action of chloral hydrate, hexobarbital, or phenobarbital. These reports are very interesting in regard with the present experiments. It is progressing to investigate the relationship between the chemical structure and stimulatory effect on the drug-metabolism.

The authors are indebted to Teikoku Hormone Mfg. Co. for their supply of testosterone and to Shionogi & Co. for that of cyclobarbital.

Summary

Some factors affecting on the metabolism of cyclobarbital (EHB) by the rat liver preparation were examined.

Sex difference was especially shown in the formation of 3-OH-EHB, but no difference in that of 3-keto-EHB was shown.

The pretreatment of female rats with EHB enhanced both the formation of 3-OH-EHB and that of 3-keto-EHB in approximately same proportion as controls. However, the pretreatment with 3-OH-EHB increased the formation of 3-OH-EHB and decreased that of 3-keto-EHB from EHB. The conversion of 3-OH-EHB to 3-keto-EHB was depressed by the pretreatment with testosterone or 3-OH-EHB. On the other hand, the conversion of 3-keto-EHB to 3-OH-EHB was stimulated by such a treatment. Another metabolite of EHB, 3-keto-EHB, has not stimulatory effect on the EHB-metabolism.

The removal of the adrenal glands did not prevent the stimulatory effect of EHB.

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153. **Shigeru Sako** : Syntheses of Pyridazine Derivatives. I. The Reactivity of Chlorine Atoms in 3- and 6-Positions of 3,6-Dichloropyridazine 1-Oxide.

(*National Institute of Hygienic Sciences*[*1])

In the previous paper,[1] it was shown that 3,6-dichloropyridazine (I) and 3-alkoxy-6-chloropyridazines gave their 1-oxide derivatives by N-oxidation. In this paper, reactivity of chlorines of 3,6-dichloropyridazine 1-oxide (II) in nucleophilic substitution will be described.

When (II) was reacted with one equivalent of sodium ethoxide at room temperature, two isomers, (A) and (B), were obtained. The former melted at 115~116°, yield 72%, and the latter melted at 138~139°, yield 11%. (A) was identified by mixed melting point determination and by comparing its infrared spectrum with 3-ethoxy-6-chloropyridazine 1-oxide (IIIb), prepared in the previous work.[1] Accordingly, a structure of 6-ethoxy-3-chloropyridazine 1-oxide (IVb) was assigned to (B). This fact seemed to be rather curious, because these seemed to have little contribution of −M effect of N-oxide, to the reactivity of 6-chlorine atom, and only −M effect of tertiary nitrogen to 3-chlorine atom could be seen. But anyhow, the chlorine atom in 3-position was found more

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1) T. Itai, S. Sako : This Bulletin, **10**, 989 (1962).

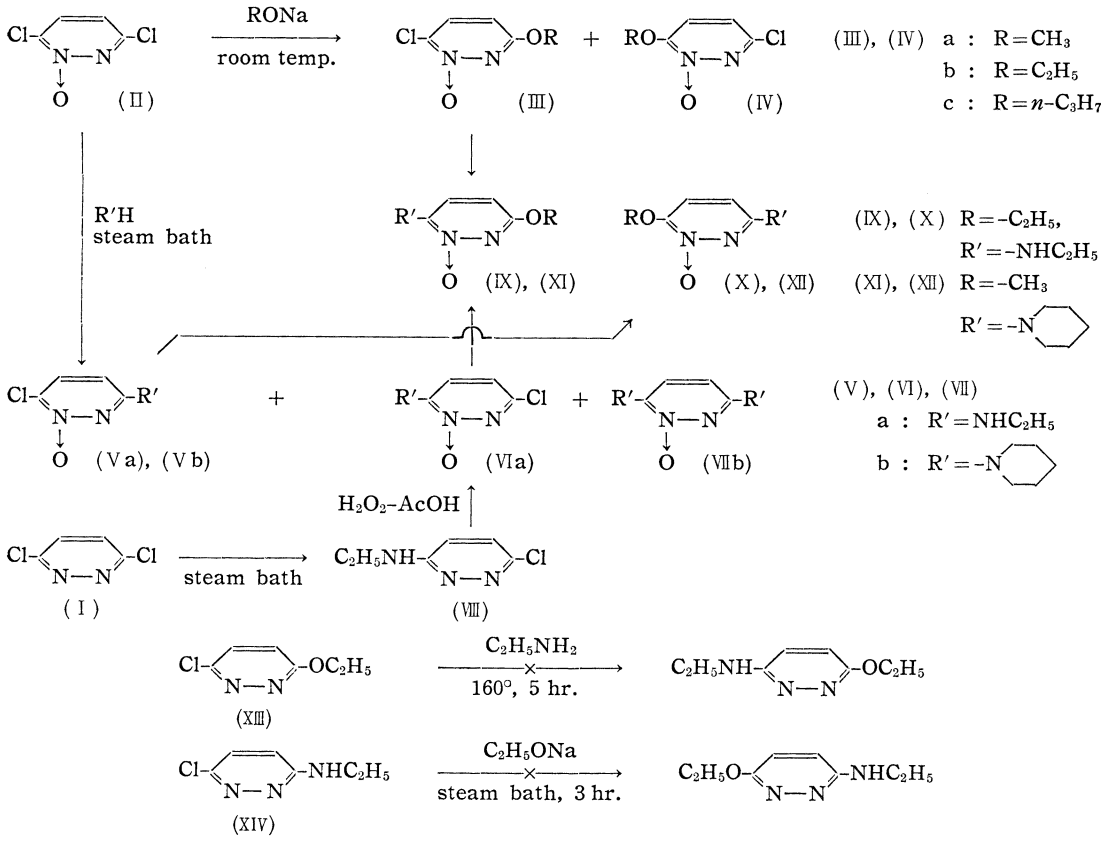
Table I. Reaction of (II) with Sodium Alkoxides and Amines

Reagents	Reaction		3-Substituted products		6-Substituted products	
	temp. (°C)	Time (hr.)	m.p. (°C)	Yield (%)	m.p. (°C)	Yield (%)
CH_3ONa	17	1	160~161	80	187~188	7.5
C_2H_5ONa	16	1	115~116	72	138~139	11
C_3H_7ONa	17	1	83~84	57		
$C_2H_5NH_2$	steam bath	4	137~138	54	75~76	14
Piperidine	steam bath	4	124~125	65	(3,6-dipiperidinopyridazine 1-oxide picrate m.p. 166°, 11.5%)	

reactive than 6-chlorine atom. Further, the same reaction was examined with sodium methoxide and propoxide, and the same results were obtained as shown in Table I.

With ethylamine, it was necessary to warm reaction mixtures on steam bath. From the reaction mixture, two isomers of $C_6H_8ON_3Cl$, (Va), m.p. 137~138° (yield 54%) and (VIa) m.p. 75~76° (yield 14%) were produced. Their structures were decided as follows: When (VIa) was reacted with sodium ethoxide, an ethylamino-ethoxypyridazine N-oxide was produced, This was identified with 3-ethoxy-6-ethylaminopyridazine 1-oxide (IX), prepared from (IIIb) and ethylamine, and this differed from 3-ethylamino-6-ethoxypyridazine 1-oxide (X), prepared from (Va) and sodium ethoxide.

Besides, a product from N-oxidation of 3-ethylamino-6-chloropyridazine (VIII) with hydrogen peroxide in glacial acetic acid was found same as (VIa). When 3-aminopyridazine derivatives were submitted to N-oxidation, they usually gave 2-oxides, as



principal products.[2] On the other hand, Newbold[3] and Katritzky[4] reported that 2-aminopyridine 1-oxide and 2-methylaminopyridine 1-oxide gave deep blue coloration with aqueous ferric chloride, and Itai and Nakashima also observed same coloration in 3-amino- and 3-amino-6-chloropyridazine 2-oxide. (VIa) and (IX) gave also deep blue coloration with ferric chloride solution, but (Va) and (X) did not. Then, it was decided that (Va) was 3-ethylamino-6-chloropyridazine 1-oxide, and (VIa) was 3-chloro-6-ethylaminopyridazine 1-oxide.

When (II) was heated with piperidine on a steam bath for 4 hours., 65% of piperidinochloropyridazine N-oxide and 11.5% of dipiperidinopyridazine N-oxide were obtained. The latter was considered as 3,6-disubstituted one. The structure of former was assigned to 3-piperidino-6-chloropyridine 1-oxide (Vb), because a reaction product from (Vb) with sodium methoxide was different from 3-methoxy-6-piperidinopyridazine 1-oxide (XI) prepared from (IIIa) and piperidine.

By higher basicity of piperidine, the substitution seemed to take place easier than with ethylamine. As the results, though 6-piperidino compound might be produced initially, it seemed likely to change immediately into 3,6-disubstituted compound owing to high reactivity of 3-chlorine atom and of piperidine.

Previously, Ochiai and Okamoto[5] reported that effect of N-oxide varied by temperature in nitration of quinoline N-oxides. Besides, it was presumed that presence of water in reaction mixture might influence to the velocity of the reaction or to the ratio of the reaction products. So, these factors were examined the results of which are summarized in Tables II and III. As the fact, any distinct difference could not be found out from these results, and chlorine atom in 3-position was always more reactive than that in 6-position of (II).

Table II. Reaction of (II) with Ethylamine

(II) mg.	$EtNH_2$ and solvents	Reaction		Yield (%)	
		Temp. °C	Time (hr.)	(Va)	(VIa)
305	70% $EtNH_2$ 0.8 cc., EtOH 10 cc.	97	4	54	14
309.1	70% $EtNH_2$ 0.6 cc., H_2O 3 cc. EtOH 0.5 cc.	97	4	54	18
320.2	5% $EtNH_2$ abs. EtOH solution 7 cc.	97	4	57	13
204.6	70% $EtNH_2$ 0.4 cc., EtOH 2 cc.	150	4	59	15

Table III. Reaction of (II) with Sodium Methoxide

(II) mg.	MeONa equivalent	Reaction Temp. and Time	Yield (%)		3,6-Dimethoxypyridazine 1-oxide
			(IIIa)	(IVa)	
201.5	1.1	0°, 1 night	81	9	—
205.4	1.1	17°, 1 hr.	80	7.5	—
214.7	1.1	MeONa was dropped into boilling MeOH solution of (II)	70	—	3
301.2	1.1	MeONa was added in MeOH solution of (II) at 120°	51	—	9

However, in under-mentioned experiments, —M effect of N-oxide may be perceptible, e.g., (IIIb) could be converted into (IX) by heating with ethylamine at 150° for 5 hours, but, 3-ethoxy-6-chloropyridazine (XIII) did not react with ethylamine under similar condition (almost all of (XIII) was recovered). Similarly, (Va) was converted into (X) by heating with sodium ethoxide on a steam bath for 1 hour, though 3-ethylamino-

2) T. Itai, T. Nakashima: This Bulletin, **10**, 936 (1962).
3) G. T. Newbold, F. S. Spring: J. Chem. Soc., **1949**, S133.
4) A. R. Katritzky: J. Chem. Soc., **1957**, 191.
5) E. Ochiai, T. Okamoto: Yakugaku Zasshi, **70**, 384 (1950).

6-chloropyridazine (XIV) did not react with sodium ethoxide under the same condition (87% of (XIV) was recovered).

Now, the results of this experiments have only been reported here. The reason why 3-chlorine is more reactive than 6-chlorine will be reported later.

Experimental

Reaction of 3,6-Dichloropyridazine 1-Oxide (II) with Sodium Ethoxide; Formation of 3-Ethoxy-6-chloropyridazine 1-Oxide (IIIb) and 3-Chloro-6-ethoxypyridazine 1-Oxide (IVb)——To a solution of 203.0 mg. of (II) in 10 cc. of EtOH, 1.6 cc. of EtONa-EtOH solution (Na : 20 mg./cc., 1.1 equivalent) was added, under ice-cooling, and allowed to stand for 1 hr. at room temperature (16°). EtOH was distilled off under reduced pressure, the residue was added with a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to dryness, and 211 mg. of white residue was obtained. The residue was dissolved in benzene, passed through an alumina column, and eluted with benzene-$CHCl_3$ and $CHCl_3$. White crystals (m.p. 112~116°) of (IIIb) were obtained from benzene-$CHCl_3$ eluate and recrystallized from isopropyl ether or ligroin to colorless needles, m.p. 115~116°. Yield, 154.3 mg., 72%. Admixture with an authentic sample[1] showed no depression of m.p. and their IR spectra had also same absorption.

White crystals of (IVb) were obtained from $CHCl_3$ eluate, and recrystallized from benzene to colorless needles, m.p. 138~139°. Yield, 23 mg., 11%. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.27; H, 4.04; N, 16.05. Found : C, 41.53; H, 4.12; N, 16.44.

Reaction of (II) with Sodium Methoxide; Formation of 3-Methoxy-6-chloropyridazine 1-Oxide (IIIa) and 3-Chloro-6-methoxypyridazine 1-Oxide (IVa)——To a solution of 205.4 mg. of (II) in 10 cc. of MeOH, 1.6 cc. of MeONa-MeOH solution (Na : 20 mg./cc., 1.1 equivalent) was added under ice-cooling, and allowed to stand for 1 hr. at room temperature (17°). MeOH was distilled off under reduced pressure, the residue was taken up in a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, $CHCl_3$ was evaporated to dryness, and 197.6 mg. of white residue (m.p. 143~148°) was obtained. The white residue was dissolved in benzene-$CHCl_3$, passed through an alumina column, and eluted with benzene-$CHCl_3$ and $CHCl_3$. White crystals of (IIIa) were obtained from benzene-$CHCl_3$ eluate, m.p. 157~161°. Yield, 159.2 mg., 80%. The crystals were recrystallized from EtOH to colorless needles, m.p. 160~161°. Admixture with an authentic sample showed no depression of m.p. and their IR spectra had also same absorption.

White crystals of (IVa) were obtained from $CHCl_3$ eluate, m.p. 188°. Yield, 15 mg., 7.5%. The crystals were recrystallized from benzene to colorless needles, m.p. 187~188°. *Anal.* Calcd. for $C_5H_5O_2N_2Cl$: C, 37.40; H, 3.14; N, 17.45. Found : C, 37.50; H, 3.08; N, 18.09.

Reaction of (II) with Sodium Propoxide; Formation of 3-Propoxy-6-chloropyridazine 1-Oxide (IIIc)——To a solution of 158.4 mg. of (II) in 8 cc. of PrOH, 1.3 cc. of PrONa-PrOH solution (Na : 20 mg./cc.) was added, and the mixture was allowed to stand for 1 hr. at room temperature. PrOH was distilled off under reduced pressure, the residue was taken up in a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was dissolved in benzene, passed through an alumina column and eluted with benzene. Benzene was distilled off from eluates, the residues which had m.p. 81~84° were collected, and recrystallized from ligroin to colorless scales, m.p. 83~84°. Yield, 118.5 mg., 65.5%. Admixture with authentic sample showed no depression of m.p. and their IR spectra had also same absorption.

Reaction of (II) with Ethylamine; Formation of 3-Ethylamino-6-chloropyridazine 1-Oxide (Va) and 3-Chloro-6-ethylaminopyridazine 1-Oxide (VIa)——A mixture of 305 mg. of (II), 10 cc. of EtOH and 0.8 cc. of 70% aqueous solution of ethylamine was placed in a sealed tube and heated on a steam bath for 4 hr. The solvent was evaporated, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated. The residue (m.p. 95~100°) was recrystallized from benzene and colorless needles of (Va) were obtained, m.p. 137~138°. Yield, 173 mg., 54%. Beilstein's reaction was positive. *Anal.* Calcd. for $C_6H_8ON_3Cl$: C, 41.51; H, 4.64; N, 24.20. Found : C, 41.04; H, 4.32; N, 23.91.

Benzene was evaporated from the mother liquor and the residue was recrystallized from petr. benzin. Colorless needles of (VIa) were obtained, m.p. 75~76°. Yield, 45 mg., 14%. *Anal.* Calcd. for $C_6H_8ON_3Cl$: C, 41.51; H, 4.64; N, 24.20. Found : C, 41.79; H, 4.72; N, 24.84. This gives a deep blue coloration with $FeCl_3$ solution.

3-Ethylamino-6-chloropyridazine (VIII)——A mixture of 1.020 g. of (I), 4 cc. of EtOH and 2 cc. of 70% aqueous solution of ethylamine was placed in a sealed tube, and heated on a steam bath for 4 hr. The solvents were distilled off, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and concentrated

to dryness. The residue was recrystallized from benzene-petr. benzin to colorless needles, m.p. 125~126°. Yield, 930 mg., 81%. *Anal.* Calcd. for $C_6H_8N_3Cl$: C, 45.72; H, 5.12; N, 26.66. Found : C, 45.87; H, 5.00; N, 26.48.

Oxidation of (VIII) with Hydrogen Peroxide; Formation of (VIa)——To a solution of 1.040 g. of (VIII) in 7 cc. of glacial AcOH, 1 cc. of 30% H_2O_2 was added, and the mixture was heated at 65° for 2 hr. To the mixture 1 cc. of 30% H_2O_2 was added and heating was continued for 7 hr. over. After distilling off the solvent *in vacuo*, the residue was neutralized with $NaHCO_3$, adding simultaneously some amount of water. The solution was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and concentrated to dryness. The residue was recrystallized from isopropyl ether or petr. benzin to colorless needles, m.p. 75~76°. Yield, 361.6 mg., 31.5%. This showed no depression on admixture with (VIa) prepared from (II).

3-Ethoxy-6-ethylaminopyridazine 1-Oxide (IX). i) Reaction of (IIIb) with Ethylamine——A mixture of 300 mg. of (IIIb), 3 cc. of EtOH and 2.5 g. of 70% aqueous solution of ethylamine was placed in a sealed tube and heated in an oil bath at 150° for 5 hr. The solvent was distilled off under reduced pressure, the residue was basified with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated. The residue (m.p. 80~90°) was recrystallized from ligroin to colorless needles, m.p. 92~93°. Yield, 100 mg., 32%. *Anal.* Calcd. for $C_8H_{13}O_2N_2$: C, 52.44; H, 7.15; N, 22.94. Found : C, 52.65; H, 7.23; N, 22.99. This gives a deep blue coloration with $FeCl_3$ solution.

ii) Reaction of (VIa) with Sodium Ethoxide——To a solution of 65 mg. of (VIa) in 1 cc. of EtOH, 2 cc. of EtONa-EtOH solution (Na : 20 mg./cc.) was added and the mixture was heated on a steam bath for 30 min. EtOH was distilled off, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The residue was recrystallized from petr. benzin to colorless needles, m.p. 92~93°. Yield, 38.8 mg., 57%. This showed no depression of m.p. on admixture with a sample prepared from (IIIb).

3-Ethylamino-6-ethoxypyridazine 1-Oxide (X)——To a solution of 400 mg. of (Va) in 2 cc. of EtOH, 7 cc. of EtONa-EtOH solution (Na : 20 mg./cc.) was added and the mixture was heated on a steam bath for 30 min. EtOH was distilled off, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The residue was recrystallized from benzene to colorless needles, m.p. 114~115°. Yield, 273.1 mg., 65%. *Anal.* Calcd. for $C_8H_{13}O_2N_2$: C, 52.44, H, 7.15; N, 22.94. Found : C, 52.65; H, 6.95; N, 23.13.

Reaction of (II) with Piperidine; Formation of 3-Piperidino-6-chloropyridazine 1-Oxide (Vb) and 3,6-Dipiperidinopyridazine 1-Oxide (VIIb)——A mixture of 205.5 mg. of (II), 3 cc. of EtOH and 0.4 g. of piperidine was placed in a sealed tube and heated on a steam bath for 4 hr. The solvent was distilled off, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The yellow residue was recrystallized from isopropyl ether, and colorless scales of (Vb) were obtained, m.p. 124~125°. Yield, 159.5 mg., 60%. *Anal.* Calcd. for $C_9H_{12}ON_3Cl$: C, 50.59; H, 5.66; N, 19.67. Found : C, 50.45; H, 5.19; N, 20.09.

Isopropyl ether was evaporated from the mother liquor and 90 mg. of red viscous liquid was obtained. Picrate of (VIIb) was deposited from the EtOH solution of this residue on addition of picric acid, m.p. 160~161°, 70.7 mg., 11.5%. This was recrystallized from EtOH to yellow needles, m.p. 165~166° (decomp.). *Anal.* Calcd. for $C_{14}H_{22}ON_4 \cdot C_6H_3O_7N_3$: C, 48.87; H, 5.13; N, 19.95. Found : C, 49.08; H, 4.96; N, 20.37.

3-Piperidino-6-methoxypyridazine 1-Oxide (XII)——A mixture of 75.0 mg. of (Vb) and 10 cc. of MeONa-MeOH solution (Na : 2 mg./cc.) was heated on a steam bath for 30 min. MeOH was evaporated, the residue was taken up in water and extracted with $CHCl_3$ repeatedly. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The residue (41.5 mg.) was recrystallized from petr. benzin-benzene, to colorless needles, m.p. 128~130°. Yield, 22.6 mg., 31%. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found : C, 57.23; H, 6.99; N, 19.94.

3-Methoxy-6-piperidinopyridazine 1-Oxide (XI)——A mixture of 100.5 mg. of (IIIa), 0.3 g. of piperidine and 4 cc. of EtOH was placed in a sealed tube and heated in an oil bath at 130° for 4 hr. The solvent was distilled off, the residue was taken up in a small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was removed. The viscous liquid was dried in a vacuum desiccator and the solid (63.5 mg.) obtained was recrystallized from petr. benzin to colorless needles, m.p. 107~108°, 17.2 mg. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found : C, 57.26; H, 6.77; N, 20.68.

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spectrometry. Elemental analyses were performed by the members of Department of Pharmaceutical Sciences, University of Tokyo, and Kowa Pharmaceutical Co. Ltd., to whom he is also thankful.

Summary

Reactivity of 3,6-dichloropyridazine 1-oxide (II) to nucleophilic substitution was examined. 3-Chlorine atom was always more reactive than 6-chlorine atom. Chlorine of 3-substituted-6-chloropyridazine 1-oxide was more reactive than that of 3-substituted-6-chloropyridazine.

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154. Masatomo Hamana, Bunsuke Umezawa, and Shoichi Nakasima : Studies on Tertiary Amine Oxides. XIII. Reactions of N-(*p*-Dimethylaminophenyl)nitrones having Pyridine N-Oxide, Quinoline or its N-Oxide as α-Substituent.

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Previously, it[1] was reported that N-(*p*-dimethylaminophenyl)-α-(1-oxido-2-pyridyl)-nitrone (PO-2) underwent a facile rearrangement to the corresponding acid anilide in the presence of several reagents, among which sulfur dioxide was most specific, and that the presence of both N-(*p*-dimethylaminophenyl) and α-(1-oxido-2-pyidyl) group in (PO-2) was shown to be favorable for the rearrangement. In order to examine the effect of heteroaromatic rings (quinoline or pyridine), ring position bearing the substituent of α-(N-dimethylaminophenylnitrone) group (2- or 4-position), and N-oxidation of the rings, syntheses of five nitrones, N-(*p*-dimethylaminophenyl)-α-(1-oxido-4-pyridyl) (PO-4), N-(*p*-dimethylaminophenyl)-α-(2-quinolyl) (Q), N-(*p*-dimethylamiophenyl)-α-(1-oxido-2-quinolyl) (QO), N-(*p*-dimetylaminophenyl)-2-(4-quinolyl) (L) and N-(*p*-dimethylaminophenyl)-α-(1-oxido-4-quinolyl)nitrone (LO) were carried out and they were subjected to the reaction with six sorts of reagent namely, sulfur dioxide, triphenyl phosphite, phosphorus trichloride, phosphoryl chloride and acetic anhydride. All nitrones used were prepared easily from the corresponding pyridinium salts by the King reaction, except (PO-4), which was obtained by the same route as employed in the synthesis of an authentic specimen of (PO-2)[2] as shown in Chart 1.

The fact that 4-picoline 1-oxide could not be converted to the corresponding pyridinium salt by King's method appeared to show -I effect of N-oxide group diminishing greatly at 4-position, which located remote for from the functional group than 2-position by two carbon atoms in pyridine ring.

Corresponding anils and acid anilides, expected as reaction products, were synthesized by the following unequivocal route.

Specificities, hitherto known, of the above reagents could be summarized as below. Sulfur dioxide was a deoxygenative reagent for aliphatic tertiary amine N-oxide[3] or

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