HETEROCYCLES, Vol. 4, No. 4, 1976

THE REACTIONS OF ETHYL 2-QUINOLYL- AND 2-PYRIDYLCYANOACETATE[1]

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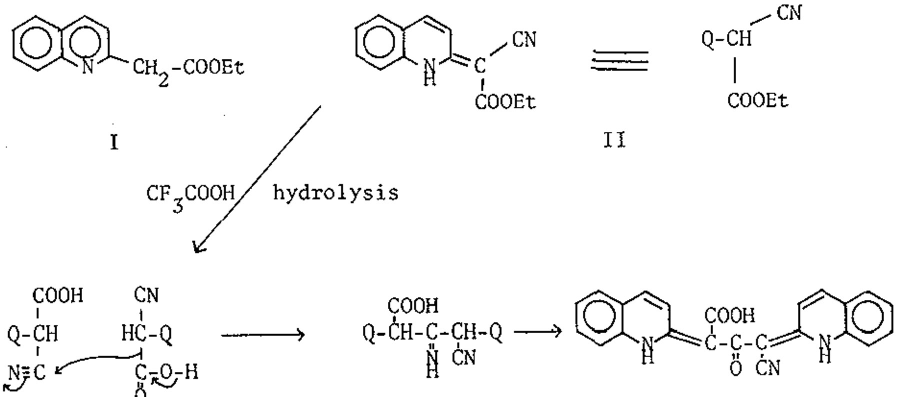
Ethyl 2-quinolylcyanoacetate(II) was refluxed in trifluoroacetic acid to give a chemically very stable substance. The potassium salt(IVa) of II reacted with methyl iodide to afford selectively the C-methylated product, which was treated with alkali in ethanol to give methyl 2-quinolyl ketone(VIIa) in good yield. On the other hand, ethyl 2-cyano-2-(2-pyridyl)-propionate(XII) gave only 2-(2-pyridyl)-propionitrile(XIV).

We have been looking for a facile route to ethyl 2-quinolylacetate(I). By Tanida[2] I has previously been synthesized starting with quinaldine in five steps. Baty et al.[3] succeeded in converting ethyl 2-quinolylacetoacetate to I by treating with sodium hydride in dimethyl cellosolve. On the other hand, Oishi et al.[4] reported that ethyl 2-piperidylideneacetate remained unchanged when refluxed in trifluoroacetic acid. On the basis of these informations, we treated II prepared by the known method[5] with trifluoroacetic acid on a water bath to give a brown precipitate, which was insoluble in most organic solvents. From the elemental analysis and the mass spectrum, the composition was shown to be $C_{23}H_{15}O_3N_3$. The nmr spectrum in trifluoroacetic acid showed only two singlets in the aromatic region. The compound was stable to overnight reflux with both concentrated hydrochloric acid and 50% aqueous potassium hydroxide, and could not be reduced with sodium borohydride or lithium aluminum hydride. On the basis of the physical and the chemical data, the following structure(III) was proposed for this adduct, and we speculated that the mechanism producing III from II might be as follows:

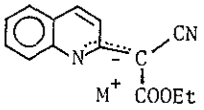


I

II

III

Next II was treated with 1∿2 molar equivalents of potassium hydroxide in aqueous ethanol at room temperature and left overnight to give a yellow solid, mp 275∿278°. The fact that the flame test of this compound exhibited purple coloration showed that it was a potassium salt. Furthermore it was shown to have the composition $C_{14}H_{11}O_2KN_2$. The structure of the potassium salt may therefore be IVa. Similarly, the sodium salt(IVb), mp 322∿324°, was obtained by treating with sodium hydroxide in ethanol. The two metal salts were neutralized with dilute hydrochloric acid to the corresponding acid. Its physical and chemical behaviors were exactly consistent with the structure, II.

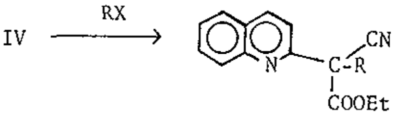


IV

a: M=K

b: M=Na

IVa and IVb, reacting with an excess of methyl iodide in a sealed tube, gave only one product in quantitative yield. The ir spectrum showed a carbonyl band at 1740 cm^{-1}, and the uv spectrum only one absorption due to the quinoline nucleus at 233.5 mμ. These facts suggest that the compound is the C-methylated product, ethyl 2-cyano-2-(2-quinolyl)-propionate(Va). In a similar fashion, ethyl 2-cyano-2-(2-quinolyl)-n-caproate(Vb) was also obtained as the sole product when IVa or IVb were treated with n-butyl bromide. However benzylation gave the C-benzylated compound, ethyl 2-cyano-3-phenyl-2-(2-quinolyl)-propionate(Vc) as the main product, and the N-benzylated compound, ethyl 1,2-dihydro-1-benzyl-2-quinolylidenecyanoacetate(VI) as the minor one. VI was a yellow crystalline substance, mp 171∿174°, which exhibited a carbonyl band at 1680 cm^{-1} in the ir spectrum.

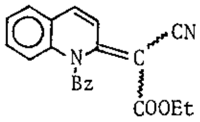


V

a: R= CH_3

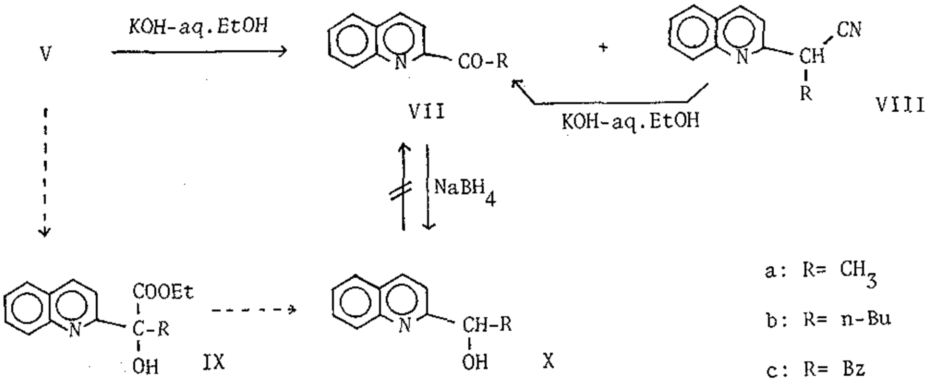
b: R= n-Bu

c: R= Bz



VI

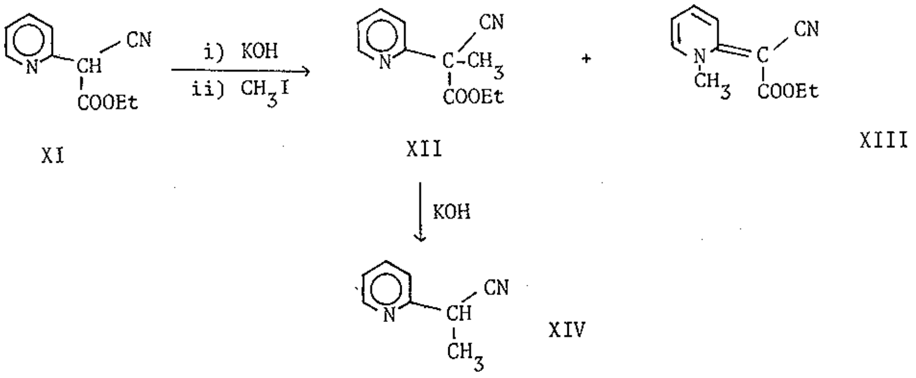
On the assumption that V should not form metal salts, the C-alkylated products were treated with 1∿2 molar equivalents of potassium hydroxide in aqueous ethanol at room temperature. In case of Va, only one product, mp 45°, was obtained. This compound exhibited a carbonyl band at 1700 cm^{-1} in the ir spectrum. The composition was shown to be $C_{11}H_9ON$ and that of its phenylhydrazone $C_{17}H_{15}N_3$. Thus this product was shown to be methyl 2-quinolyl ketone(VIIa).



In a similar fashion, Vb was treated with alkali. In this case, two products were isolated in about equal quantity. They were purified by alumina column chromatography. The physical data suggests that the white crystalline compound, mp 35°, eluted with n-hexane, is n-butyl 2-quinolyl ketone(VIIb), which was verified by comparison with an authentic sample prepared from 2-cyano-quinoline and n-butyl magnesium bromide. On the other hand, a yellow oil eluted with n-hexane-ether (4:1), exhibited a cyano band at 2250 cm^{-1} and no carbonyl band in the ir spectrum. The composition of its picrate, mp 103∿104°, was shown to be $C_{21}H_{13}O_7N_5$. This yellow oil was further treated with alkali to give VIIb. These facts suggest that this oil is an intermediate in the transformation of Vb to VIIb, 2-(2-quinolyl)-n-capronitrile(VIIIb). In case of Va, the intermediate, 2-(2-quinolyl)-propionitrile(VIIIa), may be too unstable and suffer oxidative decyanation to give VIIa[6].

An alternative possible route[7] to the ketonic compounds, VII, might be that from the secondary alcohols, X, via the ester alcohols, IX, which might be formed by the attack of hydroxyl ion on the electron deficient center of V. However this route had to be given up, because X, which was synthesized by the reduction of VII with sodium borohydride, was stable under such oxidative conditions. 3-Phenyl-2-(2-quinolyl)-propionitrile(VIIIc) obtained from Vc was very stable to oxidation under basic conditions, and could not be converted to the corresponding ketonic compound, benzyl 2-quinolyl ketone(VIIc). VIIIc was identified as the picrate.

For comparison with the reactions of the above quinoline series, the reactions of ethyl 2-pyridylcyanoacetate(XI) were examined. The potassium salt of XI did not precipitate from aqueous ethanol, but the crude crystals obtained after evaporation of the solvent on treatment with methyl iodide gave the C-methylated product, ethyl 2-cyano-2-(2-pyridyl)-propionate(XII), and the N-methylated product, ethyl 1,2-dihydro-1-methyl-2-pyridylidenecyanoacetate(XIII) in a 5:1 ratio.



Both XII and XIII were separated by silicagel column chromatography and characterized by their ir, nmr spectral and elemental analyses.

Next XII was treated with alkali for one day to give only one product, which was shown on the basis of its ir and nmr spectra, and the elemental analysis of its picrate to be 2-(2-pyridyl)-propionitrile(XIV), which like VIIIc was very stable to oxidation in basic media.

ACKNOWLEDGEMENT The authors are indebted to Mrs. Yoko Tanii (née Nakazawa) for her valuable assistance. Thank are also due to the members who undertook the elemental analyses and nmr measurements.

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Received, 13th December, 1975