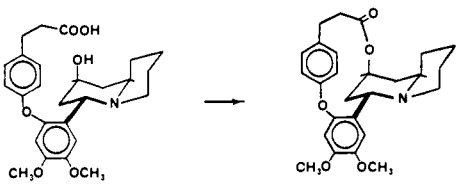
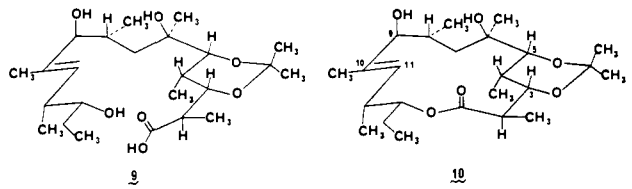
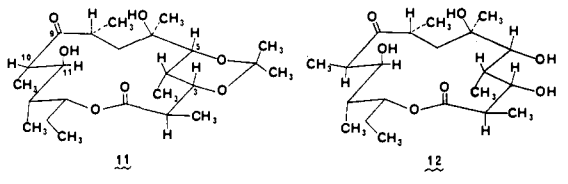


7 8

Erythronolide B (**12**), the aglycone of the antibiotic erythromycin, has been synthesized from the protected acyclic hydroxy acid **9** by application of the double activation method.[11] Treatment of **9** in THF with 2 equiv of 2,2′-dipyridyl disulfide and 2 equiv of triphenylphosphine for 22 hr at 25° led to the 2-pyridinethiol ester which could be isolated in 88% yield and which upon heating at reflux in xylene (under argon) at *ca.* 0.002 *M* concentration for 72 hr afforded the macrocyclic lactone **10,** identical with the material prepared in three steps from erythronolide[11] in 36% yield.[12] The conversion of **10** to erythronolide B[4] was effected by the sequence: (1) selective oxidation with manganese dioxide in methylene chloride to form the $\Delta^{10,11}$-en-9-one, mp 117°,[11] in 98% yield; (2) epoxidation of the 3,5-acetonide, $\Delta^{10,11}$-en-9-one by a large excess of 30% hydrogen peroxide in methanol containing 5 equiv of sodium hydroxide (per equivalent of enone) at 10° for 1 hr and 25° for 12 hr to form quantitatively 10(*R*), 11(*S*)-oxide,[4] mp 121–121.5°, $[\alpha]^{23}D$ +7.8° (*c* = 2 in CH_3OH); (3) reduction of the oxide with hydrogen (1 atm) over Pd–C catalyst in methanol containing a little sodium bicarbonate for 22 hr at 25° to form in 77% yield the 3,5-acetonide of 10-epi erythronolide B (**11**);[4] (4) epimerization of **11** at C-10 (potassium carbonate in aqueous methanol); and (5) acid-catalyzed hydrolysis of the acetonide (1:1 THF:1 *N* hydrochloric acid at 25°).



9 10



11 12

Studies in this area are continuing with the aim of achieving total syntheses of several naturally occurring macrocycles, including brefeldin A and erythronolide B, and also of improving and extending the double activation method.[13]

References and Notes

(1) E. J. Corey and K. C. Nicolaou, *J. Amer. Chem. Soc.*, **96,** 5614 (1974).
(2) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Amer. Chem. Soc.*, preceding paper.
(3) Prepared by treatment of brefeldin A (**3**) with 3 equiv of dihydropyran in methylene chloride in the presence of a catalytic amount of *p*-toluenesulfonic acid (initially at 0° then at 25° for 4 hr) to give the bis(tetrahydropyranyl) ether **2** (100%), followed by saponification of **2** with 0.13 *N* lithium hydroxide in 3:1 methanol:water at 50° for 20 hr (100%).
(4) Satisfactory infrared, proton magnetic resonance (pmr), and mass spectral data were obtained on a chromatographically homogeneous sample of this intermediate.
(5) See H. P. Weber, D. Hauser, and H. P. Sigg, *Helv. Chim. Acta*, **54,** 2763 (1971), for structure. We are indebted to Dr. Sigg for a generous gift of brefeldin A.
(6) Prepared from naturally derived carpaine (**6**) (gift of Dr. James L. Coke) by reaction with excess benzylchloroformate in 2:1 THF—4 *N* sodium hydroxide at 0° to form **5**,[4] $[\alpha]^{20}D$ −17.00° (*c* = 8.35 in $CHCl_3$), and subsequent hydrolysis with 0.3 *N* lithium hydroxide in 3:1 methanol—water at 70° for 20 hr.
(7) For the structure see (a) M. Spiteller-Friedman and G. Spiteller, *Monatsh. Chem.*, **95,** 1234 (1964); (b) J. L. Coke and W. Y. Rice, Jr., *J. Org. Chem.*, **30,** 3420 (1965), and references cited therein.
(8) Prepared from naturally derived vertaline (gift of Dr. James P. Ferris) by saponification with 20% aqueous sodium hydroxide:dimethyl sulfoxide (1:2) at 120° for 5 hr.
(9) For structure see (a) J. A. Hamilton and L. K. Steinrauf, *J. Amer. Chem. Soc.*, **93,** 2939 (1971); (b) J. P. Ferris, *J. Org. Chem.*, **27,** 2985 (1962); **28** 817 (1963).
(10) Since there was available to us only enough of the hydroxy acid **7** (15 mg) to permit a single small-scale cyclization experiment, it seems likely that substantially higher yield can be realized. The conversion of (±)-**7** to (±)-vertaline (**8**) in 41% yield by acid-catalyzed lactonization has recently been reported; see M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.*, **22,** 973 (1974). The acid–lactonization process has also been reported for other members of the Lythraceae series with yields being either low or unspecified; see (a) B. Loev, I. Lantos, and H. Van Hoeven, *Tetrahedron Lett.*, 1101 (1974); (b) M. Hanaoka, N. Ogawa, and Y. Arata, *ibid.*, 2355 (1973); and (c) M. Hanaoka, H. Sassa, N. Ogawa, Y. Arata, and J. P. Ferris, *ibid.*, 2533 (1974).
(11) The oily acid **9**[4] was prepared from naturally derived erythronolide B by the following sequence: (1) conversion of erythronolide B to the 3,5-acetonide,[4] mp 81.5°, $[\alpha]^{23}D$ −84.4° (c = 2 in CH_3OH), by reaction with 2-methoxypropene (4 equiv) in methylene chloride containing 0.7 mole % of phosphorus oxychloride at 25° for 168 hr; (2) dehydration at the β-ketol unit in the acetonide to form the $\Delta^{10,11}$ olefin,[4] mp 117°, uv_{max} 231 nm (ε 12,200); (3) reduction of the 9-keto group by 2 molar equiv of sodium borohydride in methanol at 0° to form the 3,5-acetonide, $\Delta^{10,11}$-en-9-ol **10**[4]; and (4) saponification using dimethyl sulfoxide—5.4 *N* sodium hydroxide (4:3) at 110° for 5 hr.
(12) Improvements in the efficiency of this process will be sought in further experimentation. It should be noted, however, that this represents the first successful cyclization to an erythromycin aglycone system and that, further, the cyclization was achieved without protection of the hydroxyl groups at C-6 or C-9.

(13) This investigation was assisted in part financially by a grant from the National Institutes of Health.

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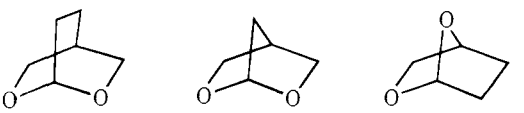
2,6- and 2,7-Dioxabicyclo[2.2.1]heptanes

Sir:

Recently[1] we reported the synthesis of a highly reactive bicyclic acetal, 2,6-dioxabicyclo[2.2.2]octane (**1**), the parent of a new ring system. We now report the synthesis of the next lower homolog, 2,6-dioxabicyclo[2.2.1]heptane (**2**), also the parent of a new ring system. Additionally we report the synthesis of the isomeric bicyclic acetal 2,7-dioxabicyclo[2.2.1]heptane (**3**), the parent of a much-investigated group of sugar derivatives.[2]



1 2 3

Alkylation of dimethyl malonate with bromoacetaldehyde diethyl acetal, followed by lithium aluminum hydride reduction, gave diol diacetal **4.** Bicyclization of this intermediate was performed in dilute dioctyl phthalate solution under high vacuum at 110° with a trace of *p*-toluenesulfonic acid as catalyst and condensation of the distillate at liquid nitrogen temperature. Compound **2** was obtained in 58% yield after distillation, bp 63–64° (30 mm).[3]

$$(HOCH_2)_2CHCH_2CH(OC_2H_5)_2 \xrightarrow{H^+} 2$$

4

Diol **5** was prepared according to the literature procedures used for the corresponding diethyl acetal.[4] Applica-

Table I. Rates of Acidic Solvolysis of Several Bicyclic Acetals[6]

Acetal	k_1, sec^{-1}	Acid concn. C_{HA}, M	Relative reactivity
2	5.3×10^{-3}	6.3×10^{-4}	6.9×10^{5}
3	1.8×10^{-3}	6.3×10^{-3}	2.5×10^{4}
1	1.8×10^{-4}	6.3×10^{-3}	2.5×10^{3}
7	5.8×10^{-5}	6.3×10^{-1}	7.7 (ref 1)
8			1 (ref 1)

tion of the bicyclization technique described above gave 2,7-dioxabicycloheptane **3** in 85% yield (by gc), bp 47° (30 mm). It could also be made from 2-methoxy-5-hydroxytetrahydropyran[5] (**6**) in 39% yield.

$$HOCH_2CHOHCH_2CH_2CH(OCH_3)_2 \xrightarrow{H^+}$$

5

$$3 \xleftarrow{H^+} HO\text{-}\langle O \rangle\text{-}OCH_3$$

6

Tremendous differences in reactivity among these compounds were indicated by measurements of their rates of acid-catalyzed solvolysis (Table I). In the series **2, 3, 1,** 6,8-dioxabicyclo[3.2.1]octane (**7**), and dimethyl acetal (**8**), the half-lives increased by a factor of $>10^2$ as the total acid concentration was increased by a factor of 10^3. The approximate relative reactivities under these conditions thus span more than five powers of ten. These differences are traceable to ring strain and anomeric effect. Work is currently under way to establish the respective contributions of undissociated acid and of oxonium ion.

These new monomers are expected to be of interest in studies of polymerization to polysaccharide analogs,[1,2,7] the thermochemistry of acetals,[8] and the study of acetal solvolysis mechanisms and lysozyme action.[9]

Acknowledgment. We are greatly indebted to the National Institutes of Health, Grant No. GM-18595, for support of this work.

References and Notes

(1) H. K. Hall, Jr., L. J. Carr, R. Kellman, and Fr. DeBlauwe, *J. Amer. Chem. Soc.*, **96**, 7265 (1974).
(2) Reviews: C. Schuerch, *Advan. Polym. Sci.*, **10**, 173 (1972); *Accounts Chem. Res.*, **6**, 184 (1973).
(3) All new compounds in this investigation gave satisfactory C and H analyses and nmr, ir, and mass spectra and were pure by gas chromatography.
(4) C. C. Price and R. B. Balsley, *J. Org. Chem.*, **31**, 3406 (1966).
(5) R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, **48**, 2334 (1970).
(6) Conditions: temperature 35°; dichloracetic acid catalyst; solutions are initially 1.25 *M* in acetal in solvent 0.6 ml acetone-d_6 and 0.2 ml D_2O; rates followed by monitoring C_1H nmr absorption intensity (C_5H for **7**) as a function of time. Good pseudo-first-order plots were obtained.
(7) H. K. Hall, Jr., and M. J. Steuck, *J. Polym. Sci., Part A-1*, **11**, 1035 (1973).
(8) M. Mansson, *J. Chem. Thermodyn.*, **1**, 141 (1969), and related articles.
(9) Review: T. H. Fife, *Accounts Chem. Res.*, **5**, 764 (1972).

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A Platinum(II) Complex Containing a Metallodithiocarboxylate Ligand

Sir:

Although thiocarbonyl complexes of several metals are now known,[1] none has been reported for Pt(II). In our attempts to prepare such a complex, we not only found evidence for the formation of a reactive platinum thiocarbonyl complex but also observed that it is slowly converted into a very stable Pt(II) complex containing the novel metallodithiocarboxylate bidentate ligand, the first ligand of this type to be observed. The molecular structure of the complex has been established by an X-ray crystallographic investigation.

When 0.46 g of *trans*-$(Ph_3P)_2Pt(Cl)[C{=}S)OMe]$[2a] in 15 ml of CH_2Cl_2 was stirred under 1 atm of BF_3 for 18 hr at 25°, the solution changed from pale to deep yellow. The BF_3 and solvent were removed under a stream of N_2 leaving a yellow oil which solidified on gently warming under vacuum. While attempts to recrystallize and purify the solid yielded only oils, the compound did exhibit a strong band in its infrared spectrum at 1400 cm^{-1} in a position characteristic of the thiocarbonyl ligand;[1] it also exhibited a broad absorption at 1050 cm^{-1} typical of the BF_4- ion. This evidence together with the presence of only phenyl proton resonances in its pmr spectrum suggested that the compound could be formulated as $[(Ph_3P)_2Pt(Cl)(CS)]BF_4$.[2b] While C, H, Cl, S, and F analyses of the compound were close to this composition, they were not satisfactory. That $[(Ph_3P)_2Pt(Cl)(CS)]BF_4$ was the predominant compound in the solid, however, was supported by its ready reaction with MeOH and Me_2NH in CH_2Cl_2 at 25° to give the following known and expected[3] products in 60–70% yield.

$$(Ph_3P)_2Pt(Cl)(CS)^+ \xrightarrow{MeOH} (Ph_3P)_2Pt(Cl)[C(=S)OMe]^2$$
$$(Ph_3P)_2Pt(Cl)(CS)^+ \xrightarrow{Me_2NH} (Ph_3P)_2Pt(Cl)[C(=S)NMe_2]^4 \quad (1)$$

When a CH_2Cl_2 solution of the impure $[(Ph_3P)_2Pt(Cl)(CS)]BF_4$ was shaken with a small amount of H_2O, the 1400-cm^{-1} absorption of the CS ligand disappeared and a new band appeared at 2115 cm^{-1}. The position of this product band was identical with that of a sample of $[(Ph_3P)_2Pt(Cl)(CO)]BF_4$ prepared by a different route.[5]

$$(Ph_3P)_2Pt(Cl)(CS)^+ + H_2O \longrightarrow (Ph_3P)_2Pt(Cl)(CO)^+ + H_2S \quad (2)$$

This reaction presumably proceeds *via* H_2O attack at the thiocarbonyl carbon atom as proposed for the conversion of the CS ligand in $W(CO)_5(CS)$ into a C≡NR group on reaction with primary amines.[6] Even the solid $[(Ph_3P)_2Pt(Cl)(CS)]BF_4$ undergoes slow hydrolysis according to eq 2 when exposed to the atmosphere for several hours.

If a solution of $[(Ph_3P)_2Pt(Cl)(CS)]BF_4$ in CH_2Cl_2–hexane is allowed to stand under an air atmosphere at 25° for 1 to 2 days, air-stable yellow crystals (35–40% yield) suitable for X-ray analysis are formed. When recrystallized from acetonitrile–ethyl ether, the compound analyzes correctly for $[Cl(Ph_3P)_2Pt(CS_2)Pt(PPh_3)_2]BF_4$. *Anal.* Calcd: C, 53.3; H, 3.65; Cl, 2.16; S, 3.91. Found: C, 52.6; H, 3.51; Cl, 1.69; S, 4.12. The compound is stable on heating in air up to its melting point, 258–261°. It is a 1:1 electrolyte in CH_2Cl_2 solution and exhibits a broad band at 1050 cm^{-1} in its infrared spectrum characteristic of the BF_4^- anion.

The crystal used for the structure determination of this compound contained approximately 0.2 mol of CH_2Cl_2 per mole of complex. Data were collected on a fully automated Syntex $P2_1$ four-circle diffractometer using monochromatic Cu Kα (1.5418 Å) radiation. There are four molecules of complex in the unit cell which belongs to the common space group $P2_1/c$. Diffractometer measured cell constants for the monoclinic unit cell are a = 15.577 (1), b = 16.539 (3),