# OBSERVATIONS ON AMINE CATALYSIS OF FORMATION AND
DEHYDRATION OF KETOLS

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We have previously suggested (1) that amine catalysis of
intramolecular aldol condensation (e.g., I⟶II) occurs via
formation of an enamine which serves as nucleophile for the
carbon-carbon bond formation. In order to gain further insight
into this type of reaction, and into amine catalysis in general,
we have studied the relative effectiveness of selected primary
(1°), secondary (2°), and tertiary (3°) amines as catalysts
for the following conversions: 1) 2-methyl-2-(3-oxobutyl)-
cyclohexane-1,3-dione (I) to cis-fused ketol II, plus, in
certain cases, bridged ketol III;   2) I to enedione IV (2),
plus, in certain cases, its dienamine V; and 3) II to IV,
plus, in certain cases, V.
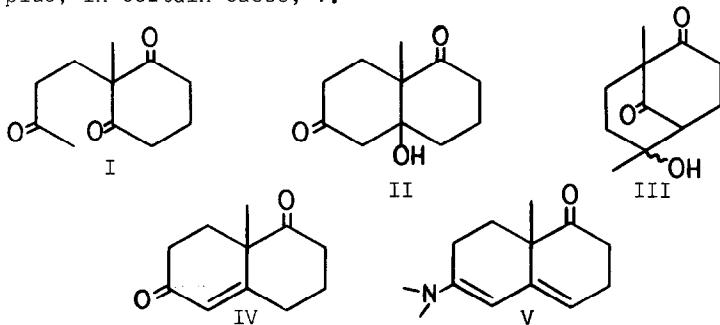
1) Cyclization of I to Ketol

   Details of the preparation and structure proof of cis-
9-hydroxy-10-methyldecalin-2,5-dione (II), m.p. 141-142°, and
1,6-dimethyl-6-hydroxybicyclo[3.3.1]nonane-2,9-dione (III),
m.p. 115-116°, will be published elsewhere (3). The best
yields of ketol obtained from I were 10% of pure II with an
equivalent of pyrrolidine as catalyst (12-min. reaction at 0°
in ether) and 33% of a 1:1 mixture, m.p. 99-100°, of II and
III with piperidine as catalyst (5-hr. reaction at 25° in
ether).

   One can envisage amine catalysis of cyclization of I in
three ways. First, the amine can serve as a proton abstractor,
as illustrated in A for I → II. All classes of amines (1°,
2°, and 3°) are theoretically capable of thus effecting
cyclization (4).

A

I ⟶   ⟶ II
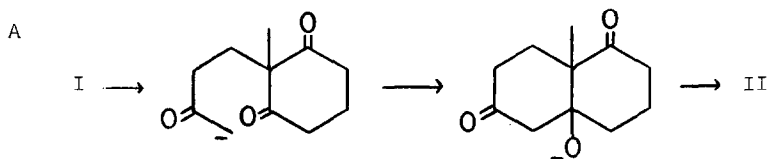
   Alternatively, an amine can bring about cyclization by
condensing with either of the two carbonyl groups involved.
Immonium salt formation, as shown in B for I → II, will
facilitate nucleophilic attack at that site (5). This
mechanism, however, can lead to II only if the intermediate
3° amine VI can be converted to II, most probably via IV.
(Bridged ketol III cannot arise by a similar elimination-
addition without a violation of Bredt's rule.)

B

I $\longrightarrow$ [structure] $\longrightarrow$ [structure] $\longrightarrow$ IV
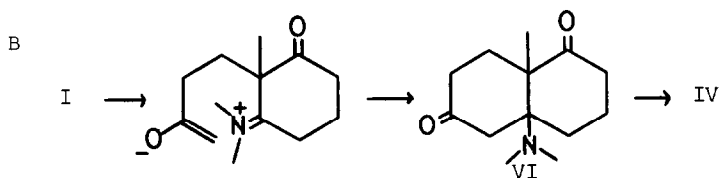
Enamine formation, as previously mentioned (1), can also lead to cyclization, as shown in C for I$\longrightarrow$II. Obviously, neither condensation mechanism is possible with 3° amines; to the extent that 3° amines are effective catalysts for any process, it must be general base-catalyzed (4).

C

I $\longrightarrow$ [structure] $\longrightarrow$ [structure] $\longrightarrow$ II
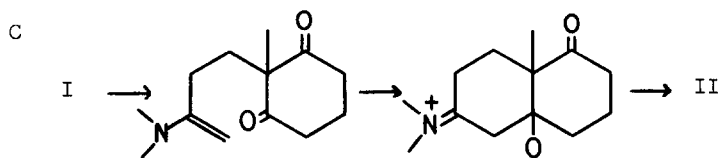
The formation of ketol from I in dioxane at 25° under the influence of different amines has been studied by thin-layer chromatography (t.l.c.). The results are given in Table I. The most striking observation is that the 3° amines, tri-ethylamine and quinuclidine, yielded no detectable ketol. This strongly suggests a condensation mechanism (B or C). Furthermore, as noted above, ketol cannot arise directly by mechanism B. The possibility that ketol II was formed by hydration of IV was tested and excluded; no ketol could be detected under the cyclization conditions or even under conditions designed to be more favorable to the addition of water to IV. Thus, the enamine-as-nucleophile mechanism (C) is the most reasonable choice for the cyclization of I to ketol II or III.

Table I

CYCLIZATION OF 2-METHYL-2-(3-OXOBUTYL)CYCLOHEXANE-1,3-DIONE
AS STUDIED BY THIN-LAYER CHROMATOGRAPHY[a]

AMINE	pK_b	KETOL DETECTED	TIME (hr.) OF APPEARANCE	TIME (hr.) OF DISAPPEARANCE
Piperidine	2.80^b	Yes[f]	< 0.017	252-260
Pyrrolidine	2.89^c	Yes[g,h]	< 0.017	7-10
Hexamethyl-eneimine	2.90^d	Yes	< 0.017	18-22
Quinuclidine	3.05^e	No	--None in 334--	
Triethylamine	3.25^b	No	--None in 312--	
n-Butylamine	3.39^b	Yes[h]	< 0.017	18-22
Morpholine	5.64^d	Yes[f]	< 0.017	90-100

[a] Reaction run in dioxane at 25°, 0.2M in I and 0.2M in amine. T.l.c. done on Silica Gel G or H, developed with 1:4 acetone-chloroform. Ketol detected with 0.2% 2',7'-dichlorofluoroescein in methanol under ultraviolet irradiation; lower limit of detection ca. 0.5%. Each "time" reported is the consistent result of at least 3 determinations.

[b] N. A. Lange, "Handbook of Chemistry", Handbook Publishers, Inc., Sandusky, Ohio, 7th Edition, 1949, p. 1408.

[c] L. C. Craig and R. M. Hixon, J. Am. Chem. Soc., 53, 4367 (1931). Ref[d] gives pK_b = 2.68 for pyrrolidine.

[d] H. K. Hall, Jr., J. Phys. Chem., 60, 63 (1956).

[e] C. A. Grob, A. Kaiser, and E. Renk, Chemistry and Industry, 598 (1957).

[f] Isolated as a mixture of II and III from preparative runs in ether.

[g] Isolated as pure II from t.l.c. plates.

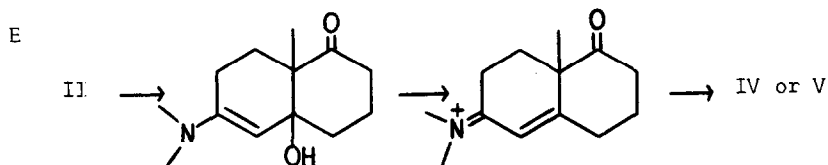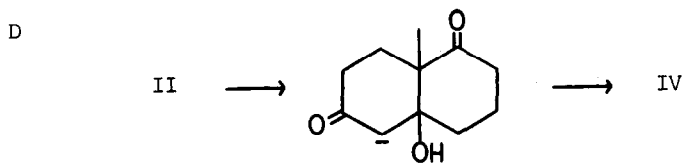[h] Isolated as pure II from preparative runs in ether.

2) Cyclization-Dehydration of I

The remote logical possibility remained that ketol II was not being detected in the cases of the two 3° amines because of very rapid formation of IV in these cases. The conversion of I to IV (which with 1° and 2° amines appears partially or exclusively as the corresponding dienamine V) can easily be followed by ultraviolet spectroscopy. The results of such a study, using the same conditions and amines used for the t.l.c. study, are given in Table II.

Again, the relative ineffectiveness of the two 3° amines, particularly the presumably unhindered quinuclidine, is striking. There is no discernible relationship between catalytic potency and base strength, nor is the possibly least hindered amine, n-butylamine, the most effective catalyst. Upon comparing the effectiveness of pyrrolidine, piperidine, and hexamethyleneimine one finds the minimum in the 6-membered ring case which is characteristic of processes in which a ring atom (in this case nitrogen) changes from tetrahedral to trigonal hybridization in or before the slow step (6). All these observations are consistent with the importance of a condensation mechanism as opposed to general base catalysis.

3) Dehydration of II

Catalysis of the elimination of water from β-hydroxy-ketones, such as II, likewise can be envisaged as occurring either by a proton abstraction mechanism (as shown in D) or by a condensation mechanism (E).

D

II $\longrightarrow$ [structure: decalin diketone with angular methyl and O⁻, OH] $\longrightarrow$ IV

E

II $\longrightarrow$ [structure: enamine with N and OH] $\longrightarrow$ [structure: iminium N⁺] $\longrightarrow$ IV or V

The preliminary results of a study of the conversion of II to the chromophoric IV and V are given in Table II. The same pattern of relative effectiveness as in the cyclization-dehydration of I is apparent, and for the reasons discussed above mechanism E is therefore implicated. In Westheimer's classic study of the conversion of diacetone alcohol to acetone (7) the inactivity of trimethylamine as catalyst led to the analogous conclusion: that the dealdolization proceeded _via_ amine condensation. The fact that ketol II can be recovered in excellent yield from a 600-hr. reaction with quinuclidine indicates that II, like diacetone alcohol, does not undergo dealdolization by general base catalysis.*

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* The possibility of course exists that II undergoes reversible dealdolization with $1°$ and $2°$ amines (by the reverse of mechanism C) during its conversion to IV and V. However, since dehydration of II is in no case slower than cyclization-dehydration of I, the dealdolization, if it occurs, does not appear to go all the way to I.

Table II

DATA FROM ULTRAVIOLET SPECTROSCOPIC STUDIES

AMINE	pK_b	APPROX. REL. RATE OF CYCLIZATION-DEHYDRATION of I[a,b]	APPROX. REL. RATE OF DEHYDRATION of II[b]
Piperidine	2.80	1	1[d]
Pyrrolidine	2.89	120	1000[d]
Hexamethyl-enimine	2.90	5	15[d]
Quinuclidine	3.05	0.03[c]	0.02[d,e]
Triethylamine	3.25	0.005[c]	0.02[a,c]
n-Butylamine	3.39	50	50[d]
Morpholine	5.64	0.4	1[d]

[a] Reaction run in dioxane at 25°, 0.2M in I, 0.2M in amine.

[b] Relative rates calculated by use of the expression: % reaction = 100 (ε_{244}/12,500 + $\varepsilon_{270-280}$/19,000). The rel. rates to 10% and 33% cyclization were used for comparison in the cases of 1° and 2° amines, and differed little. All figures are highly approximate for at least the following reasons. 1) It was assumed that each conjugated dienamine V had ε = 19,000, which was the best (highest) value obtained with pyrrolidine. (Attempts to isolate pure enamines of IV were futile.) 2) The reactions considered (particularly cyclization-dehydration of I) are not quantitative, and thromophoric by-products may be more important in some cases than in others. 3) Absorption at ~240 mμ may be due to species other than IV, such as immonium salts or enamines. 4) The figures for the cyclization-dehydration may have been affected by the fact that completely pure I could not be prepared.

[c] The rel. rates for the 3° amine cases are maximum estimates based on very small % reaction over 600-2400 hr.

[d] Reaction run in dioxane at 25°, 0.1M in II, 0.1M in amine.

[e] This figure is the result from one run which gave 1% reaction in 600 hr. Another run gave < 0.3% reaction in 2000 hr.

Several cautionary points should be made with respect to interpretation of all of the above data. First, it is not completely clear how ketol *does* arise; perhaps the isolation or detection techniques are necessary complements to the amine catalyst. Although the data of Table II do not rule out the possibility, there is no reason to assume that II is an intermediate in the over-all cyclization-dehydration. Second, there are puzzling aspects to the ultraviolet spectroscopic studies in addition to the large experimental uncertainty (see footnotes to Table II). For example, a few experiments involving changing the relative concentrations of substrate and amine did not lead to results anticipated by simple mass law considerations. It is hoped that future investigations of similar aldol condensations in less refractory systems will clarify some of these points.

Nonetheless, all the data reported herein indicate the importance of amine catalysis by condensation rather than proton abstraction, and, to the extent of ketol formation, are suggestive of enamine as nucleophile for the cyclization of I. These conclusions are in agreement with those of Yasnikov (8) based on a study of the kinetics of the aldol condensation of butyraldehyde and the dehydration of butyraldol in aqueous solution as catalyzed by primary amines and amino acids. It should also be noted that the available evidence (9) concerning aldolase catalysis suggests an enamine-as-nucleophile mechanism in the functioning of this enzyme.

References

(1) T. A. Spencer and K. K. Schmiegel, *Chemistry and Industry*, 1765 (1963).

(2) *cf.*, S. Ramachandran and M. S. Newman, "Organic Syntheses", John Wiley and Sons, Inc., New York, Vol. 41, 1961, p. 38.

(3) T. A. Spencer, H. S. Neel, D. C. Ward, and K. L. Williamson, submitted for publication.

(4) *cf.*, C. D. Gutsche, R. S. Buriks, K. Nowotny, and H. Grassner, *J. Am. Chem. Soc.*, **84**, 3775 (1962).

(5) *cf.*, T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

(6) *cf.*, G. Stork, A. Brizzolara, H. Landesman, J. Szmusz-kovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(7) F. H. Westheimer and H. Cohen, *J. Am. Chem. Soc.*, **60**, 90 (1938).

(8) T. S. Boiko, N. V. Volkova, and O. O. Yasnikov, *Ukr. Khim. Zh.*, **29**, 1179 (1963); *Chem. Abstr.*, **60**, 3964 (1964).

(9) *e.g.*, J. C. Speck, Jr., P. T. Rowley, and B. L. Horecker, *J. Am. Chem. Soc.*, **85**, 1012 (1963), and references cited therein.