The 2,3-Diazabicyclo[2.2.1]heptyl Ring System. III.[1] Synthesis and Characterization of Some 7-Substituted Derivatives

EVAN L. ALLRED AND CLYDE ANDERSON

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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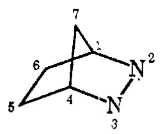
Synthesis of 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one ethyl ketal (**5**) from methyl azodicarboxylate and cyclopentadienone ethyl ketal is described. A study of the conversion of **5** and the saturated analog **7** to other 7-substituted derivatives under a variety of conditions is reported. The ketal function of **5** and **7** is unusually stable toward acidic reagents. However, ketal **7** can be transformed to 7,7-dichloro-2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptane (**11**) by treatment with aluminum chloride.

2,3-Diazabicyclo[2.2.1]heptyl ring compounds have not been subjected to a systematic study despite the fundamental character of the structure and the fact that the system has been known since 1925.[2] As part of a program of research in this area, we have been investigating the synthesis and chemistry of substituted derivatives in this ring system (**1**).[3] This paper reports the first successful synthesis of 7-substituted derivatives and also describes some aspects of the reactivity of these compounds.

The Diels–Alder reaction of azodicarboxylate derivatives like **2** with appropriately substituted cyclopentadienes would seem to provide a straightforward synthetic approach to 7-substituted 2,3-diazabicyclo[2.2.1]heptyl structures. Unfortunately, a major difficulty is that suitable simply substituted cyclopentadienes have only a fleeting existence in the monomeric state, even at low temperature. DePuy and co-workers[4] found that once formed, cyclopentadienone (**3**) dimerized extremely rapidly. Trapping experiments indicated that **3** reacted largely, if not exclusively, as a dienophile. Similarly, the ethylene ketal of **3** self-dimerized with remarkable facility and could not be trapped with other dienophiles.[5,6] More recently, Eaton and Hudson[7] have demonstrated that the reactivity of cyclopentadienone ethyl ketal (**4**) is just within the limit of synthetic utility for the usual crossed Diels–Alder reactions. These latter results prompted our investigation of the use of **4** as a starting point for the preparation of 7-substituted members of ring system **1**.



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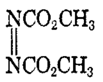
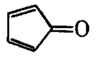


$$\begin{matrix}\mathrm{NCO_2CH_3}\\ \Vert\\ \mathrm{NCO_2CH_3}\end{matrix}$$

2



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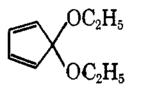

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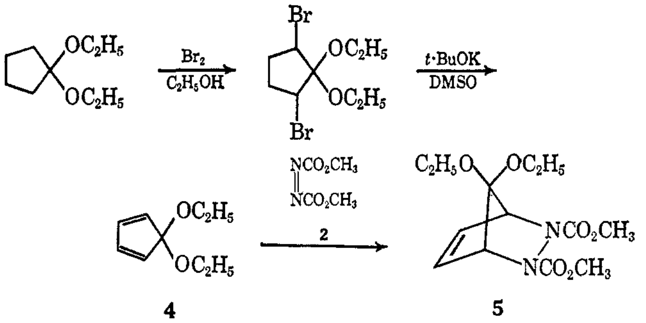
The synthesis of the first 7-substituted compound is summarized in Scheme I. Methyl azodicarboxylate (**2**) readily intercepted **4** and after a work-up by elution chromatography afforded the Diels–Alder adduct 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one ethyl ketal (**5**) in *ca.* 50% yield. Assignment of the structure was based on analyses, spectral data, and the results of the reactions illustrated in Schemes II and III. The nmr spectrum was fully consistent with the assigned structure and clearly showed the correct numbers and kinds of tertiary, vinyl, methoxyl, and ethoxyl hydrogens. As expected the ethoxyl groups are nonequivalent. A full description of nmr data is given in the Experimental Section.

SCHEME I



It was found that bromination with bromine was more convenient than the pyridinium bromide perbromide method[7] for synthesis of 2,5-dibromocyclopentanone ethyl ketal on a preparative scale. The success of direct bromination depends on the rate of addition of bromine. If the addition rate is too slow, appreciable product other than the 2,5-dibromo ethyl ketal forms. This other material presumably is an ethoxy ketal which arises from a competing solvolysis of the allylic monobromo intermediate.[8] Fortunately the ethanolysis reaction occurs at a slower rate than the second bromination step.[8] Addition of bromine at a rate which maintains the presence of a small amount of unreacted bromine throughout the reaction leads consistently to >90% yield of 2,5-dibromocyclopentanone ethyl ketal.

Ethyl ketal **5** was of considerable interest since it was expected to be synthetically useful for the preparation of variety of other 7-substituted derivatives of **1**. Accordingly, experiments aimed at converting the ketal masking group to other functions were undertaken. These are summarized in Schemes II and III.

Hydrolysis of **5** to the 7-ketone **6** was examined under rather mild conditions with both hydrochloric and sulfuric acids. In the case of treatment with 10% sulfuric acid at 50° for 17 hr **5** was recovered quantitatively. In all experiments only **5** was recovered unchanged. Because of the reported molecular frag-

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(1) For the preceding article in this series, see E. L. Allred and R. L. Smith, *J. Org. Chem.*, **31**, 3498 (1966).

(2) O. J. Diels, J. H. Blum, and W. Koll, *Ann.*, **443**, 242 (1925).

(3) E. L. Allred, C. L. Anderson, and R. L. Smith, *J. Org. Chem.*, **31**, 3493 (1966).

(4) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *ibid.*, **29**, 3503 (1964).

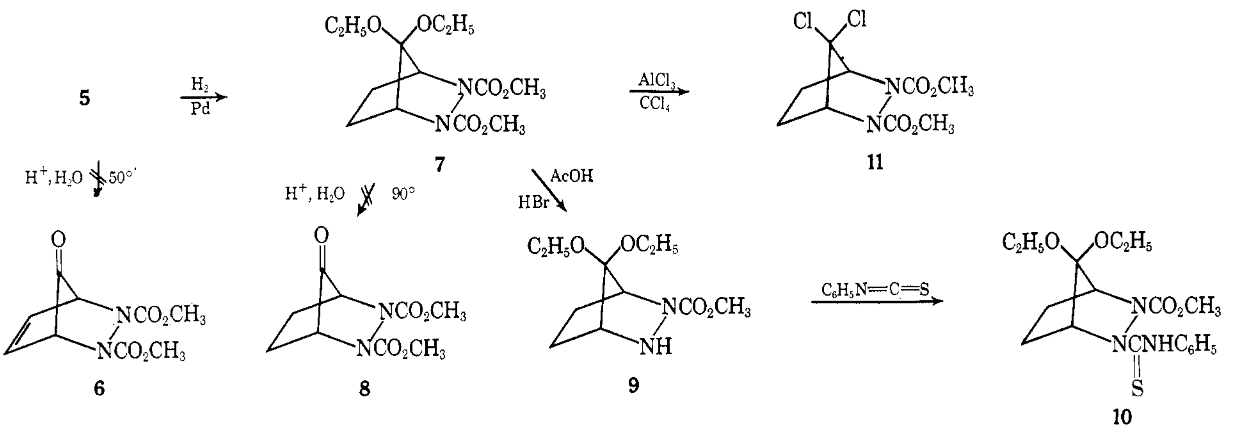
(5) C. H. DePuy, B. W. Ponder, and J. D. Fitzpatrick, *ibid.*, **29**, 3508 (1964).

(6) E. Vogel and E. G. Wyes, *Angew. Chem.*, **74**, 489 (1962).

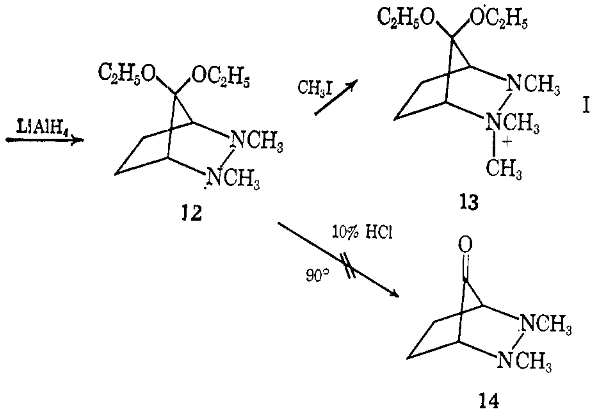
(7) P. E. Eaton and R. A. Hudson, *J. Am. Chem. Soc.*, **87**, 2769 (1965).

(8) A reaction analogous to this proposal was found in a study of dibromination of cycloalkanones in methanol; see E. W. Garbisch, *J. Org. Chem.*, **30**, 2109 (1965), Experimental Section. In the case of 2-methylcyclohexanone it was demonstrated that the competing methanolysis occurred more slowly than bromination.

SCHEME II



SCHEME III



mentation of 2,3-dicarboethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene with acid at higher temperature,[3,9] it did not appear possible to generate **6** with more vigorous conditions. For this reason **5** was converted to the saturated analog **7** by hydrogenation. The ketal **7** also proved to be remarkably stable. Treatment of **7** with concentrated hydrochloric, hydrobromic, and hydriodic acids at temperatures to 90° failed to yield the saturated 7-ketone **8**. Representative experimetal conditions and results are summarized in the Experimental Section in Table I.

When **7** was treated with 30% hydrogen bromide in acetic acid at 70°, conversion to a new compound was effected in high yield (94%). This product, however, still had the ethyl ketal grouping intact and was shown to be 2-carbomethoxy-2,3-diazabicyclo[2.2.1]heptan-7-one ethyl ketal (**9**). The structure was assigned on the basis of the nmr spectrum, and the formation of the phenyl thiosemicarbazide derivative **10**. The nmr spectrum showed the disappearance of one methoxyl group but the presence of two ethoxyl groups and the correct numbers of methylene and tertiary hydrogens. A phenyl thiosemicarbazide has been used to characterize another monocarbomethoxy-2,3-diazabicyclo[2.2.1]heptyl structure.[10]

The ethyl ketal **7** was subjected next to the action of strong Lewis acids followed by treatment with water in attempts to displace the ketal grouping. These experiments are listed in Table II (Experimental Section). Under the conditions examined **7** was unaffected by boron trifluoride. Similarly, **7** was recovered unchanged after extended treatment with aluminum chloride in dichloromethane. However, aluminum chloride in carbon tetrachloride at 60° effectively replaced both ethoxyl groups with chlorine to give 7,7-dichloro-2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptane (**11**) in good yield (75%). Elemental analysis and spectral data agreed with the assigned structure. The nmr spectrum indicated the total absence of ethoxyl groups but the presence of the six methoxyl, four methylene, and two tertiary protons.

We next turned our attention to a brief examination of N,N′-dimethyl-2,3-diazabicyclo[2.2.1]heptan-7-one ethyl ketal (**12**). This compound was obtained readily in excellent yield (*ca.* 90%) by reduction of **7** with lithium aluminum hydride in ether (Scheme III). Spectral data unequivocally allowed for the assignment of structure **12**. The infrared spectrum showed no absorptions in the 3- (NH) or 5-6-μ (C=O) regions. The nmr spectrum displayed six methyl hydrogens, the correct number of methylene and tertiary hydrogens, and two nonequivalent ethoxyl groups. Analytical data were correct for the methiodide derivative **13**.

The ethyl ketal **12** also proved to be unusually stable to hydrolysis and ketone **14** was not attained when **12** was treated with 10% hydrochloric acid at 90°.

Several aspects of the synthetic work are of particular interest. One such point concerns the factor(s) responsible for the remarkable stability of the ethyl ketal group of **5** and **7** in strongly acidic media. According to Kreevoy and co-workers[11] the rate of ketal hydrolysis of cyclic structures is decreased substantially by a small internal bond angle. For **5** and **7** the internal skeletal angle at C-7 is near 95°.[12] However, this will not account for failure of ketal cleavage since 7-ketals of the structurally similar bicyclo[2.2.1]heptyl system react under analogous conditions.[7,13] A plausible reason for the observed degree of inertness is that the hydrazino part of **5** and **7** protonates preferentially with subsequent addition of a proton to the ketal group being unfavorable. Evidence for protonation of the hydrazino function is found in the formation of the monocarbomethoxy structure **9** from treatment of **7** with hydrogen bromide in acetic acid. This reaction un-

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(9) J. K. Stille and T. Anyos, *J. Org. Chem.*, **27**, 3352 (1962).

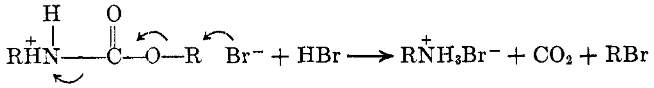
(10) S. G. Cohen, R. Zand, and C. Steel, *J. Am. Chem. Soc.*, **83**, 2895 (1961).

(11) M. M. Kreevoy, C. R. Morgan, and R. W. Taft, *ibid.*, **82**, 3064 (1960).

(12) The internal angle at C-7 for structurally similar bicyclo[2.2.1]heptane has been estimated to be 95°; see C. F. Wilcox, *ibid.*, **82**, 414 (1960).

(13) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2822 (1966); P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

doubtedly is related to the acid-catalyzed decarboxylation of carbamates with the same reagent and similar conditions.[14,15]

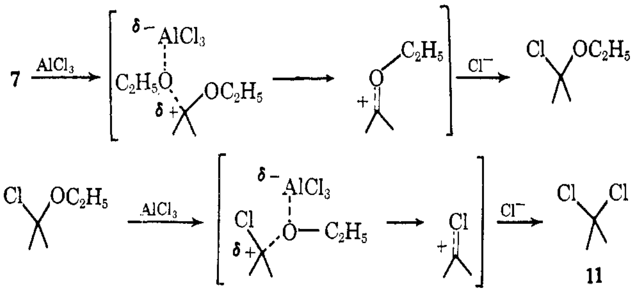


$$\mathrm{R\overset{+}{H}\overset{H}{N}—\overset{O}{\overset{\|}{C}}—O—R\ \ Br^- + HBr \longrightarrow R\overset{+}{N}H_3Br^- + CO_2 + RBr}$$

Another point of interest is the replacement of the ketal function of **7** by two chlorines with aluminum chloride in carbon tetrachloride to give **11**. This reaction also illustrates the unusual stability of the ketal. Temperatures near 60° and an excess of aluminum chloride are required for the transformation. By contrast, 7-ketals of the bicyclo[2.2.1]heptyl system are reported to react with aluminum chloride in dichloromethane (temperatures of 40° or lower).[7] For this system the product is the 7-ketone.[7] The reason for the difference in the product formed is not clear at the present time since details of experimental conditions and work-up procedure are lacking for the latter case.[7]

To the best of our knowledge the conversion of **7** to **11** is the first example of *gem*-dichloride formation from treatment of a ketal with aluminum chloride. However, heating of aliphatic ethers with aluminum chloride is reported to lead to alkyl chlorides.[16] The formation of **11** from **7** may be rationalized readily on the basis of the mechanistic formulation[17] given in Scheme IV.

SCHEME IV



Experimental Section

Melting points were taken by the capillary tube method and are uncorrected. The infrared spectra were determined as Nujol mulls or as neat films with a Beckman IR-5A spectrophotometer. Nmr spectra were obtained with a Varian Model A-60 spectrometer in deuteriochloroform or carbon tetrachloride using tetramethylsilane as an internal standard.

2,5-Dibromocyclopentanone Ethyl Ketal.—To a solution of 7.9 g (0.05 mole) of cyclopentanone ethyl ketal[18] in 125 ml of absolute ethanol at 5° was added 2 or 3 drops of bromine. After a short induction period the color disappeared. The remainder of 15.9 g (0.1 mole) of bromine was added at such a rate that the coloration of bromine was present at all times. Sufficient cooling was applied to keep the reaction temperature below room temperature. When the calculated amount of bromine had been added the reaction solution turned colorless. Addition of a few more drops of bromine caused the color to remain for several minutes. Following this, 25 g of anhydrous sodium carbonate was added to the reaction and the mixture was stirred at 5° for 10 min. After addition of 75 ml of cold pentane the mixture was poured into 65 ml of ice water. The pentane extract was recovered and dried with anhydrous magnesium sulfate, and the pentane was removed under reduced pressure keeping the temperature below 15°. The product residue was a clear, colorless oil with the same infrared spectrum as the literature[7] procedure product; the yield was 14.8 g (94%). This material was used immediately for the next reaction.

2,3-Dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one Ethyl Ketal (5).—To a vigorously stirred mixture of 20.8 g (0.19 mole) of potassium *t*-butoxide and 75 ml of dry dimethyl sulfoxide[19] at 17° was added 14.5 g (0.046 mole) of 2,5-dibromocyclopentanone ethyl ketal in 25 ml of DMSO. The addition required 3 min and the temperature was kept under 22° by cooling with a Dry Ice–acetone bath. After stirring for an additional 30 sec, 100 ml of pentane at 0° was added and the reaction mixture was poured on to 100 ml of cracked ice, water, and salt. The pentane layer was decanted into a flask at −70°. The water–DMSO layer was rapidly extracted with four more 100-ml portions of cold pentane. The combined pentane extract was transferred to a cold (−70°) dropping funnel and added dropwise to 27.2 g (0.19 mole) of dimethyl azodicarboxylate (**2**)[20] in 50 ml of ether at 25–30° during a 2-hr period. Following addition the reaction mixture was refluxed for 2 hr. The solvent was evaporated and the excess of **2** was removed at low pressure leaving 9.7 g of a viscous, yellow oil. Chromatography on Florisil (eluent, dichloromethane–ether mixtures) afforded the ketal adduct **5** as a crystalline solid in 6.7 g (48.5%) yield. Several recrystallizations from hexane produced an analytical sample, mp 100–101°.

Anal. Calcd for $C_{13}H_{20}N_2O_6$: C, 52.0; H, 6.7; N, 9.3. Found C, 52.1; H, 6.9; N, 9.0.

The infrared spectrum (Nujol) showed a strong absorption at 5.88 μ (C═O). The nmr spectrum (CCl_4) displayed the three–four pattern of lines expected for ethoxyl group protons, two triplets centered at τ 8.90 (6 H, triplet peaks offset 2.5 cps, CH_3) and a quartet at 6.48 (4 H, CH_2). Other bands were at τ 6.32 (6 H, singlet, CO_2CH_3), near 5.3 (2 H, very broad unresolved multiplet, $>$CH), and 3.56 (2 H, unresolved multiplet, HC═CH).

The above chromatographic separation also afforded a 34% yield of the Diels–Alder dimer of **4** (pentane–dichloromethane eluents). The structure was demonstrated by hydrolytic conversion to the well-known dimer of cyclopentadienone (**3**), mp 99–99.5°.[4]

2,3-Dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptan-7-one Ethyl Ketal (7).—When 1.50 g (0.005 mole) of **5** in 10 ml of ethanol was subjected to hydrogenation over 0.26 g of 10% palladium-on-charcoal catalyst at 1 atm, 0.005 mole of hydrogen was rapidly absorbed. Removal of catalyst and solvent afforded 1.51 g (100%) of **7**, mp 73–75°. An analytical sample was prepared by recrystallization from hexane, mp 74–75°.

Anal. Calcd for $C_{13}H_{22}N_2O_6$: C, 51.6; H, 7.3; N, 9.3. Found: C, 51.3; H, 7.3; N, 9.4.

Treatment of Ketals 5 and 7 with Aqueous Acids.—All experiments were carried out using the same procedure. This is illustrated by expt 1. A 0.179-g sample of **5** was heated at 50° for 17 hr with 10 ml of 10% sulfuric acid. The mixture was neutralized with sodium bicarbonate and extracted extensively with five 10-ml portions of dichloromethane. The combined extract was dried with anhydrous magnesium sulfate and the solvent removed by evaporation. This left 0.168 g (94%) of **5**, mp 99–100°. The infrared spectrum was identical with that of starting material **5**.

The results for representative conditions are summarized in Table I. In all cases no evidence was found for formation of the corresponding 7-ketone.

2-Carbomethoxy-2,3-diazabicyclo[2.2.1]heptan-7-one Ethyl Ketal (9).—A solution of 0.506 g (0.0017 mole) of **7** in 25 ml of 30% hydrogen bromide in acetic acid was kept at 70° for 1 hr. Most of the solvent was removed under reduced pressure and the residue was neutralized with aqueous 10% sodium carbonate (pH ~10). This mixture was exhaustively extracted with five 50-ml portions of dichloromethane. The combined extracts were dried with anhydrous magnesium sulfate and the solvent was removed leaving 0.385 g (94%) of **9** as a viscous liquid. This product was found to be homogeneous by chromatography on

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[14] P. Adams and F. A. Baron, *Chem. Rev.*, **65**, 567 (1965).

[15] D. Ben Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

[16] G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1963, p 149.

[17] The need for excess aluminum chloride indicates formation of a complex with the hydrazino moiety. This is omitted from the mechanistic scheme for reasons of simplicity of presentation.

[18] J. Boeseken and F. Tellegen, *Rec. Trav. Chim.*, **57**, 133 (1938).

[19] Freshly distilled from calcium hydride.

[20] J. C. Kauer, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 411.

TABLE I

RESULTS OF TREATMENT OF KETALS **5** and **7** WITH AQUEOUS ACIDS

Expt	Compd	Acid reagent, %	Time, hr	Temp, °C	% ketal recovered[a]
1	**5**	H_2SO_4, 10	17	50	94
2	**5**	HCl, 10	4	40	95
3	**7**	H_2SO_4, 10	1	60	90
4	**7**	HCl, 10	1	90	49
5	**7**	HBr, 48	1	60	80
6	**7**	HI, 40	1	70	75

[a] The starting ketal was the only material which was recovered.

Florisil. The infrared spectrum (film) showed a weak absorption at 3.09 (NH) and a strong absorption at 5.9 μ (C=O). The nmr spectrum ($CDCl_3$) displayed the ethoxyl group pattern with a triplet at τ 8.77 (6 H, CH_3) and a set of overlaid quartets with additional multiplet character[21] at 6.38 (4 H, CH_2). Other absorptions were at τ 8.17 (4 H, unresolved multiplet, CH_2), 6.74 (1 H, NH), 6.24 (3 H, sharp singlet CO_2CH_3), 5.96 (1 H, unresolved multiplet, >CH), and 5.50 (1 H, unresolved multiplet, >CH).

For further characterization, **9** was converted to the phenyl thiosemicarbazide **10** by treatment with phenyl isothiocyanate. Recrystallization from dichloromethane–pentane gave an analytical sample, mp 137–137.5°.

Anal. Calcd for $C_{18}H_{25}N_3O_4S$: C, 57.0; H, 6.6; N, 11.1; S, 8.5. Found: C, 56.8; H, 6.7; N, 10.9; S, 8.5.

Treatment of Ketal 7 with Lewis Acids.—For these experiments, 0.1–0.2 g of **7** was treated with the Lewis acid under the conditions specified in Table II. After the reaction period, water was added and the mixture was exhaustively extracted with dichloromethane. The extract was dried and the solvent removed. Typical results are summarized in Table II.

7,7-Dichloro-2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptane (11).—A mixture of 0.102 g (0.00033 mole) of **7** and 0.40 g (0.003 mole) of aluminum chloride in 10 ml of carbon tetrachloride was stirred at 60° for 1 hr. After cooling to 50°, 10 ml of water was added dropwise. The carbon tetrachloride layer was removed and the aqueous phase was extracted with five 10-ml portions of dichloromethane. The combined organic layer was dried and the solvent was removed under reduced pressure to give 0.070 g (75%) of solid **11**. An analytical sample was purified by chromatography on Florisil followed by recrystallization from hexane, mp 87.5–88°.

Anal. Calcd for $C_9H_{12}Cl_2N_2O_4$: C, 38.2; H, 4.3; Cl, 25.0; N, 9.9. Found: C, 38.3; H, 4.4; Cl, 25.3; N, 9.9.

TABLE II

RESULTS OF TREATMENT OF KETAL **7** WITH BORON TRIFLUORIDE AND ALUMINUM CHLORIDE

Expt	Reagent ratio to **7**	Solvent	Time, hr	Temp, °C	Recovered compd, %
7	$BF_3 \cdot Et_2O$[a]	None	1	45	**7**, >95
8	BF_3[a]	CH_2Cl_2	1	40	**7**, >95
9	$AlCl_3$, 3:1	CH_2Cl_2	17	40	**7**, 85
10	$AlCl_3$, 4:1	CCl_4	0.5	78	**7**, 40[b]
11	$AlCl_3$, 9:1	CCl_4	0.5	78	**11**, 40[b]
12	$AlCl_3$, 9:1	CCl_4	1	60	**11**, 75[b]

[a] Large excess of BF_3 to **7**. [b] There was no extensive attempt to work out optimum conditions.

The infrared spectrum (Nujol) displayed a strong doublet absorption at 5.72 and 5.80 μ (C=O). The nmr spectrum ($CDCl_3$) showed a total absence of the ethoxyl group pattern. Absorptions were found at τ 7.90 (4 H, center of broad quartet, $>CH_2$), 6.20 (6 H, singlet, CO_2CH_3), and 5.47 (2 H, unresolved multiplet, >CH).

N,N′-Dimethyl-2,3-diazabicyclo[2.2.1]heptan-7-one Ethyl Ketal (12).—A solution of 3.39 g (0.01 mole) of **7** in ether was added slowly to 1.7 g (0.045 mole) of lithium aluminum hydride in 150 ml of ether. After stirring for 2 hr at reflux, 3.4 ml of water was added cautiously followed by 2.9 ml of 10% sodium hydroxide. The solids were filtered and washed with ether. The ether solution was dried over magnesium sulfate, the ether was removed, and the residue was distilled to give 2.18 g (91%) of **12**, bp 51–53° (0.6 mm). The infrared spectrum showed no absorptions in the 3- (NH) or 5.8-μ (C=O) regions. The nmr spectrum ($CDCl_3$) displayed the ethoxyl group pattern at τ 8.76 (6 H, CH_3) and 6.43 (4 H, CH_2) with other bands at 8.24 (4 H, singlet, $w_{1/2}$ = 4 cps, $>CH_2$), 7.47 (6 H, singlet, CH_3), and 7.05 (2 H, singlet, $w_{1/2}$ = 4 cps, >CH).

For additional characterization, **12** was treated with methyl iodide by gentle warming to afford the methiodide derivative **13**. Recrystallization for absolute methanol gave an analytical sample, mp 178–180° dec.

Anal. Calcd for $C_{12}H_{25}IN_2O_2$: C, 40.5; H, 7.1; I, 35.6; N, 7.9. Found: C, 40.5; H, 7.0; I, 35.5; N, 7.9.

An attempt to hydrolyze ketal **12** to the 7-ketone **14** with 10% hydrochloric acid at 90° for 1 hr as described above was unsuccessful. Only starting material **12** was recovered.

Registry No.—**5**, 10277-38-0; **7**, 10293-82-0; **9**, 10293-83-1; **10**, 10293-84-2; **11**, 10293-85-3; **12**, 10293-86-4; **13**, 10293-87-5.

Acknowledgment.—This study was supported by the National Science Foundation, Grant No. GP-3534.

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(21) A case of magnetic nonequivalence owing to molecular asymmetry: W. L. Meyer, D. L. Davis, L. Foster, A. S. Levinson, V. L. Sawin, D. C. Schew, and R. F. Weddleton, *J. Am. Chem. Soc.*, **87**, 1573 (1965), and references cited therein.