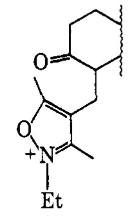
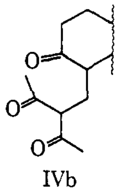
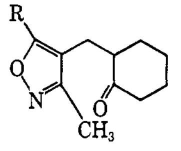
The first method examined for the crucial transformation needed for the conversion, *e.g.*, of IV into V, involved quaternization of IV with triethyloxonium fluoroborate,[6] followed by treatment with aqueous base. The latter reaction could proceed by hydration of the imonium structure IVa leading to the eventual formation of a β-diketone (*cf.* IVb) which, following cleavage and cyclization (in either order), would then produce the tricyclic diketone V. In fact, such a transformation could be realized, albeit only in ~35% yield, by allowing the quaternary salt IVa to stand overnight with 5% sodium hydroxide. It is clear that an alternative reaction, condensation of one of the methyl groups of IVa with the neighboring carbonyl group, competes with hydration. In fact, such a condensation becomes the major process when the basic solution of the salt is heated immediately. For instance, treatment of VI, R = CH_3, mp 56–57°,[7] with triethyloxonium fluoroborate followed by refluxing with 1 *N* NaOH for 2 hr gave, after chromatography of the base-soluble fraction on silica gel, a 47% yield of 3-hydroxy-2-acetyl-5,6,7,8-tetrahydronaphthalene (VII), mp 70–71° (lit.[9] 72–73°), further identified by its typical spectral properties.[10]



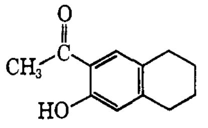
IVa



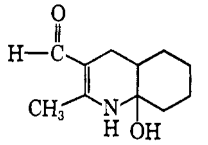
IVb



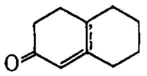
VI



VII



VIII



IX

A more satisfactory method for the transformation of the isoxazole ring was achieved by hydrogenolysis. For example, the isoxazole ring of VI, R = H[7] (2,4-dinitrophenylhydrazone mp 161–163°[8]), was cleaved with hydrogen and palladium–charcoal in 1:1 ethyl acetate–triethylamine. The solid which precipitated was separated from the catalyst with methanol and proved to be the cyclic vinylogous carbinolamide VIII, mp 165–174°,[3,11] $\lambda_{\max}^{\text{EtOH}}$ 302 mμ (log ϵ 4.41),[12] as shown by the absence of saturated carbonyl absorption in the infrared ($\lambda_{\max}^{\text{KBr}}$ 2.3, 3.13, 6.35, and 6.62 μ). The carbinolamide was transformed in high yield, by refluxing with 10% KOH for 1.5 hr, into the equilibrium mixture of $\Delta^{1,9}$- and $\Delta^{9,10}$-2-octalone (IX).[8] Similarly, starting with VI, R = CH_3, hydrogenolysis with palladium (which required 48 hr in this case)[13] and aqueous base treatment of the intermediate carbinolamide gave 50% of the octalone IX.[14]

The isoxazole route to annelation is thus established. Although either 5-unsubstituted or 5-substituted isoxazoles seem suitable for the purpose, we have concentrated further efforts[15] on the 5-substituted systems because of the higher yield obtained with II, R = CH_3, than with II, R = H, in the alkylation of α,β-unsaturated ketones.[16]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of this work.

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(6) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

(7) This was prepared either by alkylation of the pyrrolidine enamine of cyclohexanone (dioxane, 17 hr)[8] or *via* alkylation of 2-carbethoxycyclohexanone, followed by acid hydrolysis.

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(9) M. P. O'Farrell, D. M. S. Wheeler, M. M. Wheeler, and T. S. Wheeler, *J. Chem. Soc.*, 3986 (1955).

(10) *Cf.* L. Doub and J. M. Vandebelt, *J. Am. Chem. Soc.*, **71**, 2415 (1949).

(11) The wide melting point is probably due to very easy dehydration and/or epimeric or tautomeric mixtures.

(12) *Cf.* K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).

(13) Hydrogenolysis of the isoxazole ring is much faster with Raney nickel which is the catalyst of choice for fully substituted isoxazoles (*cf.* G. Stork and J. E. McMurry, *ibid.*, **89**, 5463 (1967).

(14) Variable amounts of pyridines are also produced unless oxygen is rigorously excluded from the medium. These may become the major products under somewhat different conditions. *Cf.* M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *ibid.*, **89**, 5460 (1967).

(15) See G. Stork and J. E. McMurry, *ibid.*, **89**, 5461, 5464 (1967).

(16) The ease with which the annelation reaction is carried out in the case of VI, R = H, → IX (*vide supra*) made it nevertheless worthwhile to study the case of III, R = H, mp 85–87°.[3] Two moles of hydrogen was taken up under the usual conditions and the crystalline intermediate was transformed into V in 70% yield after refluxing with 20% potassium hydroxide for 3 hr.

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Received August 11, 1967

Tranformation of 4-(3-Oxoalkyl)isoxazoles into Pyridines

Sir:

The stability of 3-substituted isoxazoles under a variety of chemical reactions, coupled with the lability of their nitrogen–oxygen linkage under special conditions, makes possible the use of these isoxazoles as masked ketoalkyl functions in the synthesis of complex molecules. We have, for instance, devised a new annelation method which makes use of 4-(3-oxoalkyl)-isoxazoles,[1–4] while Casnati, *et al.*,[5] have recently reported new furan and pyrone syntheses *via* 3-hydroxyalkylisoxazoles.

This communication deals with a new pyridine synthesis *via* 4 (3-oxoalkyl)isoxazoles which are easily prepared[2] by alkylation of ketones with the readily available 4-chloromethyl-3,5-dimethylisoxazole.[6] During the investigation of the isoxazole annelation[2] we found that hydrogenation of 2-(3,5-dimethyl-4-isoxazolylmethyl)cyclohexanone (I) gives an equilibrium mixture (IIa–c) which upon heating with base furnishes

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(1) G. Stork, *Pure Appl. Chem.*, **9**, 931 (1964).

(2) G. Stork, S. Danishefsky, and M. Ohashi, *J. Am. Chem. Soc.*, **89**, 5459 (1967).

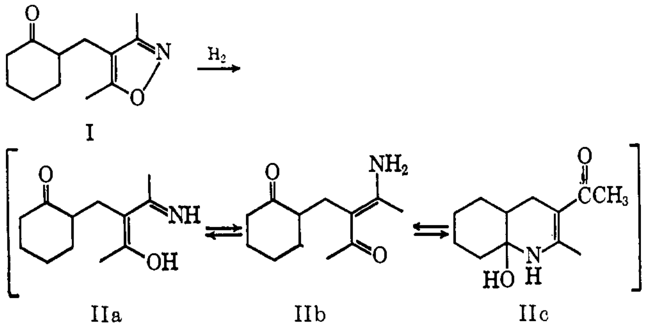
(3) G. Stork and J. E. McMurry, *ibid.*, 89, 5461 (1967).

(4) G. Stork and J. E. McMurry, *ibid.*, 89, 5463 (1967).

(5) G. Casnati, A. Quilico, A. Ricca, and V. Finzi, *Gazz. Chim. Ital.*, **96**, 1073 (1966).

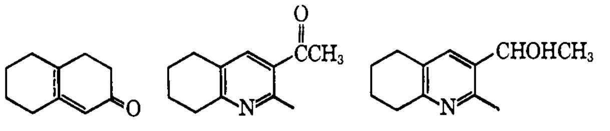
(6) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2376 (1958).

a small amount of pyridines IVa and IVb,[7] in addition to the major product, $\Delta^{1,9}$-octalone-2 (III). It became apparent that, if oxidation were to follow dehydration of IIc, β-acylpyridines (*cf.* Va) should be formed in high yield. The dehydration of carbinolamines such as IIc can be brought about by heating with base.[3] It would be expected to be particularly easy when a carbonyl group is present in the β position to the hydroxyl. In such cases, we have found that dehydration takes place under the conditions of the hydrogenolysis.



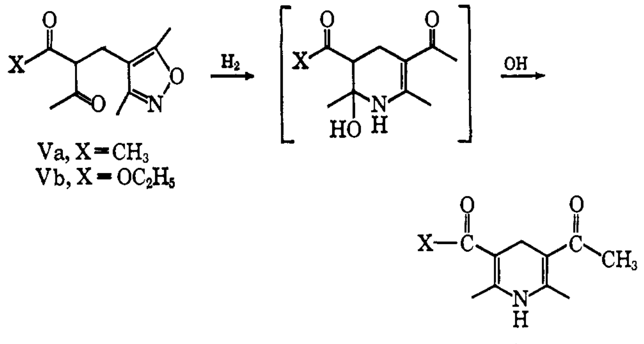
I

IIa IIb IIc



III IVa IVb

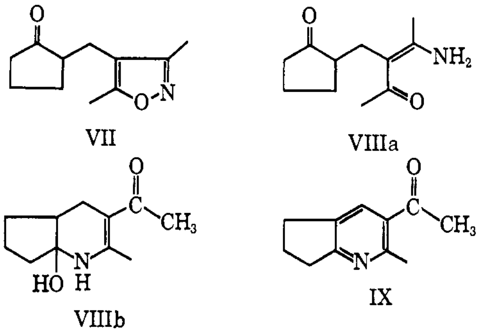
For instance, alkylation of acetylacetone with 4-chloromethyl-3,5-dimethylisoxazole gave Va, bp 134–144° (0.2 mm), catalytic hydrogenation of which in the presence of Pd–C and triethylamine afforded the known[8] dihydropyridine VIa, mp 209–216°, in 74% yield. The ethyl acetoacetate analog Vb, prepared from ethyl acetoacetate and 4-chloromethyl-3,5-dimethylisoxazole, behaved similarly and yielded ethyl 5-acetyl-2,6-dimethyl-1,4-dihydro-3-pyridinecarboxylate (VIb), mp 148–150°, $\lambda_{\max}^{\mathrm{EtOH}}$ 244, 265 and 392 mμ (log ϵ 3.90, 3.62, and 3.57, respectively), $\nu_{\max}^{\mathrm{Nujol}}$ 1700, 1650 cm^{-1}, $\delta^{\mathrm{CDCl_3}}$ 1.30 (3 H, triplet, J = 7 cps), 2.17 (9 H, singlet), 3.38 (2 H, singlet), 4.22 (2 H, quartet, J = 7 cps), and 5.80 (1 H, b), which was converted (63% yield based on Vb) into the known ethyl 5-acetyl-2,6-dimethyl-3-pyridinecarboxylate[9] by treatment with sodium nitrite and hydrochloric acid.



Va, X = CH_3
Vb, X = OC_2H_5

VIa, X = CH_3
VIb, X = OC_2H_5

In the case of 3-oxoalkylisoxazoles such as I dehydration of the hydrogenolysis product (IIa ⇆ IIb ⇆ IIc) took place under the acidic conditions used in the oxidation step. Thus, catalytic hydrogenation of I followed by treatment with sodium nitrite and hydrochloric acid gave 3-acetyl-2-methyl-5,6,7,8-tetrahydroquinoline (IVa) (mp 46–47°, $\nu_{\max}^{\mathrm{Nujol}}$ 1685 cm^{-1}, $\lambda_{\max}^{\mathrm{EtOH}}$ 245 and 285 mμ (log ϵ 3.07 and 3.67, respectively); semicarbazone mp 198–199°) in 64% yield. Enamine alkylation[9] of cyclopentanone with 4-chloromethyl-3,5-dimethylisoxazole gave the cyclopentanone VII (bp 138–148° (0.7 mm), $\nu_{\max}^{\mathrm{liquid\ film}}$ 1740 cm^{-1}, $\lambda_{\max}^{\mathrm{EtOH}}$ 223 mμ (log ϵ 3.67); semicarbazone mp 211–214°), which in turn, after hydrogenation followed by reflux in aqueous acetate buffer, furnished 2-acetyl-2-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine (IX) (mp 28–30°, $\nu_{\max}^{\mathrm{liquid\ film}}$ 1675 cm^{-1}, $\lambda_{\max}^{\mathrm{EtOH}}$ 243 and 288 mμ (log ϵ 3.50 and 3.59, respectively), $\delta^{\mathrm{CDCl_3}}$ 2.58 (3 H, singlet), 2.72 (3 H, singlet), and 7.80 (1 H, singlet); picrate mp 132–134°) in 60% yield. The formation of a pyridine without any oxidative reagent makes it obvious that air oxidation of the dihydropyridine must have taken place during the dehydration process. This assumption was confirmed in the following manner: the hydrogenation product of VII, which must exist to a considerable extent in the open form VIIIa, as shown by the presence of a strong absorption at 1735 cm^{-1} in its infrared spectrum, was allowed to stand for several days at room temperature. Under these conditions cyclization, dehydration, and air oxidation proceeded spontaneously and VIIIa was converted into the crystalline pyridine IX in more than 50% yield based on VII.[10,11]



VII VIIIa

VIIIb IX

These results establish the generality of this synthesis of β-acylpyridines *via* 4-(3-oxoalkyl)isoxazoles. Application of the method to the synthesis of more complex molecules will be published elsewhere.

Acknowledgment. This research was supported in part by the National Institutes of Health and the National Science Foundation. A Fulbright travel grant to M. Ohashi is also gratefully acknowledged.

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(7) These substances, obtained from the basic fraction after cyclization, were separated by chromatography. For the characterization of IVa *vide infra;* IVb was characterized by its mass spectral fragmentation and spectral properties.

(8) M. Scholz, *Chem. Ber.*, 30, 2295 (1897).

(9) H. Henecka, *ibid.*, 82, 41 (1949).

(10) *Cf.* G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 85, 207 (1963).

(11) All new crystalline compounds gave satisfactory elemental analyses. All new liquid compounds gave correct molecular ions in their mass spectra.

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Received August 11, 1967

A General Synthesis of 4-Isoxazolecarboxylic Acids

Sir:

One of the steps in the cyclohexenone synthesis which we have outlined elsewhere consists in the alkylation of