Specific Chemical Synthesis of Ribonucleoside *O*-Benzyl Ethers[1a]

LEON F. CHRISTENSEN[1b] AND ARTHUR D. BROOM*

Department of Biopharmaceutical Sciences, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

Received May 12, 1972

A facile new method for the one-step synthesis of 2′- and 3′-*O*-benzyl ethers of adenosine, inosine, guanosine, cytidine, and uridine by reaction of the free nucleoside with phenyldiazomethane in the presence of a Lewis acid catalyst ($SnCl_2$) is reported. A unique and rapid method of isomer differentiation by uv spectrophotometry is described. An evaluation was made of the ease of removal of the benzyl group by catalytic hydrogenolysis. An unusual example of long-range proton coupling is reported.

A great deal of interest has been generated recently in the chemical and enzymatic synthesis of oligoribonucleotides of defined chemical structure.[2-4] One of the major difficulties in the synthesis of oligoribonucleotides lies in selectively blocking the 2′-hydroxyl group of the starting ribonucleoside so that the required 3′ → 5′ internucleotide linkage may be specifically formed. The ideal blocking group must meet the following criteria: it must not undergo facile 2′ → 3′ migration, it must be stable to the conditions required for oligonucleotide synthesis, and it must be readily removable under conditions which do not permit 3′ → 2′ phosphate migration.

A number of workers have recommended the benzyl group as a protecting function which meets each of the above criteria; it is stable, does not migrate readily, and is removed by mild catalytic hydrogenolysis.[5-9]

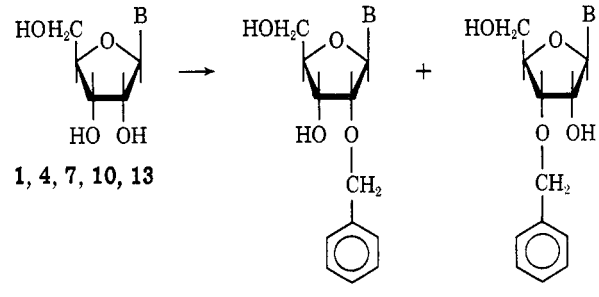
The first specific chemical synthesis of a 2′-*O*-methylribonucleoside was achieved by direct methylation of adenosine with diazomethane in a homogeneous 1,2-dimethoxyethane–water solution.[10] It has very recently been shown that this reaction is markedly catalyzed by Lewis acids such as $SnCl_2$.[11] Thus, adenosine was converted into a 99% total yield of 2′- and 3′-*O*-methyladenosine in a 1:2 ratio. In a similar reaction with cytidine the 2′:3′ ratio was 5:1.[11]

These results suggested that the Lewis acid catalyzed reaction of phenyldiazomethane with unprotected purine and pyrimidine ribonucleosides should lead directly to the desired 2′- and 3′-*O*-benzyl ethers. These syntheses, the development of a unique and facile method of structure assignment, and studies on the ease of reductive cleavage of the benzyl ethers form the basis of this report.

Results and Discussion

The presence of one and only one benzyl group in each of the benzylated nucleosides (Scheme I) was evident from elemental analysis. It was clear in all cases from examination of the uv spectra (Table I) that alkylation had occurred only on the sugar portion of the molecule. Therefore only the site of alkylation on the carbohydrate moiety remained to be determined.

SCHEME I



1–3, B = adenine
4–6, B = hypoxanthine
7–9, B = guanine
10–12, B = uracil
13–15, B = cytosine

TABLE I

UV DATA FOR SOME RIBONUCLEOSIDE *O*-BENZYL ETHERS

Compd	λ_{max}, nm ($\epsilon_{max} \times 10^{-3}$) pH 1	pH 7	pH 11
1	257 (15.1)	259 (15.1)	259 (15.3)
2	257 (12.7)	259 (13.0)	259 (12.7)
3	257 (15.6)	259 (15.8)	259 (15.5)
4	248 (12.4)	248 (12.9)	252 (13.7)
5	250 (10.6)	250 (10.6)	253 (11.5)
6	248 (13.7)	248 (13.1)	252 (14.2)
7	255 (12.3)	252 (13.5)	256 (11.3)
8	257 (10.2)	253 (11.3)	257 (9.50)
9	256 (12.7)	252 (13.9)	256 (11.7)
10	261 (10.5)	261 (10.6)	260 (7.90)
11	262 (8.90)	262 (8.70)	261 (6.65)
12	261 (10.6)	261 (10.6)	260 (7.95)
13	278 (12.9)	269 (9.05)	269 (8.95)
14	279 (11.4)	271 (7.60)	271 (7.60)
15	279 (13.7)	270 (9.50)	270 (9.40)

The two isomers obtained from the direct benzylation of uridine (**10**) were readily characterized by melting point comparisons with known compounds. Each of the three possible mono-*O*-benzyl ethers of uridine has been prepared by multistep procedures: 5′-*O*-benzyluridine reportedly melted at 162°,[12] 3′-*O*-benzyluridine (**12**) at 204–206°,[6] and 2′-*O*-benzyluridine (**11**) at 181–182°.[7,8] The 3′- and 2′-*O*-benzyluridines (**12** and **11**) reported above melted at 205–207 and 177–179°, respectively. The pmr data for **11** and **12**

(1) (a) The support of Research Grant CA 11935 and Training Grant CA 05209 from the National Cancer Institute, National Institutes of Health, is gratefully acknowledged. (b) Predoctoral Trainee of the National Cancer Institute, National Institutes of Health, 1968–1972.

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TABLE II

PMR SPECTRAL DATA FOR SOME RIBONUCLEOSIDE O-BENZYL ETHERS[a]

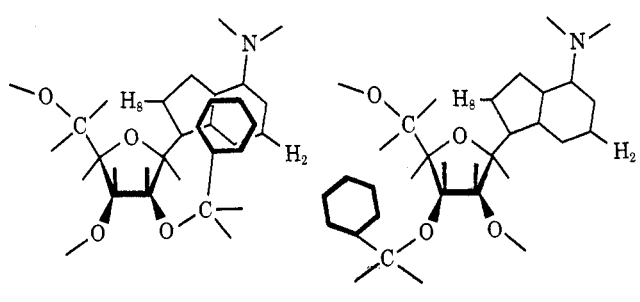
Compd	Chemical shift, δ					
	C-2 H	C-8 H	C-1′ H	C-5 H	C-6 H	Phenyl
2	7.92	8.15	5.98 (d, 5.8)			7.03
3	7.99	8.17	5.85 (d, 6.1)			7.23
5	7.88	8.13	5.97 (d, 5.1)			7.07
6	7.97	8.25	5.89 (d, 6.1)			7.29
8		7.73	5.79 (d, 4.8)			7.11
9		7.77	5.67 (d, 6.2)			7.21
11			5.83 (d, 4.4)	5.47 (d)	7.68 (d)	7.15
12			5.73 (d, 5.6)	5.55 (d)	7.68 (d)	7.20
14			5.88 (d, 3.2)	5.65 (d)	7.77 (d)	7.22
15			5.77 (d, 4.0)	5.67 (d)	7.72 (d)	7.24
1[b]	8.10	8.27	6.03 (d, 5.8)			
2[b]	7.92	7.98	5.84 (m)			6.93

[a] Unless otherwise indicated, solutions are about 6% in DMSO-d_6 with DSS (sodium 2,2-dimethyl-2-silapentane sulfonate) reference. Coupling constants in hertz are given in parentheses; d ≡ doublet, m ≡ multiplet. [b] Concentration 0.075 *M* in D_2O, DSS as internal reference.

(Table II) also correlated well with those reported earlier[13] for the two monobenzyluridines.

Assignment of the hitherto unknown 2′- and 3′-*O*-benzyl ethers of adenosine (**2** and **3**) was made using pmr and uv spectroscopy. The 5′ position was eliminated as a site of benzylation by the observation of a triplet at δ 5.37 in the pmr spectrum of **2** and a triplet at δ 5.50 in the pmr spectrum of **3** (dry DMSO-d_6 was the solvent). Both peaks disappeared rapidly upon addition of D_2O to the DMSO-d_6 solution. Such triplets have been shown to arise from the coupling of -OH (5′) to the methylene protons at C-5′.[14,15] The assignment of **2** and **3** as 2′- and 3′-*O*-benzyl isomers, respectively, was readily made using uv spectrophotometry. Examination of C-P-K molecular models reveals that a very favorable stacking interaction between the purine base and the benzene ring is possible with the 2′ isomer **2**, but impossible with the 3′ isomer **3**. A diagram of the probable conformation of each is given in Chart I. It is clear from extensive dinu-

CHART I



cleoside phosphate and model compound studies that parallel-planar overlap of "aromatic" bases results in marked hypochromicity when the bases are linked by three or more carbon atoms.[16] The finding of marked hypochromicity relative to the starting nucleoside of one of a pair of 2′(3′)-*O*-benzyl ribonucleosides would establish that isomer as 2′, since there is essentially no difference in the extinction coefficients between the 3′-*O*-benzyl nucleosides and the parent nucleosides (Table I). Table III shows clearly that this is

TABLE III

PER CENT HYPOCHROMICITY OF 2′-*O*-BENZYL NUCLEOSIDES RELATIVE TO PARENT NUCLEOSIDES

Compd	pH 1	pH 7	pH 11
2	16.0	14.0	17.2
5	14.5	17.8	16.0
8	17.1	16.3	16.0
11	15.2	17.9	17.1
14	11.6	16.0	15.1

the case for **2** and for each of the other 2′-*O*-benzyl nucleosides reported. This provides a unique and extremely facile means for determining the site of *O*-benzylation of ribonucleosides.

Each of the benzyl nucleoside pairs obeys the empirical rule of Reese and coworkers,[13] which states that the chemical shift will be at lower field and the coupling constant smaller for the anomeric proton of the 2′ isomer of a 2′(3′)-*O*-substituted pair of nucleosides. It should be noted, however, that in the case of adenosine both the chemical shift difference (δ 0.07) and the coupling constant difference (0.3 Hz) between the isomers are very small. Furthermore, *both* isomers are required before the Reese rule may be applied. The uv technique described above, however, appears to be completely general for benzyl ethers of ribonucleosides and can be utilized by comparing *either* isomer with starting material.

The demonstration of hypochromicity for 2′-*O*-benzyladenosine relative to adenosine suggested, as noted above, that stacking of the purine and the benzene ring probably occurs in aqueous solution. In order to support this concept a study of the pmr spectrum of 2′-*O*-benzyladenosine in D_2O was carried out. It is well known that intramolecular stacking in dinucleoside phosphates may be readily evaluated by pmr in D_2O solution;[17,18] the influence of the diamagnetic anisotropy of a neighboring base leads to upfield shifts of protons on an adjacent ring. Comparison of the data obtained for **2** and adenosine at equivalent con-

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centrations in D_2O (Table II) supports the intramolecular stacking illustrated in Chart I. The purine C-8 H and C-2 H protons of **2** appear 0.29 and 0.18 ppm, respectively, upfield from those of adenosine. The anomeric proton, C-1′ H, is also shielded by 0.19 ppm in **2** relative to adenosine. The pattern for the C-1′ H signal of **2** is completely unlike that of adenosine in either DMSO-d_6 or D_2O or that of **2** in DMSO-d_6. Instead of the usual doublet ($J_{1',2'} \cong 6$ Hz), the anomeric proton signal of **2** in D_2O resembles a pair of overlapping triplets containing apparent first-order coupling constants of 7.1 and 2.4 Hz. That this is a conformationally dependent long range coupling was established by recording the spectrum of **2** in D_2O at 70°; at this temperature the five-band multiplet collapsed cleanly into a doublet ($J_{1',2'} = 6.5$ Hz). The same pattern was observed in the case of 2′-*O*-benzylinosine (**5**). The spectrum of 2′-*O*-benzyluridine (**11**) in D_2O, on the other hand, shows an entirely normal doublet ($J_{1',2'} = 6.0$ Hz). The spectra of 2′-*O*-benzylguanosine (**8**) and 2′-*O*-benzylcytidine (**14**) could not be obtained because of limited solubility in D_2O. The difference between the purine nucleosides and the pyrimidine nucleoside is not surprising in view of the known conformational differences in the carbohydrate moieties of purine and pyrimidine nucleosides.[19] Decoupling experiments designed to elucidate the exact nature of the observed long-range coupling are presently in progress and will be reported elsewhere.

A very important feature of this general procedure for nucleoside O-benzylation is that little or no benzylation occurs on the purine or pyrimidine bases (as evaluated by tlc examination of the reaction mixtures), even though methylation with diazomethane of uridine[20] and inosine[21] leads in all cases to alkylation of the heterocyclic moiety. Only in the case of guanosine is the possibility of substantial N-benzylation confirmed by tlc; guanosine is quantitatively N-alkylated by diazomethane.[22] A detailed study of the reaction conditions required to optimize yields has not been undertaken, since the primary purpose of this work is to provide a *rapid* method for obtaining blocked nucleosides in reasonable yields.

Since the benzyl cation is relatively stable and N → N benzyl migration is well known in heterocyclic systems[23] it was of interest to ascertain whether O-2′(3′) → O-3′(2′) migration could occur either thermally or under the conditions used for the synthesis. When **2** and **3** were dissolved separately in methanol containing $SnCl_2 \cdot 2H_2O$ (1×10^{-3} *M*) and stirred for 6 days at room temperature, no interconversion was observed. Samples of **2** and **3** were heated above their melting points and maintained at that temperature for 2 hr. Although a small amount of decomposition occurred to give adenine, there was no isomerization detectable to tlc. Clearly isomerization will present no problem to the utilization of benzyl ethers in oligonucleotide synthesis.

As expected, hydrogenolysis under mild conditions (3 atm, room temperature) suffices to quantitatively debenzylate the *O*-benzyl purine nucleosides with no side reactions detectable by chromatography. 2′-*O*-Benzyluridine (**11**) as previously reported[7,8] may be cleanly hydrogenolyzed over palladium at 1 atm with no reduction of the ring. Contrary to a previous report,[8] in our hands hydrogenation of the ring of 2′-*O*-benzylcytidine does not proceed more rapidly than debenzylation; however, some reduction of the 5,6-double bond (10–25%) does occur by the time complete removal of the benzyl group is effected. Based upon these studies, it is clear that at least four of the five 2′-*O*-benzyl nucleosides reported herein are suitable candidates for oligonucleotide and polynucleotide synthesis.

Experimental Section

Proton magnetic resonance data were obtained using a Jeol C6OH spectrometer. A Cary 15 spectrophotometer was used for the measurement of uv spectra. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

The synthesis of phenyldiazomethane was carried out as previously described.[24] Concentrations of phenyldiazomethane solutions were measured by quantitative reaction with *p*-nitrobenzoic acid and found to be about 0.125 mmol/ml of ether solution.

General Procedure for the O-Benzylation of Ribonucleosides.—To a solution of MeOH (100 ml/g of nucleoside) containing $SnCl_2 \cdot 2H_2O$ (1×10^{-3} *M*) was added the nucleoside to be benzylated (1 g of nucleoside is *ca.* 4 mmol). A phenyldiazomethane solution (~12.5 mmol in 50 ml of 1,2-dimethoxyethane prepared by evaporating the ether *in vacuo*[25] and dissolving the oil in 1,2-dimethoxyethane) was added slowly over about 8 hr to the stirred solution at room temperature. Completion of the reaction was ascertained by the absence of starting material as judged by tlc (SilicAR 7 GF, EtOAc:H_2O:*n*-PrOH, 4:2:1, upper phase). Silica gel (5 g) was added to the solution and the solvent was removed *in vacuo*. The silica gel containing the adsorbed nucleosides and various impurities (*i.e.*, benzyl alcohol) was placed on a silica gel column (50 g) and rapidly eluted as described below to obtain a mixture of isomers free from contaminants.

2′-*O*-Benzyladenosine (2) and 3′-*O*-Benzyladenosine (3).—Adenosine (23.0 g, 86.0 mmol) was benzylated as described above. The silica gel column was washed with $CHCl_3$ (2 l.), EtOAc:$CHCl_3$ (1:1, 6 l.), and EtOAc (16 l.) Elution with EtOAc:MeOH (95:5, 15 l.) gave two fractions; the first (fraction A) contained pure 2′ isomer **2** and the second (fraction B) a mixture of **2** and **3**. Removal of the solvent *in vacuo* from fraction A followed by recrystallization from EtOH gave pure **2** (1.25 g). Evaporation *in vacuo* of the solvent from fraction B followed by fractional crystallization of the residue from MeOH gave pure **3** (11.88 g). Removal of the methanol from the filtrates followed by chromatography on Dowex-1 × 8 (OH^-, 200–400 mesh) using 20% aqueous methanol according to Dekker[26] gave, after removal of the solvent and recrystallization of the residue from acetone, **2** (7.18 g).

The total yield of **2** was 8.44 g (27%), mp 147–150° (after one recrystallization from EtOH).

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 56.89; H, 5.48; N, 19.41.

The yield of **3** was 11.88 g (38.5%), mp 195–196°.

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.03; H, 5.37; N, 19.95.

2′-*O*-Benzylinosine (5) and 3′-*O*-Benzylinosine (6).—The benzylation of inosine (2.0 g, 7.5 mmol) was carried out. The column was washed with $CHCl_3$ (1.5 l.) and EtOAc (2 l.). The isomeric mixture was eluted with EtOAc:MeOH (9:1). The solvent was removed *in vacuo*. The residue was dissolved in 1 *N* NH_4OH and applied to a column containing 500 g of DE-52 (Whatman DEAE cellulose) preequilibrated with 1 *N* NH_4OH. Elution with the same solvent gave two major bands. The pooled fractions containing the most rapidly eluted material

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were evaporated *in vacuo* and the residue was recrystallized from acetone to give **5** (572 mg, 21%), mp 218–220°.

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 56.91; H, 5.07; N, 15.62.

The pooled fractions containing the slower moving band were also evaporated *in vacuo*. The residue was recrystallized from ethanol–water to give **6** (385 mg, 14%), mp 219–221°.

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 57.17; H, 5.06; N, 15.48.

2′-*O*-Benzylguanosine (8) and 3′-*O*-Benzylguanosine (9).—Guanosine (1.0 g, 3.5 mmmol) was benzylated by the general method. The column was washed with $CHCl_3$ (1 l.) and EtOAc (2 l.). The benzylated nucleosides were eluted with EtOAc:MeOH (95:5). The solvent was removed *in vacuo* and the residue was dissolved in 1.5 *N* NH_4OH. The solution was applied to a column containing 500 g of DE-52 (Whatman DEAE cellulose) preequilibrated with 1.5 *N* NH_4OH. Elution with the same solvent gave two bands. The combined fractions corresponding to the first band were evaporated *in vacuo* and the residue was crystallized from ammonia–water to give **8** (207 mg, 16%), mp >310°, darkens at 270°.

Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.81; H, 5.24; N, 18.89.

The material from the second band was treated in the same manner to give **9** (233 mg, 18%), mp >310°, darkens above 260°.

Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.39; H, 5.16; N, 18.62.

2′-*O*-Benzyluridine (11) and 3′-*O*-Benzyluridine (12).—Uridine (5.0 g, 20.5 mmol) was benzylated. The column was washed with $CHCl_3$ (2 l.) and $CHCl_3$:EtOAc (1:3, 2 l.) and the isomers were eluted with EtOAc (4 l.). The solvent was removed *in vacuo* and the residue was crystallized from EtOAc:Me_2CO to give a mixture of **11** and **12** (4.17 g, 56%). Separation of the isomers was accomplished by fractional crystallization from EtOH. Isomeric purity of the fractions was evaluated using tlc (SilicAR 7 GF, 3% aqueous NH_4Cl). The total yield of **11** was 1.52 g (20.3%), mp 177–179°. Analytical samples were obtained by recrystallization from EtOH.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.47; N, 8.48.

The total yield of **12** was 1.08 g (14.5%), mp 205–207°.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.71; N, 8.46.

2′-*O*-Benzylcytidine (14) and 3′-*O*-Benzylcytidine (15).—Cytidine (**13**, 6.0 g, 24.7 mmol) was benzylated as described above. The column was washed with $CHCl_3$ (2 l.), EtOAc (3 l.), and EtOAc:MeOH (95:5, 3 l.). The isomeric mixture was eluted with EtOAc:MeOH (85:15). The solvent was removed *in vacuo* to give **14** and **15** as a solid foam (5.33 g, 65%).

The above mixture (1.0 g) was dissolved in a solution of MeOH (14 ml) and H_2O (28 ml). The solution was applied to a column containing Dowex 1 × 8 (OH^-) and eluted with 30% aqueous MeOH. The fractions corresponding to the first major band were combined and evaporated. The residue was recrystallized from H_2O to give **14** (530 mg, 34% from **13**), mp 160–161°.

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.74; N, 12.61. Found: C, 57.49; H, 5.94; N, 12.46.

The combined fractions corresponding to the second major band were evaporated to dryness *in vacuo*. The residue was dissolved in H_2O and lyophilized to give **15** (287 mg, 19% from **13**).

Anal. Calcd for $C_{16}H_{19}N_3O_5 \cdot 0.5H_2O$: C, 56.13; H, 5.89; N, 12.27. Found: C, 56.01; H, 5.86; N, 12.28.

Debenzylation Procedure for *O*-Benzyl Purine Ribonucleosides.—*O*-Benzyl nucleoside (50 mg) was dissolved in EtOH (25 ml) containing 1 *N* NaOH (0.5 ml). The solution was added to 5% Pd/C. The mixture was shaken under hydrogen (45 psi). After 3.5 hr, debenzylation was complete as judged by tlc (SilicAR 7 GF, EtOAc:H_2O:*n*-PrOH, 4:2:1 upper phase).

Debenzylation Procedure for *O*-Benzylpyrimidine Ribonucleosides.—2′-*O*-Benzyluridine (50 mg) was dissolved in EtOH (25 ml) containing H_2O (10 ml) and 1 *N* NaOH (2 ml). The solution was added to 10% Pd/C (25 mg) and stirred under hydrogen (1 atm). After 1 hr debenzylation was complete as judged by tlc (as above); quantitative uv evaluation showed better than 95% recovery of uridine.

Treatment of 2′-*O*-benzylcytidine (**14**) under these conditions led to complete debenzylation, but about 10–25% reduction to dihydrocytidine occurred.

Registry No.—**1**, 58-61-7; **2**, 35638-82-5; **3**, 35638-83-6; **4**, 58-63-9; **5**, 35638-84-7; **6**, 35638-85-8; **7**, 118-00-3; **8**, 35687-58-2; **9**, 35638-86-9; **10**, 58-96-8; **11**, 6554-02-5; **12**, 4710-74-1; **13**, 65-46-3; **14**, 22423-30-9; **15**, 35687-60-6.

An Unusual Spirane Synthesis

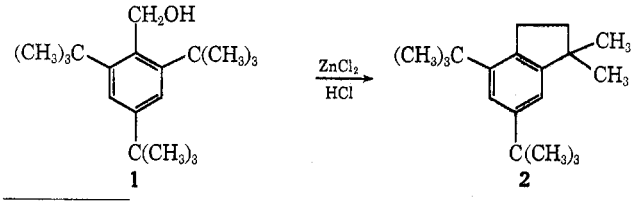
J. J. LOOKER,* D. P. MAIER, AND T. H. REGAN

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received April 27, 1972

The structure of the spirane formed by the cyclodehydration of the alcohol 5-*tert*-butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) has been established. The method used was to demonstrate the existence of a more stable isomer by lowering the barrier to ring inversion, and then to thermally isomerize the first to the second. The nmr spectra of the isomers are in agreement with the chemical results. Attempts to extend the cyclization reaction to five- and six-membered rings were unsuccessful. Two possible mechanisms for the cyclization are presented.

An unexpected cyclization is sometimes observed when a positive charge is formed near a crowded *tert*-butyl group. The positive carbon atom appears to insert itself into a carbon–hydrogen bond of one of the methyl groups of the *tert*-butyl substituent. The first example[1] of this reaction to be reported was the formation of indan **2** from alcohol **1**. Since no indan is formed when one of the ortho *tert*-butyl groups is replaced by methyl, some crowding is necessary for cyclization to occur. Other examples have subsequently appeared which include indans,[2] a benzocyclobutene,[3] and a cyclopropane.[4] We wish to report another example of this type of cyclization in which a three-membered ring is closed to form spirononatriene **4** in good yield (75%).



1 **2**

While attempting to prepare chloride **3b** for another problem, alcohol **3a** was synthesized by treating di-

(1) L. R. C. Barclay and M. C. MacDonald, *Tetrahedron Lett.*, 881 (1968).

(2) P. Martinson, *Acta Chem. Scand.*, **22**, 1357 (1968).

(3) M. H. Knight, T. Putkey, and H. S. Mosher, *J. Org. Chem.*, **36**, 1483 (1971).

(4) G. J. Abruscato and T. T. Tidwell, *J. Amer. Chem. Soc.*, **92**, 4125 (1970).