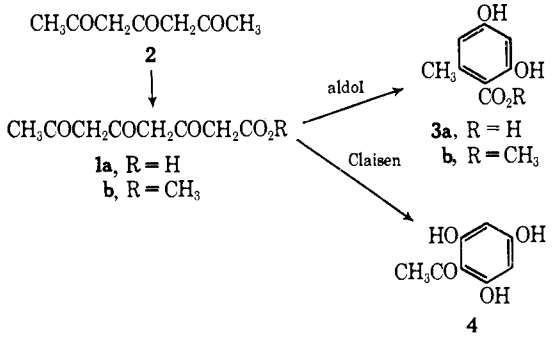
Preparation and Biogenetic-Type Aromatizations of Tetraacetic Acid (3,5,7-Trioxooctanoic Acid)

Sir:

The synthesis of oligo-β-keto compounds has attracted interest[1] since Birch proposed that certain of these, *i.e.*, the oligo-β-keto acids and/or esters, are biogenetic precursors of many phenolic natural products.[2] A recent report from this laboratory described the synthesis and biogenetically modeled cyclizations of several 3,5,7-triketo acids and esters.[3] The triketo acids were prepared by treatment of the corresponding triketones with sodium amide or potassium amide in liquid ammonia, followed by carboxylation of the intermediate trianions. Unfortunately the method was not successful for tetraacetic acid (3,5,7-trioxooctanoic acid, **1a**). Alkali metal amides failed to give appreciable conversion of diacetylacetone (**2**) to its trianion, and only a trace of the carboxylation product could be detected. Tetraacetic acid is of particular interest both as the fundamental member of the homologous series of 3,5,7-triketo acids and as the most important of these compounds in fungal metabolism. We now wish to report a practical synthesis of tetraacetic acid.



The synthesis is based on the use of lithium diisopropylamide, which is a much stronger base than the alkali amides. For example, although unactivated carboxylic acids cannot be di-ionized by alkali metal amides in liquid ammonia, Creger was able to convert isobutyric acid to the dilithium salt using lithium diisopropylamide.[4] Likewise, we find that diacetylacetone (**2**) and other 2,4,6-triketones are converted essentially completely into trianions by this reagent.

Treatment of diacetylacetone with 4 equiv of lithium diisopropylamide in tetrahydrofuran under nitrogen and carboxylation of the soluble, yellow trilithium salt with carbon dioxide gave tetraacetic acid (**1a**) as an oil. Fractionation on silicic acid gave **1a**, mp 67–71°, in 47% yield. Recrystallization from ether at −20° gave pure material, mp 74.5–75.5°; ir ($CHCl_3$) 1695–1729 (broad), 1593 cm^{-1}. The nmr spectrum of **1a** indicated that the compound existed as a mixture of enol–keto tautomers. *Anal.* Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41; mol wt, 186. Found: C, 51.74; H, 5.30; mol wt, 186 (mass spectrometric). The crude oil, obtained directly from the carboxylation reaction, underwent cyclization in aqueous sodium acetate–acetic acid (pH 5.0) to give orsellinic acid (**3a**) in 53% yield based on diacetylacetone.

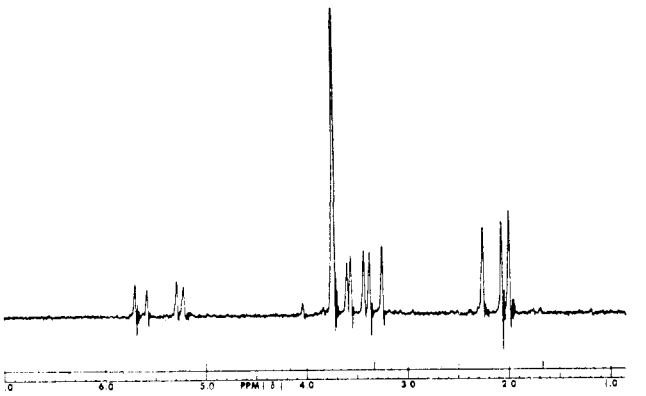
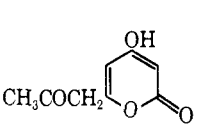


Figure 1. Nmr spectrum of methyl tetraacetate (**1b**) in $CDCl_3$.

Esterification of triketo acid **1a** with 1 equiv of diazomethane in ether gave methyl ester **1b**, mp 16–19°, in 91% yield. Recrystallization from ether at −60° raised the melting point to 24.5–26.5°; ir ($CHCl_3$) 1715–1740 (broad), 1590 cm^{-1}; uv (95% EtOH) 265 (ε 9650), 318 mμ (sh, ε 4200); nmr ($CDCl_3$ with Me_4Si standard) a mixture of enol–keto tautomers, see Figure 1. *Anal.* Calcd for $C_9H_{12}O_5$: C, 54.00, H, 6.04; mol wt, 200. Found: C, 53.93; H, 6.22; mol wt, 200 (mass spectrometric). Cyclization of ester **1b** in aqueous 0.5 *M* potassium hydroxide and fractionation of the products on silicic acid gave Claisen product **4** (39%), ester **3b** (27%), and acid **3a** (13%). On the other hand, cyclization of **1b** in 1 *M* methanolic sodium acetate gave only ester **3b** (50%). Other reactions of **1a** and **1b**, including the formation of lactone **5** and 4-pyrone **6**, are currently under investigation.



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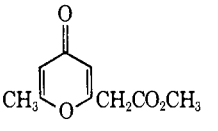

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Trace amounts of acid or base effected aldol cyclization of **1a** and **1b** in organic solvents, and it is apparent that the 3,5,7-trioxooctanoic system is more reactive than the higher homologs. The high reactivity could, in part, explain why tetraacetic acid has not yet been detected in biological systems.

Several groups have recently achieved syntheses of derivatives of tetraacetic acid. Scott and coworkers have reported[5] the synthesis of naturally occurring

(1) See, for examples, F. M. Dean, D. Steelink, and J. Tetaz, *J. Chem. Soc.*, 3386 (1958); A. J. Birch, P. Fitton, D. C. C. Smith, D. E. Steere, and A. R. Stelfox, *ibid.*, 2209 (1963); M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 3884 (1963); H. Stetter and S. Vestner, *Chem. Ber.*, **97**, 169 (1964); K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965); G. Casnati, A. Quilico, A. Ricca, and P. VitaFinzi, *Tetrahedron Letters*, 233 (1966); P. F. Hedgecock, P. F. G. Praill, and A. L. Whitear, *Chem. Ind.* (London), 1268 (1966); E. M. Kaiser, S. D. Work, J. F. Wolfe, and C. R. Hauser, *J. Org. Chem.*, **32**, 1483 (1967); T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, **23**, 3435 (1967); J. L. Douglas and T. Money, *ibid.*, **23**, 3545 (1967); K. T. Buck and R. A. Olofson, *J. Org. Chem.*, **33**, 867 (1968).

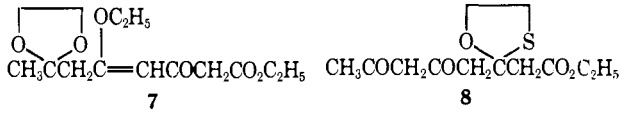
(2) A. J. Birch and F. W. Donovan, *Australian J. Chem.*, **6**, 360 (1953); A. J. Birch, *Proc. Chem. Soc.*, **3** (1962).

(3) T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **89**, 6734 (1967).

(4) P. L. Creger, *ibid.*, **89**, 2500 (1967).

(5) H. Guilford, A. I. Scott, D. Skingle, and M. Yalpani, *Chem. Commun.*, 1127 (1968).

lactone **5**. Treatment of the lactone with potassium methoxide afforded ester **3b**,[5] although ester **1b** was undoubtedly an intermediate. Bram has prepared derivative **7** in which the 7- and 5-carbonyl groups were protected as the ketal and enol ether, respectively.[6] Acid treatment of **7** afforded orcinol, presumably through a process of cyclization, hydrolysis, and decarboxylation.[6] Schmidt and Schwochau[7] have synthesized hemithioketal **8** as well as the corresponding lactone.



7 **8**

Acknowledgment. This research was supported by Research Grant GM-12848 from the National Institutes of Health, U. S. Public Health Service.

(6) G. Bram, *Tetrahedron Letters*, 4069 (1967).
(7) U. Schmidt and M. Schwochau, *Monatsh.*, **98**, 1492 (1967).
(8) Alfred P. Sloan Fellow and Career Development Awardee, K3-GM-27013, of the National Institutes of Health, U. S. Public Health Service.

T. Trefor Howarth, George P. Murphy, Thomas M. Harris[8]
Department of Chemistry, Vanderbilt University
Nashville, Tennessee 37203
Received October 24, 1968

Organometallic Conformational Equilibria. III. The Epimerization Mechanism of π-Allyl(amine)palladium(II) Chloride Complexes[1]

Sir:

Several mechanisms have been advanced to explain the dynamic behavior responsible for the variation of the pmr spectra of a large group of π-allylmetal complexes with changes of temperature or solution composition. The averaging of the AA′BB′X spectrum of π-allylpalladium chloride dimer to an A_4X spectrum in the presence of organic phosphines and arsines has generally been attributed to rearrangement *via* a σ-bonded intermediate.[2-4] This intermediate provides a pathway for interchange of *syn* and *anti* protons;[5] however, rearrangements may occur without *syn–anti* interchange, as observed in the interconversion of isomers of π-cyclopentadienyldicarbonylmolybdenum π-allyl. A process that effectively results in the rotation of the π-allyl moiety about an allyl–molybdenum axis probably accounts for the temperature dependence of the pmr of this complex.[6-8] Racemization or epimerization of π-allyl(amine)palladium chlorides could involve either of these mechanisms, a combination of them, or possibly others; we present here our investigations of this process.

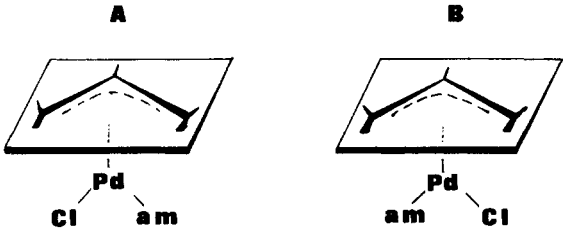


Figure 1. The enantiomers of a π-allyl(amine)palladium chloride complex.

The observation of an AA′BB′X spectrum rather than an ABCDX or A_4X spectrum for the allyl moiety in π-allyl(benzylamine)palladium chloride indicates an averaging process is occurring that interconverts the enantiomers A and B (see Figure 1), but does not involve a σ-bonded intermediate. Furthermore, preparation of the π-allyl(amine)palladium chloride from the optically active (*R*)-α-phenethylamine produces the anticipated mixture of two diastereoisomers. In the limiting low-temperature nmr two superimposed sets of ABCDX allyl resonances in a 1:1 ratio, corresponding to the two diastereoisomers, may be discerned. As the temperature is raised, the accompanying increase in proton site exchange causes broadening and coalescence of the resonances and finally produces an averaged spectrum of two superimposed AA′BB′X allyl resonances (Figure 2). Rotation of the planar allyl moiety, exchange of the amine and chloride ligands, or a planar flip of the allyl group that does not interchange *syn* and *anti* protons[12,14] (see Figure 3) could give rise to these observations. Since the chirality of the amine does not change throughout the process, the mechanisms shown in Figure 3 are all equally plausible in view of the evidence presented thus far. However, only an intermolecular exchange, which effectively averages the chirality of the amine, can account for the single AA′BB′X pattern in the averaged spectrum of the complex prepared from the racemic α-phenethylamine. Furthermore, in the low-temperature spectra of the complexes, weak resonances of the π-allylpalladium chloride dimer can be identified. The onset of broadening of the allyl resonances of the amine complex is accompanied by broadening of the dimer resonances, indicating that dissociation into dimer and

(1) Part II: J. W. Faller, *Inorg. Chem.*, in press.
(2) F. A. Cotton, J. W. Faller, and A. Musco, *ibid.*, **6**, 179 (1967).
(3) K. Vrieze, A. P. Pratt, and P. Cossee, *J. Organometal. Chem.*, **12**, 533 (1968), and references therein.
(4) J. Powell and B. L. Shaw, *J. Chem. Soc., A*, 1839 (1967).
(5) *syn* and *anti* refer respectively to the protons that are *cis* and *trans* to the proton on the central carbon atom of the allyl group.
(6) J. W. Faller and M. J. Incorvia, *Inorg. Chem.*, 7, 840 (1968).
(7) A. Davison and W. C. Rode, *ibid.*, **6**, 2124 (1967).
(8) Planar rotation of π-allyl groups has also been suggested in nickel,[9] rhodium,[10] and tris(pyrazolyl)borate molybdenum[11] complexes.
(9) H. Boennemann, B. Bogdanovic, and G. Wilke, *Angew. Chem. Intern. Ed., Engl.*, **5**, 151 (1966).
(10) J. K. Becconsall and S. O'Brien, *Chem. Commun.*, 720 (1966).
(11) S. Trofimenko, *J. Am. Chem. Soc.*, **90**, 4754 (1968).
(12) The planar flip mechanism could occur either with interchange of *syn* and *anti* sites (*via* a process similar to ring inversion in cyclohexane) or without interchange of *syn* and *anti* sites (perhaps *via* an ion pair, such that the resonance energy of the planar allyl group would not be lost). Generally these possible modes of rearrangement have not been carefully considered in transition metal rearrangements, but have been suggested as possibilities.[2,13]
(13) *Cf.* the remarks by F. A. Cotton in the discussion following the article by G. Wilke in "Proceedings of the 9th Robert A. Welch Conference on Chemical Research, November 17–19, 1965," especially p 184 ff.
(14) Since *syn* and *anti* protons are not interchanged, the rotation of the methylene groups about the carbon–carbon allyl axis, which has been suggested in some cases,[15-18] does not occur in these complexes.
(15) J. K. Becconsall, B. E. Job, and S. O'Brien, *J. Chem. Soc., A*, 423 (1967).
(16) J. K. Becconsall and S. O'Brien, *Chem. Commun.*, 302 (1966).
(17) G. Wilke, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **5**, 151 (1966).
(18) K. C. Ramey, D. C. Lini, and W. B. Wise, *J. Am. Chem. Soc.*, **90**, 4275 (1968).