The dipeptide ester hydrobromide XIII was obtained as long needles, m.p. 176–177° (gas evolution); R_f 0.61 (nin +, one spot only); $[\alpha]^{26}D$ +14° (*c* 1, methanol).

Anal. Calcd. for $C_{12}H_{16}N_2O_3 \cdot HBr$: C, 45.44; H, 5.40; N, 8.83; Br, 25.20. Found: C, 45.33; H, 5.63; N, 8.87; Br, 25.48.

Ditritylhistidylglycylphenylalanine Methyl Ester (XIV).—Ditritylhistidine[9] (6.39 g., 0.01 mole), glycylphenylalanine methyl ester hydrobromide (3.17 g., 0.01 mole), 1.50 ml. (0.011 mole) of triethylamine and 2.27 g. (0.011 mole) of dicyclohexylcarbodiimide in methylene chloride yielded the protected tripeptide XIV, 7.88 g. (92%), as a powder, m.p. 110–115°. Recrystallization from acetone–cyclohexane by concentrating to remove acetone yielded a microcrystalline powder, m.p. 110–115°, R_f 0.93 (nin −, Pauly −, *t*-BuOCl +, one spot only); $[\alpha]^{26}D$ −8° (*c* 1, methanol). Analysis and n.m.r. indicated that the product contained cyclohexane of crystallization.

Anal. Calcd. for $C_{56}H_{51}N_5O_4 \cdot C_6H_{12}$: C, 79.03; H, 6.74; N, 7.43. Found: C, 79.38; H, 6.82; N, 7.37.

Ditritylhistidylproline Methyl Ester (XV).—Ditritylhistidine[6] (7.73 g., 0.012 mole), proline methyl ester hydrochloride[10] (2.16 g., 0.013 mole), 2.0 ml. (0.014 mole) of triethylamine, 3.74 g. (0.013 mole) of dicyclohexylcarbodiimide in methylene chloride gave the protected dipeptide as a powder, 8.44 g. Chromatography on silica gel and elution with 40% ethyl acetate–benzene yielded 7.38 g. (82%) XV, m.p. 207–214°. Crystallization from acetone–cyclohexane gave needles, m.p. 212–216°, $[\alpha]^{25}D$ +29° (*c* 1, methanol); R_f 0.92 (*t*-BuOCl +, one spot only).

Anal. Calcd. for $C_{50}H_{46}N_4O_3$: C, 79.97; H, 6.18; N, 7.46. Found: C, 79.86; H, 6.28; N, 7.18.

Ditritylhistidylproline (XVI).—Protected dipeptide XV (3.75 g., 0.005 mole) was hydrolyzed as described for compound III. The crude product was crystallized from acetone–cyclohexane to yield ditritylhistidylproline, 2.66 g. (72%), gas evolution from 115°. On drying 2 hr. under vacuum at 100°, the product apparently lost solvent of crystallization and melted from 157° (no meniscus); $[\alpha]^{25}D$ −26° (*c* 1, methanol); R_f 0.92 (*t*-BuOCl +, one spot only).

Anal. Calcd. for $C_{49}H_{44}N_4O_3$: C, 79.86; H, 6.02; N, 7.60. Found: C, 79.83; H, 6.58; N, 7.32.

Compounds XV and XVI behaved quite differently on standing in 50% acetic acid at room temperature. Tr·Tr·His·Pro·OCH_3 (XV) had completely reacted after 1 hr. and yielded about equal amounts of His·Pro·OCH_3, R_f 0.24 (nin +, Pauly +, *t*-BuOCl +) and His·Pro, R_f 0.30 (nin −, Pauly +, *t*-BuOCl +). Tr·Tr·His·Pro (XVI) also had completely reacted after 1 hr. but the only product was His·Pro, R_f 0.08 (nin +, Pauly +, *t*-BuOCl +). At 90°, the initially formed dipeptide was rapidly converted to His·Pro.

Histidylproline Diketopiperazine (I).—Ditritylhistidylproline methyl ester (15.02 g., 0.02 mole) in 150 ml. of 50% acetic acid was heated 2 hr. on the steam bath and concentrated to dryness. The residue was concentrated twice more to dryness with water, slurried with water and the triphenylcarbinol (9.98 g., 96%) removed by filtration. Acetic acid was removed by passing the solution through an IR-45 ion exchange column (hydroxide form) and lyophilization of the eluate yielded the diketopiperazine (3.82 g., 82%) as a brittle foam, R_f 0.29 (nin −, Pauly +, *t*-BuOCl +, one spot only). This material proved to be extremely difficult to crystallize. On standing for 6 weeks, part of the product had solidified. From a boiling ethyl acetate extract of the partially crystallized material was obtained, on cooling, 0.12 g. of thick prisms, m.p. 167–170°. Recrystallization from ethyl acetate changed the m.p. to 168–170°. The crystalline material and the crude product behaved identically on paper chromatography; $[\alpha]^{25}D$ −66° (*c* 1, water).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C 56.39; H, 5.84; N, 24.05.

Prolylhistidine (XVII).—Carbobenzoxyproline *p*-nitrophenyl ester[17] (9.26 g., 0.025 mole), 15.86 g. (0.025 mole) of histidine *p*-nitrobenzyl ester di-*p*-toluenesulfonate and 7.6 ml. (0.055 mole) of triethylamine were dissolved in 200 ml. of methylene chloride and allowed to stand 1 week at room temperature. The reaction mixture was washed thrice with water, thrice with 0.2 *N* potassium hydroxide and with water until neutral. The organic layer was dried over magnesium sulfate and the solvent distilled to give carbobenzoxyprolylhistidine *p*-nitrobenzyl ester as a thick oil, 9.85 g. (76%), R_f 0.73 (nin −, Pauly +, *t*-BuOCl +, one spot only).

Protected dipeptide (5.43 g., 0.0104 mole) in 250 ml. of methanol plus 2.65 ml. (0.032 mole) of 12 *N* hydrochloric acid was hydrogenated over 1.2 g. of palladium black. The solution after removal of the catalyst was taken to dryness, the residue dissolved in 50 ml. of water and passed through an IR-45 anion exchange column (hydroxide form) to liberate the dipeptide from its hydrochloride salt. The eluate was distilled to dryness and the residue crystallized by dissolving in 3 ml. of water and adding 30ml. of methanol. Prolylhistidine was obtained as fine prisms, 1.90 g. (72%), m.p. 191–192° (effervescence), R_f 0.12 (nin + (yellow), *t*-BuOCl +, one spot only); $[\alpha]^{25}D$ −22° (*c* 1, water).

Anal. Calcd. for $C_{11}H_{16}N_4O_3 \cdot 1/2H_2O$: C, 50.56; H, 6.56; N, 21.45. Found: C, 50.41; H, 6.57; N, 21.41.

A sample was dried 2 hr. at 100° under high vacuum.

Anal. Calcd. for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21. Found: C, 52.28; H, 6.42; N, 22.16.

(16) B. F. Erlanger, H. Sachs, and E. Brand, *J. Am. Chem. Soc.*, **76**, 1806 (1954).

(17) M. Bodanszky and V. duVigneaud, *ibid.*, **81**, 5688 (1959).

The Effect of Initiators on the "Homogeneous" Friedel–Crafts Isomerization of Hexane

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The effect of hexene-1 and of ethylene and hydrogen bromide as co-catalysts with aluminum bromide for the isomerization of an *n*-paraffin has been studied. A kinetic analysis of the data with ethylene and hydrogen bromide suggests a dual role for the co-catalyst: that of facilitating carbonium ion formation and increasing rates at low initiator levels, and of facilitating inhibition at high initiator levels due to allylic hydride transfer between ionic and olefinic intermediates. The postulate of allylic hydride transfer leading to inhibition is supported by the effect of hexene-1 upon the reaction.

The structural rearrangement of a paraffin is customarily facilitated by the use of strong acid catalysts. Usually the reaction is conducted in a two-phase system since highly polar acids are not particularly compatible with nonpolar paraffins. Such systems are neither easily adaptable to kinetic analysis, nor to mechanistic interpretation of reaction paths.

This paper is primarily concerned with the problem of understanding the effect of a co-catalyst upon the rate of isomerization of an *n*-paraffin. The studies were

carried out in a "homogeneous" system comprised of aluminum bromide and trichlorobenzene, similar to that used by H. C. Brown[1] in studies of Friedel–Crafts alkylation.

The most important finding of this work is that co-catalysts exert a dual role in both promoting and inhibiting carbonium ion processes, the latter leading us to postulate allylic hydride transfer as a new mechanism of inhibition in these reactions. This conclusion is drawn from the behavior of ethylene and hydrogen bromide as a co-catalyst, and of hexene-1 as an inhibitor.

Several other conventional co-catalysts and inhibitors were also included in these studies and the results are reported without extensive discussion. It might, however, be noted that benzene and methylcyclohexane behaved in a manner generally expected of inhibitors and that water exerted a strong catalytic effect.[2]

Experimental

Aluminum bromide was prepared by doubly distilling commercially available material and collecting the heart cut of the second distillate in a flask which was sealed and then transferred to a drybox. The flask was broken under a nitrogen atmosphere, and the aluminum bromide was transferred to sealed bottles for storage. The drybox was continually purged with dry nitrogen during transferring operations.

The trichlorobenzenes (TCB) were obtained from the Matheson, Coleman and Bell Co. 1,2,3-Trichlorobenzene and 1,3,5-trichlorobenzene were examined by infrared spectroscopy and found to be spectrally pure. 1,2,4-Trichlorobenzene, research grade, was found to contain small quantities of the other two isomers, but the amount was usually less than 5% in different lots of commercially available material.

Technical grade 1,2,4-trichlorobenzene which contained 84% 1,2,4-trichlorobenzene, 7% 1,2,3-trichlorobenzene, and 9% 1,3,5-trichlorobenzene was used. Attempts were made to purify by distillation the technical grade 1,2,4-trichlorobenzene and the research grade 1,2,4-trichlorobenzene using a 40-plate column and a reflux ratio of 10:1, but it was not possible to lower significantly the impurity level, and these substances were simply dried and stored until needed.

Oxygen was used as a promoter by metering a dry air stream through the solution, and determining the amount of gas absorbed by difference between the total gas in and out. Hydrogen-sulfide, Matheson, 99.5% minimum purity, was added to the solutions from a constant volume system, a drop in pressure being used to determine the quantity of gas added. Benzene and methylcyclohexane were shaken with sulfuric acid, found free of impurities by gas chromatography, and stored over a zeolitic adsorbent to remove moisture and trace amounts of any olefins. No impurity was found in hexene-1 by gas chromatography or infrared spectroscopy, and it was simply dried until ready for use. Ethylene (Matheson 99.5% minimum purity) was used without further treatment.

Phillips research grade *n*-hexane was stored over a zeolitic adsorbent after no impurities were found by gas chromatography. In some experiments, particular pains were exerted to maintain a "dry" system, while in others a water-saturated hexane solution, which contained about 100 p.p.m. of water, was used to provide a reproducible amount of catalytic activity. All inhibitors were studied using a water-saturated hexane solution.

Isomerization reactions were conducted in a three-neck flask at 37.8° and 65.5°. The flask was fitted with a stirrer, a gas bag connected to an air-cooled condenser, and a rubber diaphragm through which a hypodermic could be inserted for withdrawing samples or adding promoters or inhibitors. A nitrogen atmosphere was used with the wet systems. The glass flask was baked for 16 hr. at *ca.* 200°, and it was transferred directly to the drybox before loading reagents for "dry" runs. This procedure was fairly successful in removing moisture from the glass walls, and blank runs in flasks so treated showed very little activity.

(1) H. Jungk, C. R. Smoot, and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 2185 (1960).

(2) The nature of the water–aluminum bromide system is the subject of a separate communication.

Results

Preliminary experiments showed that 1,2,4-trichlorobenzene and the mixtures of trichlorobenzenes employed in these studies were stable in the presence of the most active catalysts studied. The solvents, therefore, merely provided the medium for reaction, and, aside from influencing the stability of reactants and intermediates by normal solvation, are assumed to have behaved as essentially inert diluents.

Ethylene + Hydrogen Bromide.—Ethylene was added to a dry *n*-hexane–aluminum bromide–trichlorobenzene system containing a hydrogen bromide/aluminum bromide mole ratio of 2/1. Increasing the ethylene/aluminum bromide ratio from 0.005/1 to 2/1 increased the initial isomerization rate 20-fold (0.11 to 2.4 hr.$^{-1}$), Table 1. At the high ethylene ratio, the rapid initial rate was followed by complete cessation of reaction after only a little conversion. Isomerization at ethylene/aluminum bromide ratios of 1/1 and 2/1 also led to 15 and 32% conversion of *n*-hexane into heavier and lighter compounds within 30 min., but no further degradation with time. These results suggest that inhibitors appear after a small amount of conversion, and further that the inhibitor concentration is related to the rate of isomerization as opposed to the extent of reaction.

TABLE I

EFFECT OF INHIBITORS AND PROMOTERS ON *n*-HEXANE ISOMERIZATION

Temp., 65.5°, 25 cc. 1,2,4-trichlorobenzene, 25 cc. *n*-hexane
k_{iso} calculated assuming isomerization is irreversible

$H_2O/AlBr_3$, mole ratio[a,h]	0.0	0.13	0.25	0.50
k_c,[g] hr.$^{-1}$	.03	.26	.42	.69
$O_2/AlBr_3$, mole ratio[a,i]	.7[b]	.8	3.1	...
k_{iso},[d] hr.$^{-1}$	.068	.55	0.36	...
$C_2H_4/AlBr_3$, mole ratio[a,f,h]	.005	.05	1	2
k_{iso},[d] hr.$^{-1}$	.11	.42	1.3	2.4
$H_2S/AlBr_3$, mole ratio[a,i]	0	.05	0.1	0.15
k_{iso},[d] hr.$^{-1}$	.13	.087	.048	.015
$C_6H_6/AlBr_3$, mole ratio[c,i]	0	.01	.1	...
k_{iso},[d] hr.$^{-1}$	.31[e]	.10	.024	...
$C_7H_{14}/AlBr_3$, mole ratio[c,h]	0	.01	...	...
k_{iso},[d] hr.$^{-1}$	.31[e]	.12	...	...

[a] 0.05 mole $AlBr_3$. [b] $N_2/AlBr_3$, mole ratio. [c] 0.1 mole $AlBr_3$. [d] k_{iso} calculated for initial two hours or less of reaction time. Data deviate from first-order plots at higher reaction times. [e] Mean of two experiments. [f] Mole ratio $HBr/AlBr_3$ = 2. [g] Rate constant for cracking of *n*-C_6. [h] Technical grade 1,2,4-trichlorobenzene. [i] Research grade 1,2,4-trichlorobenzene.

Hexene-1 was studied as an inhibitor over a wet *n*-hexane–aluminum bromide–trichlorobenzene system. Although promotion was originally anticipated, the extent and rate of isomerization consistently decreased as the hexene-1/aluminum bromide ratio was raised from 0.01/1 to 5/1 (Fig. 1). Thus hexene-1 was found to be an extremely strong inhibitor of hexane isomerization.

Other Promoters and Inhibitors—Benzene and methylcyclohexane, established inhibitors of carbonium ion processes, behaved as inhibitors in the homogeneous system. Hydrogen sulfide also inhibited, while oxygen

and water promoted the isomerization. These data are summarized in Table I.

Discussion

The role of promoters and inhibitors upon the isomerization of *n*-hexane may be conveniently interpreted in terms of the results obtained with ethylene + hydrogen bromide as a promoter, and hexene-1 as an inhibitor.

A general scheme for the initiation and propagation of an ionic isomerization chain might be the following.[3]

Initiation

$$\text{Initiator} \xrightarrow{k_1} R^+ \qquad (1)$$

Propagation

$$n\text{-}C_6H_{14} + R^+ \xrightarrow{k_2} s\text{-}C_6H_{13}^+ + RH \qquad (2)$$

$$s\text{-}C_6H_{13}^+ \xrightarrow{k_3} t\text{-}C_6H_{13}^+ \qquad (3)$$

$$t\text{-}C_6H_{13}^+ + n\text{-}C_6H_{14} \xrightarrow{k_4} i\text{-}C_6H_{14} + s\text{-}C_6H_{13}^+ \qquad (4)$$

For the termination step of such a sequence, we would now like to postulate allylic hydride transfer from a hexene, with which the ions should be in equilibrium, to a chain carrying ion.[4] Such a reaction would not only stop a chain but would also lead to the formation of an allylic carbonium ion, which might well form a relatively stable salt of the type $C_6H_{11}^+AlBr_4^-$ (equations 5 and 6).

Termination-inhibition

$$C_6H_{13}^+ \underset{}{\overset{k_5}{\rightleftharpoons}} C_6H_{12} + H^+ \qquad (5)$$

$$C_6H_{12} + C_6H_{13}^+ \xrightarrow{k_t} C_6H_{14} + C_6H_{11}^+ \qquad (6)$$

Equations 1 through 6 provide a convenient qualitative and quantitative basis for the explanation of maxima as the co-catalyst concentration is increased, as well as for the behavior of hexene-1. When large amounts of initiators and hence, chain carriers are employed, the possibility of ions reacting with olefins with which they exist in equilibrium increases. Assuming ion–olefin equilibrium as in equation 5, and inhibition to follow equation 6, it is easy to show that the rate of inhibition will increase with the square of the ion concentration. Since the rate of isomerization is directly proportional to this ion concentration, increasing the initiator concentration will cause the catalytic activity to pass through a maximum. At low initiator levels, activity increases with concentration because few bimolecular encounters between ions and olefins are occurring. At high initiator concentrations, however, reactions between olefins and ions rapidly become the predominating factor, and activity decreases with increasing ion concentration.

Now, if in the case of ethylene, the initiation rate is proportional to the ethylene concentration, equation 1, and the termination rate is proportional to the square of the ion concentration, equations 5 and 6, then the steady state ion concentration is proportional to the one half power of the ethylene concentration, equation 7. This predicts that the initial isomerization rate will be linear in $[C_2H_4]^{1/2}$ (equation 8), and is in excellent agreement with the results shown in Fig. 2.

$$k_i\,[C_2H_4] = k_t[C_6H_{13}^+]^2 \qquad (7)$$

Rate of propagation

$$k_p[C_6H_{13}^+]\,[n\text{-}C_6] = \left[\frac{k_i}{k_t}\right]^{1/2} [C_2H_4]^{1/2}[n\text{-}C_6] \qquad (8)$$

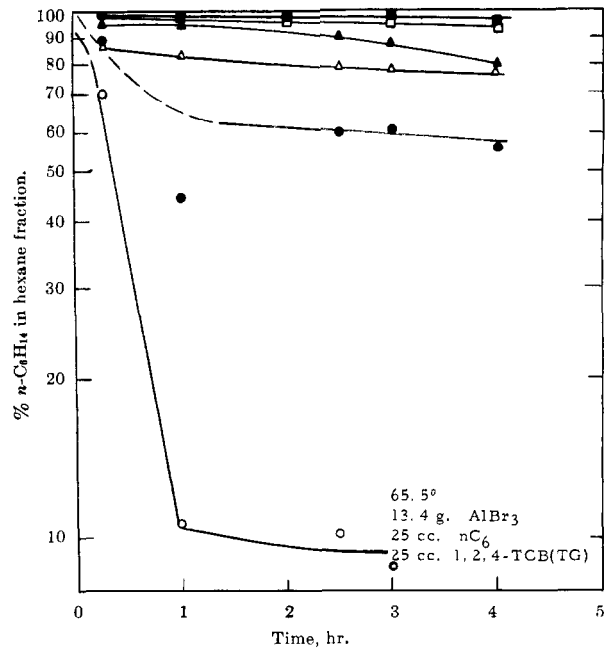

Fig. 1.—Hexene-1 inhibits the isomerization of *n*-hexane. ○ = none, ● = 0.01/1, △ = 0.1/1, ▲ = 0.5/1, □ = 1/1, ■ = 5/1 (mole ratio, hexene-1/$AlBr_3$).

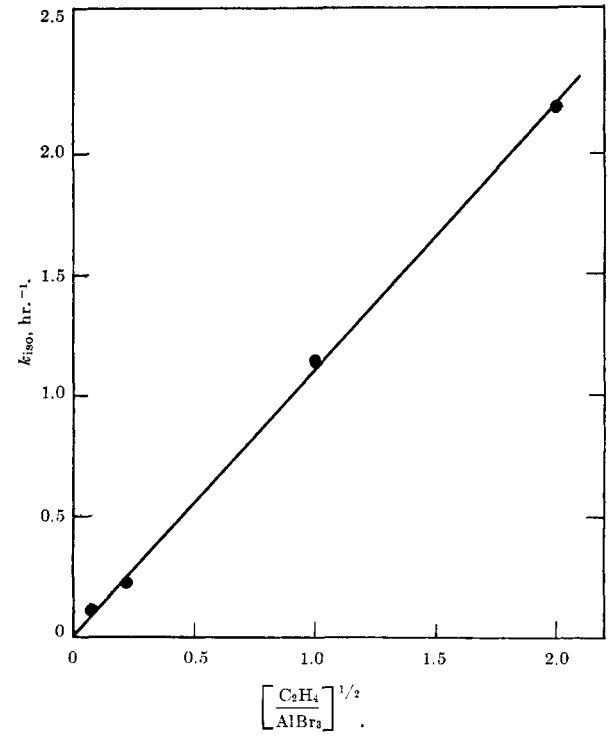

Fig. 2.—Isomerization rate is half order in ethylene concentration.

(3) H. S. Bloch, H. Pines, and L. Schmerling, *J. Am. Chem. Soc.*, **68**, 153 (1946).

(4) P. D. Bartlett, F. E. Condon, and A. Schneider, *ibid.*, **66**, 1531, (1944).

It might also be noted that the data, within experimental error, extrapolates to zero rate in the absence of ethylene, thus suggesting that hydrogen bromide does not promote aluminum bromide in the absence of trace quantities of olefin.

In summary, a co-catalyst seems to play a dual role in Friedel–Crafts catalysis in both increasing the number of chain carriers and in facilitating bimolecular chain stopping reactions.

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Reactions of α-Hydroxy Ketones with Ammonia[1,2a]

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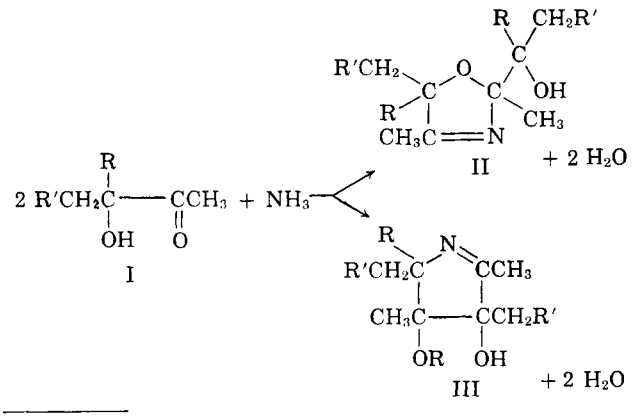
α-Hydroxy ketones react with ammonia to yield 3-oxazolines and 3,4-dihydro-2*H*-pyrrolenine-3,4-diols. The structure of the α-hydroxy ketone determines which of the two isomeric heterocyclic compounds will be formed. The 3-oxazoline structure represents a new series of heterocyclic compounds.

In 1956, Asinger and Thiel[3] published the first of a series of articles on the concomitant reactions of ketones, ammonia, and sulfur. Their reactions led primarily to the formation of 3-thiazolines. They proposed a mechanism whereby an α-mercapto ketone is formed as an intermediate.[4] In later work[5] this proposed intermediate was shown to be correct, as α-mercapto carbonyl compounds condensed with carbonyl compounds to form 3-thiazolines. Their reactions were extended to cover the formation of *m*-thiazines from β-mercapto ketones.[6]

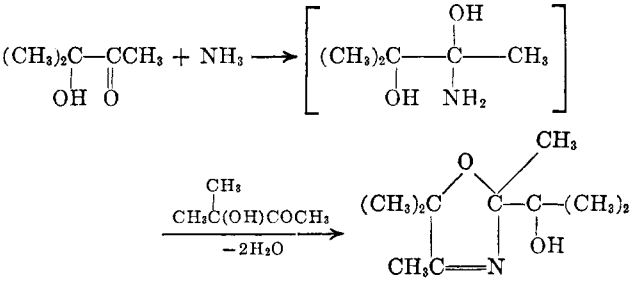
The analogy to hydroxy ketones is apparent, and research was conducted on the possibility of forming 3-oxazolines from a reaction of α-hydroxy ketones with ammonia and carbonyl compounds. The reactions, however, proved to be more complex than those of the sulfur analogs, due primarily to the high reactivity of α-hydroxy ketones with nucleophilic reagents.[7]

The general reaction of α-hydroxy ketones with ammonia is illustrated.

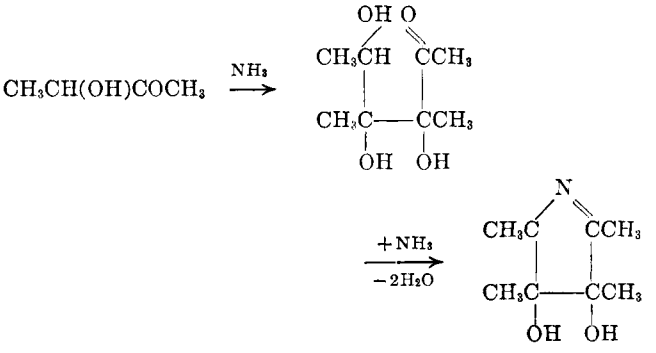


In this reaction R must be alkyl for the formation of II, and for III it must be hydrogen; R′ can be either alkyl or hydrogen.

The mechanism proposed for the formation of II is exemplified by the formation of 2-(1-hydroxyisopropyl)-2,4,5,5-tetramethyl-3-oxazoline (II, R = CH_3, R′ = H) from the reaction of 3-hydroxy-3-methyl-2-butanone with ammonia.



If R in formula I is hydrogen, the reaction apparently proceeds through an aldol condensation and final condensation of the γ-hydroxy ketone to form the isomeric 3,4-dihydro-2-*H*-pyrrolenine-3,4-diol.



The third possibility, an α-hydroxy ketone holding two α-hydrogen atoms on the hydroxy-carbon atom, should theoretically lead to pyrroleninediols. With acetol, however, extensive polymerization precluded any isolable product.

The 3-oxazolines represent a new series of heterocyclic compounds, as the only reported 3-oxazolines are actually the enolic ethers of the corresponding 4-

(1) The authors are indebted to The Petroleum Research Fund (PRF grant #685-A) for the support of the work reported in this paper.

(2) (a) Taken from the M.S. thesis of D.D.L., South Dakota School of Mines and Technology, 1962. (b) Present address, Eastman Kodak Company, Rochester, N. Y.

(3) F. Asinger, *Angew. Chem.*, **68**, 413 (1956).

(4) F. Asinger, M. Thiel, and E. Pallas, *Ann.*, **602**, 37 (1957).

(5) F. Asinger, M. Thiel, and G. Esser, *ibid.*, **610**, 33 (1957); M. Thiel, F. Asinger, and K. Schmiedel, *ibid.*, **611**, 121 (1958).

(6) F. Asinger, M. Thiel, and W. Horingklee, *ibid.*, **610**, 1 (1957); M. Thiel and F. Asinger, *ibid.*, **610**, 17 (1957).

(7) The reaction rate constant for the reduction of 3-hydroxy-2-butanone with sodium borohydride is equivalent to that of propionaldehyde: E. H. Jensen, "Sodium Borohydride—Potassium Borohydride," R. C. Wade, ed., Metal Hydrides, Inc., 1958, p. 19.