

SYNTHESIS OF IMIDAZO[4,5-b]PYRIDINES

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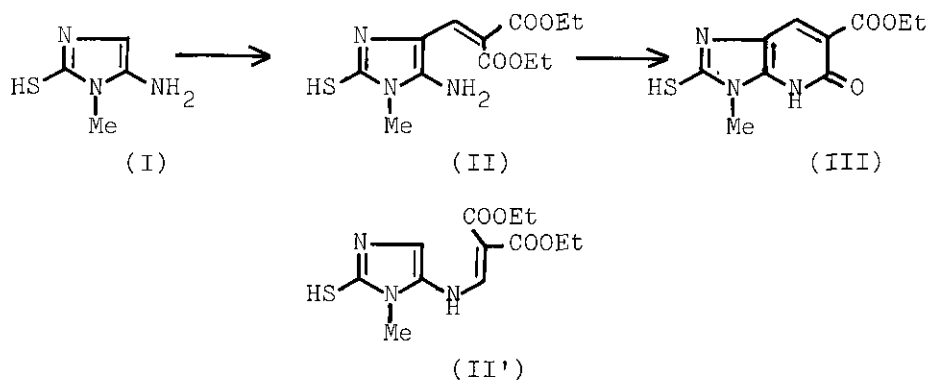
Novel syntheses of an imidazo[4,5-b]pyridine and its alkyl derivatives were studied and the structures of the products were determined. . .

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

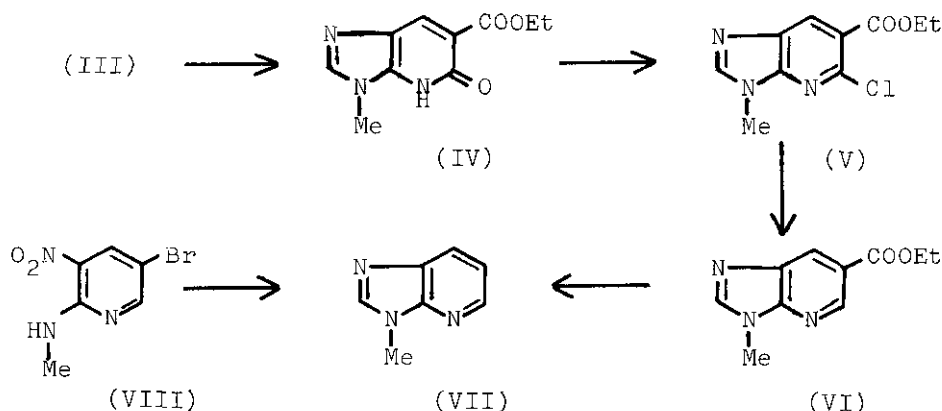
reactions was presumed to be (II'),² the spectral data of the product [nmr δ (DMSO- d_6), 1.22 (6H, t, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 4.08 and 4.17 (each 2H, q, $\text{CH}_3\text{CH}_2\text{O}$), 3.36 (3H, s, CH_3N), 7.49 (1H, s, $-\text{CH}=\text{}$), 7.73 (2H, broad s, NH_2 , disappeared on addition of D_2O), 11.16 ppm (1H, broad s, SH , disappeared on addition of D_2O); ir (KBr), 3300-3360 (NH_2), 1675 cm^{-1} (ester $\text{C}=\text{O}$)] 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 occurred 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), $\text{C}_{10}\text{H}_{11}\text{O}_3\text{N}_3\text{S}$, mp 265-267°, almost quantitatively.

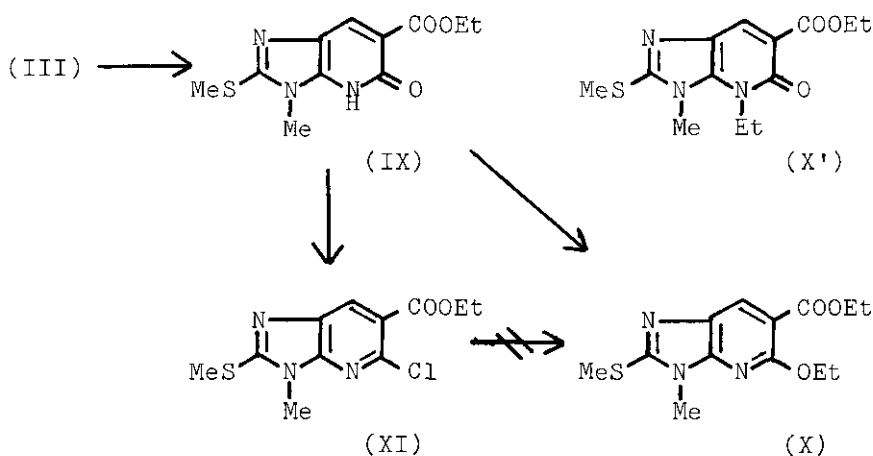


In order to confirm the skeletal structure of (III), it was converted into the compound (VII), mp 92°, by the following route : desulfurisation with HNO_3 , chlorination with "pyrophosphoryl chloride",⁴ catalytic dehalogenation with Pd/C,

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 K₂CO₃ 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, \underline{CH}_3CH_2), 2.27 (3H, s, \underline{CH}_3S), 3.26 (3H, s, \underline{CH}_3N), 4.37 and 4.51 (each 2H, q, \underline{CH}_3CH_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

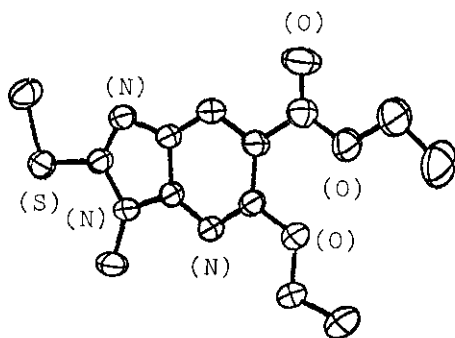


Fig. 1 Stereoscopic structure of X

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

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