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STEROIDS II. BIS-HOMOSTEROIDS VIA ENAMINES (1)

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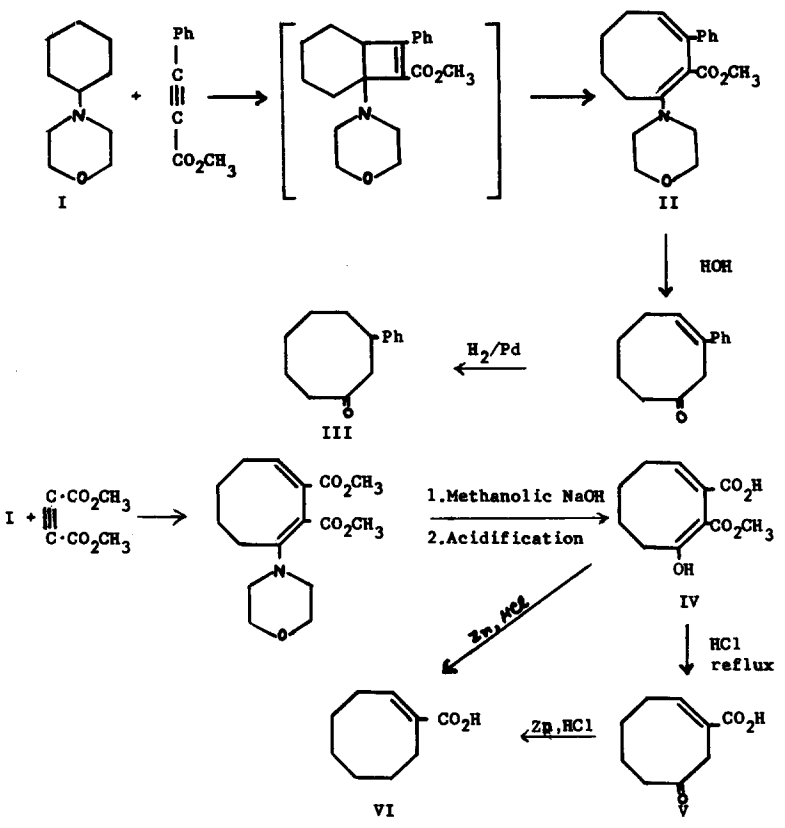
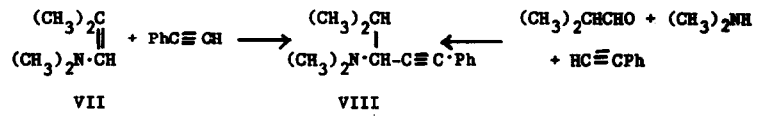
With the aim of preparing cyclobutene compounds we undertook a study of the cycloaddition of enamines to substituted acetylenes. Dimethyl acetylenedicarboxylate and methyl phenylpropiolate reacted with enamines to give 1:1-addition products (3). The spectral properties and reactions of these adducts, however, did not agree with the expected cyclobutene structure (4). The cycloaddition product (II) from methyl phenylpropiolate and the enamine I gave on vigorous hydrolysis a nitrogen-free compound which could be catalytically hydrogenated to the known 3-phenylcyclooctanone (characterized as its semicarbazone, m.p. 171-172°; lit. (5), m.p. 173-174°). The basic hydrolysis of the adduct from dimethyl acetylene dicarboxylate and I followed by acidification afforded compound IV which still contained one ester group but had lost the nitrogen function. This compound gave coloration with ferric chloride solution. When IV was heated under reflux with dilute acid the unsaturated keto acid V was obtained. It is interesting to note that its N. M. R. spectrum indicated lack of conjugation between the double bond and the keto group. Clemmensen reduction of either IV or V led to the known 1-cyclooctene carboxylic acid (6) VI, which was characterized as the amide, m.p. 105° (lit. (7), m.p. 106°). The reactions are summarized in Chart I.

CHART I



In general, therefore, a cyclooctadiene derivative can be readily obtained from a cyclohexanone via an enamine. The addition of phenylacetylene to the enamine VII, however, is an exception in that the sole product was the Mannich base VIII which could be synthesized from isobutyraldehyde, phenylacetylene and dimethylamine.

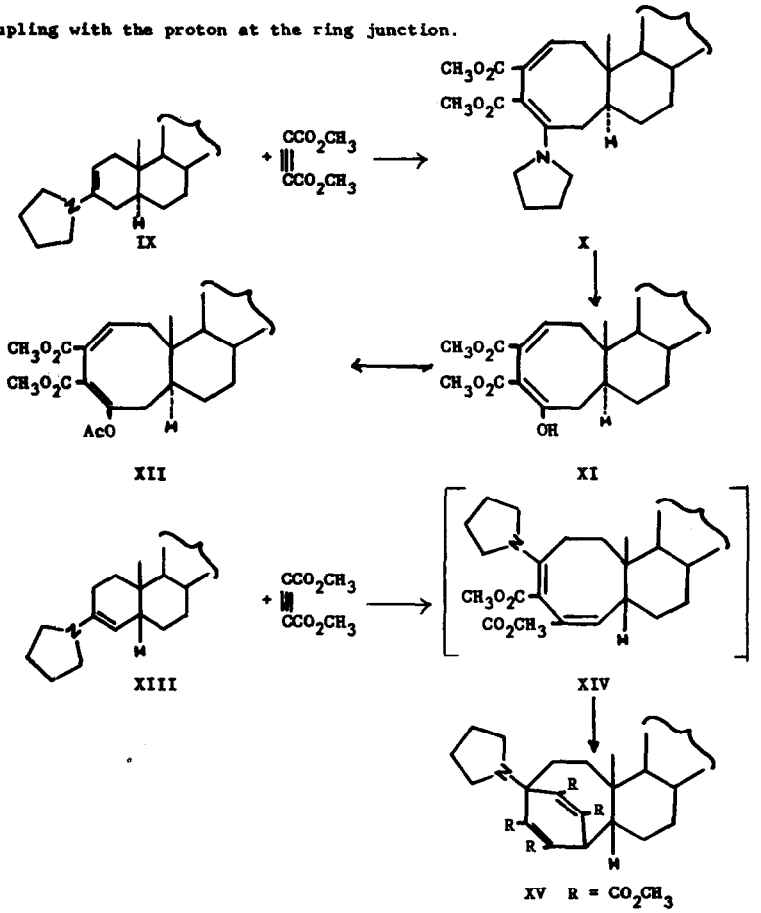


VII VIII

We have used this convenient ring expansion method for preparing bis-homosteroids. Thus, dimethyl acetylenedicarboxylate and the enamine IX from cholestane-3-one reacted at room temperature or in refluxing benzene to afford a 1:1-addition product, m.p. 212-213°, in 75% yield. The N. M. R. spectrum of this compound showed multiple peaks centered at 3.57 τ. Such a signal is consistent with the olefinic proton of the cyclooctadiene structure X but incompatible with a cyclobutene structure. Acid hydrolysis of this adduct led to a nitrogen-free compound XI, the N. M. R. spectrum of which showed a proton signal at -4.54 τ and a set of multiple peaks centered at 3.27 τ ; the former can be assigned to the proton of an enol and the latter to an olefinic proton. The enolic structure deduced for XI is supported by the observation that it gives a color with ferric chloride and that its reaction with acetic anhydride and pyridine gave acetate XII, m.p. 130-131°, which no longer showed the signal at very low field. It is worth noting that basic hydrolysis failed to saponify the ester groups of X under moderate conditions; vigorous acid hydrolysis led to intractable material.

The reaction of dimethyl acetylenedicarboxylate with the enamine from copaostan-3-one gave a crystalline product, m.p. 212-213°. The elemental analysis and the presence of four methoxy peaks in the N.M.R. spectrum showed that two moles of the acetylenic ester had added to one mole of the enamine. This adduct was not converted into a nitrogen-free compound on treatment with dilute acid. The N.M.R. spectrum of the adduct

showed no olefinic protons, but there was an unsplit peak corresponding to one proton at 6.02 τ. On the basis of this evidence we propose the structure XIII for the enamine from copreptan-3-one. The N.M.R. peak at 6.02τ is assigned to the doubly allylic proton in XV which has poor coupling with the proton at the ring junction.



It has been established that a Diels-Alder addition requires a cisoid and planar diene (8). It is worth noting that the reaction of the enamines from the two steroid ketones is sensitive to the stereochemistry of the ring junction, although both dienes X and XIV can assume a conformation in which the double bonds are cisoid and planar. Further work on the structure of XV and related compounds is in progress.

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(1) Based in part on a paper presented before the Metropolitan Meeting of the New York and New Jersey sections of the American Chemical Society in January, 1963. For Steroids I, see A. K. Bose and R. Dahill, Tetrahedron Letters 959 (1963).

(2) National Science Foundation Undergraduate Research Participant.

(3) All new compounds reported here were characterized by satisfactory elemental analysis.

(4) We are indebted to Dr. K. Brannock for drawing our attention at this stage to the facile rearrangement of the cyclobutene systems that he had prepared from enamines and substituted acetylenes.

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