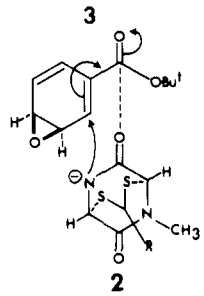
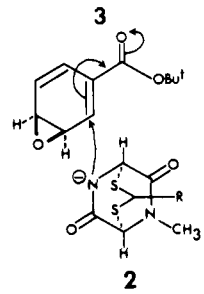
product in CH_2Cl_2–Triton B, was finally realized in dimethyl sulfoxide containing Triton B at room temperature for a short period. Retro-Michael reaction was observed with alcohols **4** and **5** in CH_2Cl_2 or Me_2SO in the presence of Triton B. Thus, an approximate 1:1 mixture of the alcohols **4** and **5** resulted from either **4**, or **5**, or **2** on Triton B treatment in CH_2Cl_2 or Me_2SO in the presence of **3** (excess) overnight.

Since overall trans-opening of the epoxide ring is expected for **3**,[7] alcohols **4** and **5** must be the epimers regarding the relative configuration of the thioacetal bridge and the alcoholic group. Two probable orientations A and B—note *d,l*-thioacetal **2** and *d,l*-benzene oxide **3**[8] are used—are considered for the transition state of the Michael reaction, when **2** and **3** approach in such a way as to cause the least steric hindrance. Interestingly, the favorable dipole interaction involved in A should make it preferred to B in nonpolar solvents such as methylene chloride. Thus, the desired stereochemistry was tentatively assigned to the alcohol **5** and the undesired stereochemistry to the alcohol **4**.[9] The importance of such a dipole interaction in the transition state determining the stereochemistry of the Robinson annelation is known in several cases.[10]

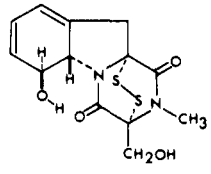


A

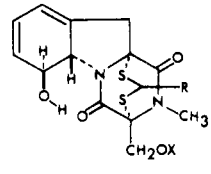


B

The alcohol **5** was converted to the acetate **6**[3] (mp 195–196 °C, Ac_2O/Py/room temperature; 90% yield) and then to the hydroxymethyl derivative **7**[3] (mp 181–182 °C) in three steps (1, TFA/room temperature; 2, $ClCO_2Et/Et_3N$-CH_2Cl_2/room temperature; 3, $NaBH_4/CH_3OH$-CH_2Cl_2/0 °C) in 70% overall yield. Mesylation of **7** ($MsCl/Et_3N$-CH_2Cl_2/room temperature), followed by lithium chloride treatment in DMF[11] and then hydrolysis ($NaOCH_3/CH_3OH$-CH_2Cl_2/room temperature), gave the chloride **8**[3] (mp 200–201 °C) in 95% overall yield.

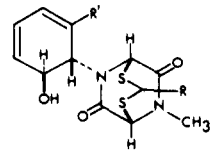


1 : gliotoxin

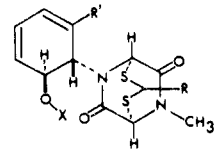


9 : X=$CH_2C_6H_5$

10 : X=H



4



5 : R'=CO_2Bu^t, X=H

6 : R'=CO_2Bu^t, X=Ac

7 : R'=CH_2OH, X=Ac

8 : R'=CH_2Cl, X=H

R=$C_6H_4OCH_3$-*p*

Phenyllithium, slowly added to a mixture of **8** and chloromethyl benzyl ether (excess) in THF at −78 °C with monitoring by TLC, gave the benzylgliotoxin anisaldehyde adduct **9**[3] (mp 210–212 °C), which was isolated in 45% yield.[12] Boron trichloride treatment of **9** in CH_2Cl_2 at 0 °C furnished the gliotoxin anisaldehyde adduct **10**[3] (mp 241–242 °C) in 50% yield.[13] *m*-Chloroperbenzoic acid oxidation of **10**, followed by perchloric acid treatment in methylene chloride at room temperature,[5] yielded *d,l*-gliotoxin **1**[3] (mp 165–166 °C) in 65% yield. Synthetic substance was identical with natural gliotoxin[14] by spectroscopic (NMR, ir, uv, MS) and TLC comparison.

Further efforts to the synthesis of an optically active form of gliotoxin and a biogenetic-type approach toward the toxin are in progress in our laboratories.[15]

References and Notes

(1) See, for example, The Merck Index 8th ed, Merck & Co., Ltd., Rahway, N.J., 1968, p 491, and references therein.

(2) The anti-series[4] with respect to the anisaldehyde residue and the NH group is used to describe the properties of the intermediates in this paper. Results parallel to the anti-series were obtained on the syn-series as well.

(3) Satisfactory spectroscopic (MS, NMR, ir, uv) data were obtained on this substance.

(4) Six steps were 1, $ClCH_2OCH_3$/*t*-BuOK/*t*-BuOH; 2, NBS/$(C_6H_5CO_2)_2$/CCl_4; 3, KSAc/CH_2Cl_2; 4, HCl/CH_3OH; 5, *p*-$CH_3OC_6H_4CHO/BF_3$·Et_2O/CH_2Cl_2; and 6, concentrated HCl/EtOH. The product was a mixture of anti- and syn-thioacetal **2** with respect to the anisaldehyde residue and the NH group. Chromatographic separation of the mixture was performed on the *N*-benzoyl derivative of **2**. Pure anti-thioacetal **2**[3] (mp 250–252 °C) and syn-derivative[3] (mp 249–251 °C) were obtained by ammonolysis of the separated *N*-benzoate. The stereochemical assignment was concluded by converting **2** into *N*-methyl-*C*-monomethyl derivative of **2** and comparing with the authentic sample.[5]

(5) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490, 6492 (1973); Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *ibid.*, **95**, 6433 (1973); S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Lett.*, 1549 (1974); K. Sasaki, T. Fukuyama, S. Nakatsuka, and Y. Kishi, *J. Chem. Soc., Chem. Commun.*, 542 (1975).

(6) R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz, and G. A. Berchtold, *J. Am. Chem. Soc.*, **96**, 1193 (1974).

(7) 1,6-Nucleophilic addition of CH_3O^- and HO^- to **3** is known to result the overall trans-opening of the epoxide ring.[6]

(8) The presence of the benzene oxide valence isomer was demonstrated by various reactions on **3**, although **3** exists predominantly as the oxepin form in solution.[6]

(9) This assignment was confirmed from the fact that the alcohol **5** yielded *d,l*-gliotoxin, while the alcohol **4** gave epigliotoxin regarding the configuration of the sulfur bridge. Detail results in the epi-series will be reported in the full paper.

(10) C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.*, **93**, 1539 (1971), and references therein.

(11) The intermediate (R' = CH_2Cl, X = Ac in structure **8**; mp 179–180 °C) was isolated at this stage.

(12) A stepwise procedure,[5] i.e., 1, $C_6H_5CH_2OCH_2Cl/BuLi/THF$; 2, PhLi/THF, gave less satisfactory results.

(13) At this stage, the synthetic gliotoxin anisaldehyde adduct **10** was found to be identical with the authentic substance, prepared from natural gliotoxin[14] in two steps (1, $NaBH_4/CH_3OH$-CH_2Cl_2; 2, *p*-$CH_3OC_6H_4CHO/BF_3$·Et_2O/CH_2Cl_2).

(14) We are indebted to Dr. R. Nagarajan, Eli Lilly Company, for providing a sample of natural gliotoxin.

(15) Financial assistance from National Institutes of Health, Harvard University, and Hoffmann-La Roche Company is gratefully acknowledged.

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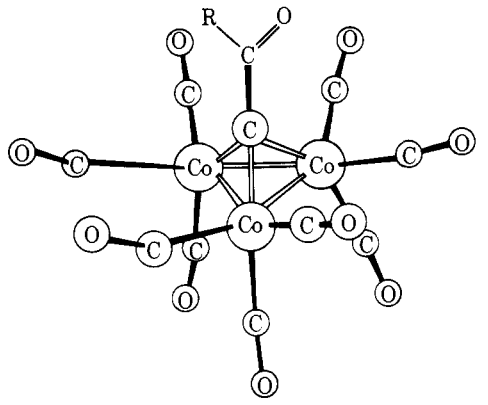
Organocobalt Cluster Complexes. 20. Novel Chemistry of Acyl- and Aroylmethylidynetricobalt Nonacarbonyl Complexes. Unusual Thermal Ketone Decarbonylation Reactions[1]

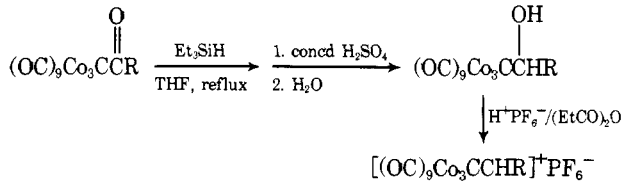
Sir:

Acyl- and aroylmethylidynetricobalt nonacarbonyl complexes, I, are readily available by reaction of the appropriate

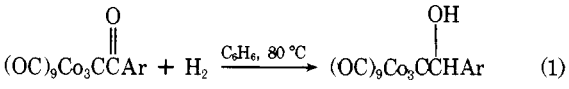


I

Scheme I



$RC(O)CCl_3$ with dicobalt octacarbonyl[2] or by reaction of the $(OC)_9Co_3CCO^+$ ion with reactive aromatic nucleophiles or with weak alkylating agents.[3,4] They are key intermediates in the synthesis of highly stable cobalt cluster carbonium ions of type $[(OC)_9Co_3CCHR]^+$ as shown in Scheme I.[5] It was found, however, that the triethylsilane reduction procedure[6] is not applicable when R is a bulky group such as *tert*-butyl or $(OC)_9Co_3C$. Since the chemistry of the Si–H bond to a remarkable extent parallels that of the H–H bond of molecular hydrogen, we examined the reaction of complexes of type I with H_2. We have found that molecular hydrogen reacts with aroylmethylidynetricobalt nonacarbonyls at atmospheric pressure in refluxing benzene with no added catalyst to produce the respective α-hydroxybenzylidynetricobalt nonacarbonyl complexes in high yield (eq 1).



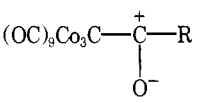
(1)

(Ar = C_6H_5, 78%; *p*-$CH_3C_6H_4$, 83%; *p*-BrC_6H_4, 79%)

In a typical experiment, hydrogen and carbon monoxide (the latter to retard decomposition of the cluster[7]) were bubbled into a solution of 1.16 mmol of *p*-$MeC_6H_4C(O)CCo_3(CO)_9$ in 50 ml of dry benzene for 30 min. Subsequently, the solution was heated at reflux for 2 h while the gas streams were continued. After this time, thin layer chromatography (TLC; silica gel sheet, benzene eluent) showed the absence of starting material and the formation of a new compound (purple spot of lower R_f). Removal of the solvent at reduced pressure was followed by isolation of the product by column chromatography (Silicar CC-7, 1:3 CH_2Cl_2/hexane) and further purification by recrystallization from hexane to give 0.56 g (83%) of *p*-$MeC_6H_4CH(OH)CCo_3(CO)_9$, mp 97.5–99 °C (lit.[6] mp 98–99 °C) whose ir spectrum was identical with that of an authentic sample.[6]

Such reactions proceeded less cleanly and gave poorer yields with acylmethylidynetricobalt nonacarbonyls. Thus similar treatment of $(OC)_9Co_3CC(O)CH_3$ during 7 h gave the desired $(OC)_9Co_3CCH(OH)CH_3$ (31%), but the completely reduced product, $(OC)_9Co_3CCH_2CH_3$, also was formed in 8% yield. Similarly, reduction of $(OC)_9Co_3CC(O)C_2H_5$ with H_2 produced a mixture of $(OC)_9Co_3CCH(OH)C_2H_5$ (23%) and $(OC)_9Co_3CCH_2CH_2CH_3$ (4%). Surprisingly, such reduction of the formyl complex, $(OC)_9Co_3CCHO$, gave only the completely reduced product, $(OC)_9Co_3CCH_3$, in 52% yield.

These hydrogenation reactions which occur so readily in the absence of an external catalyst are most surprising and it seemed reasonable to consider that at 80 °C these cobalt complexes decompose to a small extent and in this way provide catalyst species such as $HCo(CO)_4$ or $Co_2(CO)_8$. If that were so, one might expect these complexes to catalyze the hydrogenation of ketones which are by themselves unreactive toward H_2 under these conditions. However, an initial experiment gave indication that this is not the case. When a mixture of 2 mmol of $(OC)_9Co_3CC(O)CH_3$ and 4 mmol of acetylferrocene was treated with H_2 at atmospheric pressure in refluxing benzene, only reduction products of the cobalt cluster were obtained. No ferrocene derivative other than starting material (98%) was isolated. Also, hydrogenations catalyzed by $HCo(CO)_4$ and $Co_2(CO)_8$ require much more drastic conditions than those used in the present study.[8] At this point we suggest that the high stabilization of an α positive charge by the cobalt cluster[5,9-11] may be responsible for this novel chemistry. We have suggested that the resonance form



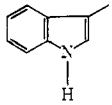
is important in the description of acylmethylidynetricobalt nonacarbonyl complexes.[3] Carbonium ions are known to react with molecular hydrogen and such hydride abstraction from H_2 could be involved in the present case. A similar suggestion was made previously in the case of the unusually facile hydrosilylation of $(OC)_9Co_3C(O)R$ compounds by triethylsilane.[6]

A complication of some interest was encountered in the attempted hydrogenation of $(OC)_9Co_3CC(O)C_6H_4NMe_2$-*p* using this procedure. The product which was formed in 41% yield was not the desired alcohol nor the completely reduced $(OC)_9Co_3CCH_2C_6H_4NMe_2$-*p*, but rather the completely unexpected decarbonylation product, $(OC)_9Co_3CC_6H_4NMe_2$-*p*. The yield of this compound could be increased to 70% simply by heating a benzene solution of $(OC)_9Co_3CC(O)C_6H_4NMe_2$-*p* at reflux under nitrogen for 45 min.

Both reduction to the alcohol and decarbonylation were observed in the attempted hydrogenation of ferrocenoylmethylidynetricobalt nonacarbonyl (17% yield of $(OC)_9Co_3CCH(OH)C_5H_4FeC_5H_5$ and 31% yield of $(OC)_9Co_3CC_5H_4FeC_5H_5$) and the isopropyl-cluster-ketone (3% yield of $(OC)_9Co_3CCH(OH)CHMe_2$ and 16% yield of $(OC)_9Co_3CCHMe_2$). This suggested that thermal decarbonylation might be a more general reaction and, as further experiments demonstrated, this proved to be the case. Table I summarizes the results. When R = aryl, the yields in general were surprisingly high. Substituent effects in $(OC)_9Co_3CC(O)C_6H_4Z$ complexes require further study, but the different reaction times in Table I which represent the time required for consumption of the starting material and the observation that $(OC)_9Co_3CC(O)C_6H_4Br$-*p* did not decarbonylate may be of mechanistic significance.

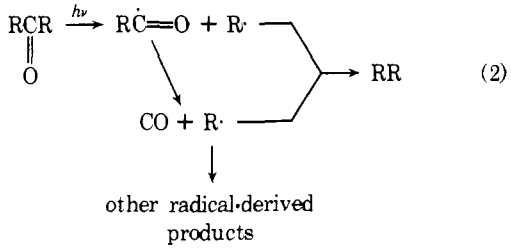
An example of such a reaction illustrates how easily such decarbonylation are effected. Two millimoles of *p*-$MeC_6H_4C(O)CCo_3(CO)_9$ in 50 ml of dry benzene was stirred and heated at reflux under nitrogen for 6 h. At the end of this time, TLC showed that all of the ketone had been consumed and that a brown product of higher R_f had been formed. The benzene was removed under reduced pressure and the residue was recrystallized from hexane to give 0.73 g (69%) of *p*-$MeC_6H_4CCo_3(CO)_9$, mp 105–106 °C (lit.[7] mp 105–107 °C) with an ir spectrum identical with that of an authentic sample.[7]

Table I. Thermal Decarbonylation of $(OC)_9Co_3CC(O)R$ Complexes

R in $(OC)_9Co_3CC(O)R$	Reaction time, h	$(OC)_9Co_3CR$, % yield
p-$Me_2NC_6H_4$–	0.75	70
p-MeC_6H_4–	6	69
C_6H_5–	5	66
p-BrC_6H_4		0[a]
	2	63
	3	71
	10	47
C_2H_5–	18	46[b]
Me_2CH–	4	31[b]
n-C_4H_9–	20	42[b]
Me_3C–		0

[a] No decarbonylation product was formed; partial recovery of starting material with complete decomposition of remaining complex. [b] Lower yields of alkyl complexes probably reflect their lower thermal stability.

This thermal decarbonylation of ketones is very unusual and finds its closest formal parallel in the Norrish type 1 photochemical fragmentation of ketones in the gas phase and, less commonly, in solution (eq 2). For instance, in the photo-



(2)

chemical decomposition of dibenzyl ketone in solution such decarbonylation and radical coupling is the predominant process following α-cleavage.[13]

The C–C bond linking the acyl or aroyl substituent to the $(OC)_9Co_3C$ cluster may well be rather weak as a result of steric factors involving the highly hindered cluster group. Thus a thermal homolytic cleavage of this bond is a conceivable process. However, other mechanistic possibilities which involve the $(OC)_9Co_3C$ unit more intimately may be conceived. Further mechanistic speculation is fruitless in the absence of further experimental information.

Finally, we note that medium effects can be important in reactions of $(OC)_9Co_3CC(O)R$ complexes. Thus ferrocenoylmethylidnetricobalt nonacarbonyl, which was for the most part decarbonylated on treatment with H_2/CO in refluxing benzene and gave only a low yield of the alcohol, reacted to give the alcohol in 72% yield with no observable decarbonylation when this reaction was carried out in refluxing benzene containing about 4% by volume of glacial acetic acid.

It is clear that our understanding of these processes which are described above is at a very rudimentary stage. However, some very novel and interesting chemistry of $(OC)_9Co_3CC(O)R$ complexes has been uncovered which can have preparative utility within the cobalt cluster area.

Acknowledgment. We are grateful to the National Science Foundation (Grant No. MPS75-21215) for generous support of this research.

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The Biosynthesis of the Lupine Alkaloids. A Reexamination[1]

Sir:

The C_{15} lupine alkaloids, e.g., sparteine (**3**) and lupanine (2-oxosparteine) (**4**), originate from three C_5 fragments,[2,3] which are derived from lysine (**1**)[4,5] via cadaverine (**2**),[2-5] and are incorporated in symmetrical fashion and with equal efficiency into each of the three C_5-segments of the alkaloids. Thus, label from [2-^{14}C]lysine is equally distributed among six carbon atoms, C-2, 6, 10, 11, 15, and 17, of sparteine[4] and of lupanine.[5,6] The biogenetic anatomy of the alkaloids is usually[2,3] represented as shown in Scheme I.

The two nitrogen atoms are also supplied by lysine.[4,10] Two of the three C_5 fragments evidently maintain a lysine nitrogen, entering the alkaloids as C_5N units, whereas the third C_5 fragment enters devoid of nitrogen.[11] Even so, it is likely, in view of the observed equal distribution of label from [2-^{14}C]lysine or [1-^{14}C]cadaverine among the three segments of

Scheme I. Incorporation of Lysine and Cadaverine into Sparteine