[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Imine–Enamine Systems and the Mechanism of their Oxidation[1]

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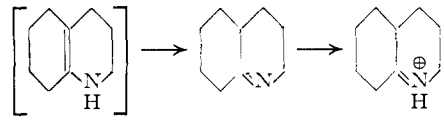
RECEIVED NOVEMBER 16, 1955

The influence of ring size, conjugation and functional groups on the enamine–imine tautomerism of some cyclic and open unsaturated organic bases has been investigated by spectrophotometric methods. Most secondary or primary vinylamines described in the literature appear to be imines. The hydroperoxides formed by rapid autoxidation of Schiff bases such as the *p*-methoxyanils of hydratropic aldehyde and diphenylacetaldehyde rapidly rearranged to the cleavage products, aceto- and benzophenone and *p*-formanisidide, also obtainable by ozonolysis. Ozonolytic cleavage, therefore, can no longer be used as a diagnostic method of proving the position of the double bond in enamine–imine systems. The structure of the cation of dihydroberberine has been proved. Several related tautomeric systems, some occurring in natural products, are discussed.

A. Cyclic Unconjugated Azomethines.—The existence of stable (cyclic) secondary vinylamines became doubtful when the tobacco alkaloid myosmine turned out to be a Δ^1-pyrroline derivative with no indication in the infrared spectrum for the presence of an enamine Δ^2-tautomer.[1]

It was, therefore, not surprising when hexahydroindole, previously expressed as the $\Delta^{8(9)}$-enamine (I),[2,3] showed no band in the NH-stretching region

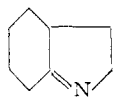
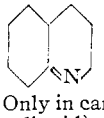


IV V VI

from a five- to a six-membered ring a shift to lower wave length of the C=N— band (−0.4 μ for the free bases as well as the salts) occurs.[5]

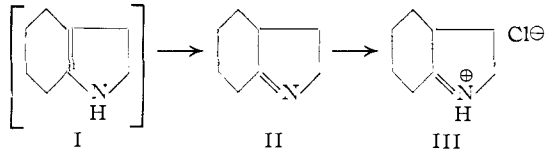
TABLE I

SPECTROPHOTOMETRIC COMPARISON OF HEXAHYDROINDOLE AND OCTAHYDROQUINOLINE AS THE FREE BASES AND THEIR HYDROCHLORIDES

Compound	Free base >C=N—	Hydrochloride: Ammonium	Immonium			>C=$\overset{\oplus}{N}$H—	$\Delta\lambda$ (λC=N base − λC=$\overset{\oplus}{N}$H)	Phase
	6.07vs (pure liquid)	3.90–4.15	4.70w	4.80vw	4.99m	5.11m	5.94s	−0.13	$CHCl_3$
	6.07s (CS_2)	3.68; 3.80	.....	4.83vw	....	5.12vw 5.25vw	5.94s	− .13	Nujol
	6.03	3.98	4.57vw 4.73vw	.....	5.02w	5.28w	5.90s	− .13	$CHCl_3$

[a] Only in carbon disulfide there is a distinct band at 3.05 and a second smaller one at 3.16. Broad and weak bands at 3.08 (pure liquid) and 3.08sh, 3.18 are observed in chloroform.

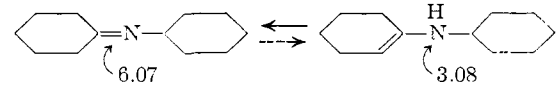
but a strong azomethine peak at 6.07 μ in accord-



I II III

ance with the imine or $\Delta^{1(8)}$-structure II. The hydrochloride III exhibited the ammonium and immonium bands (Table I) to be expected from a protonated azomethine. The homologous $\Delta^{1(9)}$-octahydroquinoline (V, Table I)[4] showed no trace of the enamine IV but exhibited the characteristic ammonium and immonium bands for the cation VI. The comparison of the data for the two homologs leads to the observation that in passing

B. Exocyclic Conjugated and Unconjugated Azomethines and Vinylamines.—The infrared spectrum of a simple unconjugated azomethine, namely, of cyclohexylidenecyclohexylamine (pure liquid), has been interpreted to indicate the presence of imine VII and enamine VIII tautomers.[6]



VII VIII

The anil of cyclohexanone(IX)[7] as the pure liquid shows a very strong >C=N— band at 6.0 μ (which makes the value for VII[6] look too high) and a very small band at 3.0 μ and a still weaker one at 3.11 μ. These data indicate that there is very little, if any, of the enamine X present. One might expect the *exo* double bond attached to a six-membered ring

(1) Infrared Diagnosis of the Hydrochlorides of Organic Bases. III. Previous paper: THIS JOURNAL, **76**, 5597 (1954). Oxidation Mechanisms. XVII. Preceding paper: L. A. Cohen and B. Witkop, *ibid.*, **77**, 6595 (1955).

(2) F. E. King, D. M. Bovey, K. G. Mason and R. L. St. D. Whitehead, *J. Chem. Soc.*, 250 (1953).

(3) B. Belleau, THIS JOURNAL, **75**, 5765 (1953). I am greatly indebted to Dr. Belleau for a liberal sample of this compound.

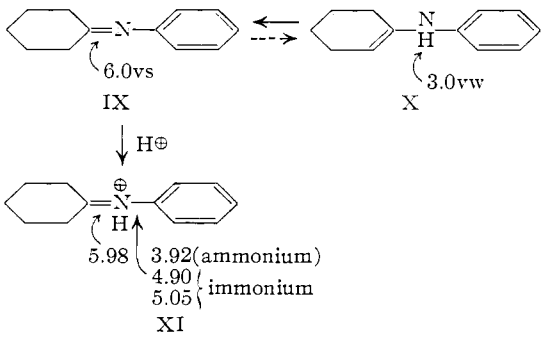
(4) L. A. Cohen and B. Witkop, *ibid.*, **77**, 6595 (1955).

(5) The analogy is to be found in the Raman spectra of cyclopentene and cyclohexene and in the infrared spectra of the series: 1-methylcyclopentene, 1-methylcyclohexene and 1-methylcycloheptene.

(6) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 186 (1952).

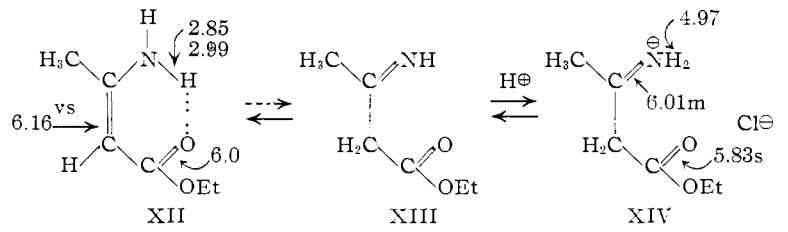
(7) G. Reddelien and O. Meyn, *Ber.*, **53**, 345 (1920).

to be relatively unstable[8] and the shift into the ring to be easier for VII than for IX, but the shift



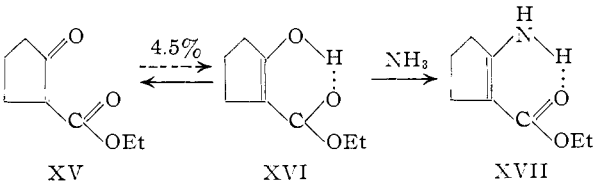
to lower wave length for $\Delta\lambda_{C=N}$ in the cation XI is smaller than expected[9,10] (see Fig. 1).

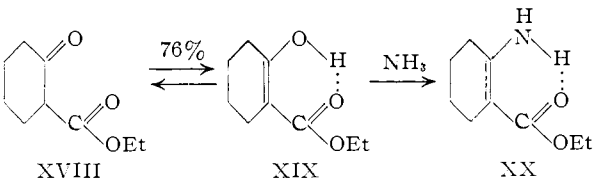
Whereas attempted catalytic oxidation of X in ethyl acetate with freshly reduced platinum led to the uptake of insignificant amounts of oxygen, considerable oxidation took place at 80° when a stream of oxygen was passed through the pure liquid. No hydroperoxide was obtained but at least six different products, some of which contained oxygen, resulting from dehydrogenation, condensation or polymerization (see Experimental), were isolated.



The infrared spectrum of ethyl β-aminocrotonate (pure liquid or chloroform solution) with its single high ester carbonyl band at 6.00 μ supports the pure chelated enamine structure XII.[11] Traces of acid (under anhydrous conditions) convert the enamine to the salt XIV of the imine XIII and not to the ammonium salt of the enamine as is commonly and erroneously believed.[12] The cation XIV displayed the expected immonium band at 4.97 μ and the carbonyl band of an unconjugated ester (possibly bonded) at 5.83 μ (Fig. 1).[13]

The reaction with ammonia of the 4.5% enolic[11] 2-carbethoxycyclopentanone (XV ⇄ XVI) and





of the 76% enolic[14] ethyl tetrahydrosalicylate (XVIII ⇄ XIX) yielded the enamines XVII and XX. The infrared spectra of these compounds showed *no trace of amine*, whereas the keto–enol tautomerism is distinctly demonstrated by the multiplicity of infrared bands.[15] It was impossible to prepare stable salts of XVII and XX. With ethereal hydrochloric or picric acid only ammonium chloride or picrate was obtained.[16]

The chelated enamine structures XII, XVII and XX display sharp and narrow NH_2 bands which appear as if they belonged to a non-bonded amino group. This phenomenon has been realized before in methyl N-methylanthranilate (XXI) in which the carbonyl band at 5.94 μ (1685 cm.$^{-1}$) indicates a strong hydrogen bond, while the NH

(8) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).

(9) B. Witkop, J. B. Patrick and H. Kissman, *Ber.*, **85**, 949 (1952).

(10) B. Witkop, *Experientia*, **10**, 420 (1954).

(11) K. v. Auwers, *Ber.*, **63**, 1072 (1930); **64**, 2748 (1931), had reached the same conclusion on the basis of molar refractivity measurements. His results have been challenged recently by Kohlrausch [K. W. F. Kohlrausch and A. Pongratz, *ibid.*, **67**, 982 (1934); *Monatsh.*, **70**, 226 (1937)], who found two bands in the double bond region of the Raman spectrum and by Seher [A. Seher, *Arch. Pharmaz.*, **284**, 371 (1951)]. The latter objected to von Auwers' comparing exaltation values of β-amino- and β-dimethylaminocrotonates and showed that there is an unexpected decrease in exaltation when passing from β,β-diphenylvinylamine to its dimethyl derivative. However, as is shown below, in our hands the reaction between diphenylacetaldehyde and ammonia yielded a compound, m.p. 89°, with a strong single imine band at 6.01 μ, but not the alleged "β,β-diphenylvinylamine," m.p. 110° (142° after recrystallization) [W. Krabbe, A. Seher and E. Polzin, *Ber.*, **74**, 1892 (1941)]. Seher's second objection is equally doubtful since it is based on the results of the questionable accuracy of bromine titration; the bromine titration gives only half the values (6.87%) of the iodine chloride titration (13.2%) of the enol of ethyl acetoacetate [A. Gero, *J. Org. Chem.*, **19**, 469 (1954)]; its use for enamines, therefore, is doubly questionable.

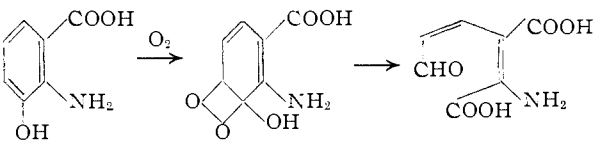
(12) *Cf.* H. Henecka, "Chemie der Beta-Dicarbonyl-Verbindungen," Springer Verlag, Berlin–Göttingen–Heidelberg, 1950, p. 191.

(13) This shift of the double bond into conjugation with the nitrogen to an immonium compound on salt formation will occur also when the C=C bond is embedded between two carboxyl or even cyano groups; the salts of diaminomaleonitrile are derived from the tautomeric aminoiminosuccinonitrile [R. L. Webb, S. Frank and W. C. Schneider, THIS JOURNAL, **77**, 3491 (1955)]. There is not enough room here to correct the erroneous formulations of many related cases in the literature.

(14) G. Schwarzenbach, M. Zimmerman and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951). XVI with lithium aluminum hydride yields more than twice as much (25%) of 2-hydroxymethylcyclopentanol as XIX which gives 11% 2-hydroxymethylcyclohexanol, an interesting demonstration that chemical analysis of tautomeric mixtures, in this case by instantaneous reduction, qualitatively may lead to similar results as physico-chemical methods; *cf.* A. Dreiding, THIS JOURNAL, **75**, 939 (1953).

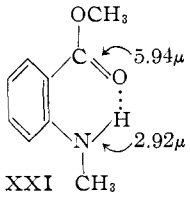
(15) N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Petersen, *ibid.*, **74**, 4070 (1952); *Cf.* R. Mayer, *Angew. Chem.*, **68**, 169 (1956).

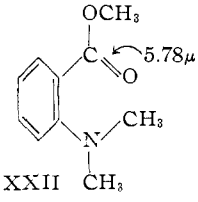
(16) The stability of the primary vinylamines, XII, XVII and XX, must be considered when formulating the labile intermediates in the tryptophan → niacin conversion



This sequence of reactions is based on new evidence obtained by A. H. Mehler (*J. Biol. Chem.*, **218**, 241 (1956)) and on the novel picture of oxidation of phenolic compounds as developed by O. Hayaishi and collaborators [THIS JOURNAL, **77**, 5450 (1955)].

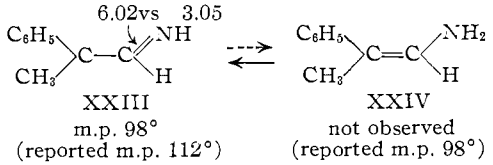
band at 2.92 μ (3361 cm.$^{-1}$) is not appreciably different from its usual position in intermolecular bonding.[17] The ester carbonyl in methyl N,N-

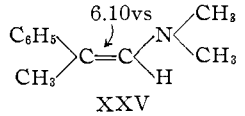




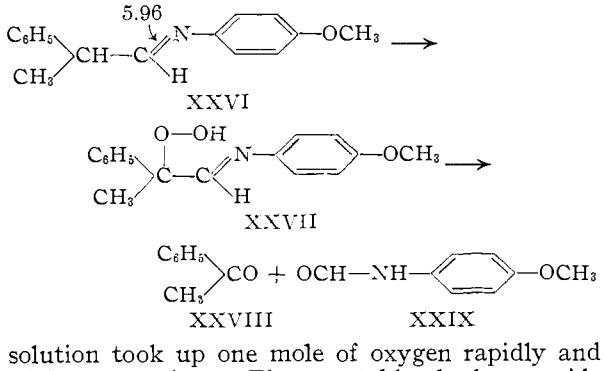
dimethylanthranilate (XXII) lies at the normal position 5.78 μ (1730 cm.$^{-1}$).

C. Schiff Bases of Hydratropic- and Diphenylacetaldehydes and their Mode of Oxidation.— These compounds deserve special interest in view of the claim that they form not only stable enamines but allegedly exist as pairs of stable tautomers (XXIII ⇄ XXIV).[18] In our hands only the imine of hydratropic aldehyde was obtained with melting points ranging according to the mode of preparation between 98 and 112°; all preparations had identical spectra: a single NH band, a single strong unconjugated imine band at 6.02 μ proving structure XXIII. The conjugated >C=C< bond of the liquid N,N-dimethyl-β-methyl-β-phenylvinylamine (XXV)[19] is distinctly different and shows up strongly at 6.10 μ.





The condensation of hydratropic aldehyde with a *p*-unsubstituted aromatic amine such as aniline yielded an unexpected condensation product $C_{19}H_{17-19}N_3$ not identical with paraleucaniline or its isomers. However, by condensation with *p*-anisidine it was possible to obtain the *p*-methoxyanil XXVI as a highly unstable compound, which in



solution took up one mole of oxygen rapidly and without catalyst. The unstable hydroperoxide

(17) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).
(18) A. Seher, *Arch. Pharmaz.*, **284**, 371 (1951).
(19) W. Krabbe, A. Seher and E. Polzin, *Ber.*, **74**, 1892 (1941).

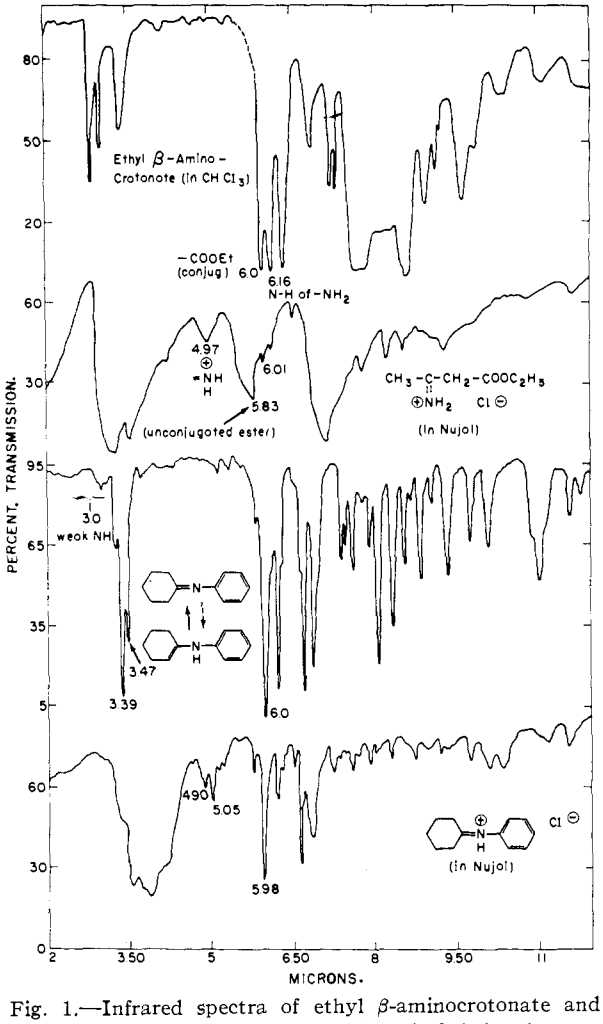
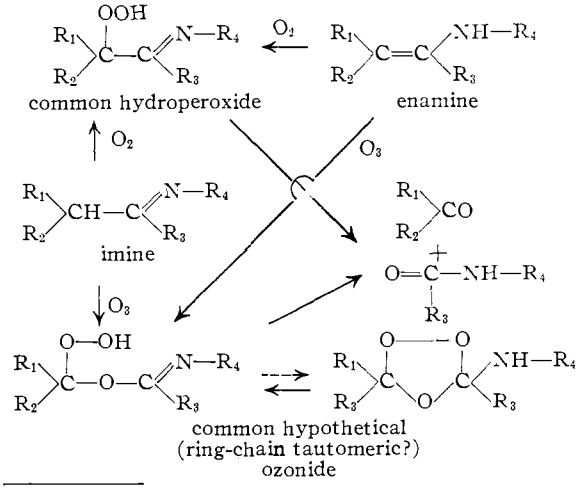


Fig. 1.—Infrared spectra of ethyl β-aminocrotonate and cyclohexanone anil (pure liquid) and of their salts.

XXVII, recognizable from its strong starch–iodide test, rearranged rapidly to acetophenone (XXVIII) and *p*-formylanisidide (XXIX) possibly *via* an ion pair intermediate[20,21] or concerted cyclic mechanism.[22]



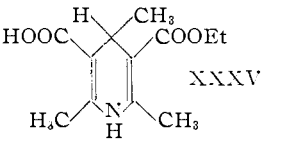
(20) P. D. Bartlett and J. L. Rice, THIS JOURNAL, **75**, 5591 (1953).
(21) B. Witkop and J. B. Patrick, *ibid.*, **73**, 2196 (1951).
(22) D. B. Denney, *ibid.*, **77**, 1706 (1955).

The Schiff bases (or vinylamines?) obtainable in the reaction of ketenimines with aromatic Grignard reagents also form unstable hydroperoxides which undergo the same type of rearrangement.[23]

This spontaneous oxidative cleavage of an azomethine between the α- and β-carbons will also happen on ozonolysis[18,19,24] so that both imine and enamine, if stable, will lead to the same cleavage products. In view of the great reactivity of the Schiff bases under discussion, it will be difficult to prove what the ratio of hydroperoxide–ozonide in ozonization is, since both intermediates would rapidly decompose to the same cleavage products Ozonolytic cleavage, therefore, is not a suitable method for the investigation of imine–enamine (and probably, in certain cases, keto–enol) tautomerism.

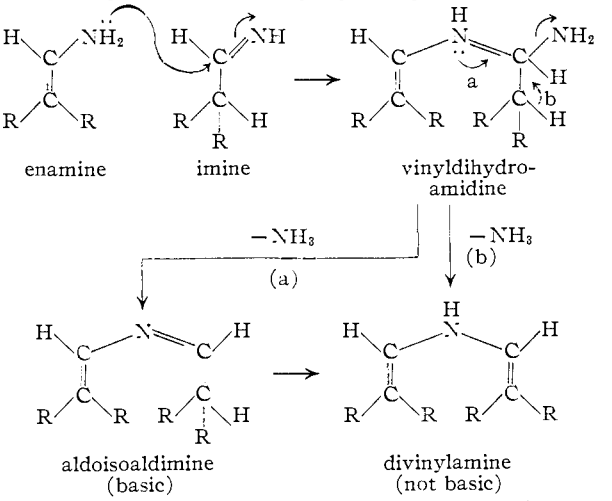
The catalytic reduction of nitro-*asym*-diphenylethylene (XXXIII) in ether[25] yielded needles (from ether) of an unstable compound, $C_{14}H_{13}N$ (no m.p. and nitrogen det. given), which resinified with air, gave benzophenone on oxidation and indicated one labile hydrogen in the Zerewitinov determination. Kohler and Drake considered the compound to be **diphenylacetaldimine (XXX)**. On warming to 90° a new compound (m.p. 129° from methanol) was obtained which is obviously not, as they believed, $C_{42}H_{36}N_2$ but impure $C_{28}H_{23}N$, m.p. 142–146°, as formed in the reduction of nitro-*asym*-diphenylethylene with aluminum amalgam in ether.[26]

By careful reaction of diphenylacetaldehyde with ammonia in ether, needles were obtained, m.p. 89°, which showed (in chloroform) a single >C=N— band at 6.01 μ. All other preparations that had come into contact with alcohols, ethyl acetate or carbon disulfide showed a more or less strong enamine band at 6.11 μ. Attempts to isolate the enamine XXXI led to the compound $C_{28}H_{23}N$, m.p. 148–150° (from carbon disulfide–petroleum ether), which is the divinylamine XXXIV for two reasons: (i) the compound is *neutral* or weakly basic (*cf.* ref. 26) as are other divinylamines, *e.g.*, the dihydropyridine derivative XXXV.[27] The addition of *p*-toluenesulfonic acid to the chloroform solution of XXXIV leads to partial hydrolysis but not to the cation of XXXII which would be recognizable from the shift to lower wave length of the C=N band[10]; (ii) a single strong band at 2.98 μ shows the compound to be a secondary *amine*.

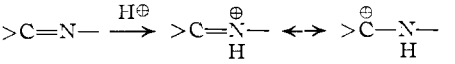


XXXV

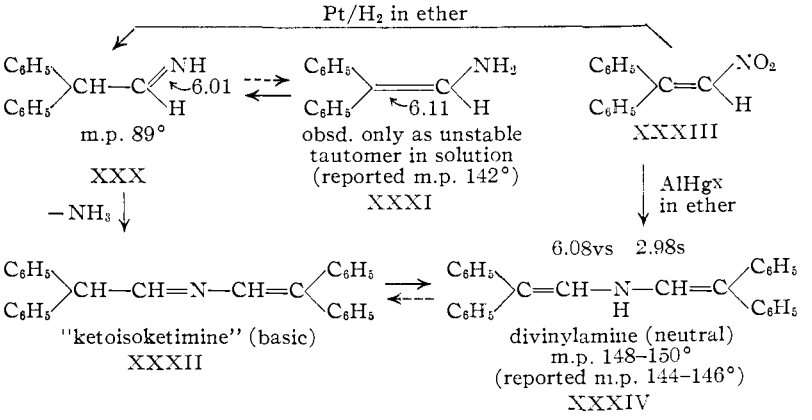
The exceptionally easy conversion of the tautomeric mixture XXX ⇄ XXXI into the divinylamine XXXIV proceeds probably by the general process.



Acid will catalyze the addition of the enamine to the imine by increasing the polarity of the azomethine



The process is analogous to the formation of ketoisoketimines from ketimine ⇄ enamine mixtures by thermal loss of ammonia.[28,29] Seher[18] assumes intermediate hydrolysis of the enamine to the enol form of the aldehyde which then reacts with another mole of intact enamine to give the divinylamine. The formation of the divinylamine under anhydrous conditions or on warming certainly does not proceed by such a mechanism.

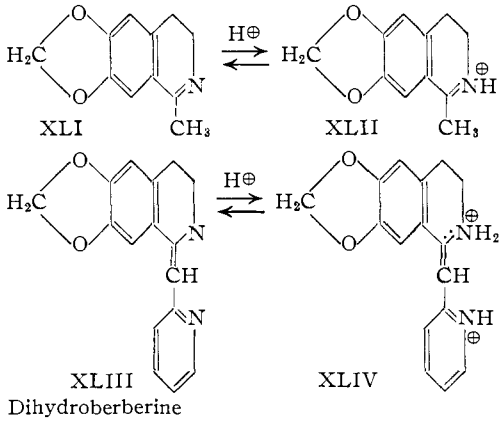


The *p*-methoxyanil XXXVI (C=N— at 6.10 μ in chloroform, at 6.02 μ in carbon disulfide), whose cation XXXVII shows the expected shift to lower wave length of 5.96 μ of the protonated azomethine group, in solution avidly absorbed oxygen. The hydroperoxide XXXVIII, present in solution, on attempted isolation rearranged and broke down to benzophenone and *p*-formanisidide.

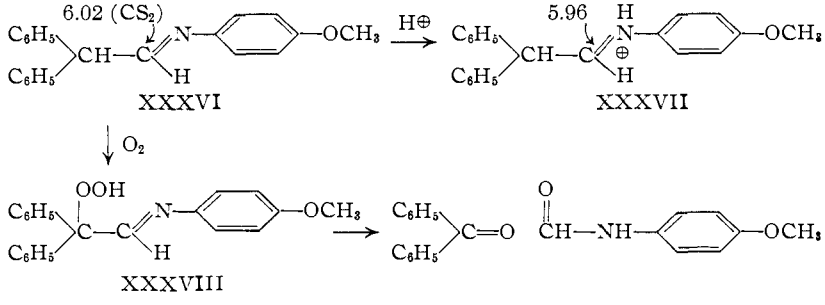
(23) C. L. Stevens and R. J. Gasser, 127th Meeting of the A.C.S., Cincinnati, Ohio, March 29–April 7, 1955, Abstracts p. 13N.
(24) B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3855 (1952).
(25) E. P. Kohler and N. L. Drake, *ibid.*, **45**, 1287 (1923).
(26) P. Lipp, *Ann.*, **449**, 24 (1926).
(27) A. Hantzsch, *ibid.*, **215**, 1 (1882).
(28) C. Moureu and G. Mignonac, *Compt. rend.*, **158**, 1395 (1914); **159**, 149 (1914).
(29) J. B. Culbertson, THIS JOURNAL, **73**, 4818 (1951).

TABLE II

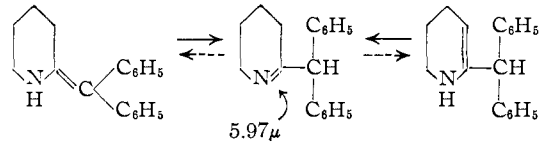
ENAMINE–IMINE TAUTOMERISM OF DIHYDROBERBERINE AS EVIDENCED BY THE SHIFT TO LOWER WAVE LENGTH, λ_{max} CATION − λ_{max} BASE, IN COMPARISON WITH THE FREE BASES AND CATIONS OF 1-METHYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE AND 1-(α-PICOLAL)-1,2,3,4-TETRAHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE[b,37]

Compound	Tertiary base: λmax	Tertiary base: log ε	Tertiary base: Present as	Cation: λmax	Cation: log ε	Cation: Present as	Δλ, mμ (λmax cation − λmax base)
 XLI ⇌ XLII	317	3.77	Imine	365	3.91	Imine	+48
XLIII ⇌ XLIV	384	4.09	Enamine	380	3.95	Enamine (+ imine)	− 4
Dihydroberberine XXXIX ⇄ XL	370	4.14	Enamine	350	4.17[a]	Imine	−20

[a] The hydrochloride of dihydroberberine in approximately 2×10^{-5} molar ethanolic solutions is appreciably dissociated into the free base; the spectrum of the hydrochloride was therefore taken in 1 *N* ethanolic HCl. [b] All spectra in ethanol.



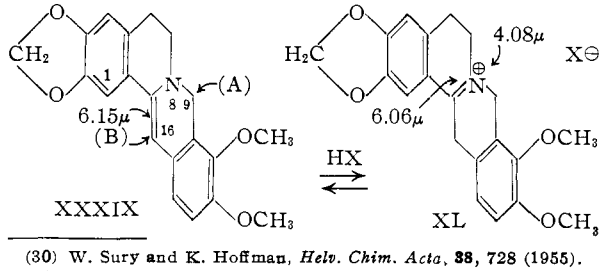
The system of diphenylacetaldimine built into a piperidine ring also exists primarily in the imine



λ_{max} (ε) 254 (3250)

form with no convincing indication of the presence of the *endo-* and *exo*cyclic vinylamines.[30]

D. The Dihydroberberinium Cation.—Dihydroberberine (XXXIX), formed together with oxoberberine in the alkali-catalyzed oxidation–reduction of berberine,[31] was one of the first enamines to undergo C- and N-alkylation with alkyl iodides.[32,33] The formulation XL for the cation of XXXIX[34–36] has not been proved. Table II provides the necessary data and conclusive proof for the structure of the dihydroberberinium cation as XL.



The free base, present as the enamine XXXIX, provides conjugation between two catechol rings. The system and absorption characteristics are very similar to 1-(2-picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (XLIII)[37] which on salt formation (double cation XLIV) stays essentially as the enamine. The small hypsochromic shift of −4 mμ is indication for the formation of some unconjugated imine. The disruption of conjugation in the cation of dihydroberberine would lead to a chromophore comparable to the cation XLII of 1-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (XLI)[37] which is indeed the case (Table II). The difference of −15 mμ is attributable to the hypsochromic effect of incorporation of $>C{=}\overset{\oplus}{N}(H)-$ in an additional ring.[38]

The infrared spectrum of dihydroberberine (XXXIX) in chloroform showed a distinct band for conjugated >C=C< at 6.15 μ. The cation XL had a new band at 6.06m μ in chloroform and 6.04m in Nujol which is close to that of cotarnine hydrochloride (Fig. 2). The ammonium bands of the quaternary azomethine group in dihydro-

(30) W. Sury and K. Hoffman, *Helv. Chim. Acta*, **38**, 728 (1955).
(31) M. Freund and K. Fleischer, *Ann.*, **409**, 230 (1915).
(32) J. Gadamer, *Arch. Pharm.*, **248**, 680 (1910).
(33) M. Freund, *Ann.*, **397**, 1 (1912).
(34) *Cf.* C. K. Tinkler, *J. Chem. Soc.*, **99**, 1344 (1914).
(35) K. Feist and W. Awe, *Arch. Pharm.*, **271**, 43 (1933).
(36) H. W. Bersch, *ibid.*, **283**, 192 (1950).
(37) J. L. Bill and C. R. Noller, THIS JOURNAL, **70**, 957 (1948).
(38) *Cf.* W. R. Rimington, *ibid.*, **67**, 1839 (1945).

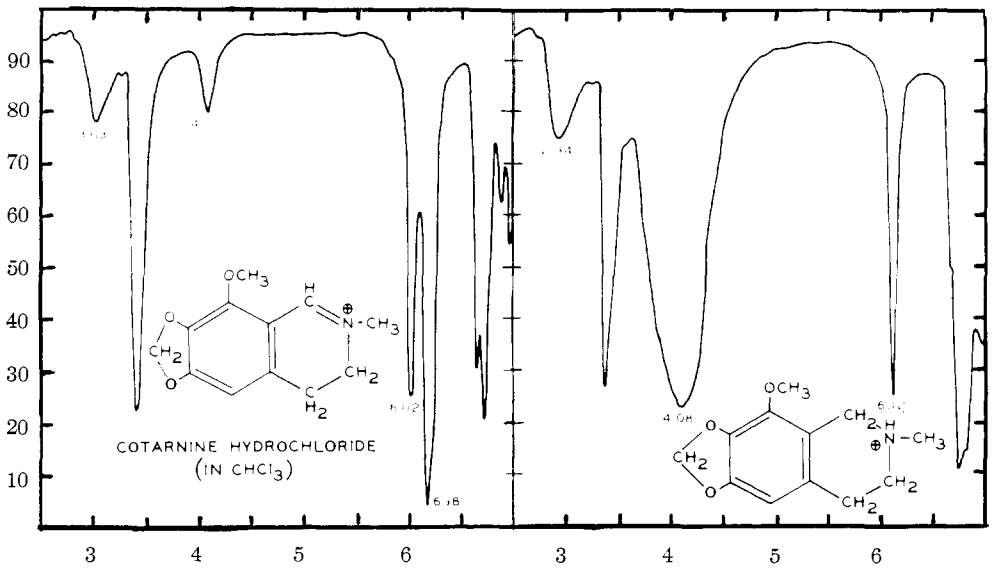
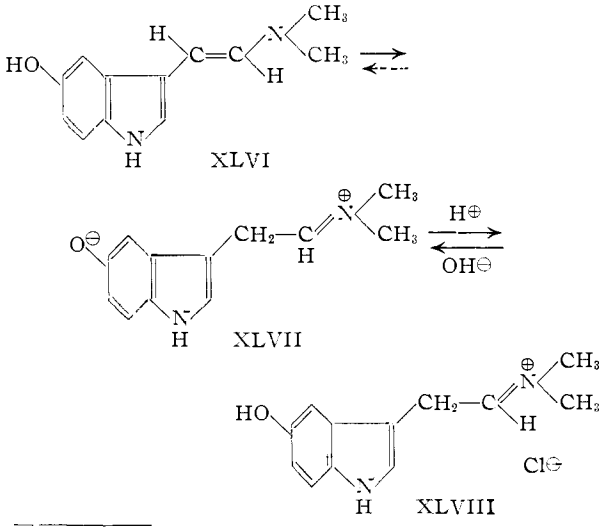


Fig. 2.—Infrared spectra of the hydrochlorides of cotarnine and hydrocotarnine (prepared from cotarnine by reduction with sodium borohydride (B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 4474 (1953)) showing the difference between a quaternary immonium and a tertiary ammonium band.

berberine and cotarnine hydrochlorides are identical (4.07w in chloroform). In hydrocotarnine hydrochloride (Fig. 2) the free proton of a saturated ammonium ion shows up at 2.94w and a strong band appears at 4.08s, a characteristic difference which would lead to the detection of tertiary (enamine) hydrochloride in the cation of dihydroberberine.[39]



(39) A word may be added regarding the mechanism of oxidation of such a system. The easy autoxidation of dihydroberberine to 9-oxoberberine (arrow A in XXXIX) is probably preceded by dehydrogenation to berberine followed by the steps: ammonium base → carbinolamine → quinolizidone as exemplified by the autoxidation of alstoniline hydrochloride [R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 685 (1954)] and numerous other dihydro(iso)-quinolines and dehydroquinolizinium compounds. Attachment of oxygen at the 16-position (arrow B in XXXIX) would parallel the course of the C-alkylation and, in conjunction with oxidation at A, lead to hydrastine by a sequence of simple reactions. Dihydroberberine, though not occurring in nature, is probably the key intermediate for the formation of corydalis (C-methylation at C16) (ref. 34), ophiocarpine (hydroxylation at C16 and reduction) and hydrastine (oxidation at C16 and C9) alkaloids. The attempted benzoylation of dihydroberberine has not yet led to N-benzoyl-*epi*cryptopine.

E. Miscellaneous Cases.—The naturally occurring enamine dehydrobufotenine is generally formulated as XLVI.[40] The data in Table III show that dehydrobufotenine has the same ultraviolet spectrum as 5-hydroxyindole,[41] *i.e.*, the vinylamine side chain makes no contribution to the spectrum. The alternate zwitterionic immonium

TABLE III

ULTRAVIOLET AND INFRARED DATA OF DEHYDROBUFOTENINE HYDROCHLORIDE

Solvent	I λmax	I ε	II λmax	II ε	Infrared in Nujol
H_2O	294	6675	224	21850	
NaOH	324	4775	[230	17325]	Shoulder at 4.28 (ammonium); weak band at 4.66 (immonium); indistinct and broad band at 5.99–6.10[a]; in other mulls sharp but weak bands at 6.10 (conjug. >C=C<) and 6.22 (phenyl)
	[298 infl. 5980]				
EtOH	288	6250	225	21680	
	325	5340			
EtOH + EtONa	275	5600			
EtOH/HCl	297	6640	226	21480	
6 *N* HCl	293	6880			

[a] Native bufothionine has a fairly broad and strong band at 5.92. On repeated recrystallization from water this band becomes weaker and shifts to 5.99, an indication that the labile sulfate group is easily lost.

structure (XLVII ⇄ XLVIII) might possibly explain the highly polar character of the base, the hydrogenation of dehydrobufotenine to bufotenine (in acidic solution),[40] the course of bromination[40] and the band at 5.99 μ in the infrared spectrum, but fails to account for the fact that dehydrobufotenine is stable to reduction with sodium borohydride,[42] stable to the action of amine oxidase[43] and to hydrolysis (open "Decker bases" hydrolyze easily). Due to lack of material the question of the exact structure of dehydrobufotenine must be left

(40) H. Wieland and Th. Wieland, *Ann.*, **528**, 234 (1937).

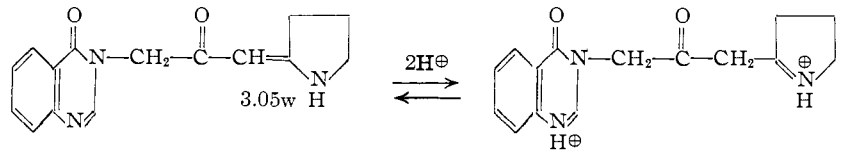
(41) A. Ek and B. Witkop, THIS JOURNAL, **76**, 5579 (1954).

(42) *Cf.* B. Witkop and J. B. Patrick, *ibid.*, **75**, 4474 (1953).

(43) S. Udenfriend, private communication. XLVII could be considered as the first intermediate in the sequence amine → aldimine → aldehyde → acid, postulated for the reaction of an amine with amine oxidase.

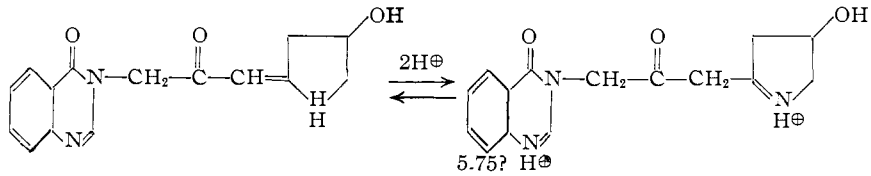
open at present. New analytical procedures (paper chromatography, ultraviolet fluorescence spectrophotometry)[43] leave no doubt about dehydrobufotenine being a uniform and pure compound distinctly different from bufotenine.

F. Competition for Conjugation in β-Aminovinyl Methyl Ketone Derivatives.—The two compounds 3-[β-keto-γ-(4,5-dihydropyrrolyl)-propyl]-4-quinazolone (XLIX)[44] and 3-[β-keto-γ-(5-hydroxy-1,4,5,6-tetrahydro-2-pyridyl)-propyl]-4-quinazolone (LI)[45] are probably *exo*- and not



XLIX λ_{max} 226, 305 (EtOH) in $CHCl_3$: 5.95vs, 6.20vs

L yellow dihydrochloride in Nujol: 5.79sh, 5.84s, 5.99s; 6.19w



LI $\lambda\lambda_{max}$ 226 (ε 25,100); 314(ε 24,600) (in EtOH) in Nujol: 5.94s, 6.15s, 6.18sh

LII colorless dihydrochloride in Nujol: 5.75m, 5.87s, 5.99m, 6.32w $\lambda\lambda_{max}$ 226 (ε 22,800), 314 (ε 20,900)

*endo*cyclic vinylamines[46] as indicated by the lack of absorption for unconjugated carbonyl. The infrared bands at 5.95 and 5.94 μ are probably those of the carbonyls conjugated with the imino groups through *exo*cyclic double bonds. In the dihydrochlorides (L and LII) the bands at 5.84 and 5.87 μ possibly indicate the migration of the double bond out of conjugation with the carbonyls and into the five- and six-membered rings to form immonium salts.[47] The assignment of bands in the dihydrochlorides L and LII is difficult since quinazolines, quinazolones[48] and their salts show a surprising number of bands in the 6 μ region which cannot readily be associated with any particular part of these complex molecules.

Experimental[49]

Hexahydroindole Hydrochloride (III).—To 50 mg. of the liquid colorless base[3] in anhydrous peroxide-free ether was added 0.8 equivalent of 0.1 *N* ethereal hydrogen chloride. The colorless crystalline precipitate, which turned pink on standing, was washed with ether. On recrystallization from chloroform–ethyl acetate very hygroscopic crystals were obtained, m.p. 160–162°.

Anal. Calcd. for $C_8H_{13}N\cdot HCl$: C, 60.15; H, 8.83; N, 8.42. Found: C, 59.89; H, 8.73; N, 8.42.

Cyclohexylideneaniline Hydrochloride (XI).—To an ethereal solution of freshly distilled cyclohexanone anil (X, b.p. 79° (0.2 mm.), prepared according to Reddelien,[7] was added ethereal hydrogen chloride. The crystalline precipitate was washed with ether; the material sublimed in colorless rods above 100° and melted at 131–133° with bubbling. On attempted recrystallization from ethanol–ether aniline hydrochloride, m.p. 198°, was isolated. Even on storage in the desiccator the anil decomposed slowly and smelled of cyclohexanone.

Anal. Calcd. for $C_{12}H_{15}N\cdot HCl\cdot{}^1/_2H_2O$: C, 65.75; H, 7.76; N, 6.37. Found: C, 65.45; H, 7.46; N, 6.77.

Infrared spectra. (a) Free base (pure liquid): 3.0vw, 3.11sh, 3.292w; 3.39vs, 3.48vs, 6.0vs, 6.25s, 6.73s, 6.90s, 7.43m, 7.49m, 7.62m, 7.80vw, 7.95m, 8.11s, 8.38s, 8.58m, 8.87m, 9.07w, 9.36m, 9.78m, 10.11m, 11.10m.

(b) Hydrochloride (in Nujol): no band in NH region, 3.90 (ammonium), 4.90w, 5.06m, 5.16vw, 5.19vw, 5.52vw (immonium bands), 5.98vs, 6.25m, 6.57m, 6.68s, 6.89s.

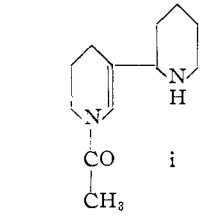
Reaction of Cyclohexylideneaniline with Oxygen.—Through 88 g. of cyclohexylideneaniline (b.p. 78° (0.3 mm.)) was bubbled a lively stream of dry oxygen at a temperature of 80° for 15 hr. Longer oxidation time and temperatures only 10–20° higher led to dark, viscous or semi-solid products.

(44) B. R. Baker, *et al.*, *J. Org. Chem.*, **17**, 58 (1951).

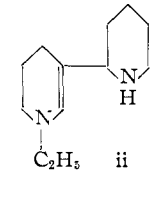
(45) B. R. Baker, *et al.*, *ibid.*, **17**, 68 (1951).

(46) This conclusion has been reached independently in the mean time by Dr. B. R. Baker, to whom we express our thanks for the donation of samples.

(47) *Cf.* N. J. Leonard, *et al.*, THIS JOURNAL, **76**, 2781 (1954); **77**, 437 (1955). Using this method, we have tried to determine or confirm the proximity of the double bond in ammodendrine (i, kindly supplied by Prof. C. Schöpf) by reduction with lithium aluminum hydride to the unknown deoxyammodendrine (ii) the double cation of which



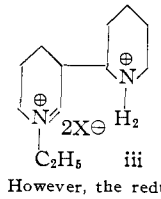
i



ii

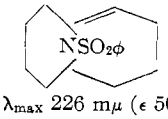
6.12 in hydrate, m.p. 74°, 6.07vs in anhydr. cpd., m.p. 53°, 6.16 in hydriodide, m.p. 222°

λ_{max} (241 (ε 10,170) in ether Hydriodide (in CH_3OH) λ_{max} 225 (ε 25,000)

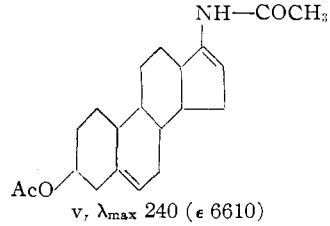


iii

should have the immonium structure (iii). However, the reduction of ammodendrine by lithium aluminum hydride, which is difficult and requires not ether but hot dioxane as a solvent, furnished an oily base with a strong and narrow band at 6.03 μ, a strong band at 6.08 and a shoulder at 6.15; the hydrochloride showed no immonium bands in the 5 μ region. The position of the maximum in ammodendrine hydriodide is the same as in iv. [A. C. Cope, XIVth National Organic Chemistry Symposium of the American Chemical Society, Lafayette, Indiana, June 13–16, 1955, Abstracts p. 37; *cf.* Cope, R. J. Cotter and G. R. Roller, THIS JOURNAL, **77**, 3590 (1955)]. The absorption of free ammodendrine seems to be in accord with that of an acylated vinylamine as the comparison with v (kindly communicated from unpublished results by Dr. F. Sondheimer) shows.



iv, λ_{max} 226 mμ (ε 5080)



v, λ_{max} 240 (ε 6610)

(48) H. Culbertson, J. C. Decius and B. E. Christensen, THIS JOURNAL, **74**, 4834 (1952).

(49) All melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and his associates of the Institutes' Analytical Service Laboratory.

Compound $C_{18}H_{20}N_2O_2$, M.p. 239–240°.—After extraction with ether, benzene and methyl alcohol there remained a solid residue which in over-oxidized, almost solid reaction mixtures constituted the major crystalline oxidation product. After recrystallization from methyl alcohol rectangular prisms were obtained, m.p. 239–240°, λ_{max} 240 mμ; infrared bands (Nujol): 3.01, 6.01vs, 6.24s, 6.55vs, 6.65s, 6.93vs.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.82; N, 9.45. Found: C, 72.83; H, 7.03; N, 9.55.

The same compound was found in neutral fraction of the dark chloroform extracts (see below).

In another run the oxidation mixture was digested with warm chloroform; the dark solution was extracted with saturated sodium bicarbonate solution. The *acidic fraction*, after neutralization of the bicarbonate solution with acetic acid and extraction with ether, consisted of 0.28 g. (0.8%) of a viscous residue showing infrared bands at 2.95 (broad and weak), 5.82 (narrow strong), 6.15w, 6.22m. From the chloroform solution the *phenolic (or weakly acidic) materials* were extracted with 2 *N* alkali. After neutralization with acetic acid and ether extraction, there was left as a phenolic fraction 0.49 g. (1.4%) of a light-brown viscous residue which darkened on exposure to air and which had infrared bands at 2.97, 5.86s, 6.16s, 6.23s, 6.66vs. The *basic compounds* were extracted from the chloroform solution with 2 *N* HCl and separated into a weakly basic and a more basic fraction by adjusting the *p*H first to 6 and then to 8. The weaker base (4–6%) was aniline, apparently formed from unreacted starting material by acid hydrolysis. The more strongly basic material gave a solid residue which after recrystallization from methanol formed plates, m.p. 157–159°. The ultraviolet spectrum resembled aniline; the major infrared bands were (in Nujol) 3.02 (very strong and sharp), 5.86s, 6.01vs, 6.24s, 6.51vs.

Anal. Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.63; H, 7.83; N, 7.29.

The residual chloroform extract contained the *neutral fraction* (80–95% of the weight of the starting material depending on the length of oxidation). After evaporation to dryness the benzene-soluble part of the neutral fraction was chromatographed on alumina. The first fractions were rechromatographed from hexane. The initial elutions gave a residue which was recrystallized from pentane and for final purification sublimed at 145° (0.3 mm.). On slow evaporation from ether and after washing with pentane large colorless plates were obtained, m.p. 109–110.5°.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.05; H, 6.36; N, 10.71.

The ultraviolet spectrum showed three peaks, 246, 273 and 291 mμ, not shifted by acid, slightly shifted to longer wave lengths by base. The longest peak came close to λ_{max} of diphenylamine 288 (log ε 4.16). The major infrared bands were 2.94, 6.26vs, 6.60s, 6.67vs, 7.15m. The part of the neutral fraction which was insoluble in benzene yielded more compound $C_{18}H_{20}N_2O_2$, m.p. 239–240°.

Ethyl β-Iminobutyrate Hydrochloride (XIV).—To an ethereal solution of ethyl β-aminocrotonate (prepared according to Glickman and Cope[50]) was added ethereal hydrogen chloride until no more precipitation occurred. The crystalline powder was carefully washed with absolute ether and, under exclusion of moisture,[51] used immediately for mulling in Nujol.

2-Carbethoxycyclopentenylamine (XVII).—The compound was prepared from 2-carbethoxycyclopentanone by reaction with dry ammonia,[52] as colorless platelets, m.p. 59° after two recrystallizations from petroleum ether.

The reaction of the enamine in ether with ethereal picric acid or hydrochloric acid led to precipitates which on isolation turned out to be ammonium picrate and chloride.

Ethyl Tetrahydroanthranilate (XX).[52]—From the reaction of 2-carbethoxycyclohexanone with dry ammonia the enamine was obtained as colorless scales, m.p. 75°. No stable salt could be obtained in ethereal solution; the precipitates which formed slowly with ethereal picric and hydrochloric acids were identified by m.p. and analysis as ammonium salts.

(50) S. A. Glickman and A. C. Cope, THIS JOURNAL, **67**, 1012 (1945).

(51) J. N. Collie, *Ber.*, **20**, 445 (1887); *J. Chem. Soc.*, **71**, 303 (1897), obtained an oil which solidified to crystals decomposing at 130°.

(52) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1677 (1945).

β-Methyl-β-phenylacetaldimine (Hydratropaldimine, XXIII).—Two grams of hydratropic aldehyde dissolved in 10 ml. of methyl alcohol was saturated at 0° with dry gaseous ammonia and kept in the cold room (−5°) for four days. The colorless rectangular prisms (1.7 g.) which separated melted at 98–105°.

In another run using the same amounts of reactants a saturated methanolic solution of ammonia gas was added at −5° to a methanolic solution of the aldehyde. The elongated prisms which separated after storage overnight at −5° melted in a range of 95–112°. Recrystallization from ethanol furnished a microcrystalline powder, m.p. 100–105°.

The reaction of hydratropic aldehyde in ethyl acetate with dry ammonia gas with or without cooling produced hexagonal crystals, m.p. 96–98°, clear melt at 102°.

Infrared Spectra.—All preparations showed identical infrared absorption bands in chloroform solution, one single NH-band at 3.05, a very sharp and strong —C=NH— band at 6.02 and bands at 6.24s, 6.70vs, 6.89vs, 7.28m (C–CH_3). In carbon disulfide solution there is again only one strong and very narrow imino band at 3.01; the C=N— band at 6.03 is, however, much less intense than in chloroform solution.

The addition of 0.1 *N* trichloroacetic acid solution in chloroform to solutions of the imine in the same solvent leads to the appearance of a carbonyl band at 5.82 (hydratropic aldehyde 5.81) but not of ammonium (4.10) or immonium bands (4.5–5.5).

Isomerization with Alkali.—When 2.5 g. of aldimine was suspended in 100 ml. of 20% methanolic caustic potash and refluxed for 2 hr., the colorless, hexagonal crystals, after washing with hot ethanol, melted at 135–137° (cloudy melt).[19] The infrared spectra in chloroform and in carbon disulfide were identical with those of the lower melting aldimine.

Reaction of Hydratropic Aldehyde with Dimethylamine. A. Compound M.p. 150–152°.—A solution of 5 g. of hydratropic aldehyde in 10 ml. of methanol was saturated at 0° with dry gaseous dimethylamine. The reaction mixture was slowly taken to a colorless liquid in a vacuum desiccator. The residue was digested with 5-ml. portions of low-boiling petroleum ether in the cold. On standing in the cold room the petroleum ether extracts deposited sheaves of glistening, colorless, hygroscopic needles, m.p. 150–152° (crystalline transformation at 112–120°, distillation to coverglass at 140–150°).

Anal. Calcd. for $C_{11}H_{15}NO_2 \cdot {}^1/_3H_2O$: C, 66.31; H, 7.93; N, 7.03. Found: C, 66.17; H, 8.16; N, 6.64.

The compound was not very soluble in chloroform and possibly underwent decomposition when solution was forced by short warming. Such solutions gave a poorly resolved spectrum, a strong band at 5.85 indicating hydrolysis. A satisfactory mull could not be prepared because of the hygroscopic nature of the crystals.

B. N,N-Dimethyl-(β-methyl-β-phenylvinyl)-amine (XXV).—Dry dimethylamine gas was passed in excess through 5 g. of hydratropic aldehyde. After a short induction period the reaction mixture warmed up and was kept below 50° by external cooling. When the temperature no longer rose the reaction was stopped. Neither on allowing to stand in the cold nor on trituration with petroleum ether could crystallization be induced. Only ether extracts on prolonged standing deposited crystals showing the same melting behavior as the solid obtained under A. The reaction product was then distilled at 52° (1 mm.), forming a colorless, mobile liquid with a very characteristic odor. On exposure to air and light the liquid turned yellow.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.70; H, 9.25; N, 7.82 (nitrogen values were constantly too low, even lower by Kjeldahl analysis).

Infrared Spectrum.—The pure liquid showed a slight dip in the OH–NH region at 3.0; three strong bands, each more intense than the following, at 5.77s, 5.93s, 6.10vs (the last band must be C=C, the other two bands remaining unexplained), 6.24s (phenyl), 6.68s, 6.88vs, 7.23m, 7.36m, 7.50m, 7.90s, 8.38w, 8.75w, 9.16s, 9.43vs, 9.74s, 10.01w, 10.43w, 10.98w, 11.56m, 13.18vs.

Hydrochloride.—When ethereal hydrogen chloride was added to a solution of the amine in ether, colorless crystals separated which were recrystallized from a mixture of methylene chloride and ethyl acetate. The hydrochloride formed extremely hygroscopic platelets which deliquesced at 60–80°, resolidified at 100–110°, formed fine needles at

140° and a clear colorless melt at 168–170°. The melting point of dimethylamine hydrochloride is 171°.

Anal. Calcd. for $C_{11}H_{15}N \cdot HCl \cdot 2.5H_2O$: C, 54.32; H, 8.72; N, 5.75. Found: C, 54.74; H, 8.72; N, 6.05.

The attempted preparation of a picrate in ethereal solution led only to the isolation of dimethylamine picrate as small buff prisms, recrystallizable from methanol, m.p. 154–156°.

Infrared Spectrum.—The solution of the hydrochloride in chloroform showed a band at 2.97, an ammonium "trough" at 3.50–3.75, a sharp ammonium band at 4.13, two strong bands at 5.78 and 5.94 and no band at 6.10.

***p*-Methoxyanil of Hydratropic Aldehyde (XXVI).**—When 4.47 g. of hydratropic aldehyde was mixed with 4.0 g. of *p*-anisidine in 15 ml. of methanol, a strong exothermic reaction occurred, and the reaction mixture solidified to a crystalline mass on cooling. The labile crystals were collected carefully and recrystallized from methanol. The colorless crystals immediately turned yellow and sticky on exposure to air or moisture. The compound was dried at room temperature and 0.1 mm. for five minutes and then used for analysis immediately. The Schiff base melted over a range at 70–80°, clear, slightly yellow melt at 92°.

Anal. Calcd. for $C_{16}H_{17}NO \cdot {}^1/_3H_2O$: C, 78.33; H, 7.26; N, 5.71. Found: C, 77.93; H, 7.25; N, 5.67.

The Schiff base autoxidized so rapidly that solutions in chloroform immediately showed the same NH (2.97) and CO bands (5.91) as exhibited by formanisidide. The band at 5.91 extended to 5.96 and was broad and intense enough to account for the presence of aromatic-aliphatic >C=N—.

Autoxidation of Hydratropic Aldehyde *p*-Methoxyanil.—When a solution of the Schiff base in ether or ethyl acetate was shaken under oxygen, exactly one mole of oxygen was taken up rapidly. The oxidized solution strongly liberated iodine during and shortly after the oxygen uptake. The intermediary hydroperoxide was too unstable to be isolated. Cautious and rapid evaporation of autoxidized solutions led only to rearranged crystalline material devoid of any peroxide function. The residue of such solutions consisted of crystals embedded in a slightly yellow oil. The latter was removed by washing with low-boiling petroleum ether in the cold. The crystals were recrystallized from ether or ethyl alcohol and formed colorless prisms, m.p. 82°, undepressed on admixture with an authentic sample of N-formyl-*p*-anisidide.

Anal. Calcd. for $C_9H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.68; H, 6.19; N, 8.96.

The petroleum ether washings contained a fragrant oil yielding brick-red needles of a dinitrophenylhydrazone, m.p. 248–250° undepressed on admixture with an authentic sample of acetophenone dinitrophenylhydrazone.

Reaction of Hydratropic Aldehyde with Aniline.—When 4.47 g. ($^1/_{30}$ mole) of hydratropic aldehyde in 20 ml. of benzene was refluxed for 30 minutes with 3.1 g. ($^1/_{30}$ mole) of aniline, 0.6 ml. of water was collected in the water separator connected with the reflux condenser. The mixture was evaporated *in vacuo*. Recrystallization from methanol yielded long silky, colorless needles, m.p. 134–136°. The same compound was obtained when an equimolar mixture of the components in methanol was left in the cold room for two days.

Anal. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.16; H, 6.31; N, 14.50. Calcd. for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52.

Infrared Spectrum.—Strong and narrow NH-band at 2.98, very strong C=N-band at 6.05, very strong phenyl at 6.28, weak C–CH_3 at 7.25.

Hydrochloride.—The hydrochloride, prepared in ethereal solution, separated as a microcrystalline, colorless powder, subliming as iridescent scales at 150°, m.p. 244–248° (*cf.* aniline hydrochloride, m.p. 198°).

Anal. Calcd. for $C_{19}H_{17}N_3 \cdot HCl \cdot H_2O$: C, 66.66; H, 5.61; N, 12.25. Found: C, 66.23; H, 5.71; N, 11.91.

Infrared Spectrum.—Sharp NH at 2.98 in $CHCl_3$, missing in Nujol; traces of ammonium and immonium bands at 3.87, 4.28, 5.17, strong band at 6.05 in chloroform and 5.87 in Nujol.

Diphenylacetaldimine (XXX). A. Reaction in Ethanol.—When 4 g. of diphenylacetaldehyde, prepared by dehydration of hydrobenzoin (obtained from benzoin by reduction with sodium borohydride), was dissolved in 10 ml. of ethanol and saturated at 0° with dry ammonia gas, hard colorless crystals separated overnight in the coldroom (−5°), m.p. 75–82°. Attempted recrystallization from methanol gave tars. The infrared spectrum of this preparation showed two strong bands of almost equal intensity at 6.02 and 6.10 indicative of a mixture of imine, enamine and possibly the compound m.p. 148–150° (see below).

B. **Reaction in Ethyl Acetate.**—The same reaction as above carried out in 10 ml. of ethyl acetate yielded after 48 hr. at −5° fine fluffy needles, m.p. 91°.

Anal. Calcd. for $C_{14}H_{13}N \cdot {}^1/_4CH_3COOC_2H_5$: C, 82.91; H, 6.96; N, 6.45. Found: C, 83.25; H, 6.85; N, 6.20.

Infrared Spectrum.—The chloroform solution of a fresh preparation measured immediately after dissolving showed NH_2 at 2.97 and 3.05, a carbonyl band at 5.75 (ethyl acetate), a strong band at 6.01 (imine) and a weaker enamine band at 6.11.

Reaction in Ether.—When ether was used as a solvent the reaction product separated after standing for 48 hr. at −5° as colorless, hard pellets of the same size and shape as the commercial pellets of caustic alkali. After washing with ether this product melted at 91°. The infrared spectrum still showed a weak band at 6.11. A further crop obtained from the ethereal mother liquor on standing for three more days at −5° finally yielded colorless needles, m.p. 89°, of pure imine.

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17. Found: C, 85.79; H, 6.56; N, 6.62.

Infrared Spectrum.—The infrared spectrum showed only the presence of pure imine 2.97, 3.06 (probably non-bonded and bonded secondary NH rather than primary amino group), 6.01 (>C=N—), 6.24 (phenyl), 6.69vs, 6.89vs, 7.23vw, 7.40vw, 7.58m, 7.83m, 8.67w, 9.0m, 9.32m, 9.70m, 9.98w, 10.27vw, 10.61w, 10.92m, 11.27vw.

Conversion of the Imine to the Compound m.p. 148–150° (XXXIV).—In an attempt to get better resolution in the NH-region, solutions of various imine preparations were dissolved in carbon disulfide. Such solutions displayed only a single, very strong band at 6.10 indicative of rearrangement of imine to an isomeric vinylamine. By cautious addition of petroleum ether to carbon disulfide solutions of the imine, silky colorless needles were obtained after storage for 24 hr. at room temperature, m.p. 148–150°.

Anal. Calcd. for $C_{28}H_{23}N \cdot H_2O$: C, 85.90; H, 6.44; N, 3.58. Found: C, 86.14; H, 6.50; N, 3.89.

Infrared Spectrum.—The solution of this compound in chloroform showed a strong and narrow NH-band at 2.98, negligible aliphatic CH at 3.30, a very strong band at 6.08 and equally strong phenyl at 6.26, 6.70s, 6.89s, 7.32vw, 7.50w, 7.67w, 7.79s, 8.84vs, 9.31m, 9.73m, 10.02vw, 11.26s. On addition of 0.1 *N* *p*-toluenesulfonic acid solution in chloroform the band of free diphenylacetaldehyde at 5.81 appears; the only other band in the 6.0 region is a strong narrow band at 6.12. The spectrum in carbon disulfide is practically identical with that of the imine in the same solvent, the only difference being a single strong and narrow band at 2.99 exhibited by the solution of the pure high-melting compound, whereas the imine after solution in carbon disulfide shows bands at 2.84, 2.93, shoulder at 2.96, the remainder of the spectrum being essentially identical.

Diphenylacetaldehyde *p*-Methoxyanil (XXXVI).—A mixture of equimolar parts of diphenylacetaldehyde and *p*-anisidine in methanol reacted under warming and deposited on standing silky needles, which were hygroscopic and very unstable; the crystals, after sintering at 40°, formed a cloudy melt at 48° which became clear at 75°.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.99; H, 6.74; N, 4.49.

Infrared Spectrum.—A sharp and narrow band at 2.97 in chloroform and at 2.98 in carbon disulfide together with a strong band at 5.91 were always present and are attributed, partly or wholly, to formanisidide formed by rapid autoxidation. In addition there was a distinct and strong band at 6.10 (6.02 in carbon disulfide) which was shifted by salt formation (addition of 0.1 *N* *p*-toluenesulfonic acid in chloroform) to 5.96 as expected from a Schiff base on protonation.

Autoxidation of Diphenylacetaldehyde *p*-Methoxyanil.—When 3 g. of the Schiff base was dissolved in 20 ml. of ethyl acetate, 235 ml. of oxygen was taken up within 20 minutes when the solution was agitated in a closed system under oxygen. The oxidized solution gave a hydroperoxide test which was negative after 2 hr. of standing at room temperature. On concentration of the solution and addition of petroleum ether, rosettes of short rectangular rods were obtained, m.p. 80–82°, identical with *p*-formanisidide. The petroleum ether mother liquors yielded benzophenone, characterized and identified by infrared comparison.

Dehydrobufotenine Hydrochloride (XLVIII).—Thirty milligrams of dehydrobufotenine picrate[53] was dissolved in 3 ml. of 2 *N* hydrochloric acid and extracted with ethyl acetate until the aqueous phase was free of picric acid.[54]

The hydrochloride crystallized on concentration in the desiccator from the aqueous acid in long colorless needles, losing their transparency above 100°, charring at 215° and progressively darkening and decomposing, no melting up to 300°.

Dihydroberberine (XXXIX).—Following the procedure of Freund and Fleischer[31] the free dihydroberberine, prepared from the yellow-red hydrochloride from the filtrate of oxoberberine, was recrystallized from benzene and obtained in the form of yellow prisms with a green tinge, m.p. 157–159° (discoloration and decomposition starting at 146°).

(53) The sample came from Prof. V. Deulofeu, Buenos Aires, and was obtained through the courtesy of Dr. M. E. Speeter, The Upjohn Co., Kalamazoo, Michigan.

(54) *Cf.* the conversion of bufotenidine picrate into the hydrochloride: H. Wieland, W. Konz and H. Mittasch, *Ann.*, **513**, 18 (1934).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, AND THE DEPARTMENT OF CHEMISTRY, STETSON UNIVERSITY]

The Conversion of L-Histidine into Hydroxy- and Allohydroxy-proline *via erythro-* and *threo*-γ-Hydroxy-L-ornithine[1,2]

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RECEIVED DECEMBER 27, 1955

α,δ-Dibenzoyl-γ-keto-L-ornithine methyl ester (IV), obtainable from L-histidine methyl ester (I) by Bamberger cleavage, on hydrogenation yielded the two diastereoisomeric lactones (VIII and IX) of *erythro* and *threo*-α,δ-dihexahydrobenzoyl-γ-hydroxy-L-ornithine. Hydrolysis furnished the dihydrochlorides of the two diastereoisomeric lactones (X and XIII) of γ-hydroxy-L-ornithine accompanied in each case by some of the D-isomers (XI and XII) arising by acid catalyzed epimerization at C(2). The various γ-hydroxyornithines were assayed and separated by chromatography on Dowex-50 columns. The mutarotation of these lactones in aqueous solution parallels the ring opening which was followed by measuring the carbon dioxide produced by reaction with Chloramine T. The reaction of the various lactones with nitrosyl chloride, before and after mutarotation, and subsequent base-catalyzed cyclization of the mixture of α- and δ-chlorohydroxyamino acids yielded mixtures of normal and allohydroxyproline (XIV and XV; XVI and XVII) which were partially fractionated *via* their remarkably different reineckates, analyzed by Dowex-50 and identified by their rotations. These transformations made possible the stereochemical correlation of C(4) in *erythro*-γ-hydroxy-L-ornithine (X) with C(4) in hydroxy-L-proline (XIV) and in *threo*-γ-hydroxy-L-ornithine (XIII) with allohydroxy-L-proline (XVII). Preliminary results on the transamination of γ-hydroxyornithine preparations are reported.

γ-Hydroxyornithine, though not isolated from natural sources, can be visualized as a precursor or labile metabolite of hydroxyproline[3] or as a building stone in the biogenesis of scopolamine,[4] and several synthetic attempts, leading to racemic mixtures of undefined purity, have been recorded in the literature.[5–9] This paper describes the synthesis of the two diastereoisomers of γ-hydroxy-L-ornithine from L-histidine and the establishment of the stereochemistry of C(4), to which the secondary hydroxyl group is attached, by conversion to (allo)-hydroxyproline.[10]

Separation and Properties of the Two Diastereoisomeric Dihexahydrobenzoyl-γ-hydroxy-L-ornithine Lactones.—The catalytic reduction (platinum in acetic acid or Raney nickel in methanol) of α,δ-dibenzoyl-γ-keto-L-ornithine (IV),[8] obtainable *via* Bamberger cleavage[11] of L-histidine methyl ester (I)[12–14] led to the continuous uptake of seven moles of hydrogen with no indication of the γ-keto group being reduced prior to reduction of the benzene rings.[15] Even the use of Raney nickel in methanol

(1) Labile Metabolites. III. Preceding paper in this series, THIS JOURNAL, **76**, 5579 (1954).

(2) Presented in part at the Meeting of the Chemical Society (London) on Natural Heterocyclic Compounds held at Exeter, England, July 13–15, 1955; *cf.* Special Publication No. 3, The Chemical Society, Burlington House, W. 1, London, 1955, pp. 60–82.

(3) Possible pathways for the biosynthesis of γ-hydroxyornithine are the transamination of γ-hydroxyglutamic semialdehyde, a metabolite of hydroxyproline [K. Lang and U. Mayer, *Biochem. Z.*, **324**, 237 (1953)] or the reduction of a hypothetical keto-ornithine, formed possibly by the condensation of aspartate with glycine in analogy to the formation of δ-aminolevulinic acid from succinate and glycine [D. Shemin and C. S. Russell, THIS JOURNAL, **75**, 4873 (1953). Dihydroxyornithine and its betaine, myokinine, are of doubtful occurrence [R. Engeland and A. Bastian, *Compt. rend.*, **207**, 945 (1938)].

(4) E. Lecte, L. Marion and I. D. Spenser, *Can. J. Chem.*, **32**, 1116 (1954).

(5) E. Hammarsten, *Compt. rend. trav. lab. Carlsberg*, **11**, 223 (1916).

(6) W. Traube, R. Johow and W. Tepohl, *Ber.*, **56**, 1861 (1923).

(7) M. Tomita and T. Fukagawa, *Z. physiol. Chem.*, **158**, 58 (1926).

(8) W. Langenbeck and R. Hutschenreuter, *ibid.*, **182**, 305 (1929).

(9) A. N. Dey, *J. Chem. Soc.*, 1166 (1937).

(10) *Cf.* I. Uematsu, H. Ando and M. Uchida Seikagaku, *J. Biochem., Japan*, **26**, 386 (1954).

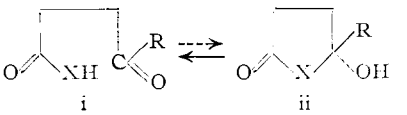
(11) *Cf.* E. Bamberger and O. Berlé, *Ann.*, **273**, 342 (1893).

(12) A. Kossel and F. Edlbacher, *Z. physiol. Chem.*, **93**, 396 (1914); A. Windaus, *et al.*, *Ber.*, **43**, 499 (1910).

(13) J. N. Ashley and C. R. Harington, *J. Chem. Soc.*, 2586 (1930). C. R. Harington and J. Overhoff, *Biochem. J.*, **27**, 338 (1933).

(14) H. Heath, A. Lawson and C. Rimington, *J. Chem. Soc.*, 2215 (1951).

(15) An equilibrium of ring-chain tautomers, i ⟶ ii, may be considered for γ-keto compounds such as the two forms of ketoglutaramic



acid [i ⟶ ii: X = NH, R = COOH; *cf.*, A. Meister, *J. Biol. Chem.*, **210**, 17 (1954)] or the γ ketoacid from furan [i ⟶ ii: X = O; R =