The Mechanism of the Reaction between Dehydroacetic Acid and Alkylamines

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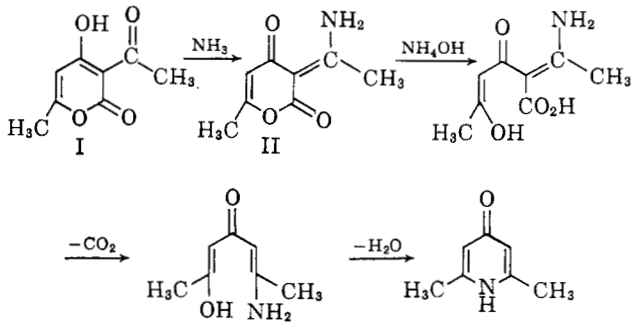
In a study of the conversion of dehydroacetic acid to N-substituted lutidones by reaction with alkylamines, two compounds have been obtained which are considered to be intermediates in the reaction. A mechanism for the reaction is suggested and its relation to a general mechanism for the conversion of γ-pyrones to γ-pyridones is considered.

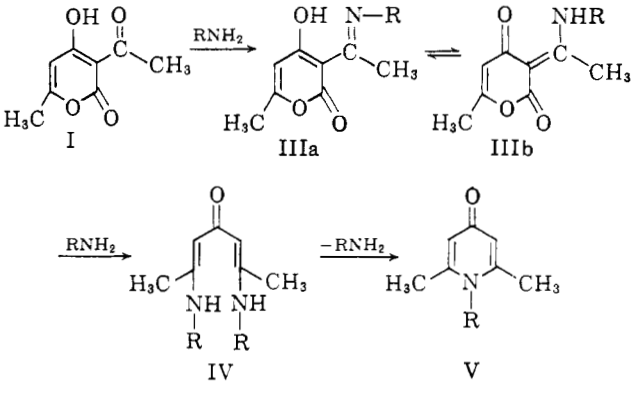
The reaction of dehydroacetic acid with ammonia or primary amines to form lutidones has been known for many years.[1,2] However, during this time there has been no comprehensive study of the reaction mechanism. In 1890, Feist[3] proposed structure II for the compound formed from dehydroacetic acid and ammonia and suggested the following mechanism for its subsequent conversion into lutidone with excess



ammonia. An analogous mechanism may be assumed for the corresponding reaction with alkylamines.

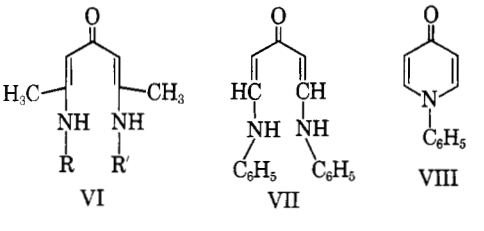
We recently undertook a study of the mechanism of the conversion of dehydroacetic acid into N-substituted lutidones and isolated two intermediates. Dehydroacetic acid reacted with an equivalent amount of aqueous methylamine forming a crystalline compound (m.p. 127–128°), with the empirical formula $C_9H_{11}NO_3$. Ultraviolet spectrum was similar to that of dehydroacetic acid [λ_{max}^{EtOH}, 235 mμ (log ε 4.08) and 311 (log 4.16)]. The compound was readily converted back to dehydroacetic acid in dilute hydrochloric acid. This evidence suggested that this compound was the Schiff base (IIIa) formed by addition of methylamine to the carbonyl group of the acetyl side chain. N.m.r. spectrum (deuteriochloroform) showed three methyl groups, one of which was a doublet, and, since the coupling constant (J = 5.0 c.p.s.) was the same as that for the N-methyl group in N-methylacetamide, the compound probably exists in the tautomeric form IIIb.[4] The compound yielded N-methylacetamide when oxidized with potassium permanganate.

When III (R = Me) was treated with methylamine it was converted into bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me). The n.m.r. spectrum of this compound also exhibited the N-methyl group as a doublet (J = 5.0 c.p.s.). The heptadienone was converted directly into N-methyllutidone with the elimination of one equivalent of methylamine by boiling in water. Similarly dehydroacetic acid when heated with excess methylamine was converted directly into bis-2,7-methylaminohepta-2,5-dien-4-one (IV). Under these conditions none of the intermediate (III) accumulated. The same series of reactions was observed when ethylamine was used.



The mechanism of the conversion of dehydroacetic acid to N-methyl- or N-ethyllutidone can be described by the series of reactions I → III → IV → V.

The simplest mechanism for the conversion of the compound IIIb to the diaminoheptadienone (IV) would be an attack by a molecule of the amine on carbon atom 6, opening the pyrone ring which, after decarboxylation, would yield product IV. In order to verify this mechanism, we attempted to prepare the dienones (VI, R ≠ R′). On treatment of compound III (R = Et) with an equimolar quantity of methylamine a mixture of products resulted. From this mixture,



3-ethylidene(α-methylamino)-6-methylpyran-2,4-dione (IIIb, R = Me) was isolated. Using an excess of methylamine the reaction with III (R = Et) yielded bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me) in greater than 50% yield. Similar results were obtained on treatment of III (R = Me) with ethylamine. In no case were mixed dienones IV (R ≠ R′) isolated. A major difficulty in a study of these reaction mixtures is the ease of conversion of the dienones

(1) L. Haitinger, *Ber.*, **18**, 452 (1885).

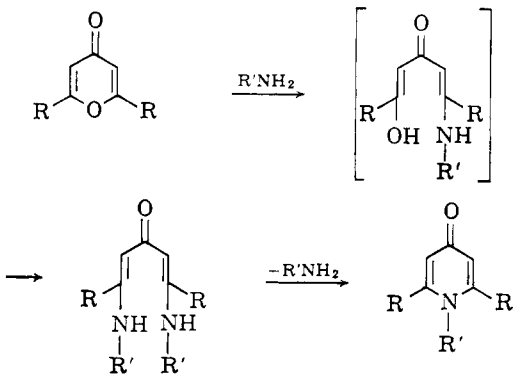
(2) See references in K. Dimroth, *Angew. Chem.*, **72**, 333 (1960).

(3) F. Feist, *Ann. Chem.*, **257**, 253 (1890).

(4) S. Iguchi, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959), have reported the formation of compounds of type IIIa from the reaction between dehydroacetic acid and various alkylamines and amino acids. However in the case of IIIa (R = Me) the melting points quoted for both the hydrated and anhydrous form of the product were exactly those of N-methyllutidone. On repeating their experimental procedure we obtained a product with the physical constants quoted and we identified this as N-methyllutidone (melting point, mixture melting point, ultraviolet, and n.m.r.).

to the N-substituted lutidones. This aspect of the work is still under review.

A considerable amount of literature exists on the conversion of γ-pyrones to γ-pyridones.[2,5] In the normal course of the reaction no intermediates were obtained, the γ-pyridone being isolated directly. However, Borsche and Bonacker[6] in 1921 observed that in the reaction of aniline with γ-pyrone bisoxymethyleneacetone dianilide (VII) was obtained. This compound could then be converted to N-phenyl-γ-pyridone (VIII). Subsequent work by Campbell, *et al.*,[7] showed that heptadienones could be obtained when 2,6-dimethyl-γ-pyrone reacted with higher alkylamines and more recently Conley, *et al.*,[8] have prepared the heptadienones IV (R = Me and R = Et) by treating 2,6-dimethyl-γ-pyrone with the alkylamine in the cold. In a recent review[5] it has been suggested that the isolation of these diaminoheptadienones does not necessarily mean that they are intermediates in the formation of the lutidone. However, we have now isolated the compounds IV (R = Me and R = Et) under the reaction conditions normally used for the preparation of the lutidone.[9] This would suggest that IV is indeed an intermediate. It would appear from our results that the mechanism proposed by Cavalieri[10] must be modified, as suggested by Conley, *et al.*,[8] to include IV as an intermediate. This is illustrated in Scheme 1.



SCHEME 1

Experimental[11,12]

3-Ethylidene-(α-methylamino)-6-methylpyran-2,4-dione (IIIb, R = Me).—Dehydroacetic acid (10.0 g.) was dissolved in 30% aqueous methylamine (10 ml.) and the solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which had formed were collected (9.5 g.). Recrystallization from ethanol gave 3-ethylidene(α-methylamino)-6-methylpyran-2,4-dione as prisms (6.6 g.), m.p. 126–127°.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.12; N, 7.70. Found: C, 59.65; H, 5.97; N, 7.70. λ_{max}^{EtOH}, 235 mμ (log ε 4.08) and 311 (4.16); infrared($CHCl_3$), 5.90, 6.03, 6.18, and 6.34 μ. N.m.r. ($CDCl_3$), τ values: 4.38 (singlet, 1H); 6.84 (center of doublet, 3H); 7.38 (singlet, 3H); 7.9 (singlet, 3H).

Oxidation of 3-Ethylidene(α-methylamino)-6-methylpyran-2,4-dione.—A solution of the foregoing compound (1.80 g.) in water (50 ml.) was stirred while 150 ml. of 5% aqueous potassium permanganate was slowly added. The temperature of the reaction was not allowed to rise above 30°. After the permanganate solution had been added, the stirring was continued for a further 30 min. The manganese dioxide then was filtered and washed well with water. The filtrate was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in absolute ethanol and the insoluble potassium chloride was filtered and washed with ethanol. The filtrate was evaporated under reduced pressure and the residue chromatographed on an alumina column. N-Methylacetamide (88 mg., 12%) was eluted with benzene–chloroform (1:3).

Treatment of 3-Ethylidene(α-methylamino)-6-methylpyran-2,4-dione with Methylamine.—The compound (III, R = Me) (0.663 g.) was dissolved in 40% aqueous methylamine by gently warming on a steam bath. When solution was complete the warming was continued and after about 5 min. crystals precipitated. The reaction mixture was cooled and the crystals were collected (0.546 g.), m.p. 158–160°. Recrystallization from absolute ethanol gave bis-2,7-methylaminohepta-2,5-dien-4-one as needles, m.p. 162–163°.

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.56; H, 9.59; N, 16.66. Found: C, 64.56; H, 9.77; N, 16.30. λ_{max}^{EtOH} 372 mμ (log ε 4.37); infrared ($CHCl_3$), 6.13 and 6.35 μ. N.m.r. ($CDCl_3$), τ values: 5.39 (singlet, 2H); 7.10 (center of doublet, 6H); 8.15 (singlet, 6H).

N-Methyllutidone (V, R = Me).—Bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me) (0.338 g.) was dissolved in water (10 ml.) and the resulting solution heated under reflux. The methylamine which formed was passed into picric acid solution (0.520 g. of picric acid in 10 ml. of ethanol). After 1 hr. the reaction was stopped and the methylamine picrate collected (0.375 g.), m.p. 210–211°, unchanged on mixing with an authentic sample. The reaction mixture was cooled and the white needles which separated were collected (0.211 g.), m.p. 247–248°, identical in all respects (melting point, mixture melting point, infrared spectrum, and ultraviolet spectrum) with a known sample of N-methyllutidone.

Bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me).—Dehydroacetic acid (10.0 g.) was dissolved in 40% aqueous methylamine (25 ml.) and the resulting solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which had formed were collected and recrystallized from ethanol yielding bis-2,7-methylaminohepta-2,5-dien-4-one (4.2 g.), m.p. 160–162°. The original mother liquor gave a second crop of crystals (0.7 g.), m.p. 246–248°, identified as N-methyllutidone (melting point, mixture melting point, and ultraviolet spectrum).

3-Ethylidene(α-ethylamino-6-methylpyran-2,4-dione (III, R = Et).—Dehydroacetic acid (10.0 g.) was dissolved in 70% aqueous ethylamine (10 ml.) and the resulting solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which formed were collected (11.0 g.). Recrystallization from ethyl acetate gave 3-ethylidene(α-ethylamino)-6-methylpyran-2,4-dione (6.5 g.), m.p. 87–88°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.58; H, 6.71; N, 7.70. Found: C, 61.39; H, 6.79; N, 7.30. λ_{max}^{EtOH} 236 mμ (log ε 4.03) and 311 (4.18); infrared ($CHCl_3$), 5.90, 6.02, 6.24, and 6.33 μ. N.m.r. ($CDCl_3$), τ values: 4.42 (singlet, 1H); 6.6 (center of multiplet, 2H); 7.40 (singlet, 3H); 7.92 (singlet, 3H); 8.69 (center of triplet, 3H).

Reaction of 3-Ethylidene(α-ethylamino)-6-methylpyran-2,4-dione (III, R = Me) with Ethylamine.—The foregoing compound (0.698 g.) was dissolved in 70% aqueous ethylamine (5 ml.) and the resulting solution was warmed on a steam bath for 3 hr. At the end of this time crystals had formed. After cooling, the crystals were collected and recrystallized from absolute ethanol yielding bis-2,7-diethylaminohepta-2,5-dien-4-one as needles (0.488 g.), m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.29; H, 10.27; N, 14.27. Found: C, 67.61; H, 10.52; N, 14.51. λ_{max}^{EtOH} 375 mμ (log ε 4.47); infrared ($CHCl_3$), 6.13 and 6.35 μ. N.m.r. ($CDCl_3$), τ values: 5.42 (singlet, 2H); 6.8 (center of multiplet, 4H); 8.15 (singlet, 6H); 8.82 (center of triplet, 6H).

N-Ethyllutidone (V, R = Et).—Bis-2,7-ethylaminohepta-2,5-dien-4-one (0.51 g.) was dissolved in water (8 ml.) and heated under reflux. The ethylamine which formed was flushed out with nitrogen into picric acid solution (0.677 g. of picric acid in 5 ml. of methanol). After 3 hr. the picrate which had formed was

(5) H. Meislich in "Pyridine and its Derivatives," Part III, E. Klingsberg, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 549.

(6) W. Borsche and I. Bonacker, *Ber.*, **54**, 2678 (1921).

(7) K. N. Campbell, A. B. Spooner, and B. K. Campbell, Abstracts of the 118th National Meeting of the American Chemical Society, 1950.

(8) R. T. Conley, E. Nowoswiat, and W. G. Reid, *Chem. Ind.* (London), 1157 (1959).

(9) K. N. Campbell, B. K. Campbell, and J. Ackerman, *J. Org. Chem.*, **15**, 221 (1950).

(10) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).

(11) All melting points are uncorrected.

(12) N.m.r. spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal reference.

collected and recrystallized from methanol yielding ethylamine picrate (0.52 g.), m.p. 167–169°, unchanged on mixing with an authentic sample. The original reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from ethyl acetate. After two recrystallizations N-ethyllutidone (0.20 g.), m.p. 160–162°, was obtained.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.45; H, 8.68; N, 9.27. Found: C, 71.04; H, 8.64; N, 9.39.

Bis-2,7-ethylaminohepta-2,5-dien-4-one (IV, **R** = **Et**).—Dehydroacetic acid (5.0 g.) was dissolved in 70% aqueous ethylamine (25 ml.) and warmed on a steam bath for 30 min. On cooling, crystals precipitated and these were collected (4.0 g.), m.p. 89–90°. Recrystallization from ethanol gave pure bis-2,7-ethylaminohepta-2,5-dien-4-one as needles, m.p. 90–91°.

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The Mechanism of the Lithium Aluminum Hydride Cleavage of Alkyl Tosylate

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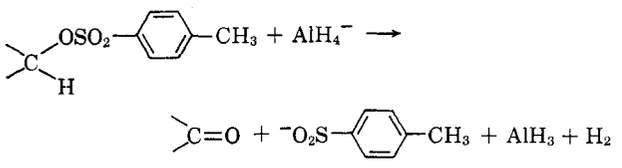
The cleavage of *trans*-9-decalylcarbinyl tosylate with lithium aluminum deuteride does not introduce deuterium into the *trans*-9-decalylcarbinol or the *p*-tolyl disulfide formed by reduction *p*-toluenesulfinate ion generated in the cleavage reaction. It is concluded that the cleavage reaction occurs by nucleophilic attack of aluminohydride ion on sulfonate sulfur.

A common side reaction in the lithium aluminum hydride reduction of alkyl tosylates is cleavage with regeneration of the parent alcohol.[1,2] The most likely stoichiometry for this process involves the formation of *p*-toluenesulfinate ion with the liberation of hydrogen. *p*-Toluenesulfinic acid and its reduction products have been isolated from the reaction when cleavage is the predominant course of the reaction.[1]

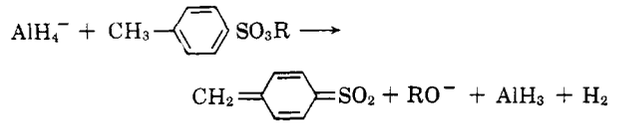
Three possible mechanisms for the cleavage reaction may be considered. The most likely is direct nucleophilic attack on sulfonate sulfur by aluminohydride ion to give an isomer of *p*-toluenesulfinic acid and alkoxide ion. Subsequent reaction with a hydride donor would liberate hydrogen to give *p*-toluenesulfinate ion. There are numerous examples of nucleophilic attack on sulfonate sulfur[3] and this mechanism requires no further comment.

A more speculative mechanism involves the base-catalyzed elimination of the elements of *p*-toluenesulfinic acid to give an intermediate carbonyl compound which would be rapidly reduced in a second step.



This type of elimination has been observed in the reaction of α-*p*-toluenesulfonyloxy ketones with alkoxides[4] and in the conversion of an α-*p*-toluenesulfonyloxylactam to an α-ketolactam with potassium *tert*-butoxide.[5]

The third possible mechanism involves a quinonoid intermediate generated by proton abstraction from the methyl group of the *p*-toluenesulfonate portion of the molecule.



This intermediate would presumably be reduced to *p*-toluenesulfinate by a hydride donor.

To test these mechanisms we have examined the products from the cleavage of an alkyl tosylate with lithium aluminum deuteride. The first mechanism predicts no deuterium incorporation in the recovered alcohol or the *p*-toluenesulfinate and its reduction products. The second mechanism requires incorporation of deuterium at the carbinol carbon atom and the third mechanism requires incorporation of deuterium into the methyl group of *p*-toluenesulfinic acid and its reduction products.

trans-9-Decalylcarbinyl tosylate was chosen as the alkyl tosylate because it is readily available and it has been shown to yield considerable cleavage product, *trans*-9-decalylcarbinol, upon lithium aluminum hydride reduction.[6,7] In the present investigation, the reduction of *trans*-9-decalylcarbinyl tosylate with lithium aluminum deuteride afforded *trans*-9-decalylcarbinol in 25% yield and *p*-tolyl disulfide in 2.5% yield. There was also a quantity of oil obtained which was undoubtedly deuterated *trans*-9-methyldecalin.[6,7] It was found that the *trans*-9-decalylcarbinol contained 0.03 atom of deuterium per molecule.[8] This evidence argues against the cleavage reaction proceeding by way of the aldehyde.

It is conceivable that part of the cleavage reaction occurs by attack of *p*-toluenethiolate ion, formed by reduction of *p*-toluenesulfinate, on sulfonate sulfur to give *p*-tolyl *p*-toluenethiolsulfonate. However, this seems unlikely because the reaction of *cis*-3-benzyloxy-*trans*-9-decalycarbinyl tosylate with benzyl mercaptide ion gives the benzyl thioether.[6]

(1) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).
(2) D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).
(3) For a leading reference, see J. F. Bunnett and J. Y. Bassett, Jr., *J. Org. Chem.*, **27**, 2345 (1962).
(4) A. S. Kende, *Org. Reactions*, **11**, 285 (1960).
(5) W. G. Kofron, Ph.D. thesis, University of Rochester, 1960.
(6) A. S. Hussey, H. O. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953).
(7) W. G. Dauben, J. B. Rogan, and E. J. Blanz, Jr., *ibid.*, **76**, 6384 (1954).
(8) Deuterium analysis were carried out by the falling drop method by Josef Nemeth, Urbana, Ill.