A NEW ALKYLATION OF PYRIDAZINES WITH NITROMETHANE AND NITROETHANE

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3-Hydroxy-4-ethoxycarbonyl-6-chloropyridazine (I) reacts with nitromethane and nitroethane to give the respective 5-methyl (I-A) and 5-ethyl (I-B) derivatives when their solution in DMSO is stirred at room temperatures in the presence of potassium carbonate. The scope of this type of nuclear alkylation of pyridazines is rather wide as shown in Table.

Recently we have reported that 3,6-dichloro-4-cyanopyridazine reacts with primary amines to give neither 3- nor 6-amino derivatives but 5-amino compound resulting from nuclear amination as exemplified below[1].

RNH_2: NH_3, $MeNH_2$, etc.

In the course of the study on such a nucleophilic reaction, we applied nitromethane and nitroethane as nucleophile to various

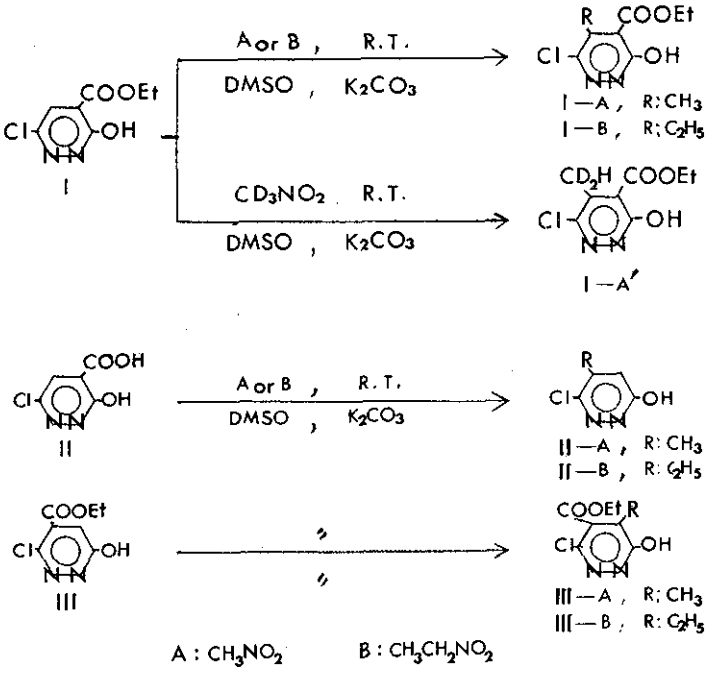
pyridazines in the presence of a basic catalyst and found that nuclear alkylation occurred instead of nitroalkylation in some cases.

For instance, when a solution of 3-hydroxy-4-ethoxycarbonyl-6-chloropyridazine (I) and nitromethane (A) (5 equiv.) in DMSO was stirred in the presence of potassium carbonate (1 equiv.) at room temperature for 12 hr, 3-hydroxy-4-ethoxycarbonyl-5-methyl-6-chloropyridazine (I-A) was obtained as colorless crystals, mp 173-175°, in 63% yield. Structure assignment of I-A is based on the elemental analysis [$C_8H_9O_3N_2Cl$], the mass spectrum [M^+: m/e 216] and the nmr spectrum [δ (DMSO-d_6): 2.15 (3H, s, CH_3)].

The reaction of I with nitroethane (B) similarly afforded the corresponding 5-ethyl derivative (I-B) in 70% yield. This result evidently indicates that the formation of I-A in the first reaction resulted from nucleophilic attack by A at the 5-position of I, the possibility of the participation of DMSO as a reactant being almost excluded. This was further confirmed by the formation of I-A' [mp 165-167°; mass spectrum m/e: 218 (M^+); nmr (DMSO-d_6) δ: 2.19 (1H, s, CD_2H)] from the reaction of I with nitromethane-d_3.

Treatment of 3-hydroxy-6-chloropyridazine-4-carboxylic acid (II) with A and B resulted in the formation of decarboxylated 5-alkyl compounds, II-A and II-B, respectively in somewhat lower yields.

3-Hydroxy-5-ethoxycarbonyl-6-chloropyridazine (III), the position isomer of I with respect to ethoxycarbonyl group, also underwent the same type of alkylation by means of A and B, giving 4-alkyl compounds, III-A and III-B in 40 and 55% yields, respectively.

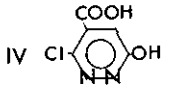


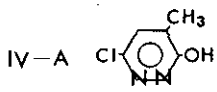
Further examination with various pyridazines revealed that the scope of this type of nuclear alkylation is rather wide at least in the pyridazine series as summarized in Table. The structure of products thus formed was established by elemental analysis, nmr and mass spectrometry, and synthesis by another route.

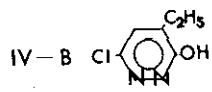
Among solvents used, DMSO was found to be most favorable; for example, the reaction of I with A in boiling THF gave I-A only in a minute amount. Potassium carbonate operated effectively as basic catalyst in most reactions, however in a few cases triethylamine was apparently more effective than potassium carbonate; the reaction of IV or V in the presence of potassium carbonate gave no product.

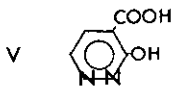
Table Reaction of Pyridazines with Nitromethane (A) and Nitroethane (B)

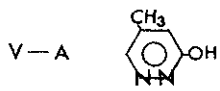
Pyridazine No	Reagent	Base	No	Product mp(°C)	yield (%)
I	A	K_2CO_3	I-A	173-175	63
	B		I-B	131-132	70
II	A	K_2CO_3	II-A	232	16
	B		II-B	205	38
III	A	K_2CO_3	III-A	112-113	40
	B		III-B	104-106	55
IV	A	NEt_3	IV-A	170-171	25
	B		IV-B	138-141	24
V	A	NEt_3	V-A	157.5	55
	B		V-B	99-101	25

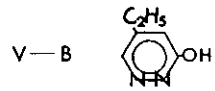




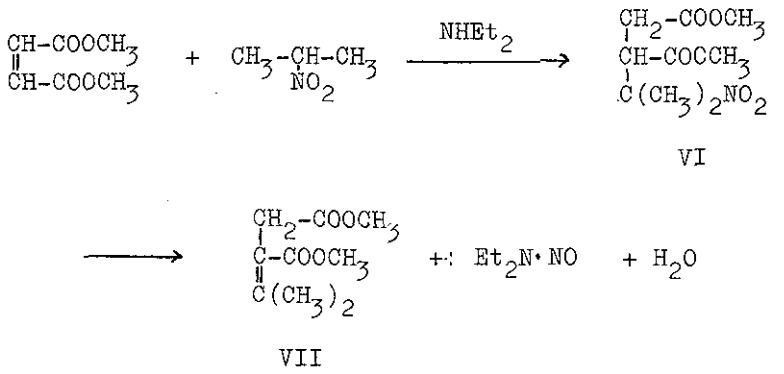








Kloetzel[2] has described that dimethyl fumarate reacts with 2-nitropropane in the presence of diethylamine to give dimethyl teraconate (VII) via dimethyl 3-methyl-3-nitro-1,2-butanedicarboxylate (VI). Although this reaction apparently resembles the above-mentioned one, the use of triethylamine gives VI instead of VII. Therefore, our reaction should be possibly assumed to



follow a different course.

All pyridazines described above are carboxylic acid derivatives of 3-pyridazinone, however this partial structure is not necessarily essential for the initiation of the reaction, because there are signs of methylation of 3,6-dichloro-4-cyanopyridazine with A, the details of which remain to be explored.

Further work is in progress to explore the essential features, the scope and the mechanism of the reaction.

REFERENCES

1 Presented at the 84th Meeting of Kyushu Branch of Pharmaceutical Society of Japan, Fukuoka, Japan, October, 1973.

2 M. C. Kloetzel, J. Amer. Chem. Soc., 1948, 70, 3571.

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