tails of the mechanisms of their thermal decompositions differ to some extent. Thus, addition of triphenylphosphine to solutions of **2** strongly inhibits its thermal decomposition, and analogs of **2** containing bidentate phosphines are more stable than **2**; in contrast, the diphos complex **4** is only moderately more stable than **3**, and addition of triphenylphosphine to solutions of **3** *increases* the rate of decomposition of this complex.[9]

Although we cannot yet provide detailed mechanisms for the thermal decomposition of the platinocycles **3–7**, the observation that all of these substances show high thermal stability indicates that resistance to thermal decomposition involving metal hydride elimination is a characteristic of this structural class, and not a peculiarity of one or two isolated platinum complexes. If the same property extends to metallocyclic derivatives of other metals, modes of thermal decomposition other than β-hydride elimination—particularly reductive elimination of two alkyl moieties with carbon–carbon bond formation and fragmentation of carbon skeletons with cleavage of carbon–carbon bonds—should be correspondingly more accessible for these substances than for analogous acyclic derivates of these metals. Since reactions of these latter types probably form the basis for many of the catalytic reactions in which metallocyclic compounds appear most promising as intermediates,[2-4] it seems possible that reaction sequences generating metallocyclic rings may offer the opportunity for unusual types of chemical transformations, by the simple expedient of suppressing the metal hydride elimination that dominates much of the chemistry of related acyclic intermediates.

(9) The rate constant for decomposition of **3** in the presence of added triphenylphosphine is given approximately by the expression $k = k_1 + k_2[PPh_3]$, with $k_2 = 2.8 \times 10^{-2}\ M^{-1}\ sec^{-1}$.

(10) John A. Lyons Fellow, 1972–1973.

(11) National Institutes of Health Predoctoral Fellow, 1968–1972.

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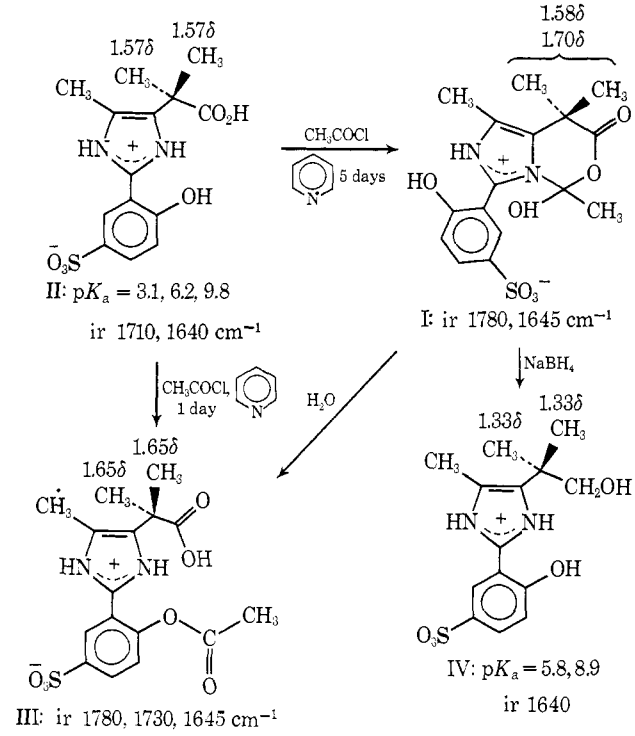
Received March 30, 1973

Isolation of a Tetrahedral Intermediate in an Acetyl Transfer Reaction

Sir:

The past 15 years have witnessed the amassing of a large body of experimental data on the mechanism of acyl transfer reactions.[1] Central to these mechanisms is the mode of disposition of tetrahedral addition intermediates of acyl functions.[2] Tetrahedral intermediates have been established to exist *via* both kinetic and ^{18}O exchange studies. The most noteworthy example has been found perhaps in the hydrolysis of ethyl trifluorothiolacetate where conclusions based on kinetic results[3] were later confirmed by oxygen exchange experiments.[4] We report herein the first isolation and unequivocal characterization of a labile acyl tetrahedral intermediate capable of an acyl migration.[5] The tetrahedral compound I (Scheme I) may be viewed to result from

Scheme I



intramolecular nucleophilic attack either of the imidazole function on a mixed anhydride intermediate or the carboxylate function on an acetylimidazole intermediate.

The tetrahedral compound was prepared by treating II[6] with 10 equiv of pyridine and 3 equiv of acetyl chloride (distilled) in dry $CHCl_3$. After 5 days, the product was collected and washed with $CHCl_3$ and Et_2O (50–55% (sometimes >80%) yield) (melting point decomposition first detected at 160° turning dark red-brown without melting by 330°; uv (H_2O–1 *M* KCl, 30° at pH 4) 310, 322 (sh), and 291 nm, reacting with $t_{1/2}$ = 1.55 min and isosbestic points at 290 and 248 nm to give a compound exhibiting a single peak at 275 nm; ir (KBr) 1780 (CO_2R), 1645 (ImH^+), 1180 (SO_3^-), and 1035 cm^{-1} (SO_3^-); nmr (C_5D_5N) δ 1.58 (s, 3), 1.70 (s, 3), 1.82 (s, 3) (this peak is not present in a sample prepared with CD_3COCl), 2.36 (s, 3), 7.19 (d, 1, J = 8.4 Hz), 8.41 (q, 1, J = 8.4, J = 2.2 Hz), and 9.13 ppm (d, 1, J = 2.2 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2O_7S$: C, 50.25; H, 4.74; N, 7.33; S, 8.39. Found: C, 50.53; H, 4.60; N, 7.05; S, 8.30). Proof

(1) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966; (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969; (c) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Proton to Proteins," Wiley-Interscience, New York, N. Y., 1971.

(2) W. P. Jencks, *Chem. Rev.*, 72, 705 (1972).

(3) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, 87, 4138 (1965).

(4) M. L. Bender and H. d-A. Heck, *ibid.*, 89, 1211 (1967).

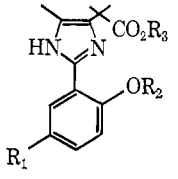
(5) While the isolation of other tetrahedral compounds has been reported, all are at the juncture of a fused ring system and none are capable of undergoing acyl migration. Furthermore those which are acyl tetrahedral adducts (*e.g.*, R. G. Griot and A. J. Frey, *Tetrahedron*, 19, 1661 (1963)) are particularly inert ("very stable" in 0.1 *N* NaOH) and those which are not inert (*e.g.*, a review of Zaugg's work in ref 1a, p 169 ff) are not *acyl* tetrahedral intermediates.

(6) II was prepared in this laboratory and has the following physical chemical properties: mp >360°; uv (H_2O–1 *M* KCl, 30° at pH 5) 310 (10.4), 273 (11.5), 285 sh (10.3), and 233 nm (14.9); ir (KBr) 1710 (CO_2H), 1640 (ImH^+), 1170 (SO_3^-), 1040 (SO_3^-), and 600 cm^{-1} (SO_3^-); nmr of K^+ salt (DMSO-d_6) δ 1.57 (s, 6), 2.28 (s, 3), 6.89 (d, 1, J = 8.5 Hz), 7.59 (q, 1, J = 8.5, J = 2 Hz), and 8.25 ppm (d, 1, J = 2 Hz); pK_a (H_2O–0.1 *M* KCl) 3.1 (CO_2H), 6.2 (ImH^+), and 9.8 (PhOH). *Anal.* Calcd for $C_{14}H_{15}N_2O_6SK \cdot H_2O$: C, 42.40; H, 4.32; N, 7.07; S, 8.09. The same sample submitted to two laboratories gave the following results: C, 42.52; H, 4.21, and C, 41.48; H, 4.20; N, 6.93; S, 7.85.

of the lactone linkage of I was accomplished through sodium borohydride (6 hydride equiv) reduction in DMF at ambient temperature for 2 days which provided IV, as white microneedles, in 60% yield (mp >340° dec; ir (KBr) 1640 (ImH^+) and 1035 cm^{-1} ($-SO_3^-$); nmr (D_2O–KOD) δ 1.33 (s, 6), 2.32 (s, 3), 3.65 (s, 2), 6.77 (d, 1, J = 8.5 Hz), 7.52 (q, 1, J = 8.5, J = 2.5 Hz), and 8.15 ppm (d, 1, J = 2.5 Hz); pK_a (H_2O, 1 M KCl) 5.8 (ImH^+) and 8.9 (PhOH). *Anal.* Calcd for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.59; S, 9.83. Found: C, 51.45 H, 5.51; N, 8.61; S, 9.73).

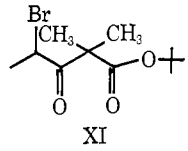
If I is dissolved in H_2O below pH 6, it rearranges quantitatively *via* a first-order process to III which is relatively stable. At higher pH's, I hydrolyzes to II *via* III following consecutive first-order kinetics. The rate constants for the two processes differ sufficiently at 3° and pH 12.4 so that it can be shown that most if not all of II arises from III and not directly from I. That III is in fact the acetyl ester was shown by comparison of uv repetitive scans recorded during alkaline hydrolysis (and the identity of the corresponding rates) with authentic III. The sample of authentic III was prepared from II employing a similar acetylation procedure as for I and a reaction time of 30 hr (mp >265° turns yellow, decomposing without melting; uv (H_2O at pH 5) 275 nm; ir (KBr) 1780 (COOPh), 1730 (CO_2H), 1645 (ImH^+), 1045 and 655 cm^{-1} (SO_3^-); nmr (DMSO-d_6) δ 1.65 (s, 6), 2.28 (s, 3), 2.38 (s, 3), and 7.2–8.1 ppm (m, 3). *Anal.* Calcd for $C_{16}H_{18}N_2O_7S$: C, 50.25; H, 4.74; S, 8.39. Found: C, 50.47; H, 4.60; S, 8.41).

The assignment of the tetrahedral structure to I rests upon five pieces of evidence. (1) I exhibits only one carbonyl peak at 1780 cm^{-1} which disallows the simultaneous presence of a carboxylic acid and an acetyl group as would be required of either a mixed anhydride or *N*-acetyl derivative of II. Seven derivatives (II, III, and V–IX) containing a free carboxyl group



V, R_1 = H; R_2 = H; R_3 = H
VI, R_1 = H; R_2 = CH_3; R_3 = H
VII, R_1 = H; R_2 = $COCH_3$; R_3 = H
II, R_1 = SO_3^-; R_2 = H; R_3 = H
VIII, R_1 = SO_3^-; R_2 = CH_3; R_3 = H
III, R_1 = SO_3^-; R_2 = $COCH_3$; R_3 = H
IX, R_1 = SO_3^-; R_2 = $COCH_2C(CH_3)$; R_3 = H
X, R_1 = H; R_2 = CH_3; R_3 = $C(CH_3)_3$

have been prepared and all exhibit a carbonyl band in the region 1710–1735 cm^{-1}. The absorption at 1780 cm^{-1} is, however, expected for a lactone carbonyl with electronegative substituents α to the ether oxygen. (2) The quantitative conversion in dilute aqueous solution of I → III *via* rate constants independent of $[I]_0$ requires an intramolecular "acetyl group" transfer. (3) The gem dimethyl groups of I exhibit magnetic nonequivalence in contrast to those in compounds II, III, V, VI, and X. This feature is invariant with solvent or the states of ionization. One possible explanation for this difference is the rigidity of the fused ring system. However, recent findings[7] concerning similarly disposed groups in another fused lactone system do not support this hypothesis. The source of nonequivalence in I is evidently the asymmetric nature of the tetrahedral carbon itself. Hence, in compound XI the α-dimethyl



XI

groups give rise to two resonances with $\Delta\delta$ = 9 Hz.[8] (4) The reducibility of the carboxyl carbonyl to an alcohol with sodium borohydride establishes that I does not possess a free carboxyl group. No reduction occurred with compounds I or III. (5) The unusually high magnetic field position of the methyl group added as acetyl chloride (1.82 ppm) indicates a unique environment. Molecular models of I show that one of two possible ring conformations forces this methyl group into the π-electronic region of the benzenoid ring. Thus, an anisotropic paramagnetic shielding of *ca.* 0.7 ppm is experienced by the methyl protons. No other structure can explain this observation.

Although the structure of I contains the "trialkyl lock" device of Cohen,[9] the ability to isolate I would appear to be a combination of insolubility and crystal lattice energy. Compound V (differing from II only by the sulfonic acid) has been repeatedly acetylated under the same reaction conditions as II with only the phenyl acetate isolated and no evidence for the formation of a tetrahedral intermediate. Further experiments are being conducted in order to deduce the mechanism of the tetrahedral to phenyl acetate rearrangement and the catalysis of this process by buffer species.

Acknowledgment. Supported by a grant from the National Institutes of Health.

(7) Personal communication from L. Cohen to J. M. Karle and I. L. Karle, *J. Amer. Chem. Soc.*, **94**, 9182 (1972).
(8) This study.
(9) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166, 9175 (1972).

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Received March 17, 1973

Specific Ortho Substitution of Aromatic Heterocyclic Amines. Conversions of 2-Aminopyridines

Sir:

Methods for the selective alkylation of aromatic heterocyclic compounds are generally quite limited.[1] In view of the recent report from our laboratory on the specific ortho alkylation of anilines,[2] we felt that a method might be at hand for the facile, specific substitution of aromatic heterocyclic amines. In order to test the validity of this premise, we have investigated the use of our alkylation process with 2-aminopyridine.

(1) For a leading reference to the known methods of alkylation of heterocyclics see E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, **94**, 2874 (1972).
(2) P. G. Gassman and G. Gruetzmacher, *ibid.*, **95**, 588 (1973).