[Chem. Pharm. Bull. 16(5) 939—943 (1968)]

UDC 547.852.2.4

The C-Alkylaminomethylation of Pyridazinol N-Oxides. IV.[1] The Mannich Reaction of 3- and 5-Pyridazinol 1-Oxides using Primary Amines

Shozo Kamiya,[2a] Genzo Okusa, Mizue Osada, Michiko Kumagai,[2b] Akitada Nakamura, and Kimie Koshinuma[2a]

National Institute of Hygienic Sciences[2a] and Showa College of Pharmaceutical Sciences[2b]

(Received February 8, 1968)

The Mannich reaction of 3-pyridazinol 1-oxide using benzylamine, gave 6-benzylaminomethyl-3-pyridazinol 1-oxide as a major, together with the 6,6′-(N-benzyl-1,1′-dimethylamino)bis(3-pyridazinol 1-oxide) as a minor.

The Mannich reaction of 5-pyridazinol 1-oxide using benzylamine, ethylamine or methylamine, also gave the corresponding 6-alkylaminomethyl-5-pyridazinol 1-oxides, but, in each case, the 6,6′-bis compound could not be isolated.

The predominance of the enol forms in the structures of 3-pyridazinol 1-oxide and 5-pyridazinol 1-oxide was discussed by comparing the IR spectra of their deuterated compounds with that of 3-pyridinol 1-oxide.

The condensation reaction of a compound containing an active hydrogen atom with formaldehyde and a primary or secondary amine, which results in the replacement of the hydrogen by an alkylaminomethyl group, is known as the Mannich reaction.

In the previous paper,[3] it has been reported that the Mannich reaction of 3-pyridazinol 1-oxide using 37% formalin and a secondary amine such as piperidine, morpholine, dimethylamine or 2,2′-dichlorodiethylamine gave 6-alkylaminomethyl-3-pyridazinol 1-oxide, together with 4,6-di(alkylaminomethyl)-3-pyridazinol 1-oxide.

As an extension of this series, the present paper deals with the Mannich reaction of 3-pyridazinol 1-oxide (I), 6-methyl-3-pyridazinol 1-oxide (IV) and 5-pyridazinol 1-oxide (VI) using a primary amine such as benzylamine, methylamine or ethylamine instead of secondary amines which are usual amine component in the Mannich reaction.

Results and Discussion

When I, suspended in ethanol, was allowed to react with an equimolar mixture of 37% formalin and benzylamine at room temperature, two kinds of products, A (mp 225° decomp.) and B (mp 224—226° decomp.) were isolated as both hydrochlorides. The analytical data fit a mono-Mannich base for A (40% yield) and an 6,6′-bis compound for B (9% yield). Although no synthetic proof has been made, the alkylaminomethylated position was determined by comparison of the NMR spectra of these Mannich bases with those of various pyridazine

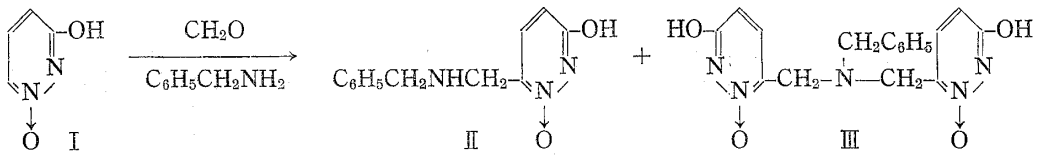


Chart 1

1) Part III: G. Okusa and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 142 (1968).
2) Location: *a*) *Tamagawayoga, Setagaya, Tokyo*; *b*) *Turumaki, Setagaya, Tokyo.*
3) G. Okusa and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **15**, 1172, 1733 (1967).

1-oxide derivatives,[1] in which the signals of these ring protons generally appear in the order of 3<6<5<4 (τ_3: 0.70—1.67, τ_6: 1.78—1.90, τ_5: 2.10—2.48, τ_4: 2.77—3.33).

As shown in Table I, the NMR spectrum of the mono-Mannich base in deuterium oxide at 60 Mc shows a singlet at 2.55 τ (5H) corresponding a phenyl ring, and an AB-type quartet at 2.24 τ and 3.10 τ (2H, J=9.0 cps) in the low field. The signal at 2.24 τ is reasonable to assign as H^5-proton and the latter as H^4-proton from the NMR parameters of various 3-pyridazinol 1-oxides reported in our previous papers.[3] Thus, the mono-Mannich base is the product of substitution at the 6-position to give 6-benzylaminomethyl-3-pyridazinol 1-oxide (II). The NMR spectrum of the 6,6'-bis derivative (Table I) also supports the proposed structure, 6,6'-(N-benzyl-1,1'-dimethylamino)bis(3-pyridazinol 1-oxide) (III) which could be obtained by the treatment of II with 37% formalin and I, though poor yield.

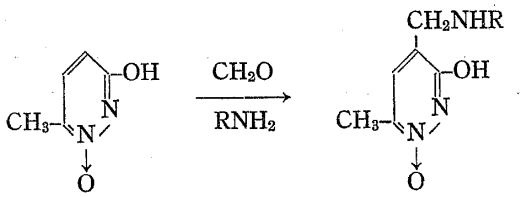
Treatment of I with excess amounts of the reagents resulted in the polymerization of the products, and the expected 4,6-disubstituted derivative could not be obtained. On the other hand the reaction using methylamine yielded a large quantity of an yellow powder which seemed to be a polymerized product from its insolubility in various solvents.

Table I. The NMR Parameters (τ) for the Ring Protons in 3- and 5-Pyridazinol 1-Oxide Derivatives in Deuterium Oxide

	I	II	III[a]	IV	Va	Vb	VI[a]	VIIa
H^3	—	—	—	—	—	—	1.71 (doub.)	2.04 (doub.)
H^4	2.92 (doub.)	3.10 (doub.)	3.40 (doub.)	3.02 (doub.)	—	—	3.25 (quart.)	3.47 (doub.)
H^5	2.16 (quart.)	2.24 (doub.)	2.15 (doub.)	2.25 (doub.)	2.57 (sing.)	2.43 (sing.)	—	—
H^6	1.77 (doub.)	—	—	CH_3: 7.56	CH_3: 7.75	CH_3: 7.56	2.08 (quart.)	—

a) Measured in DMSO-d_6.

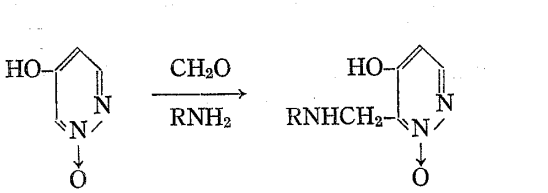
Then, the Mannich reaction of 6-methyl-3-pyridazinol 1-oxide (IV), 6-position of which was blocked, was examined. The same treatment of IV using benzylamine gave a mono-Mannich base in only 4% yield, and most of the starting material was recovered. Its structure was similarly decided to be 4-benzylaminomethyl-6-methyl-3-pyridazinol 1-oxide (Va) from the NMR spectrum which indicated H^5-proton at 2.57 τ as a singlet. Similarly, 4-methylaminomethyl-6-methyl-3-pyridazinol 1-oxide (Vb) was synthesized as the salt with IV in only 8% yield. This salt was converted to a hydrochloride by treating with hydrochloric acid. Their physical properties and analytical data were tabulated in Table II.



IV

Va : R=$C_6H_5CH_2$
Vb : R=CH_3

Chart 2



VI

VIIa : R=$C_6H_5CH_2$
VIIb : R=(*p*)CH_3O-$C_6H_4CH_2$
VIIc : C_2H_5
VIId : CH_3

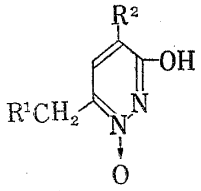
Chart 3

Continuously, the Mannich reaction of 5-pyridazinol 1-oxide (VI), in which the hydroxy group was located at the *para* position of the 2-nitrogen, was tried in connection with I. When VI reacted with an equimolar mixture of 37% formalin and benzylamine at room temperature,

a mono-Mannich base, mp 209—210° decomp., was obtained in 18% yield. Treatment of VI with excess amounts of the reagents did not give a di-Mannich base and also an 6,6′-bis compound, and only the mono-Mannich base was isolated in 70% yield.

The result obtained in the Mannich reaction of I suggests that a benzylaminomethyl group was introduced into the 6-position which is the *ortho* position from the N-oxide function and also from the hydroxy group. As a matter of fact, the NMR spectrum (Table I) of the mono-Mannich base in deuterium oxide shows an AB-type quartet at 2.04 τ due to H^3-proton and

Table II. 6- and 4-Alkylaminomethyl-3-pyridazinol 1-Oxides

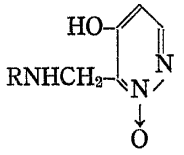


No.	R^1	R^2	mp (decomp.) (°C)	Appearance (Recryst. solv.)
II	$C_6H_5CH_2NH$	H	226—227	granules (EtOH)
III[a]	$C_6H_5CH_2N$ <	H	224—226	needles (EtOH)
Va	H	$C_6H_5CH_2NHCH_2$	219—220	granules (EtOH–(iso-Pr)$_2$O)
Vb[b]	H	CH_3NHCH_2	230	leaflets (EtOH–(iso-Pr)$_2$O)

No.	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
III	40	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.83	5.27	15.70	53.29	5.52	16.03
III[a]	9	$C_{17}H_{17}O_4N_5 \cdot HCl$	52.11	4.63	17.88	52.10	4.78	17.50
Va	4	$C_{13}H_{15}O_2N_3$	63.66	6.16	17.13	63.89	6.48	17.10
Vb[b]	8	$C_7H_{11}O_2N_3 \cdot \frac{1}{2}C_5H_6O_2N_2$	49.13	6.07	24.13	49.18	5.93	24.26

a) 6,6′-Bis compound. *b*) A salt with 3-Pyridazinol 1-oxide.

Table III. 6-Alkylaminomethyl-5-pyridazinol 1-Oxides



No.	R	mp (decomp.) (°C)	Appearance (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	$C_6H_5CH_2$	209—210	granules (MeOH)	70	$C_{12}H_{13}O_2N_3$	62.32	5.67	18.17	61.98	5.88	17.42
VIIb	(*p*)CH_3O–$C_6H_4CH_2$	219—220	granules (MeOH–EtOH)	27	$C_{13}H_{15}O_3N_3 \cdot HCl$	52.44	5.08	14.11	52.51	5.30	14.38
VIIc	C_2H_5	205	granules (MeOH)	40	$C_7H_{11}O_2N_3$	49.69	6.55	24.84	49.58	6.58	24.27
VIId	CH_3	214—218	granules (MeOH)	63	$C_6H_9O_2N_3$	46.44	5.85	27.08	46.40	5.98	27.52

3.47 τ due to H^4-proton (2H, J=10.0 cps), along with a singlet at 2.52 τ (5H) corresponding to a phenyl ring, in the low filed. Thus, the C-alkylaminomethylated position in the mono-Mannich base derived from VI was confirmed to be the 6-position.

Similarly, the Mannich reaction of VI using *p*-methoxybenzylamine, ethylamine and methylamine gave the corresponding mono-Mannich bases (VIIb, VIIc, VIId), but, in each case, a di-Mannich base and also an 6,6′-bis compound could not be obtained. Their physical properties and analytical data were tabulated in Table III.

As mentioned above, the yields of these Mannich bases arising from primary amines were generally low and their isolation from the by-products was very difficult, as compared with the same reaction using secondary amines. The reason must come from the complexities in the reaction of a primary amine with formalin and also in the reaction of NH of these mono-Mannich bases with formalin.

It has been reported that I and VI, in which their hydroxy groups are located at the *ortho* and *para* positions of the 2-nitrogen respectively, are present as the enol forms (Ia, VIa) from their UV and pK_a data.[1,4] However, they are able to tautomerize to the lactam forms (Ib, VIb) and also to the zwitterion forms (Ic, VIc) as Chart 4.

The results obtained in the Mannich reaction of I and VI using primary and secondary amines,[1,3] gave a chemical evidence that they are practically phenolic, and suggests that the contributions of the lactam form and the zwitterion form among these prototropic tautomers will be little. In addition to the UV data, pK_a values and to this chemical evidence, the predominance of the enol forms could be substantiated by comparing the IR spectra of I and VI with those of their deuterated compounds.

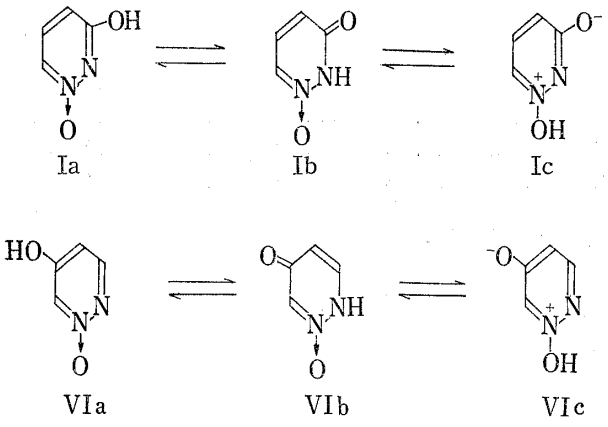


Chart 4

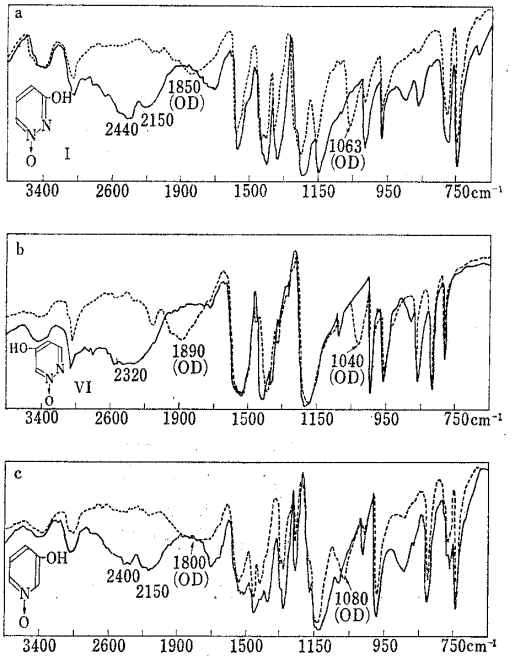


Fig. 1. The IR Spectra of 3-Pyridazinol 1-Oxide, 5-Pyridazinol 1-Oxide, 3-Pyridinol 1-Oxide and Their Deuterated Compounds in KBr

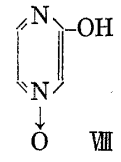
---------- : Deuterated Compound

As shown in Fig. 1-a and 1-b, it is difficult to distinguish the OH regions (3000—1800 cm^{-1}) in the IR spectra of I and VI becuase of their complication. 3-Pyridinol 1-oxide (Fig. 1-c) which has a typical phenolic hydroxy group, shows a broad absorption with two maxima at 2400 and 2150 cm^{-1}. However, these bands disappeared on deuteration with deuterium oxide, and the corresponding OD stretching absorption (νOD) appeared at 1800 cm^{-1} as a broad band, together with the OD in plane deformation frequencies (δ OD) at 1080 cm^{-1}. In Fig. 1-a and 1-b, the same result was obtained in those of the deuterated I and VI which indicated the ν OD absorptions at 1850 and 1890 cm^{-1}, respectively. The δ OD absorptions are also observed at 1063 cm^{-1} for the deuterated I and at 1040 cm^{-1} for the

4) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), 7, 938 (1959).

deuterated VI. These IR data of I and VI show that they are predominantly present as an enol form in solid, and an enol attached to a diazine nucleus as an aromatic sextet is phenolic as well as in the case of 3-pyridinol 1-oxide.

As noted in Table II and III, IV gave the Mannich bases in poor yields in striking contrast to I and VI. This fact will be explained on the basis of prototropic tautomerism. The electron-donating nature of the 6-methyl group in IV decreases the influcence of the N-oxide function to keep the enol form, and the increased basicity of the 2-nitrogen acts to increase the contribution of the alternative lactam form, of which aromaticity is considerably decreased as compared with those of I and VI. Accordingly, IV gave the Mannich bases in poor yields. This assumption was also supported by their pK_a values (I=4.0, IV=4.5, VI=4.1), in which that of IV is contrast with those of I and VI.



VIII

Emimycin,[5] an antibiotic produced by *Streptomyces* sp., has a structure of 3-pyrazinol 1-oxide (VIII) which is structurally similar to I and VI. However, none of these compounds showed bacteriostatic activities below concentrations of 1000 μg/ml against *Escherichia coli*, *Staphylococcus aureus* and *Salmonella typhosa*. Their antitumor and other tests are under investigation, results of which will be reported separately.

Experimental[6]

6-Benzylaminomethyl-3-pyridazinol 1-Oxide (II) and 6,6′-(N-Benzyl-1,1′-dimethylamino)bis(3-pyridazinol 1-Oxide) (III)——To a suspended solution of 1.12 g (0.01 mole) of 3-pyridazinol 1-oxide[4] in 20 ml of ethanol, was added 1.0 ml (*ca.* 0.01 mole) of 37% formalin and 1.18 g (0.01 mole) of benzylamine, the mixture was heated at 40–45° on a water bath for 5 min, and the clear solution was allowed to stand overnight. The reaction mixture was concentrated, and the separated crystals were filtered. These crystals, mp 160–165° (decomp.), were converted to the hydrochloride by treating with 10% hydrochloric acid. Yield, 1.07 g (40%). Colorless granules, mp 226—227° (decomp.). The filtrate was evaporated to dryness under reduced pressure, the residue was treated with 10% hydrochloric acid, and the solution was evaporated to dryness under reduced pressure. The residue was recrystallized from 95% ethanol several times to colorless needles, mp 222—226° (decomp.). 6,6′-Bis compound (III), 0.18 g (9%).

4-Benzylaminomethyl-6-methyl-3-pyridazinol 1-Oxide (Va)——A typical experiment for 4-alkylaminomethyl-6-methyl-3-pyridazinol 1-oxide is described with 4-benzylaminomethyl-6-methyl-3-pyridazinol 1-oxide (Table II). To a suspended solution of 0.63 g (0.005 mole) of 6-methyl-3-pyridazinol 1-oxide[7] was added 1.0 ml (0.01 mole) of 37% formalin and 0.54 g (0.005 mole) of benzylamine, and the mixture was allowed to stand overnight. The reaction mixture was evaporated to dryness under reduced pressure, the residue was recrystallized from a mixture of ethanol and iso-propylether several times. Yield, 0.05 g (4%), mp 219—220° (decomp.). The starting material, 0.32 g (51%) was recovered from the mother liquor.

6-Benzylaminomethyl-5-pyridazinol 1-Oxide (VIIa)——A typical experiment for 6-alkylaminomethyl-5-pyridazinol 1-oxide is described with 6-benzylaminomethyl-5-pyridazinol 1-oxide (Table III). To a suspended solution of 0.56 g (0.005 mole) of 5-pyridazinol 1-oxide[1] in 20 ml of ethanol was added 0.59 g (0.006 mole) of benzylamine and 1.0 ml (*ca.* 0.01 mole) of 37% formalin, the mixture was gently heated on a water bath till a clear solution was obtained, and the solution was allowed to stand overnight. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was triturated with a small amount of ethanol. The separated crystals were filtered and recrystallized from methanol to give 0.21 g (18%) of the product, mp 209—210° (decomp.).

Preparation of Deuterated Compounds——The replacement of the hydrogen of OH in these compounds was accomplished as follows. A sample was dissolved in an excess amount of deuterium oxide, the solution was allowed to stand overnight, and evaporated under reduced pressure. This procedure was repeated two or three times. The residue was dried over potassium hydroxide in vacuum and its IR spectrum was measured in a potassium bromide disk.

Acknowledgement The authors wish to thank Prof. T. Kato, Tohoku University, and Dr. H. Shindo, Central Research Laboratory, Sankyo Co., Ltd., for helpful discussion. Thanks are also due to Drs. T. Itai, I. Suzuki, and S. Iwahara, this institute, for their interest.

5) M. Terao, *J. Antibiotics* (Tokyo), Ser. A, **16**, 182 (1963).
6) All melting points are uncorrected. IR and UV spectra were measured on a JASCO Model IR-S infrared spectrophotometer, and on a Hitachi Model EPS-2 ultraviolet spectrophotometer. NMR spectra are determined on a Japan Electron Optics Model C-60H spectrophotometer.
7) T. Nakagome, *Yakugaku Zasshi*, **82**, 249 (1962).