

has confirmed this instability for tetrahydroalstonine.¹⁸

The greater acid stability of tetrahydroserpentine as compared to that of tetrahydroalstonine can be attributed to the difference in configuration at the D/E ring junction.¹⁹

Additional evidence for these configurations of the C/D ring junction in tetrahydroalstonine and tetrahydroserpentine is furnished by the wave lengths of the C=C bands in the infrared spectra in chloroform solution. This band is found at 6.14 μ in the former and at 6.19 μ in the latter.

The ultraviolet spectrum also corroborates the C/D ring junction as *cis* for tetrahydroserpentine and *trans* for tetrahydroalstonine. Thus the differential ultraviolet spectrum of tetrahydroalstonine *vs.* yohimbane shows distinctly two bands whereas the corresponding differential spectrum of tetrahydroserpentine has only a simple symmetrical band. (Fig. 15)

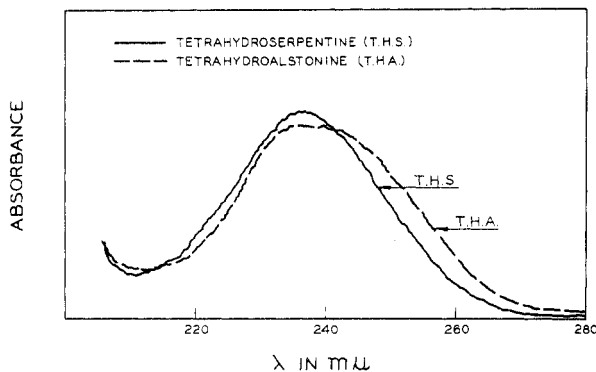
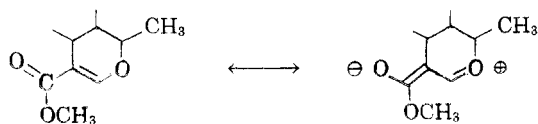


FIG. 15. DIFFERENTIAL U. V. SPECTRUM OF T. H. A. AND T. H. S. VERSUS YOHIMBANE

The configuration at C_3 and C_{15} in tetrahydroserpentine has already been proposed as *syn* by Weisenborn.²⁰ More recently Wenkert⁷ has classified

(18) We gratefully acknowledge this information from Professor Elderfield (1953).

(19) A system consisting of fused 6-membered rings with a double bond adjacent to a ring juncture has a lower energy when that juncture is *cis* than when it is *trans*. [D. A. H. Taylor, *Chemistry & Industry*, 250 (1954); Andre S. Dreiding, *Chemistry & Industry*, 1419 (1954).] If it is assumed that the disposition of atoms in dihydropyran is not unlike that in cyclohexene, then tetrahydroserpentine (*cis* D/E) should be the more stable. Resonance stabilization of the vinyl ether system will be greater in this alkaloid where the free rotation of the carbomethoxyl group allows complete coplanarity of the carbonyl and ethylenic functions:

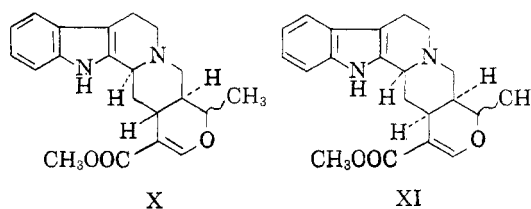


We would like to thank Dr. G. B. Kline of these laboratories for this explanation.

(20) F. L. Weisenborn *et al.*, *Chemistry & Industry*, 375 (1954).

various indole alkaloids into *normal* and *allo* products with an α -hydrogen at $C_{(3)}$ and *pseudo* or *epiallo* compounds containing a β -hydrogen at $C_{(3)}$. This assignment was given on the basis of presence or absence of certain bands in the 3.4–3.7 μ region in chloroform solution. In this classification tetrahydroserpentine and tetrahydroalstonine have an α -hydrogen at $C_{(3)}$.

All these data indicate the most probable configuration of tetrahydroalstonine (X) and tetrahydroserpentine (XI) at $C_{(3)}$, $C_{(15)}$, and $C_{(20)}$ and are represented by formulae X and XI, respectively:



On the basis of this evidence together with that cited above aricine, reserpinine, and isoreserpinine should be assigned the tetrahydroalstonine and raumitorine and tetraphylline the tetrahydroserpentine configurations.

EXPERIMENTAL

Spectra in chloroform solution were obtained in 0.11 mm. path; solutes are at concentrations of 0.18–0.2M. Spectra in carbon disulfide solution were obtained in 3 mm. path; solutes are at concentrations of 0.003–0.005M. All spectra were recorded using Perkin-Elmer, double-beam I.R. spectrophotometer, Model 21.

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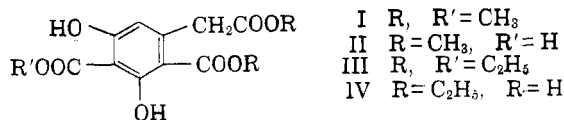
Metal-Catalyzed Condensations of Esters of Acetonedicarboxylic Acid

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Evidence is presented which suggests that the conversion of dimethyl acetonedicarboxylate (D-MADC) to methyl 2,4-dicarbomethoxy-3,5-dihydroxyphenylacetate (I) proceeds through the initial formation of a metal chelate compound. Among the reported reactions of esters of acetonedicarboxylic acid are the self-condensations of these substances to esters of 2,4-dicarboxy-3,5-dihydroxyphenylacetic acid, I, II, III, and IV, under simple experi-

mental conditions.¹⁻⁶ With no catalyst, or in the presence of catalytic amounts of sodium, sodium alkoxides, magnesium, magnesium oxide, zinc oxide, ferric oxide, and hydrogen chloride, the reaction has been reported to proceed at temperatures



of 140–180° to give yields of the condensation products up to 60%. Conventional acid and base catalyzed mechanisms have been proposed for these reactions.

In this laboratory no condensation product could be obtained from DMADC alone or in the presence of hydrogen chloride; magnesium metal gave I as reported. From a detailed examination of the literature, it appeared that a metal rather than acid or base might be the prime promoter of this reaction. Indeed, Jerdan felt that the metal was catalytically involved.⁴ More recently, Brandstrom has proposed a general hypothesis for the alkylation of tautomeric substances and has emphasized the importance of alkali metal chelate intermediates.⁷ Hauser has explained differences in products of condensations catalyzed by NaNH₂ and LiNH₂ in terms of the stabilities of the metal complexes of the products.⁸ The views of these investigators may be extended to the reaction under consideration.

The importance of the metal to the course of this reaction is shown by the data in Table I.

Clearly, I was not formed in the presence of conventional acidic and basic catalysts which contained no metals; nor was it formed with all metallic reagents. However, the reaction proceeded readily with catalytic amounts of many metals, present either as the preformed metal chelate of DMADC or as a simple organic or inorganic metal compound. The yields of I varied considerably with the catalyst, and there were other unidentified reaction products formed. The amount of a given metal used could change the course of the reaction drastically as is apparent from the early literature.^{3,4} The discrepancies of the early literature may be explained on the basis of the general use of soft glass equipment or the presence of metal impurities. When powdered soft glass was used as a catalyst, an appreciable amount of I was formed.

(1) H. Cornelius and H. von Pechmann, *Ber.*, **19**, 1446 (1886).

(2) H. von Pechmann and L. Wolmann, *Ber.*, **31**, 2014 (1898).

(3) D. S. Jerdan, *J. Chem. Soc.*, **71**, 1106 (1897).

(4) D. S. Jerdan, *J. Chem. Soc.*, **75**, 808 (1899).

(5) F. W. Dootson, *J. Chem. Soc.*, **77**, 1196 (1900).

(6) W. Theilacker and W. Schmid, *Ann.*, **570**, 15 (1950).

(7) A. Brandstrom, *Arkiv Kemi*, **6**, 155 (1953).

(8) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 4756 (1953).

TABLE I

EFFECTIVENESS OF CATALYSTS IN THE CONDENSATION OF DIMETHYL ACETONEDICARBOXYLATE

Catalyst ^a	Mole % Yield of I
None	0
Hydrogen chloride	0
<i>p</i> -Toluenesulfonic acid	0
Piperidine	0
Ammonium acetate	0
Cupric chloride dihydrate	0
Copper chelate DMADC ^b	0
Aluminum chloride hexahydrate	0
Aluminum acetate basic	0
Lithium chloride	3.5
Sodium acetate	37
Sodium hydroxide	11
Sodium iodide	8
Potassium acetate	6
Magnesium metal	14
Magnesium oxide	17
Magnesium chloride hexahydrate	36
Calcium chloride	20
Ferric chloride hexahydrate	14
Cobaltous acetate tetrahydrate	14
Zinc chloride	7
Zinc chelate DMADC ^c	15
Lead acetate trihydrate	26

^a Catalyst is A.R. and anhydrous unless otherwise noted.
^b Calcd. for C₁₄H₁₂O₁₀Cu: C, 41.03; H, 4.43; CuO, 19.4. Found: C, 40.96; H, 4.49; CuO, 19.4. ^c Calcd. for C₁₄H₁₂O₁₀Zn·2H₂O: C, 37.56; H, 4.95; ZnO, 18.18; H₂O, 8.05. Found: C, 37.70; H, 5.27; ZnO, 18.2; H₂O, 8.32.

The reactions were carried out with about 0.20 mole DMADC and 0.001 mole of catalyst heated at about 145° for 2–24 hr. The reaction mixture was distilled at 50 mm. and 145° until no further distillate came over. The residue was viscous and would crystallize when I had formed; if no I had formed, the undistilled residue remained a mobile liquid. The product was recrystallized from methanol and characterized by melting point (145–146°) and infrared curve.

That the primary step in this self-condensation reaction is probably the formation of a metal chelate compound may be readily illustrated with the reaction involving ferric chloride. Here the immediate deep-red color of the reaction mixture indicates rapid complex formation. With the zinc chelate of DMADC as catalyst the reaction proceeds smoothly. The postulated initial chelation does not exclude complex formation in further steps or the requirement of acid or base in subsequent steps of the reaction. The important fact is that the role of the metal in reactions of this type has been largely overlooked in the past and a reinterpretation of many condensation reactions may be made through the additional consideration of metal chelate formation.

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