SYNTHESIS OF IMIDAZO[4,5-b]PYRIDINES

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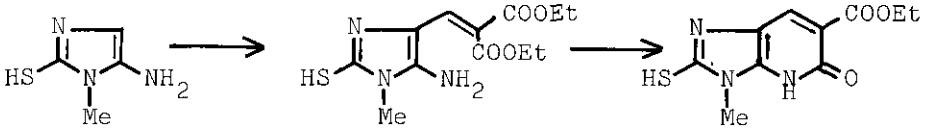
Novel syntheses of an imidazo[4,5-b]pyridine and its alkyl derivatives were studied and the structures of the products were determined.

All known imidazopyridines have been prepared by the imidazole cyclization of pyridines. We now present a new method for synthesizing imidazo[4,5-b]pyridines involving pyridine ring closure of substituted imidazole.

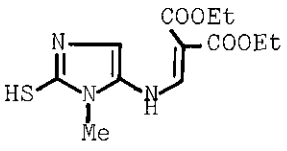
Heating equimolecular amounts of 5-amino-2-mercapto-1-methylimidazole (I)[1] and diethyl ethoxymethylenemalonate in nitrogen atmosphere gave yellow crystalline mass, $C_{12}H_{17}O_4N_3S$, mp 178°(decomp.), which was also obtained from (I)-HCl with diethyl dimethylaminomethylenemalonate in dimethylformamide (DMF) or acetic acid. Though the usual product of these

reactions was presumed to be (II'),[2] the spectral data of the product [nmr δ (DMSO-d_6), 1.22 (6H, t, 2 x $C\underline{H}_3CH_2O$), 4.08 and 4.17 (each 2H, q, $CH_3C\underline{H}_2O$), 3.36 (3H, s, $C\underline{H}_3N$), 7.49 (1H, s, -CH=), 7.73 (2H, broad s, $N\underline{H}_2$, disappeared on addition of D_2O), 11.16 ppm (1H, broad s, $S\underline{H}$, disappeared on addition of D_2O); ir (KBr), 3300-3360 (NH_2), 1675 cm^{-1} (ester C=O)] demonstrated the structure of the product to be (II) rather than (II'). O. Ceder et al[3] has reported that the reaction of 2,4-diaminothiazole with ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile occured at the 5-position of thiazole ring.

By treatment with 10% NaOH at room temperature or refluxing in EtOH in the presence of Et_3N, (II) afforded a colorless cyclized product (III), $C_{10}H_{11}O_3N_3S$, mp 265-267°, almost quantitatively.



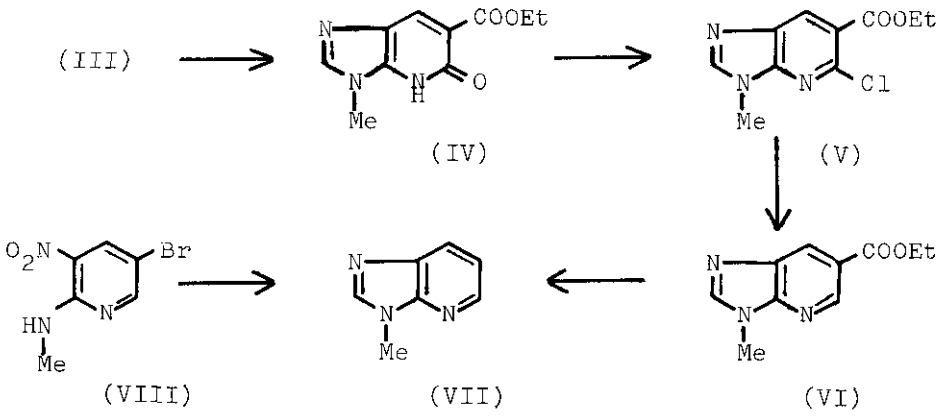
(I) (II) (III)



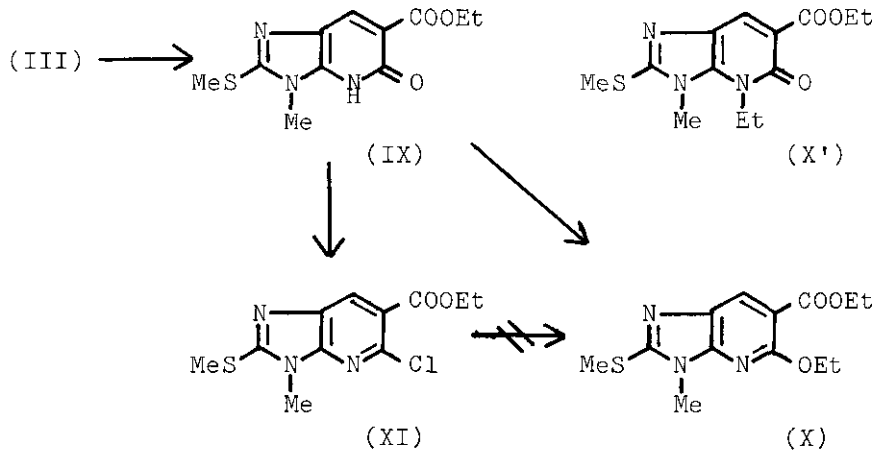
(II')

In order to confirm the skeletal structure of (III), it was converted into the compound (VII), mp 92°, by the following route : desulfurisation with HNO_3, chlorination with "pyrophosphoryl chloride",[4] catalytic dehalogenation with Pd/C,

hydrolysis with NaOEt and decarboxylation by heating in quinoline in the presence of copper chromite (via IV, V and VI). VII was identical with 3-methylimidazo[4,5-b]pyridine derived from 5-bromo-2-methylamino-3-nitropyridine (VIII)[5] by catalytic hydrogenation followed by refluxing in formic acid.



Alkylation of III with equimolecular amounts of MeI in 2% NaOH yielded the 2-methylthio derivative (IX), which was further allowed to react with EtI and K_2CO_3 in DMF to give the ethyl



compound (X or X'), $C_{13}H_{17}O_3N_3S$, mp 118-120°, ir (KBr) 1685 (ester C=O), 1610, 1440, 1260 cm^{-1}; nmr δ ($CDCl_3$) 1.37 and 1.45 (each 3H, t, $C\underline{H}_3CH_2$), 2.27 (3H, s, $C\underline{H}_3S$), 3.26 (3H, s, $C\underline{H}_3N$), 4.37 and 4.51 (each 2H, q, $CH_3C\underline{H}_2$) and 8.38 ppm (1H, s, C_7-H). The ethyl group of the product was eliminated by treatment with conc. H_2SO_4 at room temperature. The fact suggested that the alkylation of IX took place at the O-atom, not at the N-atom.

An attempt to obtain X *via* 5-chloro derivative (XI) prepared from IX with "pyrophosphoryl chloride" was unsuccessful owing to lack of reactivity of the chlorine atom. The structure of X was finally determined by X-ray analysis as shown in Fig. 1.[6]

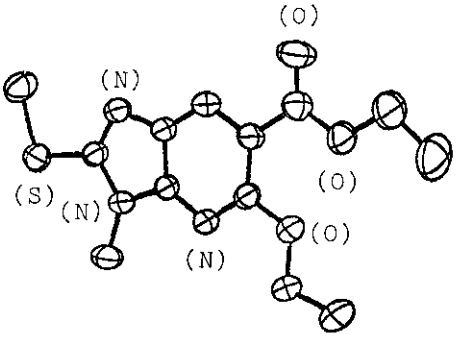


Fig. 1 Stereoscopic structure of X

REFERENCES AND NOTES

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2. In our earlier report, the structure of this compound was assigned as (II'); I. Hayakawa, H. Tanaka, R. Yoshimura, and R. Dohmori, Abstracts Papers of the 96th Annual Meeting of the Pharmaceutical Society of Japan, 1976, II, 98.

3. O. Ceder and B. Beiher, Tetrahedron, 1975, 31, 963.

4. G.B. Elion and G.H. Hitchings, J. Amer. Chem. Soc., 1956, 78 3508. IV and IX were not chlorinated by treatment with phosphoryl chloride even in drastic conditions.

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6. K. Yamazaki, R. Moroi, I. Hayakawa, and M. Sano, Details will be reported elsewhere.

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