Studies of Pyridotropolones. VII.[1,2] *Several Condensation Reactions of Isopropylpyrido[3, 2-d]tropolones*

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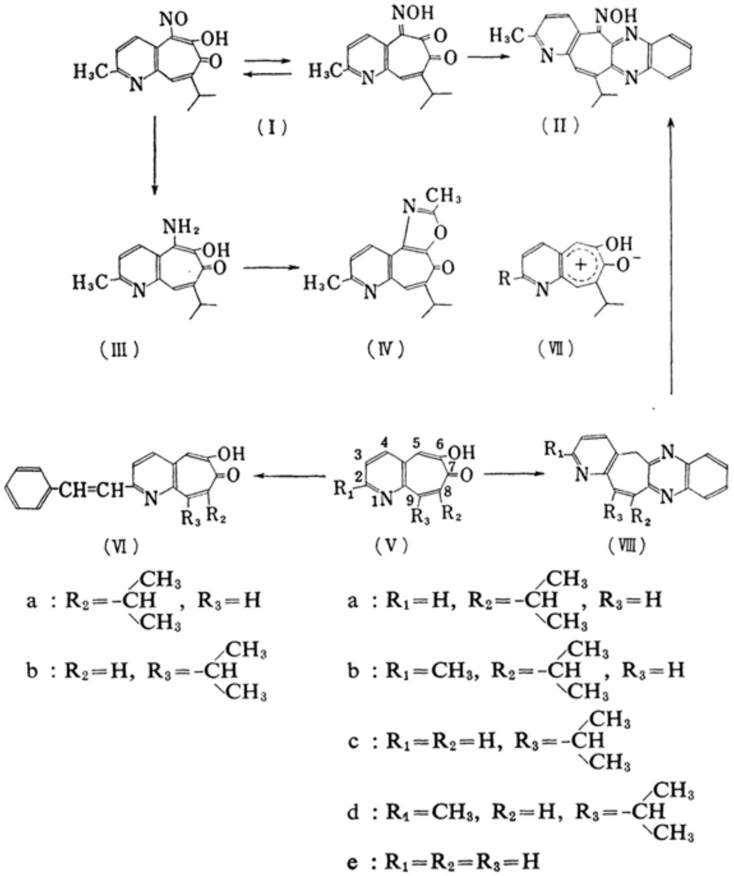
Regarding the condensation reaction of pyridotropolones, one of the present authors, Yamane,[3] has previously reported that nitroso compound I of 8-isopropyl-2-methylpyrido-[3, 2-d] tropolone afforded a quinoxalo compound II by the condensation with *o*-phenylenediamine, and that 5-amino compound III, which was obtained by the catalytic reduction of I, gave an oxazolopyridotropone derivative IV upon being treated with acetic anhydride. Kikuchi and Muroi[4] reported that pyrido-[3, 2-d] tropolone and its 2-methyl derivative gave quinoxaline derivatives by condensation with *o*-phenylenediamine, and that 2-methylpyrido [3, 2-d] tropolone afforded a 2-styryl compound by condensation with benzaldehyde. The present authors carried out similar condensation reactions of isopropylpyrido [3, 2-d]-tropolones. Furthermore, some derivatives of pyridoindolotropones were obtained by reaction with phenylhydrazine.

As was reported by Kikuchi and Muroi,[4]



a : $R_2 = -CH<^{CH_3}_{CH_3}$, $R_3 = H$

b : $R_2 = H$, $R_3 = -CH<^{CH_3}_{CH_3}$

a : $R_1 = H$, $R_2 = -CH<^{CH_3}_{CH_3}$, $R_3 = H$

b : $R_1 = CH_3$, $R_2 = -CH<^{CH_3}_{CH_3}$, $R_3 = H$

c : $R_1 = R_2 = H$, $R_3 = -CH<^{CH_3}_{CH_3}$

d : $R_1 = CH_3$, $R_2 = H$, $R_3 = -CH<^{CH_3}_{CH_3}$

e : $R_1 = R_2 = R_3 = H$

Scheme I

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[1] This work was presented at the Meeting of the Kyushu District of the Chemical Society of Japan, Fukuoka, October, 1961.

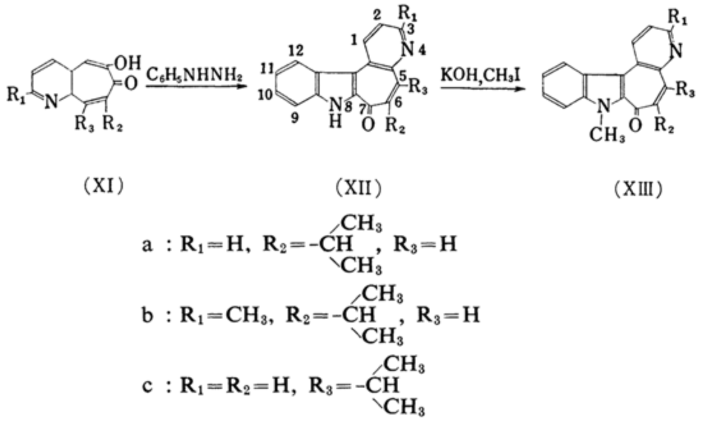
[2] Part VI: K. Yamane, This Bulletin, **34**, 42 (1961).

[3] K. Yamane, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1175 (1959).

[4] K. Kikuchi and T. Muroi, presented at the Tohoku Local Meeting of the Chemical Society of Japan, Sendai, June, 1960.

(IX) (X)

Scheme II



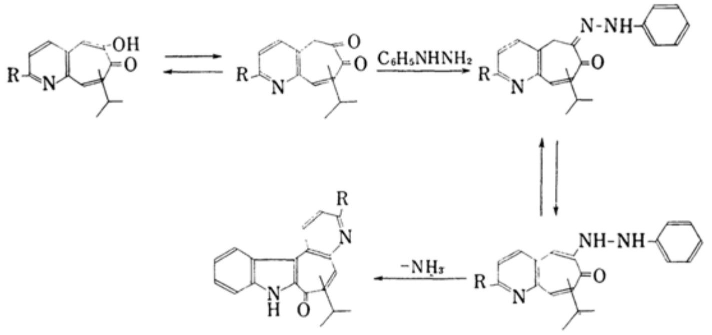
(XI) (XII) (XIII)

a : $R_1=H,\ R_2=-CH(CH_3)_2,\ R_3=H$

b : $R_1=CH_3,\ R_2=-CH(CH_3)_2,\ R_3=H$

c : $R_1=R_2=H,\ R_3=-CH(CH_3)_2$

Scheme III



Scheme IV

8-isopropyl-2-styrylpyrido[3, 2-d]tropolone (VIa) and 9-isopropyl-2-styrilpyrido [3, 2-d] tropolone (VIb) were obtained from the reaction of benzaldehyde with 8-isopropyl-2-methylpyrido-[3, 2-d] tropolone (Vb) and with 9-isopropyl-2-methylpyrido[3, 2-d]tropolone (Vd) respectively.

Attempts to prepare quaternary salts of 8-isopropylpyrido [3, 2-d] tropolones by reaction with methyl iodide, ethyl iodide and ethyl *p*-toluenesulfonate were unsuccessful. This was probably due to the decrease in the electron density at the nitrogen atom through the contribution of the structure VII.

The heating of 8- and 9-isopropyl derivatives (Va, Vb and Vc) with *o*-phenylenediamine in acetic acid afforded quinoxaline derivatives in a good yield, as in the case[4] of pyrido [3, 2-d]-tropolone. Kikuchi and Muroi[4] proposed a structure (IX or X) for the condensation product. Treating VIIIb with amyl nitrite in an acidic medium gave II.[3] VIIIe was not acylated by acetyl chloride or benzoyl chloride in pyridine. The infrared spectrum of VIIIe has no absorption bands at the NH region and exhibits an absorption band at 1453 cm^{-1} due to the CH_2 deformation vibration. From these facts, it may be concluded that the condensation product VIII exists not as formula IX but as quinoxalo structure X (Schemes I and II).

The heating of 8-isopropyl-2-methylpyrido-[3, 2-d] tropolone (XIb) with phenylhydrazine in acetic acid unexpectedly gave yellow crystals (XIIb) of formula $C_{20}H_{18}ON_2$ in place of a phenylhydrazone. This suggests that one molecule of ammonia was lost during the reaction. The crystals did not react either with carbonyl reagents or with acylating agents, but *N*-methyl compound XIII was obtained by a method similar to that used in the case of carbazole. The infrared spectrum of XIIb shows peaks at 1620 cm^{-1} and 3300 cm^{-1}. 8- and 9-isopropyl analogs (XIa and XIc) also gave similar compounds (XIIa and XIIc respectively). The ultraviolet absorption spectra of these compounds are shown in Fig. 2. From these facts it may be assumed that the condensation products have the pyrido[3, 2-d]-indolo[2, 3-b]tropone structure (Scheme III). It is interesting that the mother substance, pyrido[3, 2-d]tropolone and its 2-methyl derivative, gave no pyridoindolotropones. Further studies are now in progress. The mechanism of this condensation reaction seems to be analogous to Fischer's indole syntheses, as Scheme IV shows.

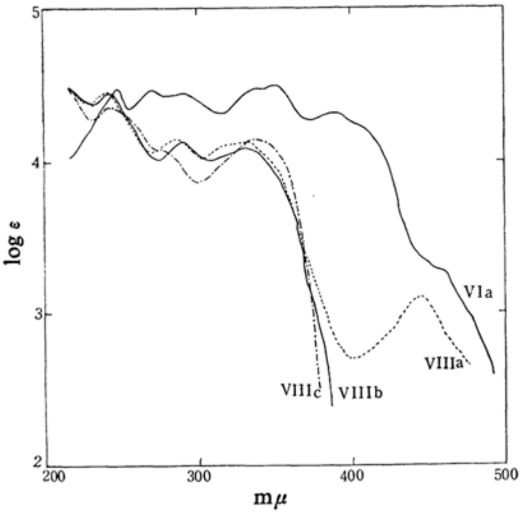


Fig. 1. Ultraviolet absorption spectra of VIa, VIIIa, VIIIb and VIIIc in methanol.

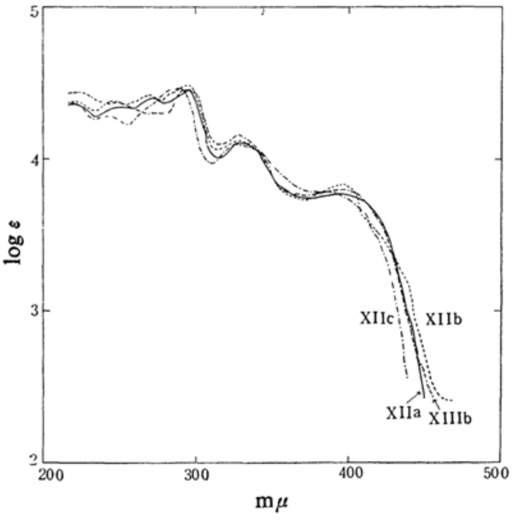


Fig. 2. Ultraviolet absorption [spectra of XIIa, XIIb, XIIc and XIIIb in methanol.

Experimental[5)]

8-Isopropyl-2-styrylpyrido[3,2-d]tropolone (VIa).—A mixture of Vb (0.4 g.), benzaldehyde (0.2 cc.) and a small amount of zinc chloride in a sealed tube was heated for 3 hr. at 150～160°C. The reaction mixture was diluted with water, and a reddish brown precipitate was then filtered out and sublimed under reduced pressure. The yellow sublimate was recrystallized from methanol to give yellow needles; m. p. 142～142.5°C.

Found: C, 79.45; H, 6.10; N, 4.21. Calcd. for $C_{21}H_{19}O_2N$: C, 79.47; H, 6.03; N, 4.11%.

9-Isopropyl-2-styrylpyrido[3, 2-d]tropolone (VIb).—This was prepared from Vd by a method similar to that described above. Yellow needles; m. p. 182～183°C.

Found: C, 79.36; H, 6.21; N, 4.23. Calcd. for $C_{21}H_{19}O_2N$: C, 79.47; H, 6.03; N, 4.11%.

The Quinoxalo Derivative of 8-Isopropylpyrido-[3,2-d]tropolone (VIIIa).—A mixture of Va (0.4 g.) and *o*-phenylenediamine (0.22 g.) in acetic acid (1.5 cc.) was refluxed for 4 hr. After being cooled, the reaction mixture was diluted with water and made alkaline with aqueous ammonia. The syrupy matter which separated was washed with water and dried in a vacuum dessicator. Recrystallization from ethanol gave pale brownish yellow needles; m. p. 133～134°C (0.43 g., yield 81%).

Found: C, 79.04; H, 5.99; N, 14.54. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62%.

The Quinoxalo Derivative of 8-Isopropyl-2-methylpyrido[3, 2-d]tropolone (VIIIb). — A mixture of Vb (0.4 g.) and *o*-phenylenediamine (0.2 g.) was treated by a method similar to that described above. Colorless cubic crystals; m. p. 149.5～150.5°C (0.45 g., yield 86%).

Found: C, 79.59; H, 6.18; N, 13.70. Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94%.

The Reaction of VIIIb with Amyl Nitrite.—To a solution of VIIIb (0.5 g.) in concentrated hydrochloric acid (2 cc.), amyl nitrite (3 cc.) was added at room temperature; the mixture was then warmed at 50°C in a water bath to deposit the hydrochloride of II. After the mixture had been allowed to stand overnight, the hydrochloride was filtered and washed with ethanol. Yield, 0.56 g. Recrystallization from ethanol gave colorless plates melting at 259～260°C (decomp.). The hydrochloride (0.12 g.) was dissolved in a large amount of 1 N sodium hydroxide solution by heating on a water bath. After insoluble matter had been removed by hot filtration, the filtrate was acidified with acetic acid and allowed to stand at room temperature to cause crystallization. Recrystallization from alcohol gave a free base, II, as pale yellow plates melting at 238～238.5°C (0.1 g.); the plates were found to be identical with the authentic sample[3)] by the mixed melting point and the infrared spectrum.

The Quinoxalo Derivative of 9-Isopropylpyrido-[3,2-d]-tropolone (VIIIc). — A mixture of Vc (0.1 g.) and *o*-phenylenediamine (0.05 g.) was

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[5)] The microanalyses were carried out by Mrs. K. Kodaira and Miss A. Iwanaga (Nozoe Laboratory), to whom deep gratitude is here expressed.

treated as in VIIIa. Colorless plates, m. p. 158.5~159°C (0.11 g., yield, 81%).

Found: C, 79.56; H, 5.61; N, 14.77. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62%.

6-Isopropylpyrido[3, 2-d]indolo[2, 3-b]tropone (XIIa).—A mixture of XIa (0.3 g.) and phenylhydrazine (0.19 g.) in acetic acid (1.5 cc.) was refluxed for 10 hr. After it had cooled, the crystals were collected by filtration and washed with water. Recrystallization from ethanol gave yellow needles; m. p. 185.5~186.5°C (0.17 g., yield 42%).

Found: C, 79.34; H, 6.22; N, 9.38. Calcd. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72%.

6-Isopropyl-3-methylpyrido[3, 2-d]indolo[2, 3-b]-tropone (XIIb).—A mixture of XIb (0.3 g.) and phenylhydrazine (0.15 g.) was treated as in XIIa. Yellow needles; m. p. 220~221°C (0.21 g., yield 53%).

Found: C, 79.50; H, 5.85; N, 9.45. Calcd. for $C_{20}H_{18}ON_2$: C, 79.44; H, 6.00; N, 9.27%.

Picrate.—Orange yellow prisms; m. p. 223~224°C (from ethanol).

Found: N, 12.94. Calcd. for $C_{26}H_{21}O_8N_5$: N, 13.18%.

N-Methyl Compound (XIIIb).—A mixture of XIIb (0.1 g.) and potassium hydroxide (0.05 g.) was heated in a test tube at 230~240°C. After the mixture had cooled, red potassium salt was refluxed with methyl iodide (1 g.) for 3 hr. The excess methyl iodide was then evaporated, and the residue was extracted with benzene. The benzene extracts were treated with charcoal, and the solvent was distilled out. The residue was recrystallized from ethanol to give yellow needles; m. p. 147~148°C, (0.08 g., yield 76%).

Found: C, 80.09; H, 6.13; N, 8.34. Calcd. for $C_{21}H_{20}ON_2$: C, 79.71; H, 6.37; N, 8.85%.

5-Isopropylpyrido[3, 2-d]indolo[2, 3-b]tropone (XIIc).—A mixture of XIc (0.13 g.) and phenylhydrazine (0.13 g.) in acetic acid (1.5 cc.) was refluxed for 8 hr. After the reaction mixture had cooled, water was added, and the product was recrystallized from ethanol to give yellow needles melting at 255°C (by Kofler block). (A very poor yield).

Found: C, 79.24; H, 5.79; N, 9.14. Calcd. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72%.

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