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Syntheses of Novel Antimicrobial Compounds: Pyrazolo[5,1-*b*]thiazole, Imidazo[1,2-*b*]pyrazole, and Thiazolo[3,2-*b*]dihydro-1,2-diazepine

In our previous communication,[1] we reported the syntheses of pyrazolo[1,5-*a*]pyridine (I), pyrazolo[1,5-*a*]pyrazine (II), and pyrazolo[1,5-*b*]pyridazine (III) derivatives which have potent antimicrobial activities. This paper deals with syntheses and reactivities of pyrazolo-[5,1-*b*]thiazole (IV, V), imidazo[1,2-*b*]pyrazole (VI), and thiazolo[3,2-*b*]dihydro-(1,2)-diazepine (VII, VIII) derivatives.

N-Amination of thiazoles (IXa, b), benzothiazoles (Xa, b, c), and imidazole (XI) with hydroxylamine O-sulfonic acid or O-mesitylene sulfonylhydroxylamine gave the corresponding N-aminothiazolium (XIIa, b), N-aminobenzothiazolium (XIIIa, b, c), and N-amino-imidazolium (XIV) compounds in a good yield. N-Amino compounds, XIIb, XIIIb, and XIV, were cyclized by treatment with acetic anhydride and anhydrous sodium acetate to the

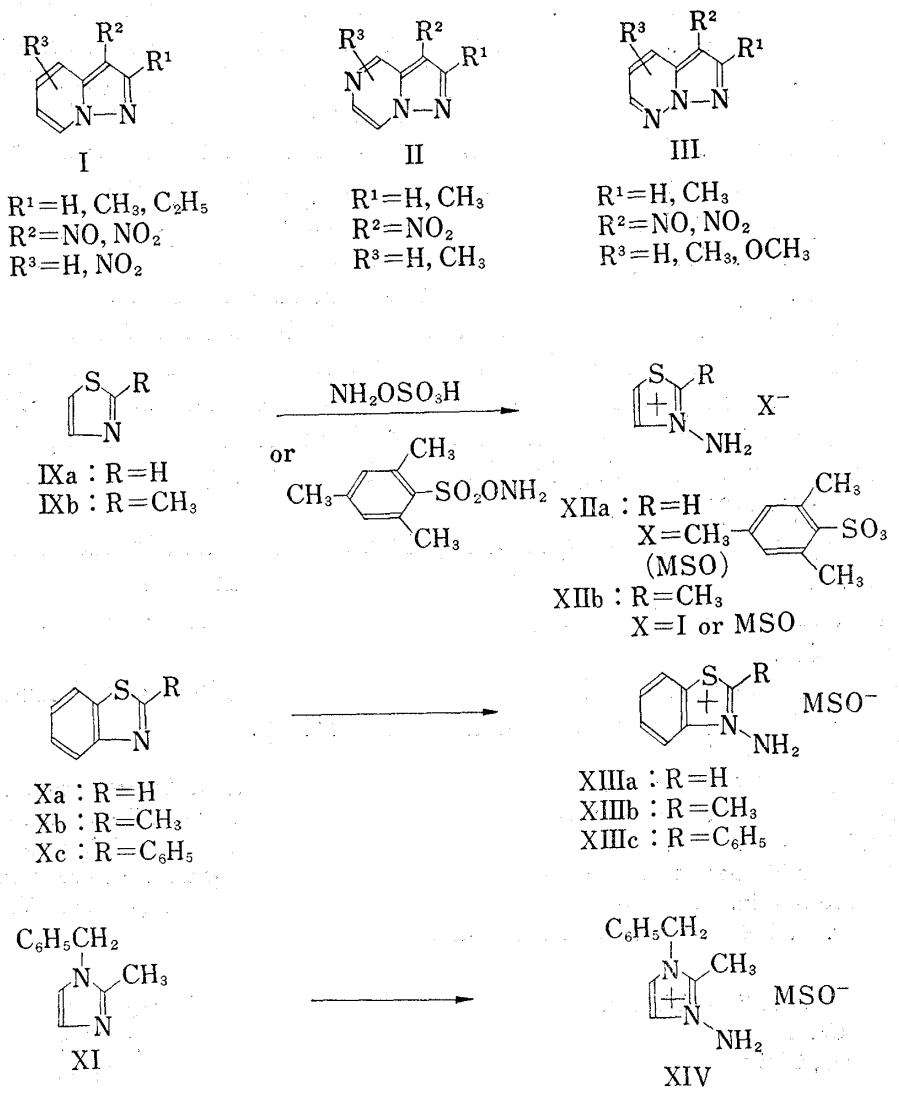


Chart 1

1) M. Hirobe, Y. Minamoto, and T. Okamoto, Abstr. Papers. 90th Annu. Meet. Pharm. Soc. Japan, 1970, II-47; S. Suzue, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 2146 (1973).

pyrazolo derivatives, IVa (42.6%, mp 130—131°), Va (21.7%, mp 148°), and VIa (25.4%, mp 128—130°), respectively.

The acetyl group of these pyrazolo derivatives was easily converted into the nitroso group or deacetylated. Nitrosation of IVa and VIa with sodium nitrite and 15% hydrochloric acid gave IVb (mp 169°) and VIb (mp 132°) in a quantitative yield. Deacetylation reactions of IVa, Va, and VIa proceeded in quantitative yields by heating with hydrochloric acid and gave IVc (oil), Vc (mp 82—83°), and VIc (oil). Deacetylated compounds, IVc and Vc, gave the corresponding nitroso compounds, IVb and Vb (mp 187—188°), by nitrosation under the above-mentioned condition and the yields were also quantitative. Reduction of VIc with sodium in liquid ammonia gave debenzylated compound, VId (mp 177—179°), in 60% yield. The structure of VId was confirmed by mixed melting point determination with an authentic sample[2] and comparison of their infrared (IR) and nuclear magentic resonance (NMR) spectra.

Huisgen, *et al.*[3] reported that pyrazolo[1,5-*a*]pyridine derivative (I, $R^1=R^2=COOCH_3$, $R^3=H$) is obtained by the reaction of N-aminopyridinium iodide and dimethyl acetylenedicarboxylate (DAC) in the presence of a base. We investigated this kind of 1,3-dipolar cycloaddition reaction with N-aminothiazole compounds to find another route for obtaining pyrazolothiazoles or their dihydro derivatives. N-Amino compounds (XIIa, b, and XIIIa, b, c) were reacted with DAC in the presence of potassium carbonate in DMF at room temperature for 48 hr. The reaction products were not pyrazolothiazole derivatives but 1:2

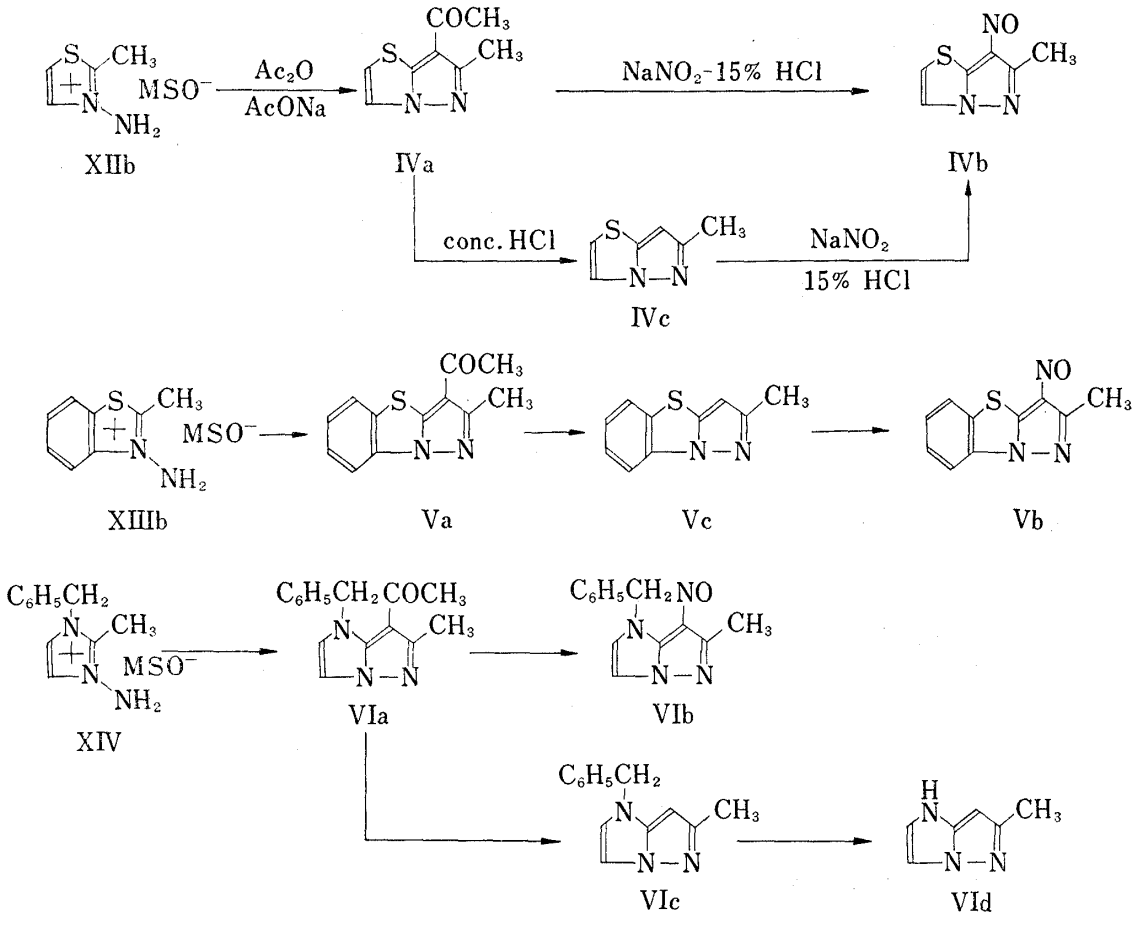
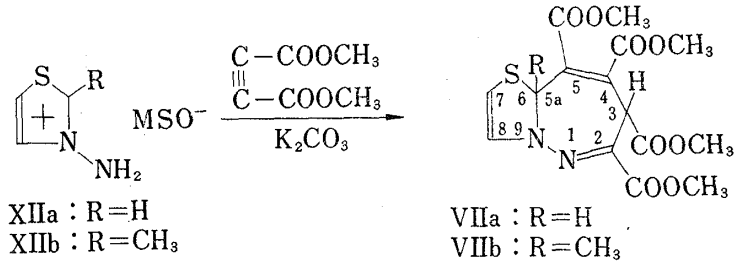


Chart 2

2) J. Elguero, R. Jacquier, and S. Mignonac-Mondon, *J. Heterocyclic. Chem.*, **10**, 411 (1973).
3) R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Letters.*, **1962**, 387.

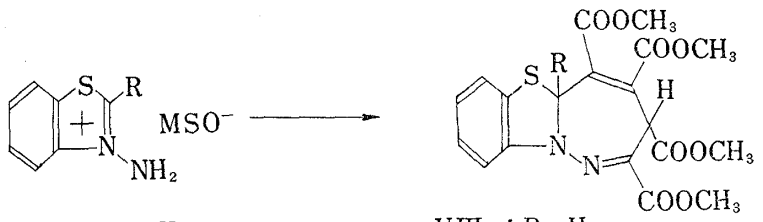
adduct (VIIa) of the starting material and DAC. The yield of VIIa was 43.3% and showed following physical constants: mp 122—124°. Mass Spectrum: Calcd. for $C_{15}H_{16}O_8N_2S$: 384. Found: 384 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1738, 1708. NMR ($CDCl_3$) δ: 3.73, 3.84, 3.90, 3.96 (each 3H, s, $COOCH_3$), 6.13 (1H, s, 3-H), 6.21 (1H, d, J=8.5 Hz, 7-H), 7.06 (1H, d, J=8.5 Hz, 8-H), 8.12 (1H, s, 5a-H). From these data the structure was assumed to be VIIa .The same type of reaction products VIIb (mp 145—146°), VIIIa (amorphous), VIIIb (amorphous), and VIIIc (amorphous) were respectively obtained from XIIb, XIIIa, XIIIb, and XIIIc under the above condition in 23—41% yield.

On the other hand, N-ethoxycarbonylaminothiazolium chloride (XV), which was obtained by the reaction of XIIa with ethyl chloroformate, gave the desired product, XVI (mp 92—93°), in 74.2% yield. IR ν_{max}^{KBr} cm^{-1}: 1730. NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.5 Hz, $COOCH_2\underline{CH_3}$), 3.82, 3.95 (each 3H, s, $COOCH_3$), 4.35 (2H, q, J=7.5 Hz, $COO\underline{CH_2}CH_3$), 6.73 (1H, d, J=8.5 Hz, 2-H), 7.04 (1H, d, J=8.5 Hz, 3-H), 7.97 (1H, s, 7a-H), Mass Spectrum: Calcd. for $C_{12}H_{14}O_6N_2S$: 314. Found: 314 (M^+). Further studies on the structure and reactivities of compound (XVI) are now in progress. Among these compounds, IVb and Vb have potent anitimicrobial activity.



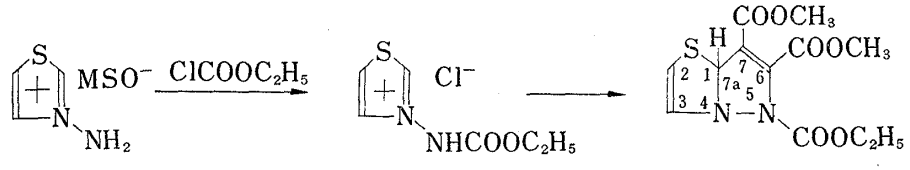
XIIa : R=H
XIIb : R=CH_3

VIIa : R=H
VIIb : R=CH_3



XIIIa : R=H
XIIIb : R=CH_3
XIIIc : R=C_6H_5

VIIIa : R=H
VIIIb : R=CH_3
VIIIc : R=C_6H_5



XIIa XV XVI

Chart 3

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