[Chem. Pharm. Bull. 28(1) 198—201 (1980)]

Pyridazines. IV.[1] Intramolecular Cycloaddition of 3-Chloro-6-(2-allyloxyphenoxy)pyridazines

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(Received July 5, 1979)

Intramolecular cycloaddition of 3-chloro-6-(2-allyloxyphenoxy)pyridazines yielded various hydroxyxanthenes, which were also prepared by similar cycloaddition of 3-substituted-6-(2-allylphenoxy)pyridazines containing methoxy groups on their benzene rings, followed by demethylation of the resulting methoxyxanthenes. The mechanism of the reaction is discussed.

Keywords——intramolecular cycloaddition; 3-chloro-6-(2-allyloxyphenoxy)pyridazines; 3-chloro-6-(2-allylphenoxy)pyridazines; 4-hydroxyxanthenes; 4-methoxyxanthenes; 4-hydroxyxanthone; [3,4]-sigmatropic rearrangement

In previous studies, the authors reported novel syntheses of xanthenes[3] and 1,9a-dihydroxanthenes[1,4] involving the thermal intramolecular cycloaddition of 3-substituted-6-(2-allylphenoxy)pyridazines.

This paper describes an unusual reaction leading to hydroxyxanthenes by the cyclization of 3-(2-allyloxyphenoxy)pyridazines.

In general, hydroxyxanthenes are important intermediates for the synthesis of naturally occurring hydroxyxanthenes[5] and also of β-adrenargic blocking agents.[6]

Heating 3-chloro-6-(2-allyloxyphenoxy)pyridazine (**3**), which has an oxygen atom between the allylic side chain and the benzene ring, in diethylaniline (DEA) at 210° for 3 hr did not give the expected compound (**4**), but provided 4-hydroxyxanthene (**5**) in 30% yield. The spectroscopic data and thin-layer chromatographic behavior of **5** were identical with those of the compound obtained by demethylation of 4-methoxyxanthene (**6**) prepared by the cycloaddition of 3-chloro-6-(2-allyl-6-methoxyphenoxy)pyridazine (**7**). Oxidation of **5** with chromic oxide gave 4-hydroxyxanthone (**8**) in 52% yield (Chart 1). The hydroxyxanthone (**8**) has been isolated from the seeds of *Mammea americana* L.[5,7] and also from wood of *Mesua ferrea* L.[8]

In order to obtain information on the mechanism of this reaction, the cyclization of 3-chloro-6-(2-allyloxyphenoxy)pyridazines with various substituents on the allylic side chains was carried out. Thus, 3-chloro-6-[2-(2-butenyloxy)phenoxy]pyridazine (**9a**) and 3-chloro-6-[2-(3-phenylallyloxy)phenoxy]pyridazine (**9b**) gave 4-hydroxy-9-methylxanthene (**10a**) and 4-hydroxy-9-phenylxanthene (**10b**), respectively, on heating. These hydroxyxanthenes (**10a** and **b**) were identical in all respects with the compounds derived from 4-methoxy-9-methylxanthene (**11a**) and 4-methoxy-9-phenylxanthene (**11b**) obtained by the cycloaddition of

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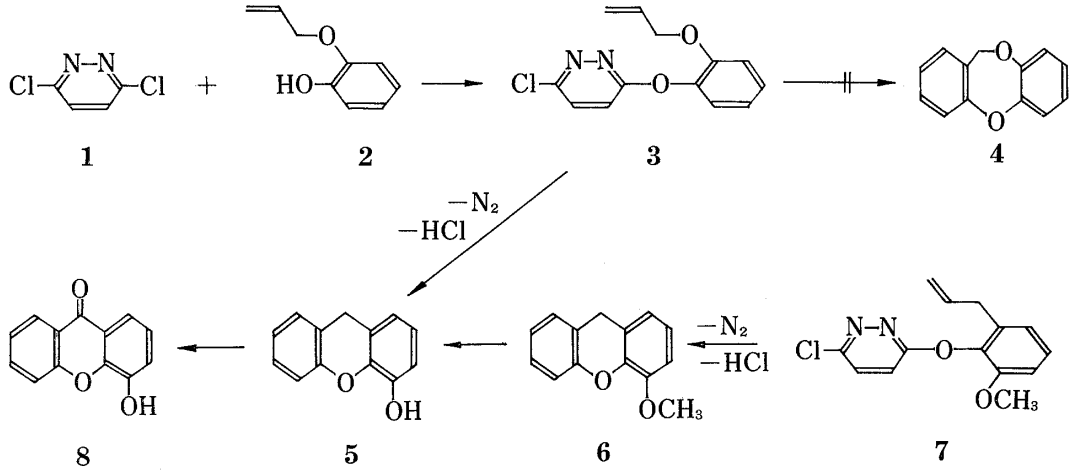

Chart 1

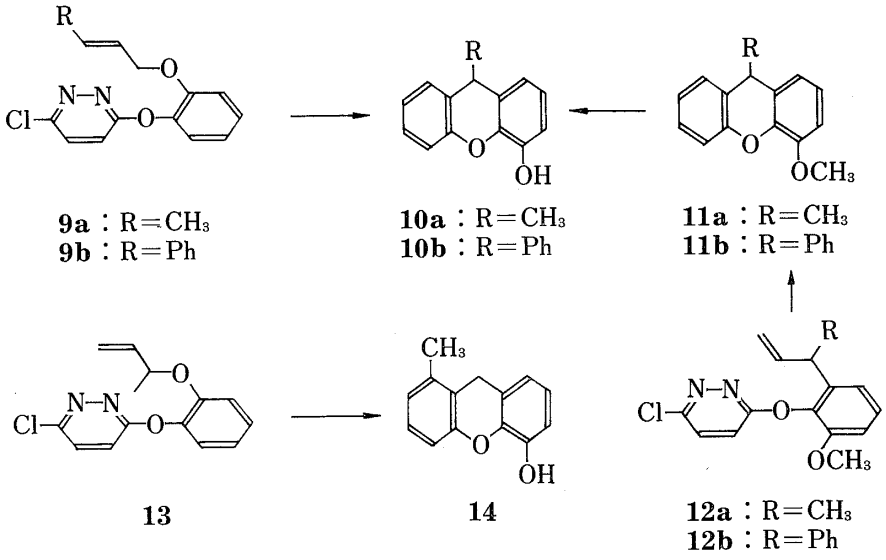

Chart 2

3-chloro-6-[2-(1-methylallyl)-6-methoxyphenoxy]pyridazine (**12a**) and 3-chloro-[2-(1-phenylallyl)-6-methoxyphenoxy]pyridazine (**12b**), respectively.

On the other hand, 3-chloro-6-[2-(1-methylallyloxy)phenoxy]pyridazine (**13**) gave 5-hydroxy-1-methylxanthene (**14**) on heating (Chart 2).

Probable pathways for the formation of these hydroxyxanthenes (**5**, **10a**, **10b** and **14**) from the corresponding (2-alkenyloxyphenoxy)pyridazines are shown in Chart 3.

The allyl groups of the starting pyridazines rearranged to the 6-position of the benzene rings to give 3-chloro-6-(2-allyl-6-hydroxyphenoxy)pyridazine (**15**). The rearrangement was presumed to be formally [3,4]-sigmatropic. However, there is no previous report on such a rearrangement of an allyl group. Intramolecular cycloaddition of **15** produced the adduct (**16**), from which nitrogen and hydrogen chloride were eliminated to give the hydroxyxanthenes (**17**).

In view of the proposed mechanism, the synthesis of xanthenes with a 4-hydroxy group and an 8- and/or 9-substituent should be facile by the intramolecular cycloaddition of suitably substituted 3-chloro-6-(2-allyloxyphenoxy)pyridazines.

The formation of hydroxyxanthenes by ring transformation of heterocyclic compounds as described above has not previously been reported.

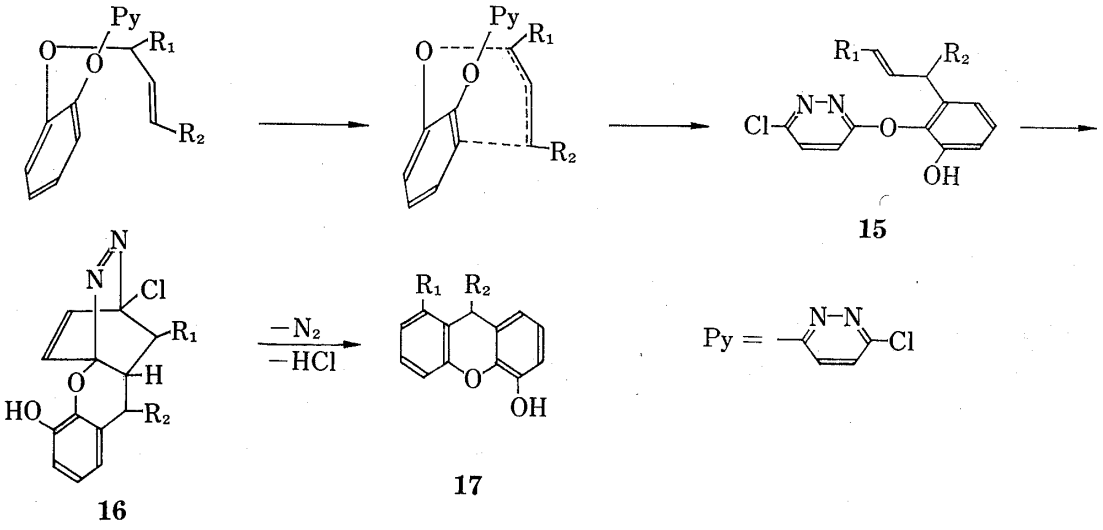

Chart 3

Further development of this reaction and its application to the synthesis of natural products are under consideration.

Experimental

All melting points are uncorrected. IR spectra were taken using a Hitachi G_3 spectrometer. NMR spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The coupling constants are given in Hz. Abbreviations used are: s, singlet; d, doublet; m, multiplet. New 2-allylphenols were prepared on the basis of the published method;[9] their physical constants are as follows: 2-(1-methylallyl)-6-methoxyphenol, bp 93—96° (4 mmHg); 2-(1-phenylallyl)-6-methoxyphenol, bp 47—49° (0.55 mmHg).

3-Chloro-6-(2-allyloxyphenoxy)pyridazines——As a typical run, the preparation of 3-chloro-6-(2-allyloxyphenoxy)pyridazine (**3**) is described below.

A mixture of 3,6-dichloropyridazine (**1**, 8.94 g), 2-allyloxyphenol[10] (9 g) and KOH (3.36 g) in dimethyl sulfoxide (40 ml) was stirred at 50° for 3 hr. The reaction mixture was poured into cold water. The resulting suspension was extracted twice with 200 ml portions of ether. The combined extracts were washed once with 2 N NaOH (100 ml) and then with water, dried over anhyd. Na_2SO_4, and the ether was removed *in vacuo* to give 13.4 g (85%) of the crude product. Recrystallization from hexane gave a pure sample, mp 78° (needles). NMR ($CDCl_3$) δ: 6.9—7.6 (6H, m, Ar, 4-H and 5-H), 5.5—6.2 (1H, m, –CH=), 5.0—5.4 (2H, m, $=CH_2$), 4.49 (2H, dt, $J=5$ and 1, $-CH_2-$). *Anal.* Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.28; N, 10.66. Found: C, 59.39; H, 4.25; N, 10.81.

Physical constants of other compounds are as follows. **9a**: mp 76° (hexane–benzene, prisms). NMR (CCl_4) δ: 6.9—7.4 (6H, m, Ar, 4-H and 5-H), 5.4—5.7 (2H, m, –CH=CH–), *ca.* 4.37 (2H, m, $-CH_2$), 1.63 (3H, d, $J=5$, $-CH_3$). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.21. Found: C, 60.82; H, 4.68; N, 9.88. **9b**: mp 111° (hexane–benzene, needles). NMR ($CDCl_3$) δ: 7.0—7.5 (11H, m, Ar, 4-H and 5-H), 6.57 (1H, d, $J=16$, –CH=C<u>H</u>–ph), 6.13 (1H, dt, $J=16$ and 5, –C<u>H</u>=CH–ph), 4.65 (2H, d, $J=5$, $-C\underline{H}_2$–CH=). *Anal.* Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.43; H, 4.43; N, 8.05. **13**: bp 165° (0.15 mmHg). NMR -CCl_4) δ: 6.9—7.5 (6H, m, Ar, 4-H and 5-H), 5.4—6.1 (1H, m, –CH=), 4.9—5.3 (2H, m, $=CH_2$), 4.3—4.8 (1H, m, $C\underline{H}(CH_3)$–CH=), 1.13 (3H, d, $J=7$, $C\underline{H}_3$–CH(O)–CH=). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; Cl, 12.81; N, 10.12. Found: C, 60.50; H, 4.71; Cl, 12.60; N, 9.89.

4-Hydroxyxanthene (**5**)——a) Cyclization of **3**: A mixture of **3** (8.4 g) and DEA (20 ml) was heated at 210° for 3 hr, and the solvent was removed *in vacuo*. The residue was extracted with a mixture of benzene–ethyl acetate (4: 1, 50 ml), and the extracts were washed twice with 20 ml portions of 6 N HCl and then with water (50 ml). The solvent was evaporated off *in vacuo*, and the oily residue was chromatographed on

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silica gel (200 g). Elution with benzene–ethyl acetate (40: 1) afforded 1.27 g (30%) of 4-hydroxyxanthene (**5**), mp 124°, lit.[6] mp 121—122°.

b) Demethylation of **6**: A mixture of conc. HCl (25 ml) and pyridine (24 ml) was gradually distilled untill the temperature reached 210°. 4-Methoxyxanthene[3] (**6**, 6.3 g) was then added to the residue, and the whole was stirred at 190° for 2 hr. After cooling, the reaction mixture was poured into cold water, and the aqueous solution was extracted with ether. Removal of the ether gave an oily residue which was recrystallized from hexane to give 3 g (48%) of **5**, mp 124°. This compound was identical in all respects with that obtained as described above.

4-Hydroxyxanthene (8)——A mixture of **5** (1.98 g) and pyridine (10 ml) was treated with chromic oxide (2.1 g) dissolved in water (3.4 ml), and the whole was stirred at room temperature for 12 hr. The reaction mixture was poured into chloroform (500 ml). After filtration, the chloroform layer was separated and concentrated *in vacuo*, then the residue was extracted twice with 20 ml portions of hot toluene. The toluene extracts were concentrated *in vacuo*, and the crude crystalline residue was recrystallized from ethyl acetate to give 1.1 g (52%) of **8** as fine needles, mp 246—248°, lit.[5] mp 245—246°. IR ν_{max}^{Nujol} cm^{-1}: 3175 (OH), 1625 (C=O).

4-Hydroxy-9-methylxanthene (10a)——This compound was obtained as described for **5** in 14 and 80% yields from **9a** and **11a**, respectively. Light-yellow oil, bp 140—144° (0.03 mmHg); IR $\nu_{max}^{liq.}$ cm^{-1}: 3430, 3520 (OH); NMR (CCl_4) δ: 6.5—7.3 (7H, m, Ar), 5.50 (1H, broad s, OH), 4.02 (1H, q, J=14 and 7, >CH–CH_3), 1.44 (3H, d, J=7, CH_3). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.43; H, 6.01.

4-Hydroxy-9-phenylxanthene (10b)——This compound was obtained in the manner described for **5** in 26 and 90% yields from **9b** and **11b**, respectively. Colorless prism, mp 126° (hexane); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3500 (OH); NMR ($CDCl_3$) δ: 6.5—7.3 (12H, m, Ar), 5.75 (1H, s, OH), 5.20 (1H, s, 9-H). *Anal.* Calcd for $C_{19}H_{14}O_2$: C, 83.20; H, 5.15. Found: C, 83.35; H, 5.09.

4-Methoxy-9-methylxanthene (11a)——A mixture of **12a** (8.93 g) and DEA (20 ml) was refluxed for 3.5 hr. Ether (50 ml) was added to the cooled reaction mixture, and the solution was repeatedly extracted with cold 6 N HCl. The ether layer was finally washed with water and dried over Na_2SO_4, then the ether was removed *in vacuo* to give 7.6 g (quant.) of **11a** as colorless prisms, mp 90° (hexane). *Anal.* Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.60; H, 6.22.

4-Methoxy-9-phenylxanthene (11b)——This compound was obtained as described above in 87% yield from **12b**. Colorless prisms, mp 138—139° (benzene–methanol). *Anal.* Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.43; H, 5.55.

3-Chloro-6-[2-(1-methylallyl)-6-methoxyphenoxy]pyridazine (12a)——Sodium (1.15 g) was added to a mixture of **1** (7.4 g) and dry toluene (20 ml), and the mixture was refluxed for 2 hr. After cooling, 2-(1-methylallyl)-6-methoxyphenol (9 g) in dry toluene (10 ml) was added, and the solution was refluxed for a further 8 hr. The reaction mixture was then poured into 2 N NaOH (40 ml), and the aqueous layer was extracted with toluene. The combined toluene extracts were washed with water, dried over anhyd. Na_2SO_4, and the toluene was evaporated off to give 12.8 g (88%) of a crude crystalline solid, mp 99° (hexane–ethyl acetate, leaflets). NMR ($CDCl_3$) δ: 7.13, 7.50 (2H, d, J=9, 4-H and 5-H). 6.7—7.4 (3H, m, Ar), 5.7—6.3 (1H, m, –C<u>H</u>=CH_2), 4.8—5.2 (2H, m, –CH=C<u>H</u>$_2$), 3.70 (3H, s, CH_3O), 3.6—3.9 [1H, m, –C<u>H</u>(CH_3)–], 1.30 (3H, d, J=9, CH_3). *Anal.* Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; N, 9.64. Found: C, 61.92; H, 5.23; N, 9.69.

3-Chloro-6-[2-(1-phenylallyl)-6-methoxyphenoxy]pyridazine (12b)——This compound was prepared as above in 99% yield from **1** and 2-(1-phenylallyl)-6-methoxyphenol, mp 111° (hexane, needles). NMR ($CDCl_3$) δ: 6.80, 7.30 (2H, d, J=9, 4-H and 5-H), 6.7—7.3 (9H, m, Ar and ph–C<u>H</u>–CH=), 6.0—6.6 (1H, m, –C<u>H</u>=CH_2), 4.8—5.3 (2H, m, =CH_2), 3.70 (3H, s, CH_3O). *Anal.* Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 68.12; H, 4.90; Cl, 10.15; N, 8.09.

Acknowledgement The authors are very grateful to the staff of the Analytical Division of the Central Research Laboratories for microanalyses and spectroscopic measurements.