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PYRIDOPYRIDAZINES. IV.[1] PYRIDO[2,3-d]PYRIDAZINE N-OXIDES. A NOVEL RING-OPENING REACTION BY MEANS OF ACETIC ANHYDRIDE

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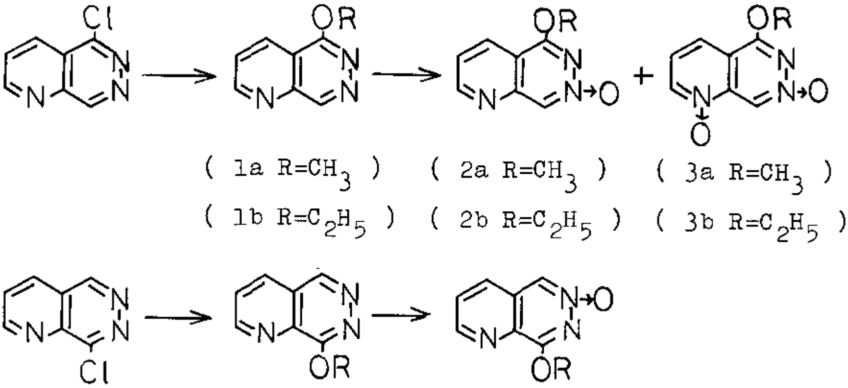
Treatment of 5-alkoxypyrido[2,3-d]pyridazines with m-chloroperbenzoic acid afforded the 7-oxides 2a and 2b, and the 1,7-dioxides 3a and 3b. 8-Alkoxypyrido-[2,3-d]pyridazines however yielded the 6-oxides 2c and 2d. Of the mono-oxides 2b and 2d on treatment with acetic anhydride gave the ring-opened esters 5b and 5d and the ketoesters 6b and 6d. 1-Methoxyphthalazine-3-oxide similarly yielded benzoate 10, acetonylbenzoate 11, and methyl stilbenedicarboxylate 12.

Previously we reported some synthetic studies of pyrido-[2,3-d]pyridazines.[2] This paper deals with the N-oxidation of 5- and 8-alkoxypyrido[2,3-d]pyridazines and with the novel reactions of 5-alkoxy-7-oxides and 8-alkoxy-6-oxides with acetic anhydride involving cleavage of the pyridazine ring accompanied by loss of the nitrogen atoms.

5- And 8-alkoxypyrido[2,3-d]pyridazines (1a, 1b, 1c and 1d) were prepared by treatment of the respective 5- and 8-chloro-derivatives[3] with the suitable alcoholic sodium alkoxide (1a, mp 132-134°, 91% ; 1b, mp 113-114°, 98% ; 1c, mp 163-164°, 77% ; 1d, mp 110-111°, 97%).



(1a R=CH_3) (2a R=CH_3) (3a R=CH_3)
(1b R=C_2H_5) (2b R=C_2H_5) (3b R=C_2H_5)

(1c R=CH_3) (2c R=CH_3)
(1d R=C_2H_5) (2d R=C_2H_5)

Chart 1

Oxidation of 5-methoxy- and 5-ethoxypyrido[2,3-d]pyridazines (1a and 1b) with m-chloroperbenzoic acid in chloroform at room temperature afforded the corresponding 7-oxides (2a, mp 200-201°, 45% and 2b, mp 170-171°, 46%) and 1,7-dioxides (3a, mp 214-215° (decomp.), 13% and 3b, mp 192-193°, 10%). On the other hand, 8-alkoxypyrido[2,3-d]pyridazines (1c and 1d) gave only 6-oxides (2c, mp 213-214° (decomp.), 52% and 2d, mp 177-178°, 71%) under the same conditions (Chart 1). N-Oxidation with 35% aq. hydrogen peroxide in acetic acid at 70° was also effective, but the products were contaminated with by-products.

The site of N-oxidation was confirmed by proton nmr spectral examinations. D. B. Paul and H. J. Rodda[4] have reported that H_3 of the pyrido[2,3-d]pyridazine 7-oxide and H_2 and H_4 of the 6-oxide all appeared at higher field than the equivalent protons of the parent heterocycle. The similar chemical shift differences were observed between 1a-d and 2a-d as shown in the following nmr data (in $CDCl_3$). 1b: δ=9.20 (H_2), 7.78 (H_3), 8.57 (H_4), 9.45 (H_8), $J_{2,3}$=4.7 Hz, $J_{3,4}$=8.0, $J_{2,4}$=1.8. 1d: δ= 9.29 (H_2), 7.83 (H_3), 8.28 (H_4), 9.26 (H_5), $J_{2,3}$=4.3 Hz, $J_{3,4}$= 8.3, $J_{2,4}$=1.8. 2b: δ=9.05 (H_2), 7.53 (H_3), 8.42 (H_4), 8.50 (H_8), $J_{2,3}$=4.7 Hz, $J_{3,4}$=8.0, $J_{2,4}$=1.7, $J_{4,8}$=0.8. 2d: δ=9.01 (H_2), 7.70 (H_3), 8.03 (H_4), 8.36 (H_5), $J_{2,3}$=4.3 Hz, $J_{3,4}$=8.5, $J_{2,4}$=1.8. The structure of the dioxides 3a and 3b was assigned on the basis that 3a and 3b were formed *via* the mono-oxides 2a and 2b (tlc), respectively and that large higher field shift of H_2 and H_4 and change of $J_{2,3}$ of 3a and 3b from 2a and 2b indicated the presence of N-oxide at the pyridine moiety. 3b: δ=8.52 (H_2), 7.36 (H_3), 7.87 (H_4), 8.89 (H_8), $J_{2,3}$=6.4 Hz, $J_{3,4}$=8.4, $J_{2,4}$=1.0.

The orientation of these N-oxidations can be explained by the steric hindrance of the alkoxy-group and the proton at the *peri* position. Such steric hindrance has been reported in the case of the N-oxidation of 3-alkoxypyridazines[5], 1-alkoxyphthalazines,[5] and 8-alkoxyquinolines.[6]

In the course of studies on the reactivity of the N-oxide function, reaction of 5-ethoxy-7-oxide (2b) and 8-ethoxy-6-oxide (2d) with acetic anhydride was found to proceed anomalously with loss of two nitrogen atoms. Thus 2b (192 mg) was heated with acetic anhydride (1.9 ml) at 95° for 12 h, and the reaction mixture was treated with semicarbazide to give ethyl 2-acetoxymethylnicotinate (5b) as an oil (picrate, mp 113-114°) and the semicarbazone of ethyl 2-(1-acetoxy-2-oxopropyl)nicotinate (6b), mp 137-138°, in 53 and 44% yields, respectively. Product 6b, mp 82-83°, could be directly isolated by diluting the reactants with cyclohexane. However the former procedure is more convenient for the quantitative separation of 5b and 6b. Pyridazinones were not detected in spite of detailed nmr examination. Hydrolysis of 5b with 10% sulfuric acid yielded the known 2-hydroxymethylnicotinic acid lactone 7[7], mp 142°, which was identified by ir spectrum and mixed melting point comparisons. Treatment of 6b with dil. hydrochloric acid gave 2-(1-hydroxy-2-oxopropyl)nicotinic acid lactone hydrochloride 8, decomp.p 192° (without melting), which was characterized by ir and nmr spectra.

A similar reaction of 8-ethoxy-6-oxide (2d) afforded ethyl 3-acetoxymethylpicolinate (5d) as an oil (39%) (the picrate, mp 100-102°) and ethyl 3-(1-acetoxy-2-oxopropyl)picolinate (6d) as an oil (38% as semicarbazone, mp 176-177°). Product 5d was hydrolyzed with 10% hydrochloric acid to give the known 3-hydroxymethylpicolinic acid lactone 9,[7] mp and mixed mp 166-167°.

Reactions of the 5- and 8-methoxyl derivatives (2a and 2d) proceeded in a similar way.

1-Methoxyphthalazine-3-oxide (4) undergoes the same type of reaction. Thus heating 4 (2.0 g) with acetic anhydride (5 ml) for 5 h produced methyl 2-acetoxymethylbenzoate (10) as an oil,

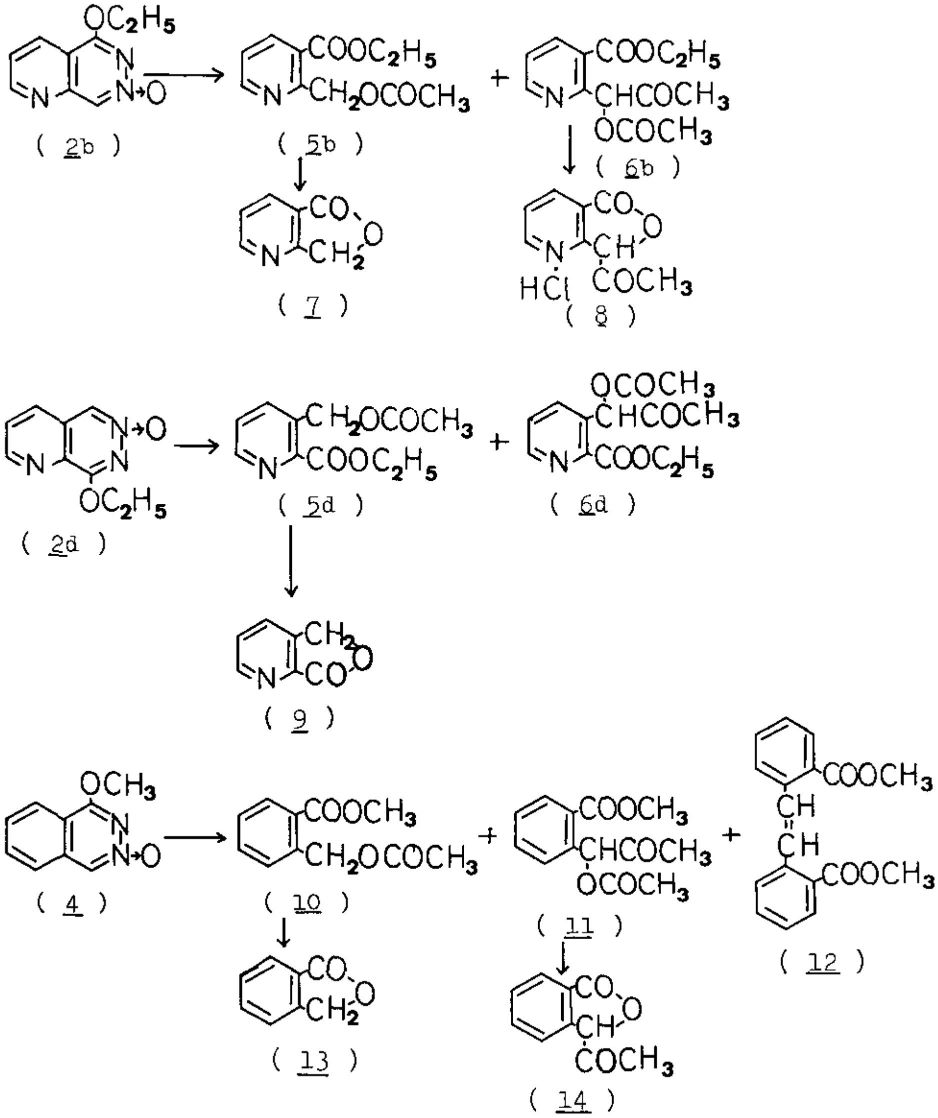

OC2H5
N→O
(2b)
COOC2H5
CH2OCOCH3
(5b)
+
CHCOCH3
OCOCH3
(6b)
CO
O
CH2
(7)
CH
COCH3
HCl
(8)
N→O
OC2H5
(2d)
(5d)
(6d)
(9)
OCH3
(4)
COOCH3
(10)
(11)
CH
(12)
(13)
(14)

Chart 2

methyl 2-(1-acetoxy-2-oxopropyl)benzoate (11) as an oil (the semicarbazone, mp 161-164°), and dimethyl stilbene-2,2'-dicarboxylate (12),[8] mp and mixed mp 102-103°, in yields of 10, 33 and 10%, respectively. The benzoate 10 gave phthalide (13), mp and mixed mp 73°, on refluxing with 10% hydrochloric acid in methanol. Product 11 was similarly hydrolyzed to give 3-acetylphthalide (14), mp 82° (lit.[9] mp 82°), in 40% yield.

These results suggest that this type of cleavage reaction is general to an appreciable degree in phthalazines and its aza-analogs.

A likely mechanism of the reaction could involve addition of acetic anhydride to give 15, which gave a quinodimethane intermediate 17 by ring-opening. The intermediate 17 gave the benzoates 10 and 11 as shown in Chart 3. Removal of acetic anhydride from 17 would then afford 1-methoxyisobenzofuran (18) as an unstable intermediate, which could be transformed into a dimer such as 19 and then isomerized into the thermally stable dicarboxylate 12[10]. Closely related reactions of pyridazine derivatives have been reported by Igeta and his co-workers,[11] involving the formation of 1,4-butadienes by treatment of pyridazine-N-oxides with Grignard reagents.

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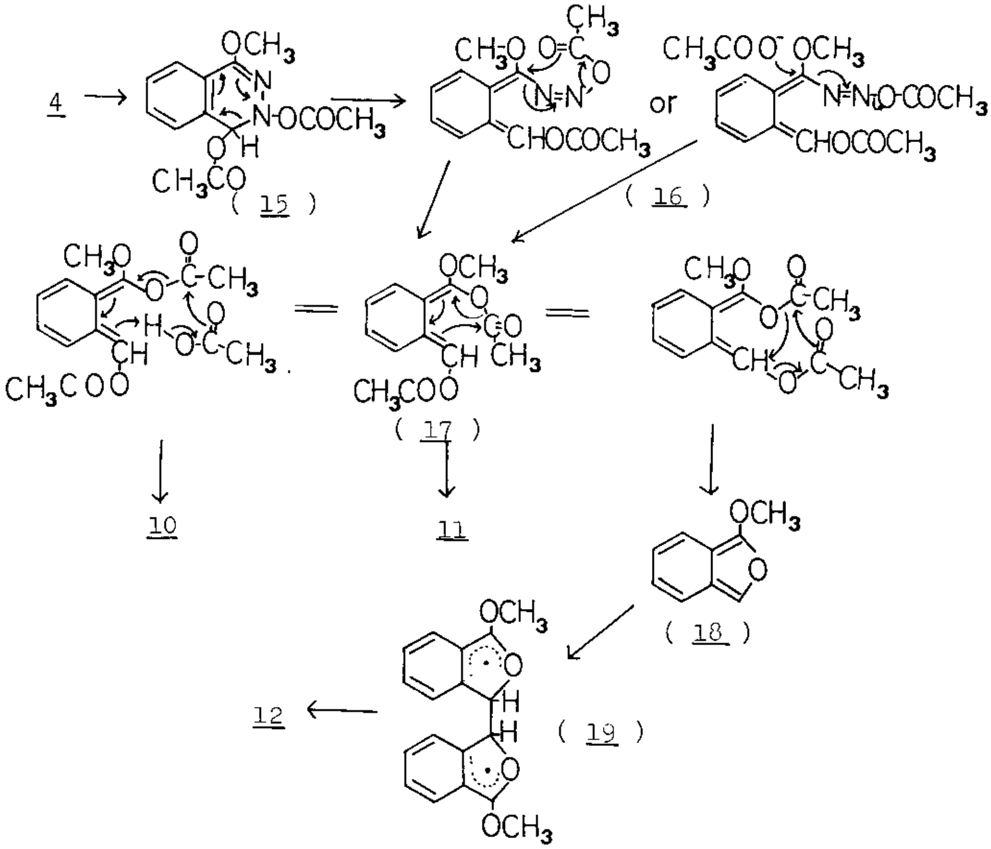

Chart 3

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