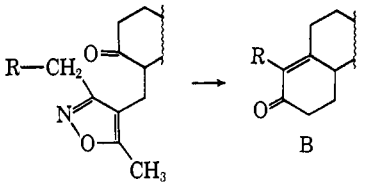
Aside from the intrinsic interest of these mechanistic details, we are now in a position to carry out the transformation A → B which utilizes the readily available 3-substituted 4-halomethyl-5-methylisoxazoles[10] in the annelation reaction.[11]



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

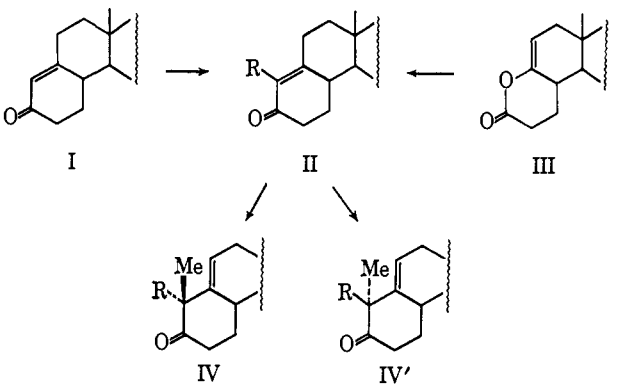
Sir:

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]

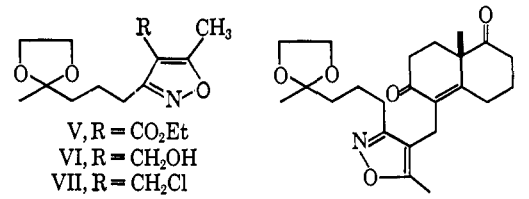


I II III IV IV'

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.

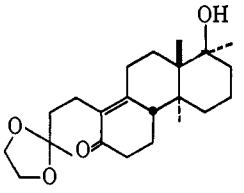
The synthesis of *dl*-D-homotestosterone successfully establishes the synthetic sequence. We nevertheless thought it worthwhile to devise a sequence for the transformation of XII into *dl*-progesterone. Dioxolanation, followed by Sarett oxidation, gave the 17a ketone XII, mp 215–216°,[7] and then (methylmagnesium 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.

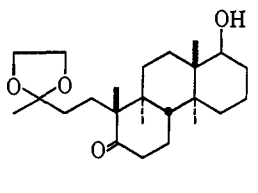


V, R = CO_2Et
VI, R = CH_2OH
VII, R = CH_2Cl

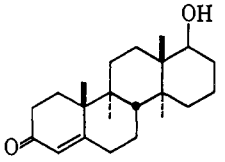
IX



X

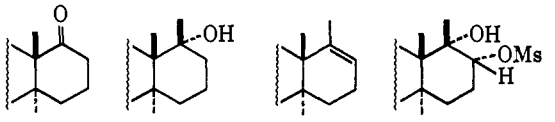


XI

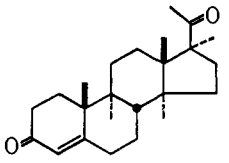


XII

to the D-homo-17a-methyl-$\Delta^{4,17(17a)}$-androstadien-3-one (XV), mp 145–146°.[7] Treatment of the crude mono-



XIII XIV XV XVI



XVII

mesylate XVI of the glycol derived from the osmium tetroxide hydroxylation of XV with potassium *t*-butoxide in dry *t*-butyl alcohol for 16 hr at 60° gave *dl*-progesterone (XVII), mp 182–184° (lit.[13] mp 183–185°), spectral properties identical with those of the natural material.

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

(13) W. S. Johnson, V. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron Suppl.*, 8, 541 (1966).

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On the Mechanism of the Paterno–Büchi Reaction

Sir:

Recently there has been considerable interest on the nature of reactive states in photocycloaddition reactions.[1] A common photocycloaddition reaction of carbonyl compounds is their addition to olefins to form oxetanes, *i.e.*, the Paterno–Büchi reaction.[2] Contributions from many laboratories suggested that the reaction of simple phenyl carbonyl compounds proceeds *via* their n,π^* triplet state. One interesting feature of this reaction is that polynuclear aromatic aldehydes with low-lying π,π^* triplet states react with olefins to yield oxetanes in much higher quantum yields than the quantum yields of photoreduction of these aldehydes. In this communication we wish to demonstrate that the Paterno–Büchi reaction of benzaldehyde proceeds *via* its n,π^* triplet state while the reaction of 9-anthraldehyde proceeds *via* a triplet state and another short-lived excited state.

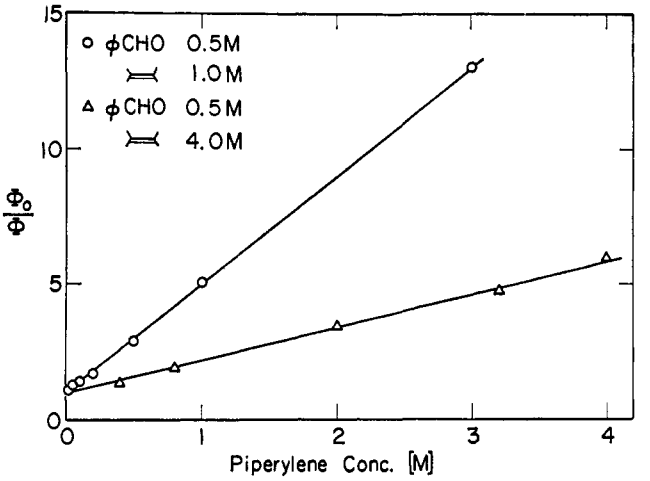

Figure 1.

When the photochemical addition of benzaldehyde (0.5 *M*) to 2,3-dimethyl-2-butene was carried out in the presence of piperylene, the reaction was quenched to various extents depending on the quencher concentration. The apparatus used has been reported earlier.[3] The formation of oxetane was followed by vpc analysis on a SF-96 (20%) on Firebrick column (0.25 in. × 5 ft) at 128° and the consumption of carbonyl compounds was analyzed by infrared spectrometry at their respective carbonyl maxima with a Beckman IR-7 infrared spectrophotometer. The reactions follow zero-order kinetics up to 25% completion. In most kinetic runs, the reaction was followed to no more than 15% completion. Linear Stern–Volmer plots were obtained for benzaldehyde at two different olefin concentrations (4 and 1 *M*) (Figure 1), indicating the reaction proceeds *via* a single reactive state which is assigned the n,π^* triplet state. In a separate experiment it was demonstrated that piperylene is just as effective a quencher as di-*t*-butyl nitroxide for the photochemical addition of benzaldehyde to 2,3-dimethyl-2-butene.

The absolute quantum yield of benzaldehyde consumption or oxetane formation was found to be de-

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(3) D. R. Coulson and N. C. Yang, *J. Am. Chem. Soc.*, 88, 4511 (1966).