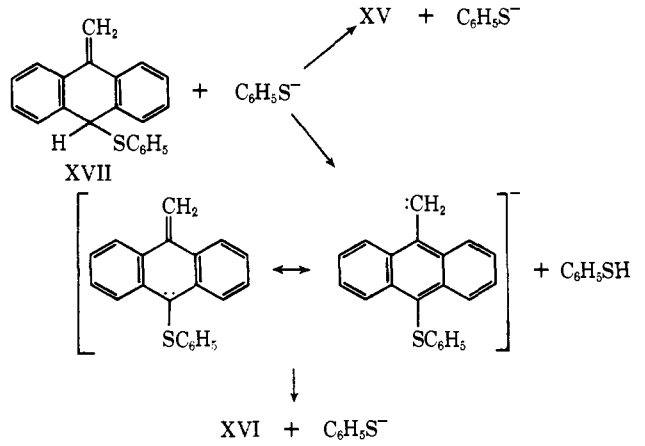
stage process, but now the intermediate XVII, unlike the other intermediates, is able to undergo the prototropic shift productive of a 9-methylanthracene, presumably because the thiophenoxy group has a relatively small steric requirement and, also, because sulfide sulfur stabilizes a carbanion.[4,5]

Sodium thiophenoxide reacts with the quaternary ammonium salt IV much more rapidly than it does with benzyltrimethylammonium chloride (half-life of 3 min as opposed to 70 hr). Whereas the reaction of the lithium salt of 2-nitropropane with the quaternary ammonium salt IV (eq 2) is 50% complete in 1 hr there is no detectable reaction between the lithium salt of



2-nitropropane and benzyltrimethylammonium chloride after 84 hr. These facts are readily intelligible on the basis of the proposed multistage mechanism.

The matter of concertedness or nonconcertedness[6] in the formation, and isomerization, of intermediates such as VI is being studied. Also under investigation are numerous interesting questions relating to leaving groups, nucleophiles, and ring systems.[7]

Acknowledgment. We thank the National Science Foundation and Eli Lilly and Co. for generous support. We are indebted to Dr. P. R. Singh for valuable preliminary studies and to Mr. D. C. Williams who prepared some of our starting materials and checked certain experiments.

(4) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, pp 55–60.

(5) Prolonged treatment of XV with sodium thiophenoxide does not isomerize it to XVI.

(6) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(7) The question arises: do we deal here with one-electron transfer processes, *i.e.*, are radicals and radical anions involved? Preliminary studies of the reaction of eq 2 do not support this possibility for the reaction is unaffected by oxygen and by di-*tert*-butyl nitroxide; the matter is being investigated further.

C. Wayne Jaeger, Nathan Kornblum*

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

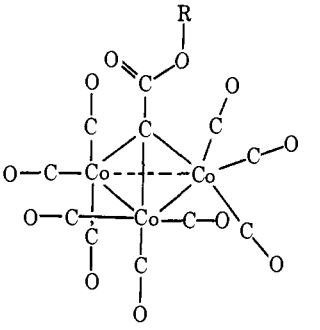
Received December 21, 1971

The Carbatricobalt Decacarbonyl Cation. A Novel Acylating Agent

Sir:

During a study of C-functional derivatives of methylidynetricobalt nonacarbonyl, we became interested in the chemistry of carboxymethylidynetricobalt nonacarbonyl (**1a**). In the course of this work, we have developed the preparation of the novel title compound (as the PF_6^- or BF_4^- salt) and have found it to be a reactive acylating agent with potentially important applications.

Carboalkoxymethylidynetricobalt nonacarbonyls (**1**, R = alkyl), generally purple to red-purple crystalline



1a, R = H
b, R = Me, mp 108–109°
c, R = Et, mp 45–46°
d, R = Me_2CH, mp 63–64°
e, R = Me_3C, mp 48–49°
f, R = Me_3Si, mp 60–62°
g, R = CH_2=$CHCH_2$, mp 40–41°

solids, can be prepared by reaction of the appropriate esters of trichloroacetic acid with dicobalt octacarbonyl in tetrahydrofuran medium.[1] However, we found that the acid itself cannot be prepared directly by this procedure and that hydrolysis of such esters (**1b–1f**) to the desired $(OC)_9Co_3CCO_2H$ in THF–water medium using added mineral acids in catalytic or above stoichiometric amounts could not be achieved. As can be seen from the disposition of the carbon monoxide ligands in **1**,[2] the ester carbonyl group is in a very sterically hindered environment and this led us to consider as a last resort the reaction conditions which were successful in the hydrolysis of esters of the highly hindered 2,4,6-trialkylbenzoic acids,[3,4] *i.e.*, a reaction in concentrated sulfuric acid.[5] Accordingly, a sample of **1c** was dissolved in concentrated sulfuric acid and the resulting yellow-brown solution was poured onto cracked ice. Extraction with ether, followed by evaporation of the dried extracts and crystallization of the residue from chloroform, gave $(OC)_9Co_3CCO_2H$, purple-black needles, which decomposes without melting, $\nu_{C=O}$ 1630 cm^{-1}, in 98% yield. Esterification of this acid by standard procedures using catalytic or above stoichiometric amounts of H_2SO_4 in the presence of the appropriate alcohol as solvent was not successful. However, here the Newman technique[4] also was applicable. When a concentrated sulfuric acid solution

(1) W. H. Dent, L. A. Duncanson, R. G. Guy, W. H. B. Reed, and B. L. Shaw, *Proc. Chem. Soc.*, 169 (1961).

(2) The structure shown for **1** is based upon the results of an X-ray crystal-structure determination for $CH_3CCo_3(CO)_9$ by P. W. Sutton and L. F. Dahl, *J. Amer. Chem. Soc.*, **89**, 261 (1967).

(3) H. P. Treffers and L. P. Hammett, *ibid.*, **59**, 1708 (1937).

(4) M. S. Newman, *ibid.*, **63**, 2431 (1941).

(5) In general, cobalt carbonyls are not stable to concentrated sulfuric acid. The conversion of acetylenedicobalt hexacarbonyl complexes, $(RC_2H)Co_2(CO)_6$, to alkylidynetricobalt nonacarbonyls, $RCH_2CCo_3(CO)_9$, by treatment of the former with dilute aqueous methanolic H_2SO_4 has been noted,[6] but nothing was known concerning the effect of concentrated H_2SO_4 on the $RCCo_3(CO)_9$ cluster compounds.

(6) R. Markby, I. Wender, R. A. Friedel, F. A. Cotton, and H. W. Sternberg, *J. Amer. Chem. Soc.*, **80**, 6529 (1958).

of $(OC)_9Co_3CCO_2H$ was poured into an excess of an alcohol, the expected ester was formed in good yield, *e.g.*, **1b** (95%), **1d** (96%), **1e** (39%), **1g** (99%), and **1** where R = $HOCH_2CH_2$ (85%). The phenyl ester could not be prepared by this procedure.

The most likely reactive species in these sulfuric acid solutions is the acylium ion, $(OC)_9Co_3CCO^+$. According to Treffers and Hammett[3] and Newman,[4] the fact that we observe the reactions described above implies that the ionization of carboxymethylidynetricobalt nonacarbonyl and its esters in sulfuric acid proceeds as shown in eq 1 and 2. The ionization process

$$(OC)_9Co_3CCO_2R + H_2SO_4 \rightleftharpoons (OC)_9Co_3CC(OH)(OR)^+ + HSO_4^- \quad (1)$$

R = H or alkyl

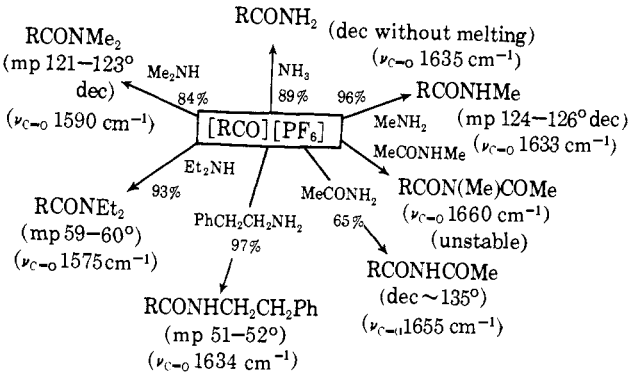
$$(OC)_9Co_3CC(OH)(OR)^+ + H_2SO_4 \rightleftharpoons (OC)_9Co_3CCO^+ + ROH_2^+ + HSO_4^- \quad (2)$$

(eq 1, 2) (*vs.* the more usual formation of $RCO_2H_2^+$ in H_2SO_4) is a consequence of both steric and electronic factors, and the observation of such behavior in the case of $(OC)_9Co_3CCO_2H$ is readily understandable in terms of steric effects. Stronger hindered acids, such as 2,4,6-tribromobenzoic acid, are merely protonated in concentrated H_2SO_4,[4] and this would imply that $(OC)_9Co_3CCO_2H$ is a fairly weak acid.

The sulfuric acid medium used in this chemistry places severely restrictive limits on the reactions of the $(OC)_9Co_3CCO^+$ ion that may be developed. However, we have found that this acylium ion may be isolated in the form of its stable hexafluorophosphate or tetrafluoroborate salts. For example, the addition of 65% aqueous HPF_6 to a solution of **1a** or **1c** in propionic anhydride solution resulted in immediate precipitation of a black solid which was quite sensitive to moisture. The analysis [Calcd for $C_{11}O_{10}F_6PCo_3$: C, 21.52; O, 26.06; Co, 28.80. Found: C, 21.56, 21.67; O, 25.62; Co, 26.51, 27.00, 31.60] and the chemistry of this solid as developed in further work are entirely in harmony with the structure $[(OC)_9Co_3CCO][PF_6]$. The BF_4^- salt, prepared in similar manner, was fairly soluble in dichloromethane, and in its CH_2Cl_2 solution ir spectrum bands at 2110 (m), 2070 (s), 2040 (vs), and 1990 (w) cm^{-1} were assigned to C≡O stretching vibrations of carbon monoxide ligands on cobalt and a band at 2260 cm^{-1} (m) to the acylium C=O frequency.

The reaction of $[(OC)_9Co_3CCO][PF_6]$ with water gave the acid **1a** in quantitative yield and treatment of the salt with alcohols produced the esters **1b** (82%), **1c** (96%), **1e** (84%), and $(OC)_9Co_3CCO_2CH_2CH_2O_2CCCo_3(CO)_9$ (35%). Use of the acylium salt allowed the synthesis of the phenyl ester (mp 63–64°) in 73% yield by its reaction with phenol in dichloromethane solution. Reactions of the acylium salt with thiols gave the expected thio esters: $(OC)_9Co_3CC(O)SEt$, mp 61–62° dec, 80%, and $(OC)_9Co_3CC(O)SPh$, mp 91.5–92.5°, 80% yield. A variety of amides was prepared by the reaction of $[(OC)_9Co_3CCO][PF_6]$ with ammonia, primary and secondary amines, and primary and secondary amides (Chart I). Ethyl glycinate was acylated with $[(OC)_9Co_3CCO][PF_6]$ by treating a mixture of the salt with $Cl^-H_3NCH_2CO_2Et^+$ in dichloromethane with pyridine. A 63% yield of $(OC)_9Co_3CCONHCH_2CO_2Et$, mp 117° dec, ν(C=O, amide) 1620 cm^{-1}, was obtained. A similar procedure was used in the synthesis of a cobalt cluster derivative of a tripeptide, $(OC)_9Co_3CCONHCH_2CONHCH(CH_2Ph)CONHCH_2CO_2Et$ (58% yield), ν(C=O, amide) 1608 cm^{-1}. Although in principle the peptide substrate contains both reactive amino and amide N–H bonds, from steric considerations, attack by the highly hindered $(OC)_9Co_3CCO^+$ would be expected to take place at the NH_2 group. That this is actually the case is indicated by the low value of ν(C=O, terminal amide) of the product (compare with values in Chart I).

Chart I[a]



[a] $\nu_{C=O}$ given are the amide C=O frequencies; R = $(OC)_9Co_3C$.

Ketone syntheses with the acylium hexafluorophosphate also are possible. This salt reacted with EtZnBr (*via* $Et_2Zn + ZnBr_2$) in THF to give $(OC)_9Co_3CCOEt$, dec ~74°, ν(C=O) 1645 cm^{-1}, in 54% yield. This ketone also could be prepared using the ($EtMgBr + ZnCl_2$) reagent system. The acylium salt also cleaves methyl groups from tetramethyltin, giving $(OC)_9Co_3CCOMe$ in 58% yield after 5 days at room temperature, in dichloromethane. Electrophilic aromatic substitution also is possible with $[(OC)_9Co_3CCO][PF_6]$, as illustrated by its reaction with ferrocene in dichloromethane to give ferrocenoylmethylidynetricobalt nonacarbonyl in 31% yield, mp 104° dec.

This work has shown $[(OC)_9Co_3CCO][PF_6]$ to be a useful, easily prepared reagent which should make possible further broad development of the chemistry of functional methylidynetricobalt nonacarbonyl complexes. The successful acylation of alcohols, amines, an amino acid ester, and a peptide suggests that the $(OC)_9Co_3CCO$ moiety should be capable of introduction as a substituent into macromolecules of biological interest *via* its reactions with OH, NH, or SH functions. The introduction of three cobalt atoms at one specific site could facilitate X-ray crystallographic and possibly electron microscopic studies of such molecules. The steric factor associated with this cation should make possible selective reactions at specific sites in a controlled fashion in these molecules. These various aspects of $(OC)_9Co_3CCO^+$ chemistry are receiving our attention.[7]

(7) All compounds reported in this communication, with the exception of **1b** and **1c**,[8] are new. All new compounds have been characterized by satisfactory (±0.3%) analyses for C and H (and if appropriate, N) and by means of their ir and nmr spectra. That portion of this work dealing with reactions in concentrated H_2SO_4 has been reported at a IUPAC Meeting; *cf.* D. Seyferth, J. E. Hallgren, R. J. Spohn, A. T. Wehman, and G. H. Williams, Special Lectures, XXIIIrd International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971, Vol. 6, Butterworths, London, 1971, p 133.

(8) G. Palyi, F. Piacenti, and L. Markó, *Inorg. Chim. Acta Rev.*, 4, 109 (1970).

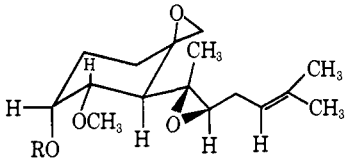
Acknowledgment. The authors are grateful to the National Science Foundation for generous support of this work (Grant No. GP 31429X).

John E. Hallgren, C. Scott Eschbach, Dietmar Seyferth*
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received January 19, 1972

A Total Synthesis of (±)-Fumagillin

Sir:

Fumagillin is an antibiotic isolated from *Aspergillus fumigatus* with antiparasitic[1] and carcinolytic[2] activity. Chemical degradation[3] and X-ray crystallographic[4] studies have led to the assignment of structure **1** to

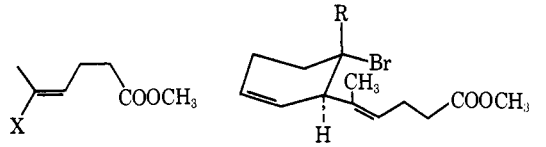


1, R = CO(CH=CH)$_4$COOH
2, R = H

fumagillin. The biological activity and novel structure of fumagillin have stimulated the interest of several groups in synthesis. However, the complications of asymmetry (six centers) and highly reactive functionality have conspired to prevent solution of the problem.[5]

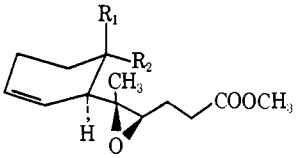
The goal of this synthesis was (±)-fumagillol (**2**), since this should be easily convertible to fumagillin. In fact, treatment of (−)-fumagillol, readily available by degradation of fumagillin,[6] with 1 equiv of methyllithium, followed by addition of this solution to 5 equiv of decatetraenedioyl chloride in tetrahydrofuran at −78°, gave fumagillin, identical with natural fumagillin by thin-layer chromatographic (tlc), infrared (ir), nuclear magnetic resonance (nmr), and mass spectral comparison.

The demonstration of the first total synthesis of (±)-fumagillol proceeded as follows. Alkylation of methyl acetoacetate with 3,3-dimethylallyl bromide[7] followed by deacetylation using the procedure of Ritter and Kaniecki[8] gave methyl 5-methyl-4-hexenoate (**3**),[9] bp 47–50° (5 mm) (57% yield). Oxidation of the olefin **3** with selenium dioxide in 97% aqueous 1,2-dimethoxyethane for 8 hr at reflux gave stereoselectively in 41% yield the α,β-unsaturated aldehyde **4**[10,11] [ir max (neat) 5.73, 5.91, 6.10 μ; nmr peaks due to CHO (δ 9.41), HC=C (6.5, br), and CH$_3$C=C (1.80)], which was converted into the triene **5** in 84% yield by reaction with allylidenetriphenylphosphorane in tetrahydrofuran (−25° for 30 min and 25° for 2 hr)[11] [found for **5**: ir max (neat) 5.72, 6.15 μ; uv max (cyclohexane) 245 (14,000), 255 (23,000), 265 (28,000), and 276 (21,000) nm].

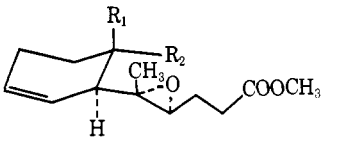


3, X = CH$_3$
4, X = CHO
5, X = CH$_2$=CHCH=CH

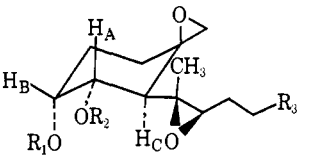
6, R = CHO
7, R = CH$_2$OH
8, R = CH$_2$OTMS



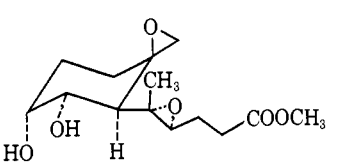
9, R$_1$ = CH$_2$OTMS; R$_2$ = Br
11, R$_1$ = R$_2$ = −OCH$_2$



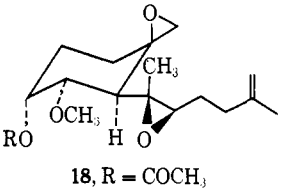
10, R$_1$ = CH$_2$OTMS; R$_2$ = Br
12, R$_1$, R$_2$ = OCH$_2$



13, R$_1$ = R$_2$ = H; R$_3$ = COOCH$_3$
15, R$_1$ = H; R$_2$ = CH$_3$; R$_3$ = COOCH$_3$
16, R$_1$ = H; R$_2$ = CH$_3$; R$_3$ = C(CH$_3$)$_2$OH
17, R$_1$ = COCH$_3$; R$_2$ = CH$_3$; R$_3$ = C(CH$_3$)$_2$OH



14



18, R = COCH$_3$
19, R = H

(1) M. C. McCowen, M. E. Callender, and J. F. Lawlis, *Science*, **113**, 202 (1951); H. H. Anderson, *et al.*, *Amer. J. Trop. Med. Hyg.*, **1**, 552 (1952); J. H. Killough, G. B. Magill, and R. C. Smith, *Science*, **115**, 71 (1952); H. Katznelson and C. A. Jamieson, *ibid.*, **115**, 70 (1952).

(2) J. A. DiPaolo, D. S. Tarbell, and G. E. Moore, *Antibiot. Annu.*, 541 (1958–1959).

(3) D. S. Tarbell, *et al.*, *J. Amer. Chem. Soc.*, **83**, 3096 (1961).

(4) (a) N. J. McCorkindale and J. G. Sime, *Proc. Chem. Soc.*, 331 (1961); (b) J. R. Turner and D. S. Tarbell, *Proc. Nat. Acad. Sci. U. S.*, **48**, 733 (1962).

(5) S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, **28**, 928 (1963); C. A. Peters, Ph.D. Thesis, University of Oklahoma, 1969; E. C. Haywood, Ph.D. Thesis, University of Rochester, 1968; G. Büchi and J. E. Powell, Jr., *J. Amer. Chem. Soc.*, **92**, 3126 (1970); J. F. O'Connor, Ph.D. Thesis, University of Rochester, 1971.

(6) J. K. Landquist, *J. Chem. Soc.*, 4237 (1956). We wish to thank Dr. Jay R. Schenk of Abbott Laboratories for generous samples of natural fumagillin.

(7) H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).

(8) J. J. Ritter and T. J. Kaniecki, *J. Org. Chem.*, **27**, 622 (1962).

(9) Satisfactory nmr, ir, and mass spectra were obtained for all intermediates.

(10) The stereochemistry of selenium dioxide oxidation of similar compounds has been examined previously; see U. T. Bhalerao and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 4835 (1971), and references contained therein.

(11) Elemental analysis or high-resolution mass spectral data for this compound are in accord with theory.

(12) The assignment of structure **6** rests on the eventual conversion of this material to (±)-fumagillol.