KETONIC CHARACTER OF ALKYL 3-HYDROXYPYRROLE-2-CARBOXYLATES: THE FIRST ENTRY INTO 2,3-UNSUBSTITUTED 4-OXO-2-PYRROLINES

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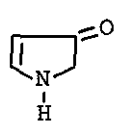
A general synthetic route to 4,5-unsubstituted 3-hydroxypyrrole-2-carboxylates (IV) has been developed, and their marked β-keto ester nature has been demonstrated on alkylation and Michael addition leading to 2,3-unsubstituted 4-oxo-2-pyrrolines.

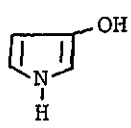
4-Oxo-2-pyrroline (I) is expected to find practical use in the synthetic chemistry as a synthon because of its versatile functionalities, i.e., enone, enamine and active methylene systems, found in its simple molecule. However, nonsubstituted pyrrolinone (I) or its tautomer, 3-hydroxypyrrole (II), is still an imaginary compound, whereas some of its derivatives, especially of 2-ethoxycarbonyl analogues of II, are known and have been used for the synthetic chemistry as in the synthesis of prodigiosin[1] (III) starting from ethyl 3-methoxypyrrole-2-carboxylate. As for the I ⇄ II tautomerism, ketonic character

of the ring enol has been reported not to exist to any extent in 3-hydroxypyrroles.[2,3]

In connection with our study on the design of alkaloid synthesis, we have developed a general synthetic route to 4,5-unsubstituted 3-hydroxypyrrole-2-carboxylates (IV) and have found their marked β-keto ester nature, the findings leading to the first entry into 2,3-unsubstituted 4-oxo-2-pyrrolines (V).



(I)



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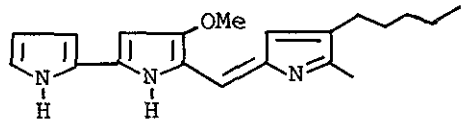

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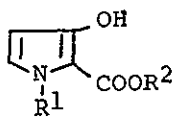
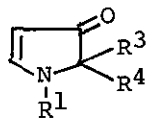


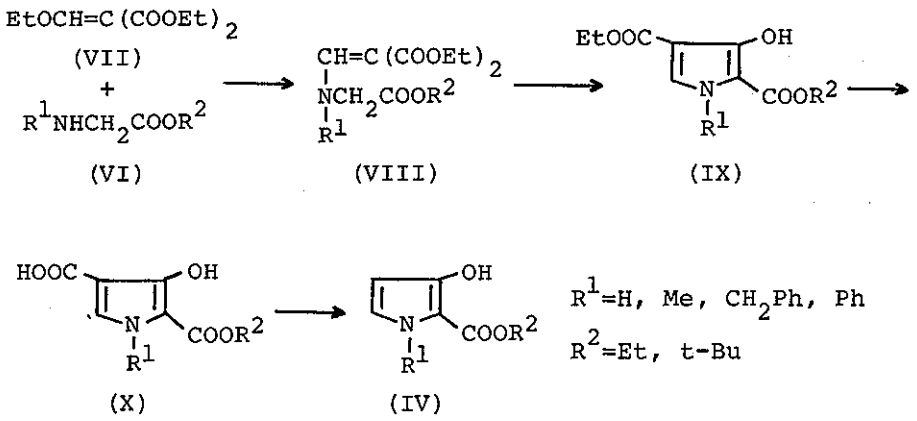
(IV)



(V)

The syntheses of relatively simple 3-hydroxypyrrole derivatives have been reported.[1,3-7] But some of them are in low yield and/or troublesome to isolate the products, and/or the reaction sequences cannot be applied to the synthesis of 4,5-unsubstituted derivatives.

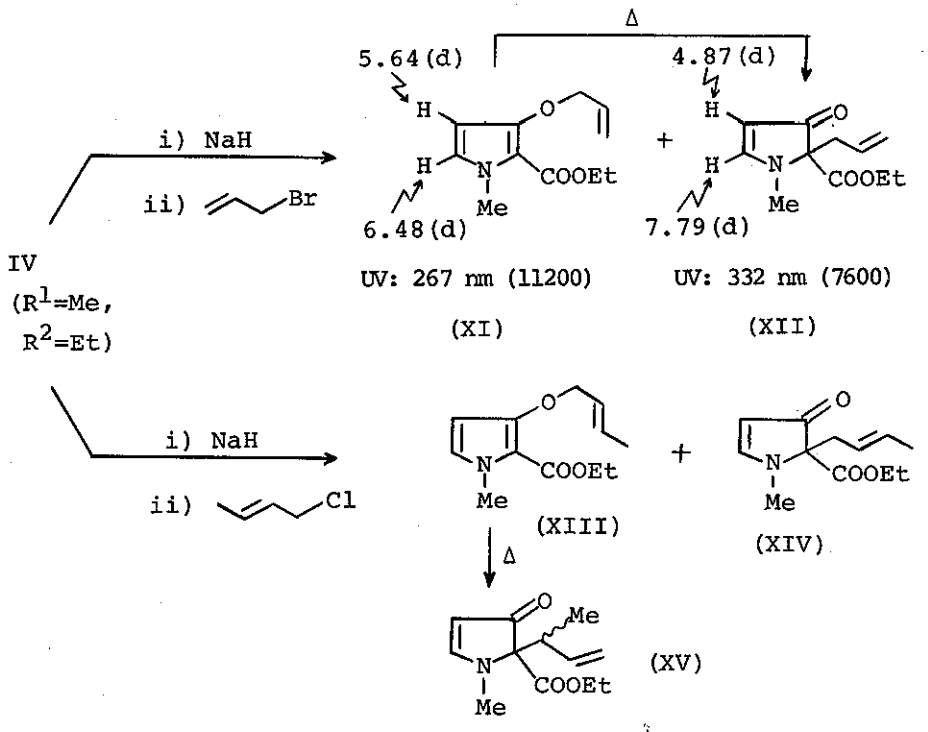
We synthesized some of 4,5-unsubstituted alkyl 3-hydroxypyrrole-2-carboxylates (IV) according to the following reaction sequences:

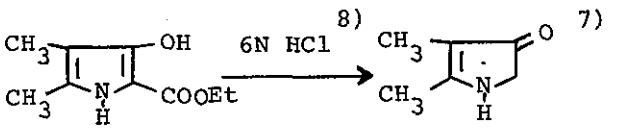


An equimolar mixture of glycine esters (VI) and diethyl ethoxymethylenemalonate (VII) gave the condensation products (VIII) with liberation of ethanol and with evolution of heat. 3-Hydroxypyrrole-2,4-dicarboxylates (IX) were obtained by Dieckmann condensation of VIII using alkoxide as condensing agent. Selective partial hydrolysis of diesters (IX) using a large excess of alkali hydroxide afforded 4-carboxylic acids (X), which readily gave IV on decarboxylation in boiling β-picoline. This synthetic route is excellent in yield and in ease of product isolation.

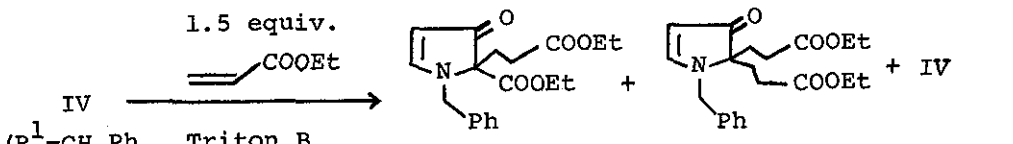
A C-alkylated product has been found to be formed from a 3-hydroxypyrrole derivative in the tetrahydropyranylation of ethyl 4,5-dimethyl-3-hydroxypyrrole-2-carboxylate catalyzed by acid.[4] And there has been reported only rare example of the C-alkylation by use of base.[3] We prepared the sodium salt of IV (R^1=Me, R^2=Et) by its treatment with sodium hydride in benzene, and examined the alkylation on it with allyl bromide

at 70-80°. An O-alkylated product (XI) and a C-alkylated one (XII) were obtained in 32 % and 63 % yields, respectively. The former (XI) was readily converted to the latter (XII) by heating at 180-200°, but not in boiling benzene, the result suggesting that a direct C-alkylation derived from its β-keto ester nature had occurred in the foregoing alkylation. This result was further supported by the alkylation with crotyl chloride as illustrated in the scheme. Ready removal of the ester group in ethyl 4,5-dimethyl-3-hydroxypyrrole-2-carboxylate (XVI) by means of hydrochloric acid seems to result from its nature of β-keto ester.[8] Further evidences were obtained from its Michael alkylation.

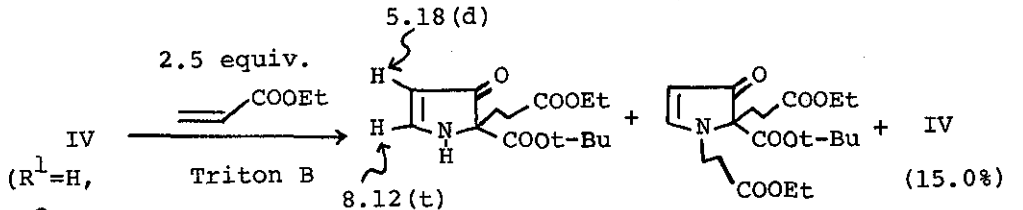




(XVI) (XVII)



(XVIII, 14.2%) (XIX, 29.3%) (45.8%)



UV: 318 nm (7000)

(XX, 32.4%) (XXI, 51.6%)

PMR spectra were measured for the solution in CCl_4 (XI, XII) and in $CDCl_3$ (XX) in δ value, and UV spectra were measured for the solution in EtOH.

Only 4-oxo-2-pyrroline type compounds, XVIII, XIX, XX and XXI were obtained on the treatment with 1.5 or 2.5 equivalents of ethyl acrylate in the presence of Triton B. Formation of the unexpected product (XIX) was rationalized by ketonic cleavage of XVIII followed by an additional Michael addition. Compounds XII, XIV, XV and XVIII-XXI are the first instance of 4-oxo-2-pyrrolines lacking substituents at the 2-

and 3-positions, especially at the 1-, 2- and 3-positions as in XX.

Other behavior toward a variety of both hard and soft electrophiles is under investigation.

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