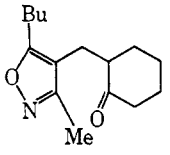
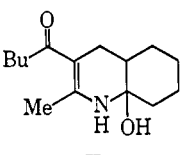
The Mechanism of the Isoxazole Annelation

Sir:

We have elucidated the sequence of steps involved in the isoxazole annelation reaction[1] and have, as a result, succeeded in extending the usefulness of this synthetic method.

An important clue was provided by the study of the annelation sequence starting with the two ketones I and II.[2] Hydrogenolysis of I (2,4-dinitrophenylhydrazone[3] mp 108–110°) over W-4 Raney nickel in ethanol gave a substance which, on the basis of its spectral properties (λ_{max}^{EtOH} 308 mμ (ε 11,500), λ_{max} 3230, 1625 cm^{-1}), was clearly the cyclic carbinolamine III.[4] Refluxing with 20% sodium hydroxide[5] in 10:1 water–ethanol for 3 hr gave a neutral[6] fraction which consisted (vpc) of 66% of $\Delta^{1,9}$-2-octalone[7] (IV, R = H) and 24% of the octalone IV, R = Pr (λ_{max}^{EtOH} 253 mμ). The same annelation sequence starting with the ketone II[2] (2,4-dinitrophenylhydrazone[3] mp 161–163°) gave neutral products shown to consist of 4% of the octalone V, R = H,


I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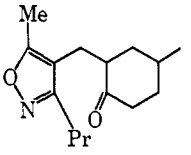
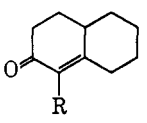

II

and 92% of the α-substituted ketone V, R = Et, λ_{max} 249 mμ, 2,4-dinitrophenylhydrazone mp 194–195°.[3]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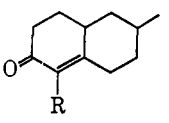
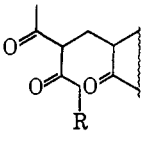
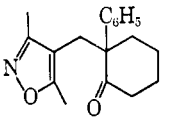
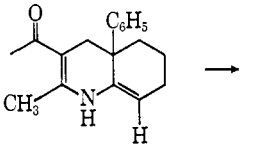

V

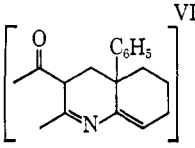

VI

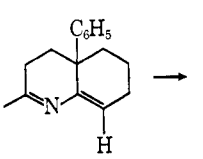
The major route to the octalones cannot involve initial hydrolysis of the cyclic carbinolamines to β-diketones such as VI. The only relevant difference between the two β-diketones (*cf.* VI) derivable from I and II is that R is propyl in the first case and ethyl in the second, a difference which cannot account for a change in the ratio of the α-substituted to the α-unsubstituted octalone from 1:3 in the first case to 23:1 in the second. In fact, the relationship between I and II and their respective major products suggests that *a mechanism must exist which leads to the incorporation in the product of the substituent initially in position 3 of the isoxazole ring, next to the nitrogen atom.*

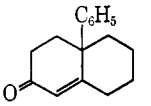
The mechanism which was devised to account for these observations is illustrated by the annelation sequence starting with the ketone VII, mp 133–133.5°,[3] in which the angular phenyl group was used to prevent the possible aromatization of various intermediates to pyridines.


VII


VIII


IX


X


XI

Evidence for this mechanism was obtained as follows. Quantitative dehydration of the solid cyclic carbinolamine from the usual hydrogenolysis of VII took place quantitatively, merely by shaking its ether solution for a few minutes with 10% aqueous sodium hydroxide, to give the hexahydroquinoline VIII as a solid, mp 55–60°, *m/e* 267, λ_{max}^{EtOH} 345 mμ (ε 10,000) and 215 (3000), λ_{max}^{KBr} 1600, 1620, and 3300 cm^{-1}, vinyl hydrogen triplet at δ 5.21. The two methyls appear together at δ 2.08. Refluxing of VIII with 20% ethanolic potassium hydroxide for 20 hr gave, in addition to some phenyloctalone XI, an air-sensitive base assigned structure X (*m/e* 225, λ_{max}^{EtOH} 218 mμ (ε 6000) and 235 (5000), λ_{max}^{KBr} 1620 and 1650 cm^{-1}, vinyl hydrogen triplet at δ 6.1 allylic methyl at 1.87). The dihydropyridine X gave the known[8] 10-phenyl-$\Delta^{1,9}$-2-octalone (XI) (2,4-dinitrophenylhydrazone mp 154–155°)[3] on prolonged heating with aqueous base or (71% yield) by hydrolysis with acetate buffer[9] to the diketone followed by cyclization with hot 5% ethanolic potassium hydroxide.

The major products from the annelation with I and II are thus explained. That they were not the exclusive products could be due to the incursion of variable amounts of hydrolysis *via* the β-diketone pathway. This side reaction should be eliminated by excluding water from the basic medium until after the cleavage of the superfluous acyl group (*cf.* IX → X).

In fact, when III was refluxed for 6 hr with 20% sodium ethoxide in *anhydrous* ethanol, followed by refluxing for another 6 hr after dilution with water, the annelated product was now exclusively the unsubstituted $\Delta^{1,9}$-2-octalone (IV, R = H), while similar treatment of the carbinolamine from II gave the α-substituted octalone V, R = Et, in 70% yield as the only product of annelation.

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

(2) These ketones were prepared in high yield by acid hydrolysis of the alkylation products (NaH, benzene–DMF) of 2-carbethoxycyclohexanone with the appropriate 4-chloromethylisoxazoles. The latter could be made either by Kochetkov's chloromethylation procedure (N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, 2762 (1958)) applied to 5-butyl-3-methylisoxazole made by the procedure of G. Bianchi and P. Grunanger, *Tetrahedron*, **21**, 817 (1965), or from ethyl 2-propyl-5-methyl-4-isoxazole-carboxylate by lithium aluminum hydride reduction followed by thionyl chloride.

(3) Satisfactory analytical data were obtained for this compound.

(4) The hydrogenolysis products we obtained from Raney nickel cleavage all seemed to exist as cyclic carbinolamines (*e.g.*, III). The reactions were conveniently followed by the disappearance of the isoxazole absorption at 231 mμ (ε 1700) and the appearance of the typical absorption at 308 mμ.

(5) This and similar reactions in basic medium should be carried out in degassed solvents under nitrogen.

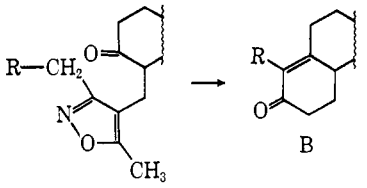
(6) Variable amounts of pyridine bases formed by oxidation of dihydropyridine intermediates were encountered (*cf.* ref 5). This reaction has been discussed previously: M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *J. Am. Chem. Soc.*, **89**, 5460 (1967).

(7) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).

(8) V. Boekelheide, *ibid.*, **69**, 790 (1947).

(9) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *ibid.*, **78**, 430 (1956).

Aside from the intrinsic interest of these mechanistic details, we are now in a position to carry out the transformation A → B which utilizes the readily available 3-substituted 4-halomethyl-5-methylisoxazoles[10] in the annelation reaction.[11]



A B

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

(10) G. Stork and J. E. McMurry, *ibid.*, **89**, 5461 (1967).
(11) *Cf.* G. Stork and J. E. McMurry, *ibid.*, **89**, 5464 (1967), for an application to steroid synthesis.

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Stereospecific Total Synthesis of Steroids *via* Isoxazole Annelation. *dl*-D-Homotestosterone and *dl*-Progesterone

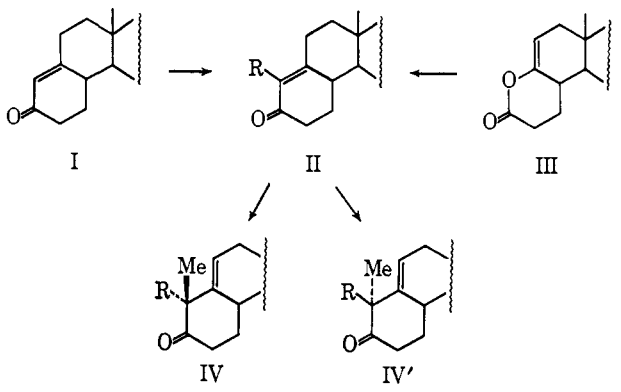
Sir:

A particularly successful route to steroids starts with a potential C/D system and proceeds *via* successive addition of rings A and B.[1] This became particularly attractive with the demonstration that monoalkylation of a tricyclic α,β-unsaturated ketone could be effected readily with a halide which served as a latent precursor of ring A (*cf.* I → II).[2,3a] This particular scheme requires preliminary construction of a tricyclic enone, although a variant in which completion of the construction of ring B through introduction of the latent precursor of ring A (*via* the reaction of an enol lactone with a suitable Grignard reagent,[2,3b] *cf.* III → II) could also be used.

In all the schemes involving eventual construction of ring A, introduction of the C_{18}-methyl group always leads to epimeric mixtures at C_{10} (*cf.* II → IV, IV').[4]

The elucidation of the details of the isoxazole annelation method[5] has made possible a simple synthesis of steroids in which the elements of rings B and A are added at once to a cyclic system. We illustrate this with a synthesis of *dl*-D-homotestosterone and of *dl*-progesterone and demonstrate at the same time the first stereospecific introduction of the C_{18}-methyl group.

The dioxolane of ethyl 3-(4-oxopentyl)-5-methyl-4-isoxazolecarboxylate (V)[6] was transformed (lithium aluminum hydride) to the alcohol VI (2,4 dinitrophenylhydrazone mp 143°[7]) which was converted (thionyl chloride–chloroform–triethylamine, −10°) to the 4-chloromethylisoxazole VII. The latter alkylated the enolate (sodium hydride–glyme) from 10-methyl-$\Delta^{1,9}$-octalin-2,5-dione[8] to form crude IX in 55% yield. The alkylated octalindione IX was successively treated with 1 equiv of sodium borohydride in ethanol (to reduce the saturated carbonyl), hydrogenated (palladium–charcoal in 3:1 ethyl acetate–triethylamine), hydrogenolyzed with Raney nickel and hydrogen in ethanol,[9] and finally refluxed first with oxygen-free methanolic sodium methoxide for 7 hr[10] and then with 3% aqueous sodium hydroxide for 15 hr to produce, in an over-all yield of 60% from crude IX, the crystalline tricyclic enone X, mp 93–94°,[7] benzoate mp 124–125°.[7]



I II III IV IV'

Introduction of the C_{18}-methyl group by the classical method (sodium *t*-amylate or sodium hydride, and methyl iodide) led to the usual mixtures of $\Delta^{9,11}$ 10β and 10α epimers (*cf.* IV, IV'). We have, however, made the remarkable observation that *the alkylation–trapping method*[11] *directly converts X into a single* (β) *isomer* in almost quantitative yield, thus solving an old and vexing problem. Addition of 500 mg of X in 30 ml of dry ether to 240 mg of lithium in 150 ml of liquid ammonia, followed after 20 min by 4 ml of methyl iodide in 20 ml of ether and further stirring for 3 hr, gave, after the usual work-up, 460 mg of the pure 10β-methyl compound XI, mp 83–84°.[7] Transformation of XI into *dl*-D-homotestosterone (XII), mp 158°,[7,12] was effected in 80% yield by successive treatment with dilute aqueous acid at room temperature and with hot dilute aqueous methanolic sodium hydroxide.

The synthesis of *dl*-D-homotestosterone successfully establishes the synthetic sequence. We nevertheless thought it worthwhile to devise a sequence for the transformation of XII into *dl*-progesterone. Dioxolanation, followed by Sarett oxidation, gave the 17a ketone XII, mp 215–216°,[7] and then (methylmagnesium bromide) the 17aβ-methyl-17aα-ol XIV, mp 190–191°,[7] dehydrated (thionyl chloride–pyridine, 0°) and deketalized (aqueous methanolic hydrochloric acid at reflux)

(1) *Cf.*, *inter alia*, R. B. Woodward, F. Sondheimer, D. Taub, K. Hensler, and W. M. McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).
(2) G. Stork, H. J. E. Loewenthal, and P. C. Mukharji, *ibid.*, **78**, 501 (1956).
(3) (a) L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960); (b) L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *Compt. Rend.*, **257**, 3086 (1963).
(4) Formation of only the 10β-methyl isomer is reported in such an alkylation by Velluz, *et al.*[3a] Careful repetition of this work in our laboratory shows actually a 2:1 mixture of the 10β and 10α compounds.
(5) G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, **89**, 5463 (1967).
(6) G. Stork and J. E. McMurry, *ibid.*, **89**, 5461 (1967).
(7) Satisfactory analytical and spectra data were obtained for this substance.
(8) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).
(9) Followed by the disappearance of the 230-mμ isoxazole absorption and appearance of the strong peak of the cyclic carbinolamine[5] at 310 mμ.
(10) Until disappearance of absorption at λ_{max} >240 mμ.
(11) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).
(12) This gave solution spectra identical with those of an authentic sample of the natural material obtained through the courtesy of Dr. D. Taub, Merck Sharp and Dohme.