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FORMYLATION OF CYCLIC β,γ-UNSATURATED KETONES*

by

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It has been well established that formylation of trans--2-decalone I[1], and their steroidal analogues[2] occurs exclusively at C-3 (decalone numbering). While the corresponding cis-2-decalone II[3] and a number of 5β-3-ketosteroids[4] behave in an analogous manner, the formylation of 5β-stigmast-22-en-3-one has been reported to yield both C-2 and C-4 (steroid numbering) substituted products[4,5].

In connection with our interest in the availability of α-formylated cyclic ketones as potential intermediates for the synthesis of aza-steroids and aza-anthra-steroids, we have examined the influence of a β,γ double bond, present either as an

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* This paper should be regarded as the fifth paper in the heterocyclic steroid series. Part IV see Tetrahedron, 1965 (in press).

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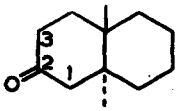
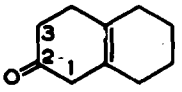
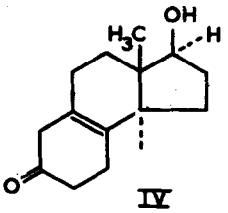
isolated function, as in the ketones III and IV, or as part of an aromatic system as in ketone V, on the direction of formylation.



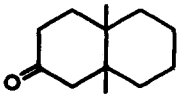
I



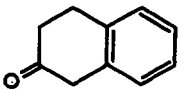
III



IV



II



V

Formylation of III[6] in <u>toluene</u>, with one equivalent of sodium methoxide as the condensing agent, results in the formation of a hydroxymethylene-ketone which was isolated as a pure crystalline product in 76 p.c. yield (m.p. 90-92°; ν_{max}^{KBr}: 3280,1700,1610 cm^{-1})*.

That the structure of the latter ketone is VI and not VII is suggested from its U.V. spectrum which exhibits a characteristic absorption λ_{max}^{EtOH}: 275 nm (7600), indicating thereby the presence of a <u>non-conjugated</u> hydroxymethylene function[7]. In agreement with structure VI, reaction with hydrazine hydrate gave a crystalline pyrazole derivative (83 %)(m.p. 141-142°;

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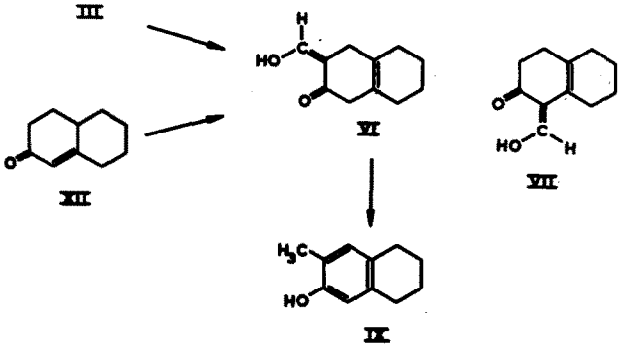
* All new compounds gave satisfactory analyses and had I.R. and N.M.R. spectra consistent with the assigned structures.

ν_{max}^{KBr}: 3160,3110,1605,965 cm^{-1}) in which the heterocyclic ring was as expected not conjugated with the double bond, as evidenced from its U.V. spectrum: λ_{max}^{EtOH}: 221 nm (4000)[7].



Further confirmation of the assigned structure of VI was also obtained from its reduction products. Catalytic hydrogenation of VI over Pd/C (10 %) till the hydrogen uptake had ceased resulted in a mixture of products from which IX (m.p. 89,5-90,5°(litt.: 88-89°[8])) was isolated in an appreciable yield*. While the unexpected formation of IX deserves some comment and will be discussed in detail elsewhere, it is obvious that, barring unusual molecular rearrangement(s), the methyl group in IX must arise from the original formyl function. The position of this methyl group clearly establishes the direction of formylation of ketone III.

A completely analogous behaviour is exhibited by ketone IV[9]. Formylation results in a single product X (65 %) (m.p.

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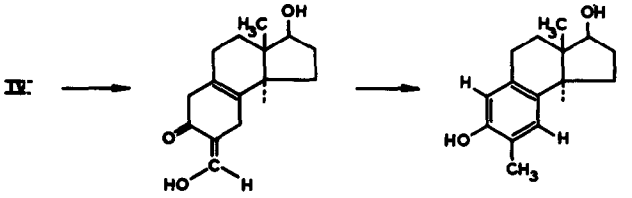
* According to its I.R., U.V. and N.M.R. spectra a mixture of isomeric 3-methyl-decalones was isolated in addition to IX.

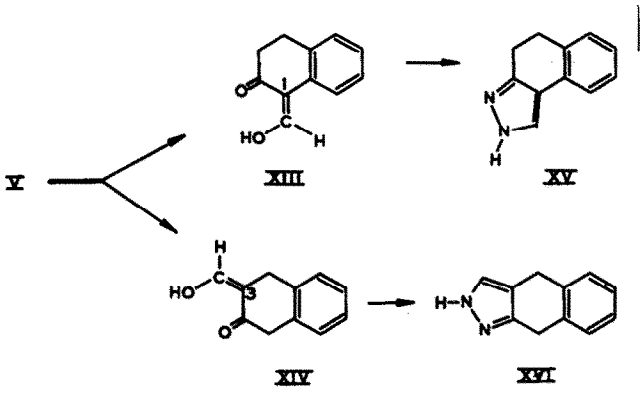
162-165°; λ_{max}^{EtOH}: 277 nm (8100); ν_{max}^{KBr}: 3140,1680,1600 cm^{-1}) which could be hydrogenated to the tricyclic diol XI (m.p. 72-74°; λ_{max}^{EtOH}: 212 nm (11.500), 283 nm (4400); ν_{max}^{KBr}: 3460,1615,1580,1500,1060 cm^{-1}). A structurally significant feature of the N.M.R. spectrum of XI in deuteriochloreform solution was the presence of a pair of sharp singlets (at δ = 6,55 and 6,70 p.p.m.) for the two aromatic protons.



X XI

Formylation of III in ethanol, using sodium ethoxide as a base, resulted in a low yield of VI (15-25 %) and a mixture of the starting ketone and its conjugated isomer XII. Since in a separate experiment it was possible to show that formylation of XII also gave VI in an excellent yield under conditions of the experiment, its formation from III in alcohol may arise either directly or via the intermediacy of XII.

Formylation of tetralone-2 (V) gives a mixture of two hydroxymethylene-ketones in which the formyl group is introduced at position C-1 (XIII) or C-3 (XIV). The composition of the mixture is dependent on the solvent employed[10]; namely, formylation in toluene yields a 1:1 mixture, while in ethanol a mixture of 80 p.c. of XIII and 20 p.c. of XIV is formed, as could be estimated from the N.M.R. spectra.



Reaction of the mixture with hydrazine hydrate gave, in a corresponding ratio, a mixture of the pyrazoles XV and XVI*, which could be separated. Compound XVI was isolated from the mixture as a crystalline compound (m.p. 149-149,5°), XV as a reddish oil, that after standing partially crystallized (m.p. after two crystallizations from ether/hexane: 134-136°). The U.V. spectrum of the phenyl-conjugated pyrazole XV (λ_{max}^{EtOH}: 215 nm (16.500), 259 nm (13.800)) permits to distinguish it from its non-conjugated isomer XVI (λ_{max}^{EtOH}: 215 nm (10.300), 258 nm(s), 264 nm (805), 272 nm (580)). The N.M.R. spectra of the two pyrazoles also supports their structural assignments; however, in view of their complexity they are not discussed here.

The formation of a mixture of the C-1 and C-3 formylated products from V, in which the former is present to at least 50 p.c. is in contrast with the recently reported beha-

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* Possible tautomerism of the pyrazole nucleus being undiscussed.

viour of 5-methoxy-tetralone-2 in a similar reaction[11] and corresponds to the results described earlier[12] for the latter ketone.

The differences in the formylation reaction of tetralone--2 and the non-aromatic ketones III, IV, and XII, as well as the influence of polar and non-polar solvents is of considerable mechanistic and synthetic interest. A complete account of these features will be presented in a further communication.

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