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# Studies on the Syntheses of N-Heterocyclic Compounds. XXVIII.[1] Syntheses of Pyrido[3,4-*d*]pyridazine Derivatives. (4)[2]

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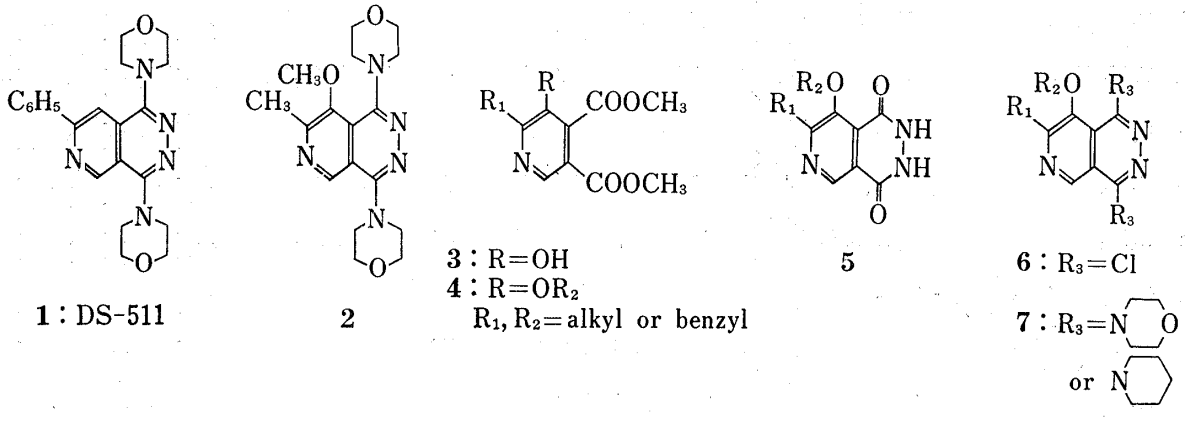
A variety of 7,8-disubstituted 1,4-dimorpholinopyrido[3,4-*d*]pyridazine derivatives were synthesized in connection with the structure-activity relationships on diuretic activity. 1,4-Dipolar cycloaddition of 4-alkyl- and 4-benzyl-5-ethoxyoxazoles with dimethyl maleate afforded dimethyl 6-alkyl- and 6-benzyl-5-hydroxy-pyridine-3,4-dicarboxylate (**3**), which were alkylated to give the corresponding 5-alkoxypyridine derivatives (**4**). The cycloaddition of 5-alkyl- or 5-benzyl-4-phenyloxazole (**9**) with N-phenylmaleimide gave an adduct (**10**), heating of which under acidic condition effected dehydration to give 5-alkyl- or 5-benzyl-N,6-diphenylpyridine-3,4-dicarboximide (**11**). Reactions of **4** and **11** with hydrazine gave pyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione derivatives (**5** and **12**), chlorination of which followed by substitution with morpholine afforded 7-alkyl- and 7-benzyl-8-alkoxy-pyrido[3,4-*d*]pyridazine derivatives (**7a**—**k**) and 8-alkyl- and 8-benzyl-7-phenyl derivatives (**14a**, **14b**, and **14c**). Also prepared were 8-methyl-7-substituted phenyl (**14d** and **15**), 8-chloro- (**19** and **21**), 8-alkoxy-7-phenyl (**26a**, **26b**, and **26c**), and 7-methyl-8-phenyl (**43**) derivatives. Stereochemistry of the adduct (**8**) obtained by the 1,4-cycloaddition reaction of 4-phenyloxazole and N-phenylmaleimide was discussed.

In connection with the relationship between the structure and the diuretic activity, we have synthesized a variety of pyrido[3,4-*d*]pyridazine derivatives, among which 1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**1**: DS-511) has proved to be a potent diuretic.[2,4–6]



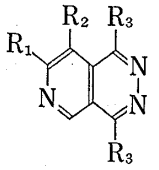

**1**: DS-511 **2** **3**: R=OH **4**: R=OR$_2$ R$_1$, R$_2$=alkyl or benzyl **5** **6**: R$_3$=Cl **7**: R$_3$=N O or N

Chart 1

1) Part XXVII: M. Tomimoto, H. Ikeda, Y. Oka, S. Yurugi, N. Miyazaki, M. Funado, N. Matsumoto, S. Chiba, and K. Kawai, *J. Takeda Res. Lab.*, **34**, 455 (1975).
2) Part (3): Y. Oka, K. Itoh, A. Miyake, N. Tada, K. Omura, M. Tomimoto, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2306 (1975).
3) Location: *Juso, Yodogawa-ku, Osaka 532, Japan.*
4) S. Yurugi, T. Fushimi, H. Sugihara, and M. Hieda, *Yakugaku Zasshi*, **92**, 1333 (1972).
5) Y. Oka, K. Omura, A. Miyake, K. Itoh, M. Tomimoto, N. Tada, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2239 (1975).
6) K. Nishikawa, H. Shimakawa, Y. Inada, Y. Shibouta, S. Kikuchi, S. Yurugi, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **24**, 2057 (1976).

However, derivatives bearing a substituent at the 8-position of the ring have remained unknown with an exception of 8-methoxy-7-methyl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (**2**) which showed a fairly potent diuretic activity.[7] The present paper deals with the chemical modifications of 7-substituted pyrido[3,4-*d*]pyridazines by introducing substituents at the 8-position.

TABLE I. 1,4,7,8-Tetrasubstituted Pyrido[3,4-*d*]pyridazines



| No. | $R_1$ | $R_2$ | $R_3$ | mp (°C) | Rec. solv. | Yield (%) | Formula | Analysis (%) Calcd. (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | $CH_3$ | $C_2H_5O$ |  | 175—177 | acetone–ether | 28 | $C_{18}H_{25}O_3N_5$ | 60.15 (60.14) | 7.01 (6.97) | 19.49 (19.57) |
| **7b** | $CH_3$ | $C_2H_5O$ |  | 134—135 | hexane | 33 | $C_{20}H_{29}ON_5$ | 67.57 (67.61) | 8.22 (8.28) | 19.70 (19.34) |
| **7c** | $CH_3$ | $C_4H_9O$ |  | 108—110 | hexane | 37 | $C_{20}H_{29}O_3N_5$ | 61.99 (61.85) | 7.54 (7.58) | 18.08 (17.95) |
| **7d** | $C_2H_5$ | $CH_3O$ |  | 207—209 | EtOH–ether | 34 | $C_{18}H_{15}O_3N_5 \cdot 2H_2O \cdot 2HCl$ | 46.15 (45.66) | 6.67 (6.21) | 14.95 (15.22) |
| **7e** | $C_3H_7$ | $CH_3O$ |  | 117—119 | $H_2O$ | 44 | $C_{19}H_{27}O_3N_5$ | 61.10 (61.19) | 7.29 (7.21) | 18.75 (18.82) |
| **7f** | $(CH_3)_2CH$ | $CH_3O$ |  | 193—196 | EtOH | 49 | $C_{19}H_{27}O_3N_5$ | 61.10 (61.05) | 7.29 (7.28) | 18.75 (18.82) |
| **7g** | $C_4H_9$ | $CH_3O$ |  | 104—105 | hexane | 60 | $C_{20}H_{29}O_3N_5$ | 61.99 (61.93) | 7.54 (7.61) | 18.08 (17.93) |
| **7h** | $(CH_3)_2CHCH_2$ | $CH_3O$ |  | 121—123 | $H_2O$ | 49 | $C_{20}H_{29}O_3N_5$ | 61.99 (61.99) | 7.54 (7.51) | 18.08 (18.02) |
| **7i** | $(CH_3)_2CHCH_2$ | $CH_3O$ |  | 104—110 | EtOH–ether | 39 | $C_{22}H_{33}ON_5 \cdot 2HCl$ | 57.90 (57.46) | 7.71 (7.94) | 15.35 (15.40) |
| **7j** | $C_2H_5(CH_3)CH$ | $CH_3O$ |  | 150—153 | hexane–ether | 13 | $C_{20}H_{29}O_3N_5$ | 61.99 (61.98) | 7.54 (7.66) | 18.08 (18.05) |
| **7k** | $C_6H_5CH_2$ | $CH_3O$ |  | 174—175 | EtOH | 14 | $C_{23}H_{27}O_3N_5$ | 65.54 (65.65) | 6.46 (6.29) | 16.62 (16.70) |
| **14a** | $C_6H_5$ | $CH_3$ |  | 187—189 | EtOH–ether | 43 | $C_{22}H_{25}O_2N_5$ | 67.50 (67.24) | 6.44 (6.48) | 17.89 (17.31) |
| **14b** | $C_6H_5$ | $C_2H_5$ |  | 197—198 | EtOH | 74 | $C_{23}H_{27}O_2N_5$ | 68.12 (67.80) | 6.71 (6.75) | 17.27 (17.50) |
| **14c** | $C_6H_5$ | $C_6H_5CH_2$ |  | 185—187 | MeOH | 45 | $C_{28}H_{29}O_2N_5$ | 71.92 (71.92) | 6.25 (6.03) | 14.98 (15.02) |
| **14d** | $C_6H_5CH_2O$- | $CH_3$ |  | 212—213 | EtOH | 72 | $C_{29}H_{31}O_3N_5$ | 70.00 (70.30) | 6.28 (6.41) | 14.08 (13.65) |
| **15** | HO-  | $CH_3$ |  | 264—266 | MeOH | 72 | $C_{22}H_{25}O_3N_5$ | 64.85 (65.20) | 6.18 (6.48) | 17.19 (16.55) |
| **19** | $C_6H_5$ | Cl |  | 201—204 | EtOH | 23 | $C_{21}H_{22}O_2N_5Cl$ | 61.23 (60.92) | 5.38 (5.34) | 17.00 (16.79) |
| **21** | $CH_3$ | Cl |  | 147—148 | acetone | 31 | $C_{16}H_{20}O_2N_5Cl$ | 54.93 (54.88) | 5.76 (5.62) | 20.02 (19.89) |
| **26a** | $C_6H_5$ | $CH_3O$ |  | 182—188 | MeOH | 49 | $C_{22}H_{25}O_3N_5$ | 64.85 (64.62) | 6.18 (5.97) | 17.19 (16.88) |
| **26b** | $C_6H_5$ | $C_2H_5O$ |  | 167—170 | ether | 49 | $C_{23}H_{27}O_3N_5$ | 65.54 (65.70) | 6.46 (6.31) | 16.62 (16.53) |
| **26c** | $C_6H_5$ | $C_3H_7O$ |  | 212—215 (decomp.) | EtOH | 69 | $C_{24}H_{29}O_3N_5 \cdot H_2SO_4$ | 54.02 (54.29) | 5.86 (5.90) | 13.13 (12.71) |
| **43** | $CH_3$ | $C_6H_5$ |  | 129—135 | ether | 57 | $C_{22}H_{25}O_2N_5$ | 67.50 (67.66) | 6.44 (6.64) | 17.89 (17.51) |

7) T. Matsuo and T. Miki, *Yakugaku Zasshi*, **92**, 703 (1972).

According to Matsuo's method,[7,8] a variety of 4-alkyl- and 4-benzyl-5-ethoxyoxazoles were allowed to react with dimethyl maleate to undergo 1,4-dipolar cycloaddition and elimination of ethanol affording dimethyl 6-alkyl- and 6-benzyl-5-hydroxypyridine-3,4-dicarboxylates (**3**), which were alkylated with alkyl halide to give the corresponding 5-alkoxy derivatives (**4**). The reaction of **4** with hydrazine afforded 8-alkoxy-7-substituted pyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**5**). Chlorination of **5** with phosphorus oxychloride in the presence of N,N-dimethylaniline or α-picoline followed by treatment with cyclic amines yielded the analogues of **2** (**7a—k**) as listed in Table I.

It was found, however, that the rate of the cycloaddition reaction of 4-aryloxazoles with dimethyl maleate was extremely retarded probably because of the reduced electron density at the diene moiety by the inductive effect of the aryl group. An extensive search to find a more reactive dienophile has finally revealed that N-phenylmaleimide reacts with 4-phenyloxazole more smoothly affording an adduct, N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-3,4-dicarboximide (**8**), which was led to **1** *via* the subsequent several steps.[9] By this route, several 7-aryl-8-substituted pyrido[3,4-*d*]pyridazine derivatives were prepared. Thus, the reaction of 5-alkyl- and 5-benzyl-4-phenyloxazole (**9**) with N-phenylmaleimide afforded adduct **10**, which were dehydrated by heating in dioxane-hydrochloric acid to give 5-alkyl- and 5-benzyl-N,6-diphenylpyridine-3,4-dicarboximide (**11**). Treatment of **11** with hydrazine gave 8-alkyl- and 8-benzyl-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**12**). Chlorination of **12** to give 1,4-dichloro derivative (**13**) followed by substitution with morpholine yielded **14a—c**, in which the 8-position of compound (**1**) was substituted with methyl, ethyl, and benzyl group respectively. Similarly 7-(*p*-benzyloxyphenyl)-8-methyl derivative (**14d**) was prepared from 4-(*p*-benzyloxyphenyl)-5-methyloxazole (**9**: $R_1$=*p*-$C_6H_5CH_2OC_6H_4$, $R_2$=$CH_3$). In this case heating of the oxazole with N-phenylmaleimide effected the addition and dehydration simultaneously to give **11**. Treatment of **14d** with trifluoroacetic acid[2] afforded 7-(*p*-hydroxyphenyl)-8-methyl derivative (**15**).

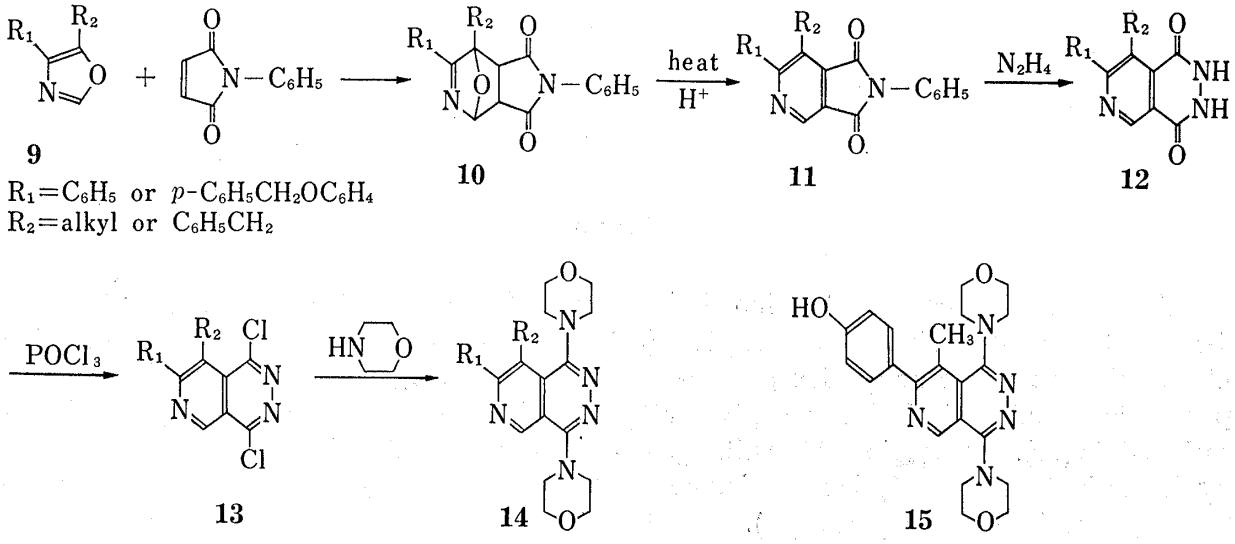


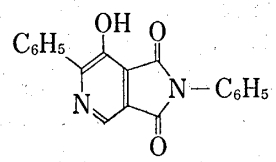

Chart 2

Subsequently, attempts were made to introduce a chlorine, oxygen or nitrogen functional group at the 8-position of **1**. The addition reaction of 5-ethoxy-4-phenyloxazole with N-phenylmaleimide followed by heating with hydrochloric acid gave 5-hydroxy-N,6-diphenylpyridine-3,4-dicarboximide (**16**), which was converted to 8-hydroxy-7-phenylpyrido[3,4-*d*]-pyridazine-1,4-(2H,3H)-dione (**17**) by treatment with hydrazine. Compound (**17**) was obtained

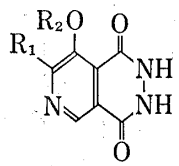
8) T. Miki and T. Matsuo, *Yakugaku Zasshi*, **91**, 1030 (1971).
9) Y. Usui, Y. Hara, N. Shimamoto, S. Yurugi, and T. Masuda, *Heterocycles*, 3, 155 (1975).

also by the reaction of diethyl 5-hydroxy-6-phenylpyridine-3,4-dicarboxylate (**22**)[10] with hydrazine, although yields in the preparation of **22** was rather unsatisfactory. Chlorination of **17** with phosphorus oxychloride in the presence of α-picoline gave 1,4,8-trichloro-7-phenylpyrido[3,4-*d*]pyridazine (**18**), substitution of which with excess morpholine occurred selectively at the 1- and 4-positions affording 8-chloro-1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**19**). Likewise 8-chloro-7-methyl derivative (**21**) was obtained from 8-hydroxy-7-methylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**20**).[7]

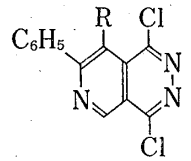
8-Alkoxy-1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**26a**, **26b**, and **26c**) was prepared from **22** by alkylation, cyclization with hydrazine, chlorination and 1,4-disubstitution with morpholine *via* compounds **23a—c**, **24**, and **25**.



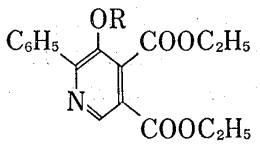
**16**



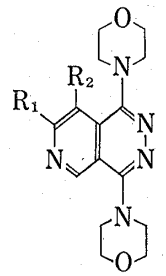
**17** : $R_1=C_6H_5$, $R_2=H$
**20** : $R_1=CH_3$, $R_2=H$
**24** : $R_1=C_6H_5$, $R_2=CH_3$, $C_2H_5$ or $C_3H_7$



**18** : $R=Cl$
**25** : $R=OCH_3$, $OC_2H_5$ or $OC_3H_7$



**22** : $R=H$
**23a** : $R=CH_3$
**23b** : $R=C_2H_5$
**23c** : $R=C_3H_7$



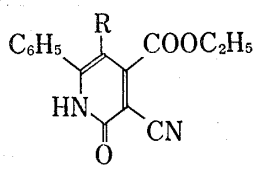
**19** : $R_1=C_6H_5$, $R_2=Cl$
**21** : $R_1=CH_3$, $R_2=Cl$
**26a** : $R_1=C_6H_5$, $R_2=OCH_3$
**26b** : $R_1=C_6H_5$, $R_2=OC_2H_5$
**26c** : $R_1=C_6H_5$, $R_2=OC_3H_7$

Chart 3

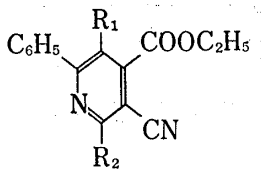
An attempt to prepare 8-amino derivatives of **1** was undertaken starting with ethyl 3-cyano-6-phenyl-2-pyridone-4-carboxylate (**27**).[11] Nitration of **27** with a mixture of fuming nitric acid and acetic anhydride gave 5-nitro derivative (**28**), which was chlorinated with phenylphosphonic dichloride to give ethyl 2-chloro-3-cyano-5-nitro-6-phenylpyridine-4-carboxylate (**29**). Reduction of the nitro group with iron-hydrochloric acid to give **30**, followed by dechlorination by catalytic reduction over palladium-charcoal, gave ethyl 5-amino-3-cyano-6-phenylpyridine-4-carboxylate (**31**). Treatment of **31** with hot conc. sulfuric acid gave 3,4-dicarboximide (**32**), which afforded 8-amino-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**33**) by the reaction with hydrazine. However, chlorination of **33** under a variety of conditions was unsuccessful, giving rise to a number of unidentified products.

On the other hand it was found that compound (**31**) provided a third synthetic route to **17**. Thus, hydrolysis of **31** to 3,4-dicarboxylic acid (**34**) followed by diazotization and hydrolysis gave 5-hydroxy-6-phenylpyridine-3,4-dicarboxylic acid (**35**). Heating of **35** with

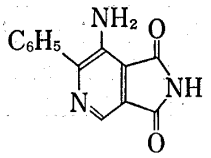
10) H. Davoll and F.B. Kipping, *J. Chem. Soc.*, **1953**, 1395.
11) D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux, and A. Rouaix, *Bull. Soc. Chim. France*, **1958**, 687.



27 : R=H
28 : R=$NO_2$



29 : $R_1$=$NO_2$, $R_2$=Cl
30 : $R_1$=$NH_2$, $R_2$=Cl
31 : $R_1$=$NH_2$, $R_2$=H



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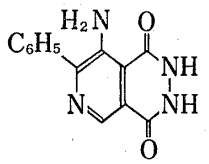

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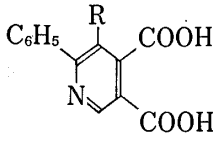
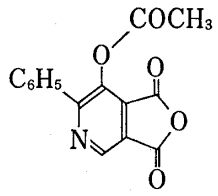


34 : R=$NH_2$
35 : R=OH



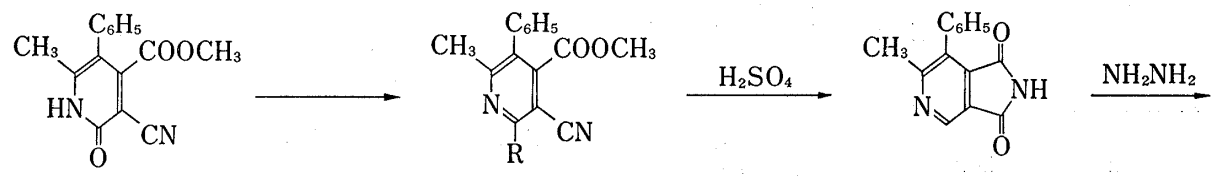
36

Chart 4

acetic anhydride effected dehydration and acetylation to yield 5-acetoxy-6-phenylpyridine-3,4-dicarboxylic anhydride (**36**), the reaction of which with hydrazine led to **17.**

Pharmacological studies in rat revealed that most of the above 8-substituted pyrido[3,4-*d*]-pyridazine derivatives showed potent diuretic activity. Especially the activities of **14a, 19** and **26a** were comparable to that of DS-511 (**1**).[6]

The result led us further to the synthesis of 7-methyl-8-phenyl derivative (**43**), a position isomer of **14a.** 7-Methyl-8-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**41**), prepared from methyl 3-cyano-6-methyl-5-phenyl-2-pyridone-4-carboxylate (**37**)[12] by a sequence of reactions, *i.e.* chlorination, catalytic reduction, treatment with sulfuric acid, and treatment with hydrazine, by way of compounds **38, 39** and **40,** was allowed to react with phosphorus oxychloride to give 1,4-dichloride (**42**), which was treated with morpholine to yield **43.** However, no diuretic activity was observed in **43.**



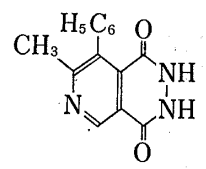
37



38 : R=Cl
39 : R=H



40



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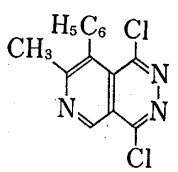
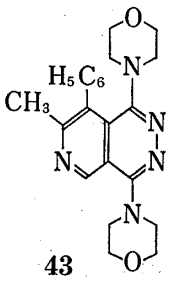


42

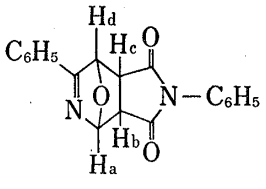


43

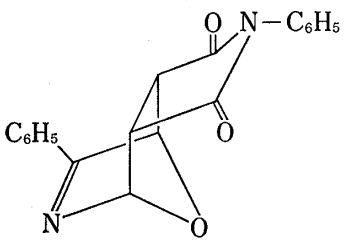
Chart 5

12) G.N. Walker and B.N. Weaver, *J. Org. Chem.*, **26, 4441 (1961).**

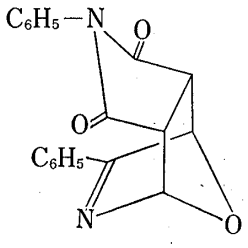
In the aforementioned 1,4-cycloaddition reaction of 4-phenyloxazole and N-phenylmaleimide, some investigations were undertaken concerning the stereochemistry of the adduct (**8**). When the reaction was carried out under room temperature in benzene, two isomeric products were isolated. In the nuclear magnetic resonance (NMR) spectrum, the coupling constant between Ha and Hb ($J_{ab}$) (Chart 6) and that between Hc and Hd ($J_{cd}$) for one compound were both zero, while $J_{ab}$ and $J_{cd}$ for the other were both 4.5 Hz. The result indicates that the configuration of the former is *exo* (**8a**) and the latter is *endo* (**8b**). The adduct obtained by refluxing 4-phenyloxazole and N-phenylmaleimide during the synthesis of **10**[9] proved to be identical with **8a**. In the *exo* derivative (**8a**), the *trans* configuration of C–O bond with respect to Hb and Hc would facilitate the subsequent dehydration to **10**. In fact **8a** was readily dehydrated to afford **10** on heating in dioxane-hydrochloric acid, while **8b** resisted the dehydration under the same condition. Although Diels-Alder reaction generally follows the "*endo* rule,"[13] it is also known that *endo* compound is often changed into thermodynamically stable *exo* compound at an elevated temperature.[14] In our present reaction, it was observed that the *exo*/*endo* ratio was increased as the reaction temperature was raised and that a considerable part of **8b** was changed into **8a** when **8b** was refluxed in benzene. The ratio seemed to be affected also by a steric factor: The ratio decreased as the substituent at the 5 position of the 4-phenyloxazole ring was changed from hydrogen to methyl, and to




8



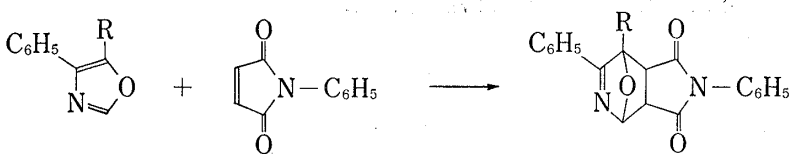

**8a**




**8b**

Chart 6

TABLE II. The Reactions of 5-Alkyl-4-phenyloxazoles with N-Phenylmaleimide



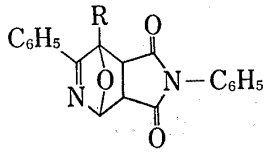

| R | Solvent | Reaction condition | Reaction time (hr) | Yield (%) *endo* | Yield (%) *exo* | Yield (%) *exo*/*endo* | Yield (%) **11** |
|---|---|---|---|---|---|---|---|
| H | $C_6H_6$ | room temperature | 170 | 16[a] | 38[a] | 2.4 | — |
| H | $C_6H_6$ | reflux | 7 | 7[a] | 64[a] | 9.1 | — |
| H | — | 110—120° | 3 | trace | 95[a] | ∞ | — |
| $CH_3$ | $C_6H_6$ | room temperature | 90 | 30[b] | 40[b] | 1.3 | — |
| $CH_3$ | $C_6H_6$ | reflux | 7 | 20[b] | 55[b] | 2.7 | — |
| $CH_3$ | — | 110—120° | 3 | 17[b] | 52[b] | 3.1 | 9.2 |
| $(CH_3)_2CH$ | $C_6H_6$ | room temperature | 170 | — | — | — | — |
| $(CH_3)_2CH$ | $C_6H_6$ | reflux | 7 | — | — | — | — |
| $(CH_3)_2CH$ | — | 110—120° | 50 | 10[a] | 3[a] | 0.3 | — |

*a*) The yield was calculated after separating by column chromatography.
*b*) The yield was calculated from integral intensity of a methyl group in NMR.

13) K. Alder and G. Slein, *Angew. Chem.*, **50**, 510 (1937).
14) D. Craig, *J. Am. Chem. Soc.*, **73**, 4889 (1951).

isopropyl group. When the reaction was conducted at 110—120° without solvent, the ratio was 3.1 for the methyl derivative and 0.3 for the isopropyl derivative whereas the value was almost infinity for unsubstituted derivative. The results are summarized in Table II and Table III.

Table III. N,6-Diphenyl-5-substituted 2,3,4,5-Tetrahydro-2,5-epoxypyridine-3,4-dicarboximides (**10**)



| R | *endo* Form mp (°C) | $J_{ab}$ (cps) | *endo* Form Analysis (%) Calcd. (Found) C | H | N | *exo* Form mp (°C) | $J_{ab}$ (cps) | *exo* Form Analysis (%) Calcd. (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 155—156 | 4.5 | 71.69 (71.74) | 4.43 (4.23) | 8.80 (8.80) | 196—198 | 0 | 71.69 (71.44) | 4.43 (4.10) | 8.80 (8.79) |
| $CH_3$ | — | 4.5 | — (—) | — (—) | — (—) | 144—145 | 0 | 72.28 (72.30) | 4.85 (4.70) | 8.43 (8.35) |
| $C_2H_5$ | — | — | — (—) | — (—) | — (—) | 145—147 | 0 | 72.82 (72.43) | 5.24 (5.20) | 8.09 (7.81) |
| $(CH_3)_2CH$ | 138—140 | 4 | 73.31 (73.34) | 5.59 (5.55) | 7.77 (7.69) | — | 0 | — (—) | — (—) | — (—) |
| $C_6H_5CH_2$ | 152—153 | 4 | 76.45 (76.53) | 4.94 (4.83) | 6.86 (6.83) | 139—141 | 0 | 76.45 (76.68) | 4.94 (4.83) | 6.86 (6.72) |
| $C_2H_5O$ | 153—155 | 4 | 69.60 (69.66) | 5.09 (4.81) | 7.73 (7.66) | — | 0 | — (—) | — (—) | — (—) |

## Experimental[15]

**5-Ethoxy-4-substituted Oxazole**——General Procedure: To a stirred suspension of $P_2O_5$ (79 g) and Hyflo Super-Cel (30 g) in $CHCl_3$ (400 ml) was added dropwise a solution of ethyl 2-alkyl-N-formylglycinate (0.3 mole) in $CHCl_3$ (50 ml) at 60—70°. After the mixture was stirred at 60—70° for 2 hr, the cooled mixture was neutralized with $NaHCO_3$ and the resulting insoluble substance was filtered off. The filtrate was extracted with $CHCl_3$ and the extract, dried over $Na_2SO_4$, was evaporated *in vacuo*. The residue was distilled under reduced pressure to give 4-alkyl-5-ethoxyoxazole. 5-Ethoxy-4-propyloxazole: Yield 32%, $bp_{29}$ 89—90°, *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.85; H, 8.26; N, 9.12. 5-Ethoxy-4-*sec*-butyloxazole: Yield 8%, $bp_{26}$ 80°, *Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.61; H, 8.80; N, 8.01. 4-Ethyl-,[16] 4-isopropyl-,[17] 4-butyl-,[17] 4-isobutyl-,[8] 4-benzyl-[8] and 4-phenyl-5-ethoxyoxazole[8] were prepared according to the methods described in literatures.

**Dimethyl 5-Hydroxy-6-substituted Pyridine-3,4-dicarboxylate** (**3**)——General Procedure: A mixture of 5-ethoxy-4-substituted oxazole and two equimolar dimethyl maleate was heated at 110—120° for 6 hr. Distillation or recrystallization of the reaction mixture gave **3**. Dimethyl 5-hydroxy-6-propylpyridine-3,4-dicarboxylate: Yield 59%, mp 89—91°, *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.93; H, 6.06; N, 5.28. Dimethyl 6-*sec*-butyl-5-hydroxypyridine-3,4-dicarboxylate and dimethyl 6-ethyl-5-hydroxypyridine-3,4-dicarboxylate were used for the subsequent procedure without distillation. Dimethyl 6-isopropyl-,[17] 6-butyl-,[17] 6-isobutyl-,[8] and 6-benzyl-5-hydroxypyridine-3,4-dicarboxylate[8] were prepared according to the methods described in literatures.

15) All melting points were measured on Kofler-type apparatus (Yanagimoto Co.) and are uncorrected. NMR spectra were measured on Varian T-60 high resolution spectrometer. Thin-layer chromatography (TLC) was carried out on SPOTFILM "Silica Gel f" (Tokyo Kasei Co.).

16) P.F. Muhlradt, Y. Morino, and E.E. Snell, *J. Med. Chem.*, **10**, 341 (1967).

17) N.D. Doktorova, L.V. Ionova, M. Ya. Karpeisky, N. Sh, Padyukova, K.F. Turchin, and V.L. Florentiev, *Tetrahedron*, **25**, 3527 (1969).

**Dimethyl 5-Alkoxy-6-alkylpyridine-3,4-dicarboxylate (4)**——General Procedure: To a solution of 3 (15 g) in anhydrous dimethylformamide (DMF) (100 ml) was added equimolar NaH and the mixture was stirred for 15 min at room temperature. To the mixture was added equimolar alkyl halide and stirring was continued for 1 hr. The mixture was poured into water (500 ml), extracted with $CHCl_3$. The extract was washed with 5% NaOH and then water, and dried over $Na_2SO_4$. Removal of the solvent gave crude **4** as a brown oil which was used for the subsequent process without purification.

**4-Phenyl-5-substituted Oxazole (9: $R_1=C_6H_5$)**——To a solution of benzylacetophenone[18] (21 g) in $CHCl_3$ (50 ml) was added $Br_2$ (1 g) at 50°. When the reaction was initiated, another 15.6 g of $Br_2$ was added dropwise with stirring under ice cooling. After removal of the solvent *in vacuo* at room temperature, to the residue were added formamide (58 ml) and acetic acid (45 ml). The resulting mixture was heated at 130° for 4 hr. After removal of acetic acid *in vacuo*, the residue was extracted with ether. The extract was washed with aq. $NaHCO_3$ and dried over $Na_2SO_4$. Removal of the solvent gave crude 5-benzyl-4-phenyloxazole (21 g) as a brown oil which was used for the subsequent process without purification. 5-Methyl-, 5-ethyl-, and 5-isopropyl-4-phenyloxazole were prepared according to the literature.[19]

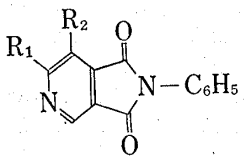
**4-(*p*-Benzyloxyphenyl)-5-methyloxazole (9: $R_1=p$-$C_6H_5CH_2OC_6H_4$, $R_2=CH_3$)**——To a solution of *p*-benzyloxypropiophenone (50 g) in $CHCl_3$ (200 ml) was added dropwise $Br_2$ (34 g) stirring at room temperature. Removal of the solvent gave crude *p*-benzyloxyphenyl-α-bromopropiophenone, which was heated with AcOH (63 ml) and formamide (80 ml) at 150° for 16 hr. After removal of AcOH, the residue was poured into water and extracted with benzene. The extract was washed with 2% KOH and water, and dried over $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was refluxed with hexane (700 ml) for 1 hr. Hexane layer was separated by decantation, decolorized with charcoal and cooled to give 13 g (24%) of **9** ($R_1=p$-$C_6H_5CH_2OC_6H_4$, $R_2=CH_3$) as colorless crystals, mp 67—68°. *Anal.* Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.19; H, 5.69; N, 5.34.

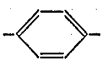
**5-Alkyl (or Benzyl)-N,6-diphenylpyridine-3,4-dicarboximide (11: $R_1=C_6H_5$) (Table IV)**——General Procedure: A mixture of 5-alkyl (or benzyl)-4-phenyloxazole (9: $R_1=C_6H_5$), (10 g) and equimolar N-phenylmaleimide was heated at 130—140° for 12 hr to give crude 5-alkyl (or benzyl)-N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-3,4-dicarboximide (**10**: $R_1=C_6H_5$), which, without purification, was heated with a mixture of dioxane (40 ml) and 5 drops of conc. HCl at 110° for 1 hr. After evaporation *in vacuo*, the residue was recrystallized from EtOH to give **11** ($R_1=C_6H_5$).

**6-(*p*-Benzyloxyphenyl)-5-methyl-N-phenylpyridine-3,4-dicarboximide (11: $R_1=p$-$C_6H_5CH_2OC_6H_4$) (Table IV)**——A mixture of 4-(*p*-benzyloxyphenyl)-5-methyloxazole (3 g) and equimolar N-phenylmaleimide was heated at 120—130° for 6 hr. The resulting solid was recrystallized from AcOEt to give **11** ($R_1=p$-$C_6H_5CH_2OC_6H_4$).

**5-Hydroxy-N,6-diphenylpyridine-3,4-dicarboximide (16)**——A mixture of 5-ethoxy-4-phenyloxazole (9: $R_1=C_6H_5$, $R_2=OC_2H_5$) (6.3 g) and N-phenylmaleimide was heated at 130—140° for 4 hr and then dissolved in hot EtOH. After cooling, the resulting precipitates were removed by filtration. To the filtrate was added

Table IV. N-Phenyl-5,6-disubstituted Pyridine-3,4-dicarboximides (11)



| No. | $R_1$ | $R_2$ | mp (°C) | Yield (%) | Formula | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **a** | $C_6H_5$ | $CH_3$ | 204—205 | 69[a] | $C_{20}H_{14}O_2N_2$ | 76.42 | 4.49 | 8.91 | 76.59 | 4.31 | 8.94 |
| **b** | $C_6H_5$ | $C_2H_5$ | 160—161 | 38[b] | $C_{21}H_{16}O_2N_2$ | 76.81 | 4.91 | 8.53 | 76.39 | 4.73 | 8.41 |
| **c** | $C_6H_5$ | $C_6H_5CH_2$ | 170—171 | 34[a] | $C_{26}H_{18}O_2N_2$ | 79.98 | 4.65 | 7.18 | 79.98 | 4.49 | 6.99 |
| **d** | $C_6H_5CH_2O$-  | $CH_3$ | 198—201 | 56[b] | $C_{27}H_{20}O_3N_2$ | 77.12 | 4.79 | 6.66 | 77.49 | 4.76 | 6.80 |

*a*) The yield based on **10**.
*b*) The yield based on **9**.

18) R. Adams, J.W. Kern, and R.L. Shriner, "Organic Syntheses," Vol. VIII, ed. by R. Adams, John Willey and Sons, Inc., New York, N.Y., 1928, p. 36.
19) H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 700 (1954).

10 drops of conc. HCl, and the mixture was refluxed for 1 hr. After cooling, the resulting precipitate was collected by filtration and recrystallized from AcOEt to give 2.6 g (25%) of **16**, mp 225—228°. *Anal.* Calcd. for $C_{19}H_{12}O_3N_2$: C, 72.14; H, 3.82; N, 8.86. Found: C, 71.95; H, 3.71; N, 8.52.

**Diethyl 5-Methoxy-6-phenylpyridine-3,4-dicarboxylate Hydrochloride (23a)**——To a solution of diethyl 5-hydroxy-6-phenylpyridine-3,4-dicarboxylate hydrochloride (**22**)[10] (4.2 g) in anhydrous DMF (40 ml) was added NaH (50% in oil: 1.4 g) with stirring under cooling. After the addition was completed, the stirring was continued for 30 min, and then methyl iodide (5 ml) was added to the mixture. After stirring for 1 hr, the resulting solution was poured into water (300 ml), made alkaline (pH 9) with 10% aq. NaOH, and extracted with benzene. The extract was dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was dissolved in ether, and the solution was acidified with EtOH–HCl. After cooling in an ice bath, the resulting precipitate was filtered and recrystallized from benzene–ether to give 3.3 g of **23a** as colorless needles, mp 86—98°. *Anal.* Calcd. for $C_{12}H_{19}O_5N \cdot HCl$: C, 59.10; H, 5.51; N, 3.83. Found: C, 59.09; H, 5.26; N, 3.85.

**Diethyl 5-Ethoxy-6-phenylpyridine-3,4-dicarboxylate Hydrobromide (23b)**——To a solution of **22** (5 g) in anhydrous DMF (30 ml) was added NaH (50% in oil: 1.6 g) with stirring and cooling. After the addition was completed, the stirring was continued for 10 min, ethyl iodide (4.5 g) was added to the mixture and the whole mixture was heated at 80° for 1 hr with stirring. After cooling, the resulting solution was poured into water (300 ml), made alkaline (pH 9) with 10% aq. NaOH, and extracted with AcOEt. The extract was washed with water, dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was dissolved in ether, and to the solution was added 30% HBr–AcOH (8 ml). The resulting precipitate was filtered, washed with ether and recrystallized from EtOH–ether to give 4.6 g (76%) of **23b** as colorless needles, mp 143—152°. *Anal.* Calcd. for $C_{19}H_{21}O_5N \cdot HBr$: C, 53.78; H, 5.23; N, 3.30. Found: C, 53.69; H, 5.26; N, 3.35.

**Diethyl 6-Phenyl-5-propoxypyridine-3,4-dicarboxylate Hydrobromide (23c)**——To a solution of **22** (5 g) in anhydrous DMF (30 ml) was added NaH (50% in oil: 1.6 g) with stirring and cooling. After the addition was completed, the stirring was continued for 10 min, and then propyl iodide (4.9 g) was added to the mixture. The subsequent procedures similar to those described for **23b** afforded 5.1 g (81%) of **23c** as colorless prisms, mp 148—154°. *Anal.* Calcd. for $C_{20}H_{23}O_5N \cdot HBr$: C, 54.80; H, 5.52; N, 3.20. Found: C, 54.77; H, 5.47; N, 3.16.

**Ethyl 3-Cyano-5-nitro-6-phenyl-2-pyridone-4-carboxylate (28)**——A mixture of fuming nitric acid ($d$= 1.52) (15.4 ml) and acetic anhydride (14 ml), which was prepared under cooling, was added to a well-stirred suspension of ethyl 3-cyano-6-phenyl-2-pyridone-4-carboxylate (**27**) (48 g) in acetic anhydride (100 ml) at such a rate that the temperature was kept between 40° and 50°. After the addition was completed, the mixture was stirred for another 30 min at room temperature. The resulting mixture was poured into a mixture of cracked ice (300 g) and water (100 ml) and stirred for 4 hr. After standing overnight, the resulting light yellow precipitate was filtered, thoroughly washed with water and dried by suction. The resulting crystals were washed with 30 ml of EtOH–ether (1: 2) and then with ether to give 34.4 g (61.5%) of **28**, mp 219—222°. *Anal.* Calcd. for $C_{15}H_{11}O_5N_3$: C, 57.51; H, 3.54; N, 13.42. Found: C, 57.52; H, 3.26; N, 13.52.

**Ethyl 2-Chloro-3-cyano-5-nitro-6-phenylpyridine-4-carboxylate (29)**——A mixture of **28** (20 g) and phenylphosphonic dichloride (30 ml) was heated at 170—180° for 2 hr. After cooling, the resulting mixture was poured into ice water to give crystals which were filtered and recrystallized from MeOH to give 19.6 g (93%) of **29** as colorless tablets, mp 110—112°. *Anal.* Calcd. for $C_{15}H_{10}O_4N_3Cl$: C, 54.31; H, 3.04; N, 12.67. Found: C, 54.18; H, 2.99; N, 12.81.

**Ethyl 5-Amino-2-chloro-3-cyano-6-phenylpyridine-4-carboxylate (30)**——To a mixture of iron powder (15 g), **29** (10 g) and EtOH (100 ml), vigorously stirred and warmed at 60°, was added dropwise conc. HCl (65.6 ml). During the addition, the mixture started to reflux vigorously. After the addition was completed, the mixture was stirred for 15 min at 60°, 2 hr at room temperature, and then 15 min cooling with ice. Resulting precipitate was filtered, washed with water and recrystallized from EtOH to give **30** (7.9 g: 87%) as yellow needles, mp 147—149°. *Anal.* Calcd. for $C_{15}H_{12}O_2N_3Cl$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.71; H, 3.89; N, 14.00.

**Ethyl 5-Amino-3-cyano-6-phenylpyridine-4-carboxylate (31)**——A mixture of **30** (10 g), 5% Pd–C (10 g), triethylamine (15 ml) and AcOEt (200 ml) was hydrogenated under atmospheric pressure at room temperature. When the theoretical amount of hydrogen was absorbed, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. To the residue was added water (200 ml) and the resulting crystals were filtered. Recrystallization from MeOH gave **31** (7.4 g: 84%) as yellow needles, mp 136—138°. *Anal.* Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.43; H, 4.91; N, 15.41.

**5-Amino-6-phenylpyridine-3,4-dicarboximide (32)**——A mixture of **31** (1 g) and conc. $H_2SO_4$ (1.5 ml) was heated at 100—110° for 1 hr. After cooling, the resulting solution was poured into ice water and adjusted to pH 3 with dil. NaOH and aq. $K_2CO_3$. The resulting precipitate was filtered and recrystallized from EtOH to give **32** (0.8 g: 91%) as orange yellow needles, mp 221—224°. *Anal.* Calcd. for $C_{13}H_9O_2N_3$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.02; H, 3.80; N, 17.73.

**5-Amino-6-phenylpyridine-3,4-dicarboxylic Acid (34)**——A mixture of **31** (5 g) and conc. HCl (50 ml) was refluxed for 15 hr. After removal of the solvent, water (50 ml) was added to the residue. The resulting crystals were filtered, washed with water and recrystallized from 50% EtOH to give **34** (4.5 g: 93%) as pale

yellow powder, mp 120—123°. *Anal.* Calcd. for $C_{13}H_{10}O_4N_2$: C, 60.46; H, 3.90; N, 10.85. Found: C, 59.97; H, 3.77; N, 10.69.

**5-Hydroxy-6-phenylpyridine-3,4-dicarboxylic Acid (35)**——To a solution of **34** (2 g) in 10% HCl (34 ml) was added dropwise a solution of $NaNO_2$ (1.9 g) in water (10 ml) with stirring at 90°. After the addition was completed, the stirring was continued for further 15 min. After cooling, water was added to the residue and the resulting crystals were filtered to give **35** (1.4 g: 70%) as pale yellow powder, mp 212—222° (decomp.). *Anal.* Calcd. for $C_{13}H_9O_5N$: C, 60.23; H, 3.50; N, 5.40. Found: C, 59.74; H, 3.49; N, 5.29.

**20-B**

**5-Acetoxy-6-phenylpyridine-3,4-dicarboxylic Anhydride (36)**——A mixture of **35** (1.2 g) and $Ac_2O$ (20 ml) was heated at 130—140° for 3 hr. After evaporation of $Ac_2O$ *in vacuo*, the residue was recrystallized from ether to give 0.7 g (53%) of **36** as pale yellow needles, mp 180—187° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}O_5N$: C, 63.61; H, 3.20; N, 4.59. Found: C, 63.25; H, 3.09; N, 4.92.

**Methyl 2-Chloro-3-cyano-6-methyl-5-phenylpyridine-4-carboxylate (38)**——A mixture of methyl 3-cyano-6-methyl-5-phenyl-2-pyridone-4-carboxylate (**37**: 6 g)[12] and phenylphosphonic dichloride (8.5 g) was heated at 180—190° for 2 hr. After cooling, the mixture was poured into ice water. The resulting precipitate was filtered and recrystallized from MeOH to give 5.7 g (88%) of **38** as colorless tablets, mp 99—100°. *Anal.* Calcd. fcr $C_{15}H_{11}O_2N_2Cl$: C, 62.83; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 63.16; H, 3.64; N, 9.61; Cl, 12.36.

**Methyl 3-Cyano-6-methyl-5-phenylpyridine-4-carboxylate (39)**——A solution of **38** (2 g) and triethylamine (1 g) in MeOH (40 ml) was hydrogenated over 5% Pd–C (200 mg) under atmospheric pressure at room temperature. After absorption of hydrogen ceased, the catalyst was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with AcOEt and the extract was dried over $Na_2SO_4$. After removal of the solvent, the residue was cooled on ice to give **1.4** g (80%) of **39**, mp 39—40°. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.46; H, 4.78; N, 10.63.

**6-Methyl-5-phenylpyridine-3,4-dicarboximide (40)**——A mixture of **39** (2.75 g) and conc. $H_2SO_4$ (3 ml) was heated at 100° for 2 hr. After cooling, water was added to the mixture. The resulting crystals were filtered and recrystallized from EtOH to give 2.2 g of **40** as pale yellow needles, mp 200—206° (decomp.). *Anal.* Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.44; H, 3.90; N, 11.55.

**7,8-Disubstituted Pyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (5 and 12) (Table V)**——a) To a solution of **4** (8 g) in EtOH (150 ml) was added 80% $N_2H_4 \cdot H_2O$ (16 g), and the mixture was refluxed for 7 hr. After cooling, the resulting precipitate (hydrazinium salt of **5**) was collected by filtration and suspended in water (150 ml). The suspension was adjusted to pH 1—2 with 10% HCl and stirred for 2 hr. The resulting crystals were filtered, washed and dried to give **5**. Compounds **5** obtained in pure form are listed in Table V. **5** ($R_1$=$CH_3$, $R_2$=$C_2H_5$), **5** ($R_1$=$C_3H_7$, $R_2$=$CH_3$), **5** ($R_1$=$C_2H_5(CH_3)CH$, $R_2$=$CH_3$) and **5** ($R_1$=$C_6H_5CH_2$, $R_2$=$CH_3$) were used for the subsequent reaction without purification.

b) A mixture of **11** (5 g) and 80% $N_2H_4 \cdot H_2O$ (35 ml) was heated at 150° for 2 hr. After removal of the excess $N_2H_4 \cdot H_2O$, EtOH was added to the residue. The resulting crystals were filtered and suspended in water. The suspension was adjusted to pH 1—2 with 10% HCl and stirred for 2 hr. The resulting crystals were filtered, washed and dried to give **12**.

**8-Hydroxy-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (17) (Table V)**——General Procedure: A mixture of **16**, **22**, or **36** (0.6 g) and 80% $N_2H_4 \cdot H_2O$ (10 ml) was heated at 120° for 1 hr. After removal of excess $N_2H_4 \cdot H_2O$ *in vacuo*, EtOH was added to the residue. The resulting crystals (hydrazinium salt of **17**) were filtered and suspended in water. The suspension was stirred and adjusted to pH 1—2 with 10% aq. HCl. After stirring was continued for 1 hr, the resulting crystals were filtered to give **17** as pale yellow powder.

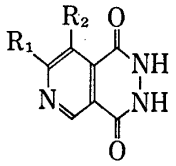
**8-Alkoxy-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (24) (Table V)**——A mixture of **23** (1.5 g), 80% $N_2H_4 \cdot H_2O$ (3 ml) and EtOH (30 ml) was refluxed for 4 hr. After cooling, the resulting crystals were filtered to give hydrazinium salt of **24** as yellow needles, which was suspended in water (15 ml) and the suspension was acidified with AcOH. After stirring for 1 hr, the resulting crystals were filtered to give **24** as pale yellow powder.

**8-Amino-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (33) (Table V)**——A mixture of **32** (1 g) and 80% $N_2H_4 \cdot H_2O$ (20 ml) was heated at 140° for 1 hr. After removal of excess $N_2H_4 \cdot H_2O$ *in vacuo*, water was added to the residue. The resulting suspension was acidified with 10% HCl and adjusted to pH 1. The mixture was filtered and the filtrate was adjusted to pH 5 with dil. $NH_4OH$. The resulting precipitate was filtered, washed with water and dried to give **33** as yellow powder.

**7-Methyl-8-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (41) (Table V)**——A mixture of **40** (2 g), AcOH (20 ml) and 80% $N_2H_4 \cdot H_2O$ (4 ml) was refluxed for 30 min. After cooling, the mixture was diluted with water. The resulting precipitate was filtered, washed with water and dried by succion to give **41** as pale yellow powder.

**7,8-Disubstituted-1,4-bis-(substituted amino)pyrido[3,4-*d*]pyridazine (7, 14, 26, and 43) (Table I)**——General Procedure: A mixture of **5**, **12**, **24**, or **41** (1 g), $POCl_3$ (15 ml) and N,N-dimethylaniline or α-picoline (1.5 g) was heated at 110—120° for 3 hr. The excess $POCl_3$ was evaporated *in vacuo* and the residue was poured into ice water. The resulting crystals were filtered to give crude 1,4-dichloro-7,8-disubstituted pyrido[3,4-*d*]pyridazine (**6**, **13**, **25**, and **42**), which, without purification, was refluxed with morpholine or piperidine (10

TABLE V. 7,8-Disubstituted Pyrido[3,4-*d*]pyridazine-1,4(2H,3H)-diones



| No. | $R_1$ | $R_2$ | mp (°C) | Yield (%) | Formula | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | $CH_3$ | $C_4H_9O$ | 275—285 (decomp.) | 87 | $C_{12}H_{15}O_3N_3$ | 57.82 | 6.07 | 16.86 | 57.87 | 6.07 | 16.70 |
| **5b** | $C_2H_5$ | $CH_3O$ | 248 (decomp.) | 46 | $C_{10}H_{11}O_3N_3$ | 54.29 | 5.01 | 19.00 | 54.11 | 4.97 | 18.88 |
| **5c** | $(CH_3)_2CH$ | $CH_3O$ | 241—245 (decomp.) | 37 | $C_{11}H_{13}O_3N_3$ | 56.16 | 5.57 | 17.86 | 55.98 | 5.45 | 17.51 |
| **5d** | $C_4H_9$ | $CH_3O$ | 255—259 (decomp.) | 47 | $C_{12}H_{15}O_3N_3$ | 57.82 | 6.07 | 16.86 | 57.46 | 6.01 | 17.07 |
| **5e** | $(CH_3)_2CHCH_2$ | $CH_3O$ | 270—273 (decomp.) | 71 | $C_{12}H_{15}O_3N_3$ | 57.82 | 6.07 | 16.86 | 57.77 | 6.03 | 17.16 |
| **12a** | $C_6H_5$ | $CH_3$ | >300 | 87 | $C_{14}H_{11}O_2N_3$ | 66.39 | 4.38 | 16.59 | 65.96 | 4.39 | 16.61 |
| **12b** | $C_6H_5$ | $C_2H_5$ | >300 | 91 | $C_{15}H_{13}O_2N_3$ | 67.40 | 4.90 | 15.72 | 66.95 | 4.79 | 15.89 |
| **12c** | $C_6H_5$ | $C_6H_5CH_2$ | >300 | 100 | $C_{20}H_{15}O_2N_3$ | 72.93 | 4.59 | 12.76 | 72.95 | 4.45 | 12.47 |
| **12d** | $p$-$C_6H_5CH_2O$-$C_6H_4$- | $CH_3$ | >300 | 91 | $C_{21}H_{17}O_3N_3$ | 70.18 | 4.77 | 11.69 | 70.24 | 4.63 | 11.79 |
| **17** | $C_6H_5$ | OH | >300 | 74 | $C_{13}H_9O_3N_3$ | 61.17 | 3.55 | 16.47 | 60.79 | 3.46 | 16.48 |
| **24a** | $C_6H_5$ | $CH_3O$ | 245—250 (decomp.) | 64 | $C_{14}H_{11}O_3N_3$ | 62.45 | 4.12 | 15.61 | 62.07 | 4.33 | 15.74 |
| **24b** | $C_6H_5$ | $C_2H_5O$ | 227—231 (decomp.) | 92 | $C_{15}H_{13}O_3N_3$ | 63.59 | 4.63 | 14.87 | 63.38 | 4.74 | 14.92 |
| **24c** | $C_6H_5$ | $C_3H_7O$ | 230—238 (decomp.) | 83 | $C_{16}H_{15}O_3N_3$ | 64.63 | 5.09 | 14.14 | 64.55 | 4.88 | 14.28 |
| **33** | $C_6H_5$ | $NH_2$ | >300 | 75 | $C_{13}H_{10}O_2N_4$ | 61.40 | 3.96 | 22.04 | 61.09 | 3.93 | 22.24 |
| **41** | $CH_3$ | $C_6H_5$ | 293—300 (decomp.) | 82 | $C_{14}H_{11}O_2N_3$ | 66.39 | 4.38 | 16.59 | 66.69 | 4.10 | 16.56 |

ml) for 4 hr. After removal of the excess amine, water was added to the residue. The filtration and recrystallization of the resulting crystals gave **7**, **14**, **26**, or **43**.

**7-(*p*-Hydroxyphenyl)-8-methyl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (15) (Table I)**——A mixture of 7-(*p*-benzyloxyphenyl)-8-methyl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (**14d**, 2 g) and trifluoroacetic acid (20 ml) was refluxed for 40 min. The excess trifluoroacetic acid was removed by evaporation *in vacuo* and subsequently by azeotropic distillation with benzene. The residual oil was neutralized with aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over anhydrous $Na_2SO_4$ and evaporated to dryness. Recrystallization of the residue from MeOH gave **15** as yellow prisms.

**8-Chloro-1,4-dimorpholino-7-substituted Pyrido[3,4-*d*]pyridazine (19 and 21) (Table I)**——A mixture of **17** (0.4 g), $POCl_3$ (6 ml) and $\alpha$-picoline (0.4 ml) was heated at 120° for 8 hr. After removal of the excess $POCl_3$, the residue was poured into ice water and the resulting crystals were filtered and purified by column chromatography on silica gel eluted with benzene–acetone (10: 1) to give 1,4,8-trichloro-7-phenylpyrido[3,4-*d*]-pyridazine (**18**). **18** was heated with morpholine (8 ml) at 140° for 3 hr. After removal of excess morpholine by evaporation *in vacuo*, water was added to the residue. The resulting crystals were filtered and recrystallized from EtOH to give 8-chloro-1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**19**) as yellow needles. 8-Chloro-7-methyl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (**21**) was prepared from 8-hydroxy-7-methylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**20**)[7] by the similar procedure.

**Reactions of 4-Phenyloxazole Derivatives with N-Phenylmaleimide (Table II and Table III)**——a) 4-Phenyloxazole (**9**: $R_1$=$C_6H_5$, $R_2$=H) (1 g) and N-phenylmaleimide (1.4 g) were reacted under the conditions shown in Table II. In the cases that benzene (20 ml) was used as the solvent, N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide (**8a**) was precipitated as colorless needles after cooling. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel eluted with benzene–acetone (20: 1) to give N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*endo*-3,4-dicarboximide (**8b**) as colorless prisms. In the case that the reaction was carried out without solvent, addition of ether

to the reaction mixture afforded the crystals of **8a**, **8b** being observed only trace quantities on TLC of the filtrate.

b) 5-Methyl-4-phenyloxazole (**8**: $R_1=C_6H_5$, $R_2=CH_3$) (1 g), N-phenylmaleimide (1.25 g) and benzene (10 ml) were reacted under the conditions shown in Table II. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with benzene-acetone (15: 1) to give 5-methyl-N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide as colorless crystals. *endo*-Adduct could not be isolated in a pure form. The yields in Table II were calculated by integral intensity of the methyl groups in NMR ($CH_3$ of oxazole: 7.49 $\tau$, $CH_3$ of *endo*-adduct: 7.85 $\tau$, $CH_3$ of *exo*-adduct: 7.98$\tau$).

c) 5-Isopropyl-4-phenyloxazole (**8**: $R_1=C_6H_5$, $R_2=CH(CH_3)_2$) (1 g) and N-phenylmaleimide (1 g) were allowed to react under the conditions shown in Table II. The reaction mixture was purified by column chromatography on silica gel eluted with benzene–acetone (20: 1) to give 5-isopropyl-N,6-diphenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide as colorless prisms. The *endo*-adduct could not be crystallized. No addition reaction proceeded when the reaction was carried out in benzene.

d) A mixture of 5-ethyl-4-phenyloxazole (1 g), N-phenylmaleimide (1.1 g) and benzene (10 ml) was refluxed for 7 hr. After removal of the solvent, EtOH was added to the residue and cooled. The resulting crystals were filtered and recrystallized from EtOH to give 0.5 g (24%) of 5-ethyl-6-phenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide as colorless prisms.

e) A mixture of 5-benzyl-4-phenyloxazole (17 g) and N-phenylmaleimide (12.5 g) was heated at 130—140° for 4 hr. The resulting mixture was dissolved in $CHCl_3$ (150 ml). Ether (500 ml) was added to the solution and the resulting solution was allowed to stand at room temperature to precipitate 5-benzyl-6-phenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide (4.3 g: 15%) as the first crop. The second crop was a mixture of *exo*-adduct and *endo*-adduct, and finally 5-benzyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*endo*-3,4-dicarboximide (3 g: 10%) was precipitated. The respective recrystallization from AcOEt gave pure *exo*-adduct as colorless prisms and *endo*-adduct as colorless granules.

f) A mixture of 5-ethoxy-4-phenyloxazole (5 g) and N-phenylmaleimide (4.8 g) was heated at 140° for 4 hr and dissolved in hot EtOH. After cooling, the resulting precipitate was filtered and recrystallized from EtOH to give 5-ethoxy-6-phenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*endo*-3,4-dicarboximide (1.5 g: 16%) as colorless needles. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give 5-ethoxy-6-phenyl-2,3,4,5-tetrahydro-2,5-epoxypyridine-*exo*-3,4-dicarboximide (6.2 g: 65%) as an oil.

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