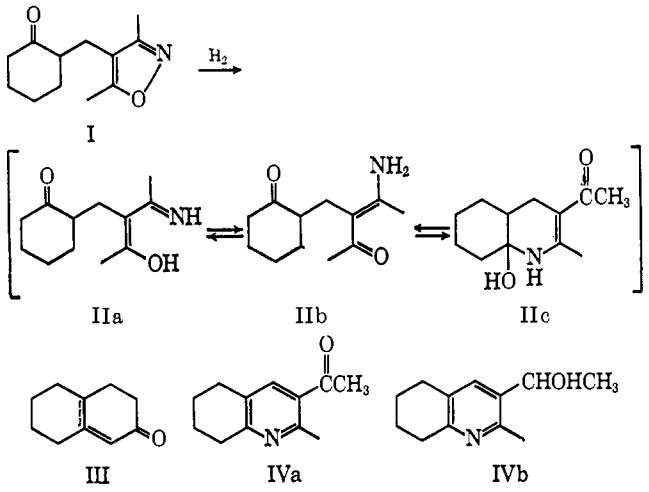
a small amount of pyridines IVa and IVb,[7] in addition to the major product, $\Delta^{1,9}$-octalone-2 (III). It became apparent that, if oxidation were to follow dehydration of IIc, β-acylpyridines (*cf.* Va) should be formed in high yield. The dehydration of carbinolamines such



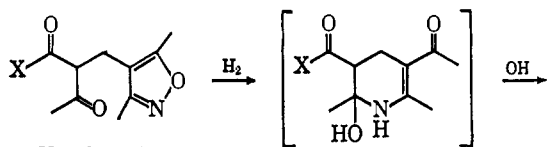
I

IIa IIb IIc

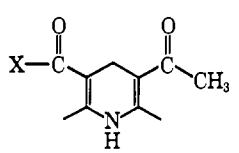
III IVa IVb

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.

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°, λ_{max}^{EtOH} 244, 265 and 392 mμ (log ε 3.90, 3.62, and 3.57, respectively), ν_{max}^{Nujol} 1700, 1650 cm^{-1}, δ^{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.

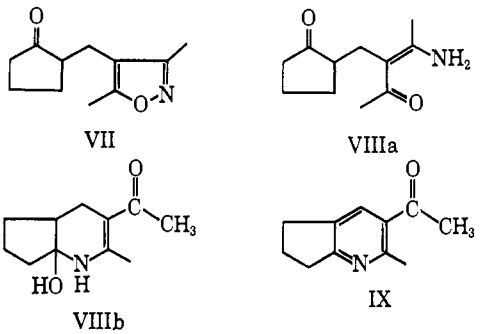


Va, X = CH_3
Vb, X = OC_2H_5



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°, ν_{max}^{Nujol} 1685 cm^{-1}, λ_{max}^{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), $\nu_{max}^{liquid\ film}$ 1740 cm^{-1}, λ_{max}^{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°, $\nu_{max}^{liquid\ film}$ 1675 cm^{-1}, λ_{max}^{EtOH} 243 and 288 mμ (log ε 3.50 and 3.59, respectively), δ^{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



VII VIIIa

VIIIb IX

converted into the crystalline pyridine IX in more than 50% yield based on VII.[10,11]

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.

(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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A General Synthesis of 4-Isoxazolecarboxylic Acids

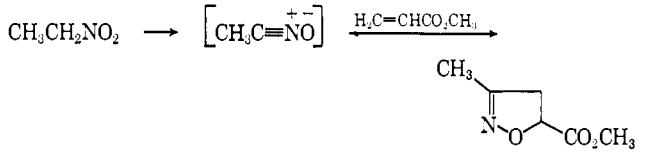
Sir:

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

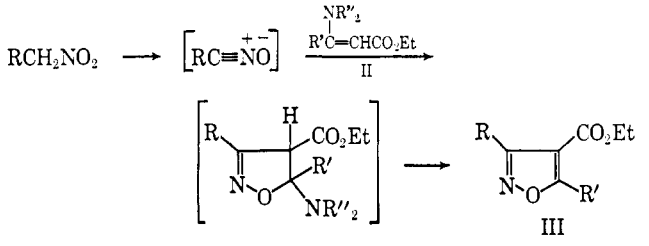
a carbonyl compound with a 3-alkyl-4-halomethylisoxazole.[1] The existing method for the synthesis of such substances, the chloromethylation of 3-alkylisoxazoles,[2] cannot be used with substituents which are incompatible with the drastic conditions required for that operation.

The most desirable general route to 3-alkyl-4-halomethylisoxazoles would involve the intermediacy of the corresponding 4-isoxazolecarboxylic acids or esters.[3] The present communication reports a general synthesis of considerable flexibility for these substances.

It is known that the potential nitrile oxide represented by a mixture of nitroethane, triethylamine, and phenyl isocyanate[4] reacts with methyl acrylate to form methyl 3-methyl-4,5-dihydro-5-isoxazolecarboxylate (I).[5] We anticipated that acrylic ester derivatives with an electron-releasing group in the β position might reverse this orientation. We have now found that the readily accessible derivatives of β-aminoacrylic esters take part in this reaction to give directly 4-isoxazolecarboxylic esters in which a variety of groups can be present in the 3 and the 5 positions.[6] The aminoacrylic ester necessary for the synthesis of 5-unsubstituted isoxazoles is obtained by addition of pyrrolidine to ethyl propiolate, while the β-substituted amino esters are simply the enamines derived from the appropriate β-keto esters.



I

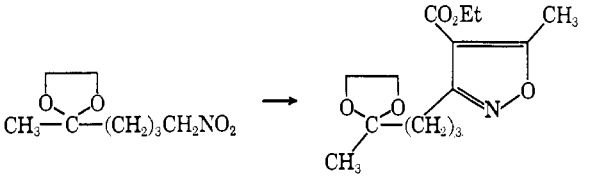


III

As an illustration, a mixture of 3.6 g of ethyl β-pyrrolidinoacrylate (II, R′ = H),[7] 1.75 g of nitroethane, and 5 g of phenyl isocyanate was treated with 0.5 ml of triethylamine in 15 ml of benzene. Stirring at room temperature for 5 hr and refluxing for 0.5 hr, followed by filtration of the diphenylurea and distillation, gave ethyl 3-methyl-4-isoxazolecarboxylate (III, R = CH_3, R′ = H) in 85% yield (bp ~110° (3 mm), nmr τ 0.98 (1 H, singlet), 5.54 (2 H, quartet), 7.55 (3 H, singlet), and 8.58 (3 H, triplet). Hydrolysis with aqueous sodium hydroxide gave 3-methyl-4-isoxazolecarboxylic acid, mp 183–183.5°.[8]

Similarly, the pyrrolidine enamine derived from ethyl benzoylacetate (II, R′ = C_6H_5) gave, with nitroethane, an ester (III, R = CH_3; R′ = C_6H_5) saponified to the known[9] 3-methyl-5-phenylisoxazole-4-carboxylic acid, mp 188–189°.

The generation of the nitrile oxide can also be done with phosphorus oxychloride at 0° in chloroform.[10] Using this procedure, the pyrrolidine enamine of ethyl acetoacetate (II, R′ = CH_3) and nitroethane gave ethyl 3,5-dimethyl-4-isoxazolecarboxylate (III, R = R′ = CH_3), bp ~75° (0.1 mm), in 72% yield (nmr τ 5.53 (2 H, quartet), 7.25 (3 H, singlet), 7.50 (3 H, singlet), and 8.59 (3 H, triplet). The corresponding acid had mp 141–142°, as reported.[2] With the same pyrrolidine enamine and 1-nitrobutane, we similarly obtained an ester III (R = Pr, R′ = CH_3) saponified to 3-propyl-5-methylisoxazole-4-carboxylic acid, mp 114°,[11] while 1-nitropropane gave ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate (III, R = Et, R′ = CH_3), saponified to the corresponding acid, mp 120–121.5°.[11] The versatility of the new synthesis is well illustrated by the preparation of an isoxazole with an acid-labile side chain, the dioxolane of ethyl 3-(4-ketoamyl)-5-methyl-4-isoxazolecarboxylate (IV), an important intermediate for the construction of steroid and other polycyclic ring systems.[12] The required dioxolane of 6-nitro-2-hexanone (2,4-dinitrophenylhydrazone mp 115–115.5°)[11] was prepared by the reaction of the ketal of 6-bromo-2-hexanone[13] with sodium nitrite.[14] Reaction under the usual conditions, using phosphorus oxychloride in chloroform, gave in 80% yield the required ketal ester IV, characterized as the semicarbazone, mp 167–168°,[11,15] of the corresponding ketone.[16]



IV

(1) G. Stork, S. Danishefsky, and M. Ohashi, *J. Am. Chem. Soc.*, **89**, 5459 (1967); G. Stork and J. E. McMurry, *ibid.*, **89**, 5463 (1967).

(2) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, 2762 (1958).

(3) 4-Halomethylisoxazoles are easily obtained in high yield from these esters by lithium aluminum hydride reduction, followed by treatment with thionyl chloride or phosphorus tribromide.

(4) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).

(5) G. Bianchi and P. Grünanger, *Tetrahedron*, **21**, 817 (1965). The addition of nitrile oxides to acetylenic esters gives unpredictable orientation resulting either in 5- or 4-isoxazolecarboxylic acids; *cf.* A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **76**, 148 (1946). In any event, we were unable to obtain an isoxazolecarboxylic ester from the reaction of nitroethane, phenyl isocyanate, and triethylamine with ethyl propiolate.

(6) In contrast, the related β-alkoxyacrylic esters did not lead to the desired isoxazoles.

(7) F. Strauss and W. Voss, *Ber.*, **59**, 1681 (1926).

(8) 3-Methyl-4-isoxazolecarboxylic acid has been reported to melt at 121–122°.[2] This is apparently an error. Analytical and spectral data on our compound, together with its comparison with an authentic sample made by dichromate oxidation of the known 4-chloromethyl-3-methylisoxazole, leave no doubt as to its structure.

(9) M. Betti and L. Alessandri, *Gazz. Chim. Ital.*, **45**, 462 (1915).

(10) G. B. Bachman and L. E. Strom, *J. Org. Chem.*, **28**, 1150 (1963).

(11) Satisfactory analytical data were obtained on this compound.

(12) G. Stork and J. McMurry, *J. Am. Chem. Soc.*, **89**, 5464 (1967).

(13) E. P. Anderson, J. Crawford, and M. Sherrill, *ibid.*, **68**, 1294 (1946); M. Guiducci, Ph.D. Thesis, Columbia University, 1965, p 21.

(14) Procedure of N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

(15) The crude product is easily purified by chromatography on Florisil; unchanged 3-pyrrolidinocrotonate is hydrolyzed under these conditions to ethyl acetoacetate which is then removed by washing with base.

(16) We thank the National Science Foundation and the Petroleum Research Fund for their support of this work.

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