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Synthesis of 2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazines[1]

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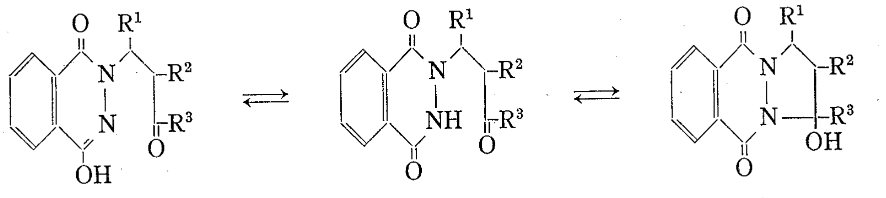
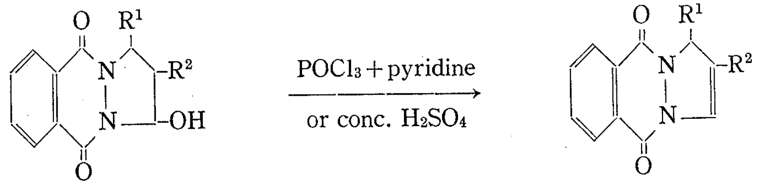
2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine (IVa) and its 2-methyl derivative (IVd), which have two bridgehead nitrogen atoms in a fused ring system, were synthesized by lithium aluminum hydride reduction of the corresponding 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (IIIa, IIId). On the other hand sodium borohydride reduction of IIIa and IIId gave 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-one (VIa) and its 2-methyl derivative (VId).

These compounds afforded the corresponding monomethiodides (Va, Vd, VIIa, VIId).

Previously, the present authors[3] have reported on a stereospecificity in ring–chain tautomerism (I–A⇄I–B⇄I–C) in the compounds having a general formula 3-(3-oxoalkyl)phthalic hydrazide (I–A), which are prepared by the Michael-type addition reaction of phthalic hydrazide to α,β-unsaturated carbonyl compounds. In this system, when R^3=H (*i.e.* aldehyde), the ring form (I–C) is predominant,[3] and when R^3=CH_3 (*i.e.* ketone), the chain form (I–A) is the prefered.[4] We have also reported that the compounds of the type illustrated by I–C are easily dehydrated to give the corresponding 5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (II) in good yields.[3]


I–A I–B I–C


I–C II

This paper deals with the synthesis of 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazines (IV), which have two bridgehead nitrogen atoms in a fused 6/5 ring system, as an application of this type of ring–chain tautomerism.

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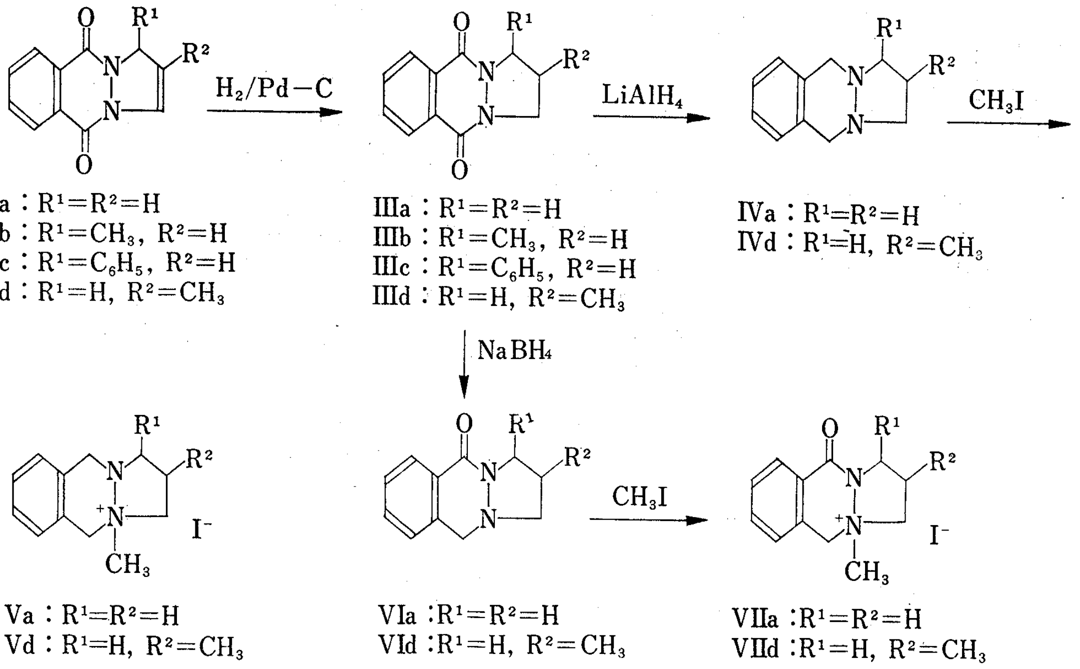
[1] A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 4, 1969.
[2] Location: *Kamiyoga 1-18-1, Setagaya, Tokyo.*
[3] A. Nakamura and S. Kamiya, *Yakugaku Zasshi*, **90**, in Press.
[4] S. Kamiya and A. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **15**, 949 (1967).



IIa : $R^1=R^2=H$
IIb : $R^1=CH_3$, $R^2=H$
IIc : $R^1=C_6H_5$, $R^2=H$
IId : $R^1=H$, $R^2=CH_3$

IIIa : $R^1=R^2=H$
IIIb : $R^1=CH_3$, $R^2=H$
IIIc : $R^1=C_6H_5$, $R^2=H$
IIId : $R^1=H$, $R^2=CH_3$

IVa : $R^1=R^2=H$
IVd : $R^1=H$, $R^2=CH_3$

Va : $R^1=R^2=H$
Vd : $R^1=H$, $R^2=CH_3$

VIa : $R^1=R^2=H$
VId : $R^1=H$, $R^2=CH_3$

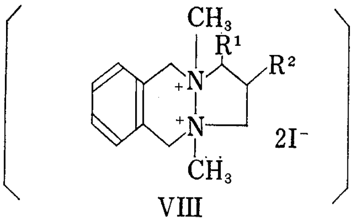
VIIa : $R^1=R^2=H$
VIId : $R^1=H$, $R^2=CH_3$

Chart 1

As shown in Chart 1, catalytic hydrogenation of the dehydrated compounds (IIa—d) in the presence of palladium charcoal gave the corresponding 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (IIIa—d) in good yields.

When IIIa and IIId were treated with lithium aluminum hydride in tetrahydrofuran, the desired 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine (IVa) and 2-methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine (IVd) were obtained in 38 and 44% yields, respectively. These new compounds gradually decompose on contact with air, but their hydrochlorides and picrates are all stable. In this lithium aluminum hydride reduction, any rearrangement reaction did not occur because of the presence of four protons at 6.31τ for IVa and at 6.34τ for IVd both as a singlet in their nuclear magnetic resonance (NMR) spectra.

Treatment of IVa and IVd with excess amount of methyl iodide gave only their monomethiodides (Va, Vd), and the bisquaternary salt of the type illustrated by VIII could not be obtained even after heating both reactants for five hours.



VIII

On the other hand, sodium borohydride reduction of IIIa in ethanol gave 2,3,5,10-tetrahydro-1*H*-pyrazolo-[1,2-*b*]phthalazin-5-one (VIa) in 64% yield. The structure of VIa was proved on the basis of the infrared (IR) spectrum showing the presence of a lactam-CO at 1643 cm^{-1} and of the NMR spectrum showing a singlet at 5.90τ (2H) due to the six-membered ring methylene group. Analogously, the same treatment of IIId gave 2-methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-one (VId) in 63% yield.

Similarly, as shown in Chart 1, VIa, and VId gave the corresponding methiodides (VIIa, VIId).

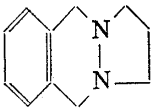
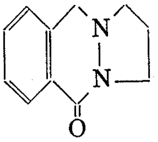
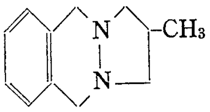
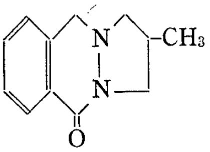
Stereochemistry of the parent compounds (IVa, IVd), which have a fused 6/5 ring system with two bridgehead sp$_3$ nitrogen atoms, was then considered by means of IR and NMR spectroscopy.

As a matter of fact IVa and IVd are able to exist in variety of either *cis* or *trans* fused conformations because of the presence of two conformationally mobile nitrogen atoms. These possible conformations for *trans* and *cis* 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazines (IVa, IVd) are shown in Chart 2.

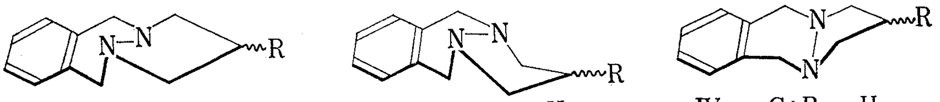
It is well known that the IR spectra of quinolizidines,[5] in which the lone pair of electrons on the nitrogen is *trans* to at least two axial hydrogens on adjacent carbon atoms, indicate a set of strong bands in the 2800—2600 cm^{-1} region. As shown in Table I, the IR spectra of IVa and IVd exhibit intense Bohlmann bands in the 2830—2600 cm^{-1} region.

There is no literature that Bohlmann band criterion was applied to fused 6/5 ring systems with two bridgehead nitrogen atoms like IV and VI. However, since the apparent extinction coefficients in the Bohlmann bands of VIa and VId are almost half as compared with those of IVa and IVd (Table I), this criterion should be applicable to this ring system.

Table I. 2850—2600 cm^{-1} Region in the IR Spectra of 2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine Derivatives (CCl_4)

Compound	cm^{-1}	ε	Compound	cm^{-1}	ε
	2830	148		2825	84
	2800	136		2790	71
	2719	45		2725	25
	2815	214		2822	109
	2725	66		2800s	89
	2690	42		2760s	33

On the basis of the strong Bohlmann bands of IVa and IVd, possibility of the conformation (IV-B) having a *cis* ring fusion (half-chair conformated, six-membered ring) can be ruled out, because they have only one *trans*-axial hydrogen to the lone pair of electrons on each nitrogen.[5] Finally, the prefered conformer between IV-A and IV-C could be confirmed to be IV-A having a *trans*-fusion by means of NMR spectroscopy. The details on the conformational analysis of this interesting ring system will be reported in a separate paper.



IVa−A: R = H
IVd−A: R = CH_3

IVa−B: R = H
IVd−B: R = CH_3

IVa−C: R = H
IVd−C: R = CH_3

Chart 2. Possible Conformations for 2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]-phthalazines (IVa, IVd)

Experimental[6]

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (IIIa—d)——A general method for this catalytic hydrogenation is described with 1-methyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIb).

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[5] F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958).
[6] All melting points are uncorrected. IR spectra were measured on a JASCO Model IR-S infrared spectrophotometer. NMR spectra were measured on a Japan Electron Optics JNM-C-60H spectrometer, and tetramethylsilane was used as an internal standard.
[7] J. Godin and A. LeBerre, *Bull. Soc. Chim. France*, **1968**, 4210.

1-Methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIIb): A solution of 3.21 g (0.015 mole) of IIb[7] in 30 ml of methanol was shaked in the presence of 0.5 g of 30% palladium charcoal under hydrogen atmosphere till hydrogen absorption ceased. After removal of the catalyst by filtration, the solution was evaporated to dryness, and the residue was recrystallized from a mixture of ethyl acetate and diisopropyl ether to give yellow dices, mp 131—132° (reported,[7] 138°). Yield, 56%. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.59; H, 5.89; N, 12.93.

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIIa): Colorless plates (from ethyl acetate), mp 199—202°. Yield, 86% from IIa.[7] *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.53; H, 4.98; N, 13.86. Found: C, 64.91; H, 5.01; N, 14.17.

1-Phenyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIIc): Pale yellow needles (from ethanol), mp 153—154°. Yield, 38% from IIc.[8] *Anal.* Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.05. Found: C, 72.51; H, 5.03; N, 10.32.

2-Methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIId): Pale yellow needles, mp 186° (from ethanol). Yield, 88% from IId.[7] *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.75; H, 5.58; N, 12.66.

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazines (IVa, IVd)——A general procedure for this lithium aluminum hydride reduction was described with 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (IIIa).

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine (IVa): A mixture of 7.07 g (0.035 mole) of IIIa, 4.56 g (0.12 mole) of lithium aluminum hydride and 160 ml of dehydrated tetrahydrofuran, was stirred for 110 hr at room temperature. The reaction mixture was carefully poured into ice-water, and the mixture was filtered. The insoluble substance on the filter paper was washed with tetrahydrofuran and ether. The filtrate and the washings were combined, and the mixture was extracted with ether. The ether was evaporated to dryness and the oily residue was distilled under reduced pressure. Colorless solid, mp 70—72°, bp 122° (5 mmHg). Yield, 2.38 g (38%). NMR (CS_2)τ: 7.75—8.30 (m), 2H; 7.18 (t), 4H; 6.31 (s), 4H; 3.05 (m), 4H. Picrate of IVa: Yellow leaflets (from ethanol), mp 148—150°. *Anal.* Calcd. for $C_{11}H_{14}N_2 \cdot C_6H_3O_7N_3$: C, 50.62; H, 4.25; N, 17.36. Found: C, 50.26; H, 4.41; N, 17.52. Picrate of the methiodide (Va): Yellow leaflets (from ethanol), mp 139—142°. *Anal.* Calcd. for $C_{12}H_{17}N_2 \cdot C_6H_2O_7N_3$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.15; H, 4.58; N, 16.82.

2-Methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazine (IVd): Colorless liquid, bp 114° (4 mmHg). Yield, 44%. NMR (CS_2) τ: 8.88 (d), 3H; 7.0—7.85 (m), 3H; 6.8—7.30 (m), 2H, 6.34 (s), 4H; 3.15 (m), 4H. Picrate of IVd: Yellow leaflets (from ethanol), mp 127—130°. *Anal.* Calcd. for $C_{12}H_{16}N_2 \cdot C_6H_3O_7N_3$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.91; H, 4.77; N, 17.07.

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-ones (VIa, VId)——A general procedure for this sodium borohydride reduction was described with 2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-one (VIa).

2,3,5,10-Tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-one (VIa): A mixture of 2.02 g (0.01 mole) of IIIa, 1.5 g (0.03 mole) of sodium borohydride and 30 ml of ethanol, was stirred for 22 hr at room temperature. The reaction mixture was evaporated under reduced pressure, and to the residue was carefully added 30 ml of 10% aqueous hydrochloric acid. The solution was warmed at 80° for 30 min, basified with a 10% aqueous potassium hydroxide solution after being cooled to room temperature, and the solution was then extracted with chloroform several times. The chloroform extract was washed with water, dried over anhydrous sodium sulfate, and the chloroform was evaporated to dryness. The residue was distilled under reduced pressure to give pale yellow liquid, bp 167—170° (3 mmHg). Yield, 1.21 g (64%). IR (CCl_4) cm^{-1}: 1655 (s), 1643 (CO). Picrate of VIa: Yellow leaflets (from ethanol), mp 209—212° (decomp.). *Anal.* Calcd. for $C_{11}H_{12}ON_2 \cdot C_6H_3O_7N_3$: C, 48.92; H, 3.62; N, 16.78. Found: C, 49.15; H, 3.69; N, 16.79. Methiodide of VIa: Colorless leaflets (from methanol), mp 198—203° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}ON_2I$: C, 43.65; H, 4.58; N, 8.48. Found: C, 43.48; H, 4.71; N, 8.54.

2-Methyl-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]phthalazin-5-one (VId): Yellow liquid, bp 169—170° (3 mmHg). Yield, 63%. IR (CCl_4) cm^{-1}: 1659, 1648 (CO). Picrate of VId: Yellow leaflets (from ethanol), mp 203—205° (decomp.). *Anal.* Calcd. for $C_{12}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 50.12; H, 3.97; N, 16.24. Found: C, 50.21; H, 3.53; N, 16.16. Methiodide of VId: Colorless plates (from ethanol), mp 178—183°. *Anal.* Calcd. for $C_{13}H_{17}ON_2I$: C, 45.36; H, 4.98; N, 8.14. Found: C, 45.17; H, 5.18; N, 8.23.

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8) H.O.K. Drew and H.H. Hat, *J. Chem. Soc.*, **1937**, 16.