The Pyridine Salts of Hydroxymaleic Anhydride

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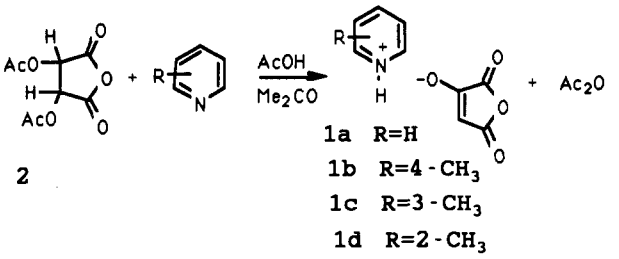
Introduction

The pyridine salt of hydroxymaleic anhydride (**1a**) was first described by Wohl and Oesterlin 90 years ago.[1]



2

1a R=H
1b R=4-CH_3
1c R=3-CH_3
1d R=2-CH_3

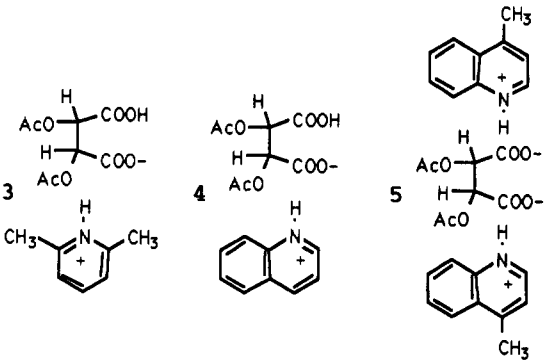
The hydroxymaleate is a useful synthon. Readily had from tartaric acid, it has been used extensively in the synthesis of complex molecules. Two of its four carbon atoms have been incorporated into $\alpha\beta$-unsaturated aldehydes,[2] three into methylpyrrolones,[3] methylnaphthoxazinones,[4] methyloxindoles,[5] and a variety of pyruvic acid derivatives,[1,5-7] and all four into oxaloacetates,[1,8] into penicillic acid,[9] and into a key intermediate in the synthesis of chlorothricolide.[10,11] We have used it in the preparation of a variety of pyruvamides and pyruvanilides and currently are developing from it a convenient access to indoles via cyclization of N-substituted pyruvanilides to hydroxyoxindoles.[5,12]

In the course of our work using pyridine salt **1a**, we remarked that although improved preparations of the compound had been described,[1,2,8,10] homologs and analogs such as might be derived from methylpyridines and quinolines have not been reported. It occurred to us that such variants, in addition to their intrinsic interest, might offer advantages as synthetic intermediates over the somewhat cantankerous parent compound. We noted also with some surprise that the structure of the compound has never been rigorously proved. That so weak a base as pyridine should form a stable salt with an enol clearly was surprising even to the original authors,[1] for they considered a variety of nonsalt formulations including several small-ring structures which today look decidedly quaint. It is unusual, moreover, to recrystallize an acid anhydride from ethanol. There is no doubt that structure **1** was adopted with reluctance. Nevertheless, it seems to have been accepted without question by all subsequent investigators.

Results and Discussion

4-Picoline, 3-picoline, and even 2-picoline react with diacetyltartaric anhydride (**2**) very much as pyridine does. Of the four cognate oxymaleates **1a-1d**, the 4-picolinium homolog **1b**, is worthy of particular mention. It is higher melting and less soluble, separates in better yield, crystallizes better, keeps better, is more resistant to destruction by adventitious moisture, yet undergoes synthetic conversions fully as satisfactorily as the pyridine compound does. In all ways it is a most convenient synthon, greatly to be preferred in synthetic applications.

In sharp contrast to the behavior of pyridine and the picolines, no oxymaleate salts were obtained when anhydride **2** was reacted with 2,6-lutidine, with quinoline, or with lepidine. Instead, there crystallized from the reaction mixtures the respective salts of diacetyltartaric acid; the acid salt (**3,4**) with lutidine and quinoline, and the normal salt (**5**) with lepidine.



The striking difference in behavior is definitely not attributable to adventitious moisture. In the earliest paper[1] Wohl and Oesterlin reported that damp pyridine reacts with **2** to give the salt of diacetyltartaric acid, and all seven bases examined by us behaved likewise. However, while dry pyridine and the picolines in ordinary reasonably dry acetone gave instead the hydroxymaleate salts **1a-1d**, lutidine, quinoline, and lepidine gave diacetyltartrate salts **3**, **4**, and **5** not only in scrupulously dry acetone but also in dry acetone containing substantial amounts of acetic anhydride. Authentic samples of these salts were prepared for comparison by adding appropriate amounts of the respective bases to diacetyltartaric acid in water.

The hydroxymaleate salts of these bases are in no way incapable of existing. We had found that salts **1a-1d** may be recrystallized from the corresponding bases; salt **1a** crystallizes beautifully from pyridine, for example. Moreover, interchange can be effected; recrystallization of salt **1a** from 4-picoline gives salt **1b**, etc. In similar fashion, recrystallization of any of salts **1a-1d** from 2,6-lutidine gave lutidine salt **1e**, and recrystallization from lepidine gave lepidine salt **1f**.

In order to arrive at a credible explanation for these differences in behavior, we found it necessary to be more certain of the structures of the hydroxymaleate salts than existing literature allowed. It is known that simple reagents convert salt **1a** into such derivatives as acetoxy-

(1) Wohl, A.; Oesterlin, C. *Ber.* **1901**, *34*, 1139-1148.
(2) van Dorp, D. A.; Arens, J. F. *Recl. Trav. Chim. Pays Bas.* **1948**, *67*, 459-468.
(3) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656-3663.
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(7) Haeusler, J.; Schmidt, U. *Chem. Ber.* **1974**, *107*, 145-151.
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(10) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041-3052.
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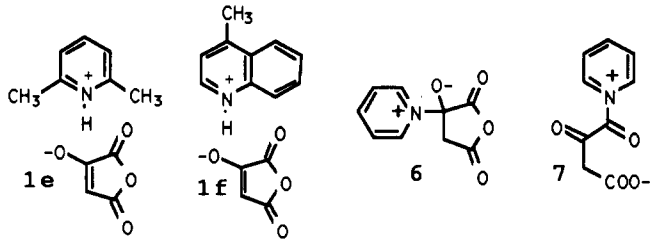
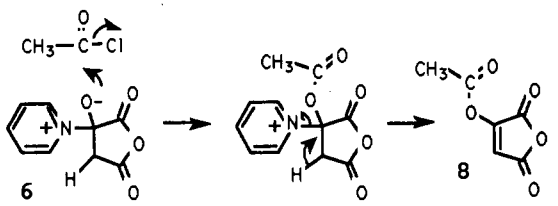


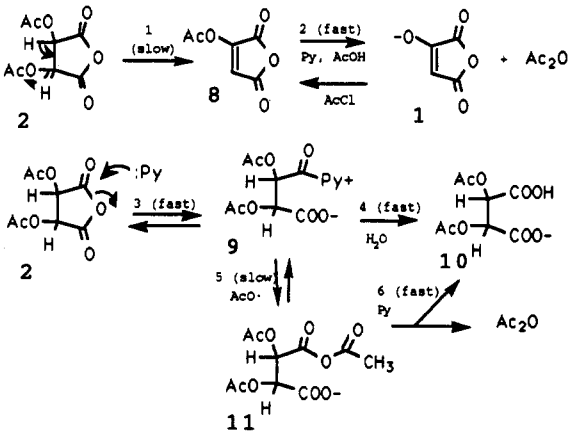
maleic anhydride (8)[1] and cognate esters,[10,11] into methoxymaleic anhydride,[9] and into ((trimethylsilyl)oxy)maleic anhydride.[13] The structures of these derivatives and transformation products of them are beyond doubt, and this chemistry serves to exclude conclusively cyclic and polymeric enol esters. It does not, however, exclude carbonyl coordination structures such as **6**. Covalently linked zwitterionic structures such as **6** and **7** were not envisioned at the turn of the century. However, such adducts are now known to be ubiquitous as intermediates in pyridine-catalyzed acyl-transfer processes and related carbonyl reactions.[14,15] In favorable cases they accumulate to substantial concentrations, and *N*-acetylpyridinium chlorides have even been crystallized.[16] With a highly electron-deficient and sterically undemanding ketone such as oxaloacetic anhydride, and given favorable solubility relationships, the zwitterionic complex might well crystallize. The enol ester and enol ether derivatives serve to exclude **7** fairly conclusively. Structure **6**, however, could perfectly well give rise to these derivatives, reaction of the oxyanion with the electrophile being followed by protolysis from the adjacent carbon and decoordination of pyridine.



The proton NMR spectra of the picoline compounds afford an unambiguous decision between structures **1** and **6**. In all three a single, sharp, one-proton vinyl peak at δ 4.8–5.2 is observed, with an integral exactly one-third of that of the nearby methyl singlet. Accordingly, salt structure **1** stands vindicated. This continues to occasion surprise. In order to form a stable salt with pyridine the enol must be about as acidic as chloroacetic acid (pK_a ~2). Concomitantly, the acyl-transfer potential of the enol ester, acetoxymaleic anhydride, must be sufficient for it to acylate acetic acid to acetic anhydride[1] and to prevent the formation of dimeric and polymeric enol esters. Ordinary enolizable ketones are easily acylated by acetic anhydride even against disfavorable enolization free energies of 20 kJ/mol or more. These characteristics certainly are mutually consistent, but a plausible explantion for them escapes us.

We return now to consider the behavior of diacetyltartaric anhydride **2** with the several pyridine and quinoline bases. Referring to Scheme I, the formation of oxymaleates

Scheme I



1 undoubtedly proceeds through acetoxymaleic anhydride (**8**) as intermediate (step 1).

Enol ester **8** is obtained as an isolatable product when oxymaleate **1a** is treated with acetyl chloride and is known[1] to react with pyridine–acetic acid mixtures to give acetic anhydride and **1a**. Proton abstraction from such a highly hindered site as the sp^3 carbon of **2**, even by such an unhindered tertiary amine as pyridine, is certain to be much slower than coordination of pyridine to anhydride carbonyl (step 3) to give acylpyridinium zwitterion **9**.[15] If the amine is wet, hydrolysis (step 4) of **9** (a rapid reaction[15] rendered even faster by intramolecular carboxylate catalysis[14] of water attack) produces diacetyltartrate salt **10**. The formation of diacetyltartrate salts rather than oxaloacetate salts confirms the slowness of step 1 relative to step 3, for anhydrides **8** and **1** doubtless would coordinate with pyridine as rapidly as **2**. In the absence of water, step 1, essentially irreversible, takes control and oxymaleate **1** is produced. 4-Picoline, a stronger base and no more hindered than pyridine, reacts similarly and even more readily. The other picolines also react well. Plausibly, steric hindrance, even with 2-picoline, is offset by greater basicity. 2,6-Lutidine is highly hindered. Quinoline and lepidine are little if any more hindered than 2-picoline but are distinctly weaker bases. With all three, proton abstraction is slowed down to such a degree that *acetolysis* of **9** to give mixed anhydride **11** (step 5) becomes significant. The mixed anhydride **11** then is rapidly cleaved (step 6) by coordination of base to the distal carbonyl giving **10**, the observed product, and acetyllutidinium (quinolinium) ion which is cleaved by acetate to acetic anhydride.

It is in the context of competition between steps 1 and 5 that sense can be made of the several improved procedures for the preparation of **1**. These all call for adding acetic acid a short time, seconds to minutes, after adding pyridine to anhydride **2**, development of a characteristic greenish color being the signal for adding the acid. Acetoxymaleic anhydride **8** is unstable to pyridine and must be acetolyzed (step 2) as fast as it is formed. Added acetic acid, over and above the low steady-state concentration produced in step 1 and consumed in step 2, enhances this trapping, and hence the yield of oxymaleate **1**. The acid must not be added too early, however, for acetate will accelerate step 5 (and, to the extent that it protonates pyridine, will decelerate step 1) and starting material will go to **11** rather than to **8**. Just when to add the acid, and how much to add, is critical. There can be

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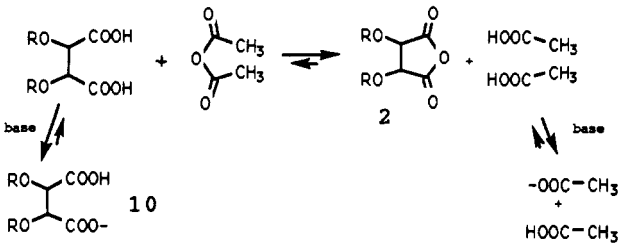
(14) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.
(15) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 2125–2126; **1970**, *92*, 5432–5442.
(16) Sheinkman, A. K.; Portnova, S. L.; Sheinker, Yu. N.; Kost, A. N. *Dokl. Akad. Nauk SSR* **1964**, *157*, 1416–1419.

Scheme II



no question but that the variable yields bewailed in the literature are attributable to these kinetic knife-edges.

An interesting minor point is the equilibrium preference for **10** and acetic anhydride rather than **2** and acetic acid. Diacetyltartaric acid reacts very completely with acetic anhydride, even in the presence of much acetic acid, to give the cyclic anhydride **2** (Scheme II). The driving force for the cyclic anhydride, largely entropic, is sufficient to reverse the otherwise predictable preference for a predominance of the anhydride of the weaker acid. In the presence of a base, however, neutralization occurs, and the energy of neutralization of the stronger acid is sufficiently greater than that of the weaker that the equilibria are displaced in favor of the more stable salt **10**; a manifestation, in effect, of the time-honored precept that a stronger acid displaces a weaker acid from its salt. Solubility relationships and crystal lattice energies doubtless are responsible for the formation of the normal salt rather than the acid salt when lepidine is the base.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were determined at 60 MHz in $CDCl_3$–DMSO (2:1) mixture using tetramethylsilane as internal reference. Diacetyltartrate salts of quinoline, lepidine, and 2,6-lutidine were not analyzed; authentic samples for comparison were prepared by simple neutralization reactions.

4-Picolinium Salt of Hydroxymaleic Anhydride (1b). To a solution of (+)-diacetyl-L-tartaric anhydride[2] (48 g, 0.22 mol) in acetone (50 mL) at 10 °C was added 4-picoline (36 mL, 0.37 mol) followed after 5 min by acetic acid (29 mL). Separation of product soon began. After 4 h at 0 °C, the buff solid (35 g, 77%) was isolated by suction filtration and washed three times with ether. Crystallization from DMF gave the analytical sample, mp 122–3 °C; ^{1}H NMR: δ 2.2 (s, 3 H), 5.4 (s, 1 H), 7.7 (m, 2 H), 8.7 (m, 2 H), 12.4 (s, 1 H).[17] Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38. Found: C, 58.03; H, 4.42%.

The isomeric picolinium salts and the pyridinium salt were prepared similarly.

3-Picolinium salt (1c): 62%, mp 97.5–99 °C; ^{1}H NMR δ 2.5 (s, 3 H), 4.9 (s, 1 H), 7.7 (m, 1 H), 8.2 (m, 1 H), 8.7 (m, 2 H), 14.2 (s, 1 H).[17] Anal. Calcd as for **1b**. Found: C, 58.08; H, 4.40.

2-Picolinium salt (1d): 67%, mp 90–91.5 °C; ^{1}H NMR δ 2.7 (s, 3 H), 4.8 (s, 1 H), 7.8 (m, 2 H), 8.4 (m, 1 H), 8.7 (m, 1 H), 15.0 (s, 1 H).[17] Anal. Calcd as for **1b**. Found: C, 58.15; H, 4.35.

Pyridinium salt (1a): 63%, mp 112 °C (lit.[2] mp 108–110 °C); ^{1}H NMR δ 5.1 (s, 1 H), 7.8 (m, 2 H), 8.2 (m, 1 H), 8.9 (m, 2 H), 12.3 (s, 1 H).[17]

Acid 2,6-Lutidinium Salt of Diacetyltartaric Acid (3). Reaction of 2,6-lutidine (51 mL, 0.44 mol) and acetic acid (29 mL) with (+)-diacetyl-L-tartaric anhydride (48 g, 0.22 mol) in dry acetone (100 mL) under conditions closely similar to those described above gave no trace of the hydroxymaleic anhydride salt. Instead, the product which crystallized (40%) proved to be the monolutidinium salt of diacetyltartaric acid, mp 148–149 °C: ^{1}H NMR δ 2.2 (s, 6 H), 2.5 (s, 6 H), 5.5 (s, 2 H), 7.1 (m, 2 H), 7.6 (m, 1 H), 12.2 (s, 2 H).[17] The identical compound crystallized (60%) when 2,6-lutidine (5 mmol) was added to a solution of diacetyl-L-tartaric acid (5 mmol) in water (10 mL).

Salts **4** and **5** were prepared as described above for **3**.

Acid quinolinium salt (4): 55%, mp 118.5–120 °C; ^{1}H NMR δ 2.2 (s, 6 H), 5.7 (s, 2 H), 7.8 (m, 6 H), 8.9 (m, 1 H), 10.7 (s, 2 H).[17]

Normal lepidinium salt (5): 62%, mp 111–112.5 °C; ^{1}H NMR δ 2.2 (s, 6 H), 2.7 (s, 6 H), 5.8 (s, 2 H), 7.7 (m, 10 H), 8.7 (m, 2 H), 9.5 (s, 2 H).[17]

2,6-Lutidinium Salt of Hydroxymaleic Anhydride (1e). 4-Picolinium salt **1b** (0.5 g) was warmed with dry 2,6-lutidine (4 mL) until it dissolved. Upon cooling, crystals of exchanged compound **1e** separated and were recrystallized from fresh 2,6-lutidine. The crystals, leached overnight with dry ether to remove solvent, had mp 76–77 °C: ^{1}H NMR δ 2.8 (s, 6 H), 4.7 (s, 1 H), 8.0 (m, 2 H), 8.7 (m, 1 H), 12.0 (br s, 1 H).[17] Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 4.98. Found: C, 59.85; H, 5.13.

Lepidinium salt (1f) was similarly prepared, mp 129–130 °C: ^{1}H NMR δ 2.7 (s, 3 H), 4.8 (s, 1 H), 7.7–8.5 (m, 5 H), 9.2 (d, J = 5.6 Hz, 1 H), 10.9 (br s, 1 H).[17] Anal. Calcd for $C_{14}H_{10}NO_4$: C, 65.63; H, 3.91. Found: C, 65.75; H 4.05.

Acknowledgement is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(17) The position of the NH resonance in these compounds is concentration and solvent dependent and varies between 9 and 16 ppm downfield from TMS.