalate would involve the steps shown in Scheme I. The 3,4-dihydroisocoumarin **10** is analogous to the paraconic esters formed during the Stobbe condensation of succinic esters, but until now **10** has not been isolated under Stobbe conditions. Instead, **11** is the isolated product. Under acidic conditions, however, **11** may be isomerized to **10**.[4b]

In the present work it was demonstrated that an analog of **10** was obtainable by reaction of **1** with 4-benzyloxybutyraldehyde (**4**) under Stobbe conditions. Two products were isolated, one of which is the expected half-ester **7**, and the other of which is the 3,4-dihydroisocoumarin **12**. The latter product was converted quantitatively into **7** by treatment with sodium

(1) (a) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, MEDI 28. (b) G. D. Searle International Co., P. O. Box 5486, Chicago, Ill. 60680.

(2) R. N. Hurd and D. H. Shah, *J. Med. Chem.*, in press.

(3) W. S. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).

(4) (a) W. Dieckmann, *Chem. Ber.*, **47**, 1432 (1914); (b) H. J. E. Loewenthal and R. Pappo, *J. Chem. Soc.*, 4799 (1952); (c) J. B. Jones and A. R. Pinder, *ibid.*, 2612 (1958); (d) J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 (1960); (e) J. H. Chatterjea, K. D. Banerji, and H. Mukherjee, *ibid.*, **40**, 45 (1963).

(5) G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, **72**, 501 (1950).

(6) J. B. Cloke, R. J. Anderson, J. Lachmann, and G. E. Smith, *ibid.*, **53**, 2791 (1931).