Keten. Part X.[1] The Reaction of Dimethylketen with Pyridine *N*-Oxide

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The reaction of dimethylketen with pyridine *N*-oxide gives acetone, pyridine, 4-isopropylpyridine and a bicyclic compound for which two alternative structures are suggested, which may arise by reaction of pyridine *N*-oxide with an α-lactone.

PREVIOUS studies[2] on the reaction of dimethylketen with heteroaromatic *N*-oxides have shown that phenanthridine and isoquinoline *N*-oxides form adducts containing oxazepinedione rings and also undergo deoxygenation. We now report the results of an investigation of the reaction between pyridine *N*-oxide and dimethylketen.

Dimethylketen failed to react with pyridine *N*-oxide in ethyl acetate, but reaction in benzene solution gave a mixture of products. Pyridine and 4-isopropylpyridine were isolated and characterised as their picrates, and acetone was isolated and identified as its dinitrophenylhydrazone. In addition, a very low yield of a crystalline solid, $C_{13}H_{17}NO_4$, was isolated having a composition corresponding to the combination of one molecule of pyridine *N*-oxide and two molecules of dimethylketen with one extra atom of oxygen.

Spectroscopic study of the last product showed two absorptions in the i.r. region at 1802 and 1738 cm.$^{-1}$ and u.v. absorption at 262 nm. The n.m.r. spectrum showed two singlets in the C-Me region, each corresponding to six protons, and lower-field multiplets whose position, intensity, and coupling strongly suggested a 1,4-dihydropyridine derivative, an assignment consistent with the u.v. spectrum.[3] The very high frequency for the carbonyl absorption in the i.r. spectrum indicates the presence of either a carboxylic anhydride group or an *O*-acyl hydroxylamine,[2,4] and the presence in the mass spectrum of a significant peak at 120 mass units, corresponding to a dimethylpicolyl cation, $Me_2C^+C_5H_4N$, leads to the assignment of either of the structures (I) or (II) to this compound. This is partly confirmed by formation of 4-isopropylpyridine on acidic hydrolysis of the

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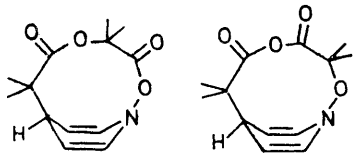
[3] E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, 1962, **27**, 3764.
[4] O. Exner and B. Kakac, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2530 (*Chem. Abs.*, 1961, **55**, 3482).

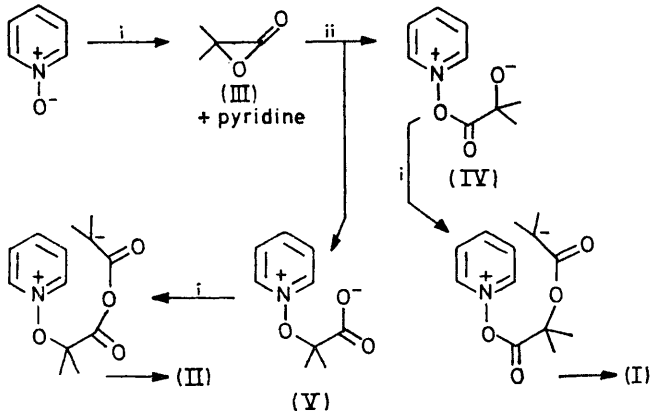
compound, which presumably arises *via* decarboxylation of 2-(4-pyridyl)isobutyric acid formed by cleavage of the ester ring in (I) or (II) followed by 1,4-elimination from the dihydropyridine system. The very low yield of the compound, coupled with the difficulty of purification



(I) (II)

precluded further work to distinguish between the possible structures (I) and (II).

The mechanism of formation of this compound must account for the incorporation of the extra oxygen atom into the structure, and in view of the reagents employed, this can only reasonably be derived from the pyridine *N*-oxide. It has already been shown [2] that deoxygenation of isoquinoline *N*-oxide by dimethylketen proceeds by formation of an α-lactone and we propose that the compound arises as shown in the Scheme; here the



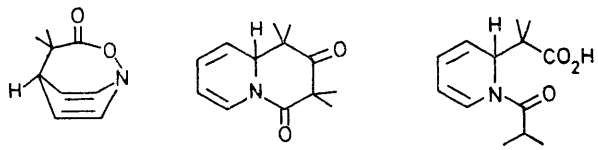
i, $Me_2C{=}C{=}O$; ii, Pyridine *N*-oxide

SCHEME

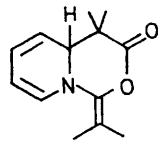
α-lactone (III) reacts with a further molecule of the *N*-oxide to give either zwitterion (IV) or (V) which further reacts with dimethylketen and then undergoes ring closure to give the isolated product. Nucleophiles usually attack α-lactones at the 3 position [5] to give carboxylate anions, but α-lactams are known to react with nucleophiles at both the carbonyl group and the adjacent carbon atom.[6] The very low yield of the bicyclic product may well be due to the ability of both (IV) and (V) to decompose to pyridine, acetone, and carbon dioxide. In an unsuccessful attempt to trap the α-lactone (III), pyridine *N*-oxide was treated with dimethylketen in methanol, but was recovered unchanged. Presumably the *N*-oxide catalyses the reaction of the keten with methanol.[7]

The 4-isopropylpyridine isolated from the reaction mixture might arise either by hydrolysis of (I) or (II) during work-up, or by spontaneous decomposition of a possible 1 : 1 adduct (VI). We have been unable to detect anything corresponding to (VI), but on prolonged storage the compound (I) or (II) decomposes slowly forming some 4-isopropylpyridine.

The formation of a 1,4-bridged product in this reaction calls into question the structure of Staudinger's adduct of pyridine with dimethylketen,[8] to which the structure (VII) was originally assigned. We have prepared the adduct and characterised its hydrolysis product, which from the occurrence in the n.m.r. spectrum of a one-proton doublet at low field due to H-6 of the dihydropyridine ring is clearly the 1,2-dihydropyridine derivative (VIII). In view of previous studies [9] and the ease



(VI) (VII) (VIII)



(IX)

of hydrolysis of the adduct, we assign the structure (IX) to the adduct of pyridine and dimethylketen.

The reactions of dimethylketen with 2-picoline-*N*-oxide, 4-picoline *N*-oxide, and 2,6-lutidine *N*-oxide were also examined. In each case the alkyl pyridine was the sole characterisable product. After work-up involving treatment with water, isobutyric acid was also identified, possibly derived from isobutyric anhydride. Examination of the reaction mixtures by v.p.c. coupled directly to a mass spectrometer showed the presence of numerous products formed in very low yield, which could not be isolated in quantities sufficient to permit structural investigation.

EXPERIMENTAL

N.m.r. spectra were measured for deuteriochloroform solutions with a Varian A60 or HA100 spectrometer, i.r. spectra with a Unicam SP100 spectrometer, u.v. spectra with a Unicam SP 700C or Cary 14 spectrometer, and mass spectra with an A.E.I. MS9 spectrometer.

Dimethylketen was prepared by the pyrolysis of tetramethylcyclobutane-1,3-dione in a modified version of Johnson and Witzel's apparatus [10] and was used without further purification.

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[10] J. R. Johnson and J. M. Witzel, *Org. Reactions*, 1946, **3**, 136.

The Reaction of Pyridine N-*Oxide with Dimethylketen.*—(*a*) Dimethylketen (*ca.* 6 g.) was passed into a solution of freshly distilled pyridine *N*-oxide (3·4 g.) in dry benzene (180 ml.) and the mixture was set aside for 2 days. Evaporation of the solvent left an oil which, on addition of light petroleum (50 ml., b.p. 60—80°) deposited the *bicyclic compound* as a colourless solid (0·12 g., 2·7%), m.p. 128° (decomp.) (from benzene–light petroleum) (Found: C, 61·9; H, 6·8; N, 5·6. $C_{13}H_{17}NO_4$ requires C, 62·1; H, 6·8; N, 5·6%), $\lambda_{max.}$ (EtOH) 262 nm.; $\nu_{max.}$ (KBr disc) 1802 and 1738 cm.$^{-1}$; τ 3·37 (2H, dd, *J* 8, 1 Hz), 5·15 (2H, dd, *J* 8, 4·5 Hz), 7·05 (1H, m), 8·52 (6H, s,), 8·78 (6H, s); *m/e* 251 (1%), 120 (8), 95 (26), 80 (11), 79 (100), 78 (14), 71 (42), 70 (53), 58 (32), 52 (71), 51 (32), 50 (18), 44 (93), 43 (83), and 41 (62).

Evaporation of the mother-liquors left an evil-smelling oil from which pyridine was isolated as its picrate, identified by a mixed m.p.

(*b*) A sample of the original reaction mixture was distilled, and the distillate was added to freshly prepared solution of 2,4-dinitrophenylhydrazine in methanolic sulphuric acid. Acetone dinitrophenylhydrazine was deposited and was identified by a mixed m.p.

(*c*) Repetition of the preparation above was followed by extraction of the reaction mixture with cold dilute hydrochloric acid. Work-up of the organic layer gave the bicyclic compound. The aqueous extract was basified and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to leave an oil which was separated chromatographically (alumina and chloroform) into pyridine and 4-isopropylpyridine, both of which were identified by comparison of their picrates with authentic specimens.

Hydrolysis of the Compound $C_{13}H_{17}NO_4$.—A mixture of the compound $C_{13}H_{17}NO_4$ (70 mg.), acetic acid (0·2 ml.), and dilute hydrochloric acid (20 ml.) was boiled under reflux for 1 hr. The resultant solution was cooled and extracted with ether (2 × 10 ml.), the ether extract being discarded. The aqueous layer was neutralised with sodium hydrogen carbonate and extracted with ether (2 × 25 ml.). The ethereal solution was washed with water, dried ($MgSO_4$), and evaporated to leave a colourless oil (25 mg. 76%) identified as 4-isopropylpyridine by comparison of its picrate with an authentic sample.

4-*Isopropylpyridine.*—This compound was prepared by methylation of 4-picoline with sodamide and methyl iodide following a published procedure.[11] Distillation of the product gave a fraction, b.p. 182—188°, shown by the n.m.r. spectrum to be a mixture of 4-isopropyl- and 4-t-butyl-pyridine. The mixture was separated by preparative v.p.c. (di-isodecyl phthalate, 150°), and the 4-isopropylpyridine was converted into its picrate, m.p. 135° (lit.,[12] 135°) (Found: C, 47·8; H, 3·8; N, 15·9. Calc. for $C_8H_{11}N,C_6H_3N_3O_7$: C, 48·0; H, 4·0; N, 16·0%).

2-(1-*Carboxy*-1-*methylethyl*)-1,2-*dihydro*-1-*isobutyrylpyridine* (VIII).—Dimethylketen (*ca.* 7·5 g.) was passed into a solution of pyridine (3 ml.) in ether (140 ml.) at 0° and the mixture was then stirred with dilute sulphuric acid (80 ml., 1N) for 12 hr. The ethereal solution was extracted with ice-cold sodium hydroxide solution, and the extract was acidified at 0° and extracted with ether. This extract was dried (Na_2SO_4) and evaporated leaving a viscous oil which crystallised slowly giving the carboxylic acid as prisms, m.p. 86—87° (from aqueous methanol) (lit.,[8] 94—95°) (Found: C, 65·8; H, 8·0; N, 5·9. Calc. for $C_{13}H_{19}NO_3$: C, 65·8; H, 8·0; N, 5·9%), $\lambda_{max.}$ (EtOH) 299 nm. (log ε 3·71); $\nu_{max.}$ (KBr disc) 1700, 1662, and 1644 cm.$^{-1}$; τ −0·66br (1H, s), 3·31 (1H, d, *J* 7·5 Hz), 3·88 (1H, dd, *J* 8·5, 5·5 Hz), 4·2—4·7 (3H, m), 7·05 (1H, sept, *J* 7 Hz), 7·7—7·9 (overlapping signals, total 12H).

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