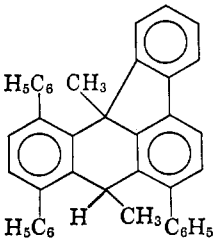
ring current, as has been suggested by both Dailey[8] and Pople.[9]

Treatment of the mixture of **1** and **2**, obtained by hydrogenation, with trifluoroacetic acid gave the cyclization product **3**, mp 213–214°.[3,10] Although this



3

side reaction prevents a quantitative measure of the relative thermodynamic stabilities of **1** and **2**, it is clear from equilibration studies of the mixture and of **1** alone in benzene–trifluoroacetic acid that **2** is the more stable tautomer. Equilibration of **1** and the hydrogenation mixture of **1** and **2**, with 0.025 *M* sodium methoxide in DMSO containing 0.02 wt % methanol[11] at room temperature, gave mixtures composed of 0.30–0.35% **1** and 99.70–99.65% **2**. However, identical treatment of **2** failed to yield **1** in amounts that could be detected by ultraviolet spectroscopy. Therefore, the equilibrium constant for the reaction **1** $\rightleftarrows$ **2** has a minimum value of about 300, and $\Delta G \leq -3.4$ kcal/mole at room temperature. Since methylene–methylanthracene tautomerism of 1,4-diphenyl-9,10-dimethylanthracene has not been detected, the introduction of two additional phenyl groups into the 5,8 positions in this compound essentially reverses the usual pattern of thermodynamic stability.[12] The observation that **2** is the more stable tautomer must mean that the loss in delocalization energy is more than compensated by relief of steric compression. In this connection the crowded nature of **1** is almost self-evident. Thus, if **1** possesses a more or less normal geometry, the distance between the nodal planes of the **1** and **8** phenyl groups is about 4.8 A, in contrast to the 7.4 A represented by twice the sum of the van der Waals radii of a methyl and two phenyl groups.[13]

(8) B. P. Dailey, *J. Chem. Phys.*, **41**, 2304 (1964).
(9) J. A. Pople, *ibid.*, **41**, 2559 (1964).
(10) There is ample precedent for this type of reaction. For an example in the anthracene series, see C. Weizmann, E. Bergmann, and L. Haskelberg, *J. Chem. Soc.*, 391 (1939).
(11) E. C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, **87**, 382 (1965).
(12) There is no real precedent for this finding in that **1** appears to be the first example of a 1,4,5,8-tetrasubstituted 9,10-dimethylanthracene. However, 1,5-dichloro-9-methylene-10-methyl-9,10-dihydroanthracene was prepared many years ago under conditions that imply thermodynamic stability by E. deB. Barnett and J. W. Cook, *Ber.*, **61B**, 314 (1928); recently P. de Bruyn [*Bull. Soc. Chim. Belges.*, **69**, 328 (1960)] has reported the synthesis of 1,5-dichloro-9,10-dimethylanthracene and has shown that this is indeed the less stable tautomer. Furthermore, both 1,4-dimethoxy-9,10-dimethylanthracene and its methylene tautomer, as well as evidence that the former is the stable isomer, have been reported by Y. Lepage, *Compt. Rend.*, **246**, 954 (1958).
(13) Supported in part by an Institutional Grant from the National Science Foundation.
(14) National Science Foundation Trainee, 1965–1967, and National Institutes of Health Predoctoral Fellow, 1967.

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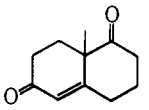
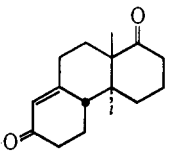
The Isoxazole Annelation Reaction. A Method for the Construction of Cyclohexenone Rings in Polycyclic Systems

Sir:

The annelation of ketones has engaged our attention for some time as we have sought a method of some generality which would serve, for instance, to transform the bicyclic dione I into the annelated tricyclic substance V. We started from the assumption that suitably



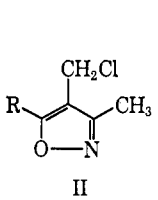
I



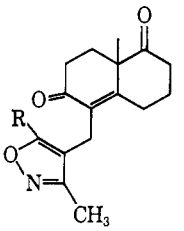
V

substituted 4-halomethylisoxazoles (*cf.* II) might be used in a new annelation method provided they could meet the following requirements: (a) they must be capable of monoalkylating α,β-unsaturated ketones (I → III); (b) the isoxazole ring must be able to survive chemical transformations in other parts of the molecule, such as hydrogenation (III → IV); (c) conditions must be found for the eventual transformation of the substituent into the desired new ring (IV → V).

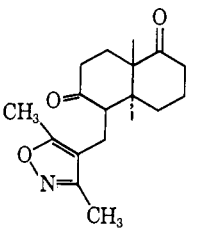
We now consider in a general way the problems involved in this scheme, while the application to the specific case of steroid syntheses is taken up in accompanying communications. We were encouraged to find that alkylation of the sodium enolate from 10-methyl-$\Delta^{1,9}$-octalin-2,5-dione (I)[1] (sodium hydride–glyme) with 3,4-dimethyl-4-chloromethylisoxazole[2] led to III, R = CH_3, mp 85–86°, λ_{max}^{EtOH} 252 mμ (ϵ 10,000), in 70% yield.[3]



II



III

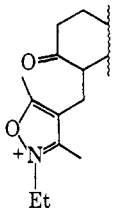


IV

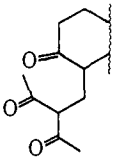
The transformation of III, R = CH_3, into IV put a severe requirement on the isoxazole ring because of its well-documented[4] lability to chemical or catalytic reduction. We found that hydrogenation with palladium–charcoal reduced the double bond considerably more rapidly than it cleaved the isoxazole ring in a variety of media. The desired *trans* stereochemistry was produced most selectively by using 3:1 ethyl acetate–triethylamine when IV, mp 164–165°,[3] was obtained in 70% yield.[5]

(1) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).
(2) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, 2762 (1958).
(3) Satisfactory analytical and spectra data were obtained for this substance.
(4) N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.*, 2, 416 (1963).
(5) In a number of other cases which we have examined, hydrogenolysis of the isoxazole ring competes with hydrogenation at other points in the molecule. We have made the potentially important observation that the rate of hydrogenolysis of isoxazole rings is *dramatically affected by the pH of the medium.* For instance, although the isoxazole ring of the simple model VI, R = H, was completely hydrogenolyzed with palladium charcoal in 3 hr in 1:1 ethyl acetate–triethylamine, it was essentially unaffected in 5:1 ethyl acetate–acetic acid in 20 hr.

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

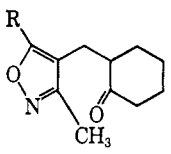


IVa

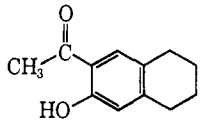


IVb

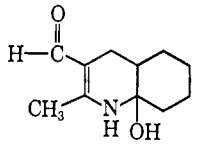
the major process when the basic solution of the salt is heated immediately. For instance, treatment of VI, R = CH_3, mp 56–57°,[7] with triethyloxonium fluoroborate followed by refluxing with 1 *N* NaOH for 2 hr gave, after chromatography of the base-soluble fraction on silica gel, a 47% yield of 3-hydroxy-2-acetyl-5,6,7,8-tetrahydronaphthalene (VII), mp 70–71° (lit.[9] 72–73°), further identified by its typical spectral properties.[10]



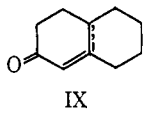
VI



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] λ_{max}^{EtOH} 302 mμ (log ε 4.41),[12] as shown by the absence of saturated carbonyl absorption in the infrared (λ_{max}^{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.

(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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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

(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).