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Structures of Reaction Products from 1-Hydrazinophthalazine and Some Carbonyls[1]

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Reaction of 1-hydrazinophthalazine (**1**) with mesityl oxide gave five crystalline compounds, including hydrazones and their cyclization products. Isomerization of the hydrazones which were elucidated to be two geometrical isomers was discussed briefly. Structures of several products obtained by reactions of **1** with acetylacetone, tiglic aldehyde were also discussed on the basis of their spectral properties.

Hydralazine (1-hydrazinophthalazine, **1**), a clinically useful antihypertensive agent, forms a hydrazone by treatment with a simple ketone, *e.g.* acetone, methyl ethyl ketone and acetophenone.[3] In a search for biologically active compounds, we have examined reactions of **1** with a diketone and unsaturated carbonyls which were presumed to introduce an additional heterocycle to the phthalazine ring, to give compounds of biological interest.

Reaction of **1** with acetylacetone at reflux temperature gave 1-(3,5-dimethyl-1-pyrazolyl)-phthalazine (**2**), identical with a product prepared from 3,5-dimethylpyrazole and 1-chlorophthalazine.

Similar treatment of **1** with tiglic aldehyde (*trans*-2-methyl-2-butenal) gave two compounds, **3a** and **3b**. The main product, **3a** revealed in its nuclear magnetic resonance (NMR) spectrum a signal for an azomethine proton at 8.14 ppm, in its infrared (IR) spectrum a characteristic NH band at 3240 cm^{-1}, and in its ultraviolet (UV) spectrum absorptions at 288 and 355 nm; the former was attributable to a phthalazine ring and the latter to a hydrazone group. Consequently, **3a** was assigned the structure of 1-[2-(2-methyl-2-butenylidene)hydrazino]-phthalazine.

The minor product, **3b** exhibited in its UV spectrum a maximum at 252 nm, no absorption due to a hydrazone group, in its NMR spectrum no azomethine proton signal, and in its mass spectrum an M^+ ion 2 mass units less than that of **3a**. The structure of 3-(1-methyl-1-propenyl)-*s*-triazolo[3,4-*a*]phthalazine was therefore assigned to **3b**, which apparently was yielded by oxidative ring closure of **3a**. A similar ring closure has been reported for 1-hydrazinoisoquinoline derivatives.[4]

Reaction of **1** with mesityl oxide (4-methyl-3-penten-2-one) under reflux afforded five crystalline compounds, **4a** (mp 132—133°), **4b** (mp 80—86°), **4c** (mp 170.5—172.5°), **4d** (mp 112—114°), **4e** (mp 82—83°). The mass spectrum of **4a** showed molecular formula $C_{14}H_{16}N_4$, and the UV spectrum contained absorptions at 208, 240, 289 and 357 nm; the last absorption indicated the presence of a hydrazone group. The NMR spectrum showed the presence of three methyl groups (1.92, 2.10 and 2.30 ppm), an olefinic proton (5.92 ppm), an NH proton (10.30 ppm) and five aromatic protons of the phthalazine ring (7.30—7.72, 8.20—8.60 ppm). On the basis of these data, **4a** was assigned as the hydrazone of mesityl oxide and **1**. Of the

1) This work was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
3) J. Druey and B.H. Ringier, *Helv. Chim. Acta.*, **34**, 195 (1951).
4) C. Hoogzand, *Recueil*, **90**, 1225 (1971).

possible geometric isomers of the hydrazone (Chart 2), Vc was proved as the structure of **4a** by an NMR spectrometry using a shift reagent, details of which will be reported separately.

Thin-layer chromatography (TLC) of **4b** indicated that it was contaminated with a small amount of **4a**. Since **4b** was apt to change **4a**, **4b** could not be obtained in a pure state. From these results **4b** was elucidated to be a geometric isomer of **4a**, and this view was supported by the following experiments. While no significant differences were observed between the mass spectra of **4a** and **4b**, or their IR spectra, the UV absorptions of **4b** at 275, 282 and 352 nm were slightly shifted (*ca.* 7 nm) from those of **4a**. The NMR spectrum of **4b** contained a characteristic olefinic proton signal at 6.62 ppm together with a weak signal at 5.92 ppm due to the olefinic proton of the contaminant (**4a**). The ratio of **4b** to **4a** could be calculated from the peak areas of these signals, which changed slowly even when **4b** was dissolved in a purified neutral solvent. The presence of acids, as in commercial chloroform, affected significantly the ratio but bases had little effect. Fig. 1 shows the time course of the change, observed for **4a** and a mixture of **4a** and **4b** in purified deuteriochloroform and in deuteriomethanol at room temperature. At the equilibrium point, the ratio of **4a** to **4b** in deuteriochloroform (after 7 days) was 88: 12 and in deuteriomethanol was approximated as 80: 20. These results clearly showed that **4b** is a less stable isomer of **4a**.

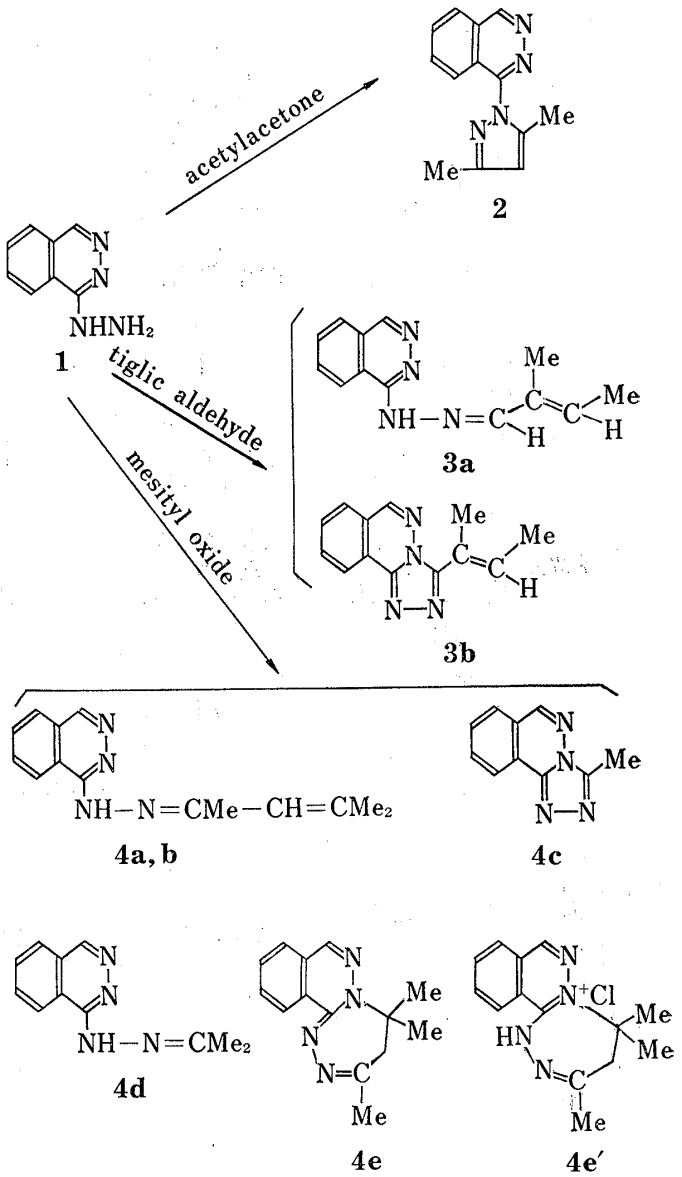

Chart 1

The configuration of **4b** has not fully been determined, but the chemical shift of its C-8 proton (8.37 ppm), being almost the same as that observed for **4a**, indicated that both compounds have the same configuration in the proximity of this proton. In contrast, 1-[1-methyl-2-(1-methyl-ethylidene)hydrazino]phthalazine, which probably takes configuration VII due to the steric hindrance of the N-methyl group, exhibited the C-8 proton signal at 7.80 ppm. Hydrazones having no N-methyl group of the present series, show the C-8 proton signal at about 8.4 ppm. The olefinic proton of **4b** resonates at lower field than that of **4a** does, showing that the difference between **4a** and **4b** is associated with the configuration of the C–N double bond. Further consideration of the effect of steric hindrance led to assignment of VIa as the most probable configuration for **4b**.

Compound **4c** was identified as 3-methyl-*s*-triazolo[3,4-*a*]phthalazine by comparison with an authentic sample prepared from **1** and ethyl acetate.[3)]

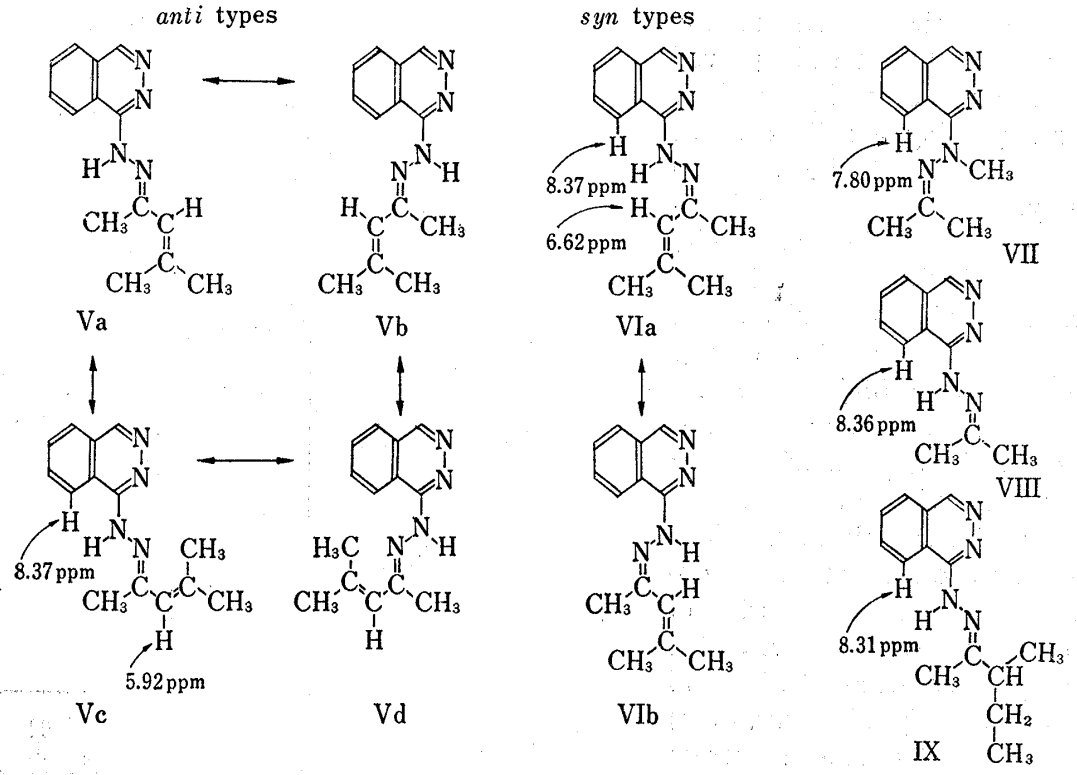

Chart 2

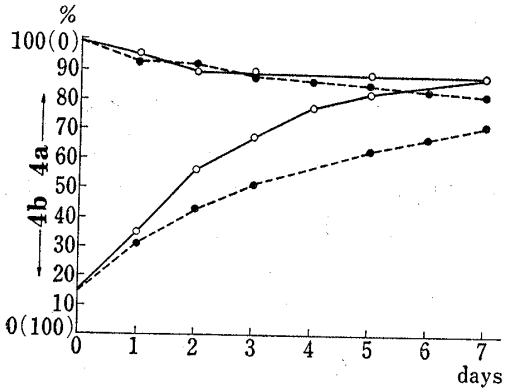

Fig. 1. Time Course of the Change of **4a** and **4b**

—○—: $CDCl_3$
---●---: CD_3OD

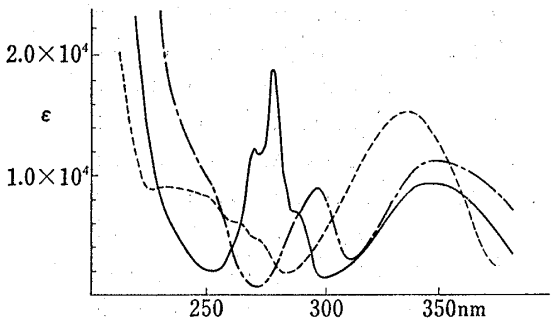

Fig. 2. UV Spectra

——: **4d** in MeOH
--------: **4e** in MeOH
——: **4e** in 1NHCl

The structure of **4d** was proved as the hydrazone of acetone and 1-hydrazinophthalazine. The compound was probably yielded by reaction of **1** with acetone, derived from mesityl oxide, or by hydrolytic elimination of the isopropyl group of **4a**.

Compound **4e**, having the same molecular formula as **4a**, exhibited in its NMR spectrum signals for three methyl groups, a methylene group and a phthalazine ring, and in its UV spectrum a maximum at 341 nm, but no absorption due to a phthalazine ring. However, the UV spectrum of **4e** in 1N HCl showed an absorption at 295 nm attributable to a phthalazine ring together with a hydrazone absorption (Fig. 2). This indicated that the aromatic system of **4e** in 1N HCl was analogous to that of **4d** (Chart 1, **4e'**). Therefore the structure of **4e** was assumed as 3,5,5-trimethyl-4,5-dihydro-1,2,4-triazepino[3,4-*a*]phthalazine.

5) A. Akashi, T. Chiba, and A. Kasahara, *European. J. Pharmacol.*, **29**, 161 (1974).

In the above reaction **4a** was obtained in better yields when the mesityl oxide was allowed to react with hydrochloride of **1** in refluxing MeOH. Pharmacological screening showed that **4a** has an antihypertensive activity.[5]

Experimental

Melting points were uncorrected. UV spectra were taken in MeOH on a Hitachi 323 Spectrophotometer and IR spectra in KBr on a Hitachi 285 Spectrometer. NMR spectra were measured in $CDCl_3$ with Me_4Si as an internal standard on a Hitachi R-20B Spectrometer; chemical shifts from Me_4Si were given in ppm. Mass spectra were determined at 75 eV on a JEOL JMC-OISG-2 Spectrometer. TLC was carried out on silicagel F-254 (Merck).

1-(3,5-Dimethyl-1-pyrazolyl)phthalazine (2)——a) A mixture of acetylacetone (1.05 g) and **1** (1.97 g) in ethanol was heated under reflux for 2 hr, cooled and concentrated. The residue was poured into H_2O, neutralized with $NaHCO_3$ and extracted with benzene. After concentration of the benzene solution, the residue was chromatographed on silicagel and eluted with benzene. The eluate was crystallized from ether–petroleum ether to give **2** (208 mg), mp 100—102°, identical with a sample described below. *Anal.* Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.99. Found: C, 69.56; H, 5.36; N, 25.30. UV λ_{max}^{MeOH} (ε): 220 (3.5×10^4), 285 (7.3×10^3), 349 (9.6×10^3). Mass M$^+$: Calcd. 224.1061. Found: 224.1080. NMR: 2.37, 2.49 (s, 6H, Me×2), 6.15 (s, 1H, CH), 7.80—9.48 (m, 5H, aromatic H).

b) A mixture of 3,5-dimethylpyrazole (96 mg) in dimethylsulfoxide (DMSO) (4 ml) and NaH (60 mg) was heated at 60° for 15 min, and cooled. 1-chlorophthalazine (165 mg) was added and the mixture was kept at room temperature for 2 hr, and poured into ice-water. Extraction with ether and crystallization of the extract from ether–petroleum ether afforded **2** (157 mg) mp 100—102°.

1-[2-(2-Methyl-2-butenilidene)hydrazino]phthalazine (3a) and 3-(1-Methyl-1-propenyl)-*s*-triazolo[3,4-*a*]-phthalazine (3b)——A solution of tiglaldehyde (6.43 g) and **1** (11.4 g) in MeOH was refluxed for 2 hr under N_2, cooled and concentrated *in vacuo*. The residue was chromatographed on silica gel and eluted with benzene. The eluate was crystallized from ether to give **3a** (10.4 g), mp 145—148.5°. *Anal.* Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 68.71; H, 6.23; N, 25.07. UV λ_{max}^{MeOH} (ε): shoulder 240 (7.8×10^3), shoulder 279 (2.4×10^4), 288 (3.4×10^4), 355 (2.1×10^4). Mass M$^+$: Calcd. 224.1071. Found: 224.1080. NMR: 1.87 (d, J=7.5 Hz, 3H, Me), 1.94 (s, 3H, Me), 6.01 (q, J=7.5 Hz, 1H, CH), 8.14 (s, 1H, N=CH), 7.30—8.11 (m, 5H, aromatic H).

Further elution of the chromatogram with benzene–$CHCl_3$ (1: 2) and crystallization of the eluate from ethyl acetate gave **3b** (70 mg), mp 64—66°. *Anal.* Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.99. Found: C, 69.59; H, 5.24; N, 25.27. UV λ_{max}^{MeOH} (ε): 252 (2.7×10^4), shoulder 259 (2.5×10^4), 270 (2.0×10^4). NMR: 1.95 (d, 3H, =CH–Me), 2.33 (s, 3H, Me), 7.06 (q, 1H, =CH–Me), 7.70—8.80 (m, 5H, aromatic H).

Reaction of 1 with Mesityl Oxide——a) A solution of **1** (4.0 g) in mesityl oxide (100 ml) was refluxed for 5 hr and concentrated. The residue dissolved in benzene was washed with H_2O and dried. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (40 g). Fractions eluted with benzene–$CHCl_3$ (2: 1) were collected and crystallized from isopropyl ether to give 1-[2-(1,3-dimethyl-2-butenylidene)hydrazino]phthalazine (**4a**) (1.8 g), mp 132—133°. *Anal.* Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.08; H, 6.70; N, 23.60. UV λ_{max}^{MeOH} (ε): 208 (2.7×10^4), 240 (8.9×10^4), 289 (2.0×10^4). 357 (1.5×10^4). Mass M$^+$: Calcd. 240.1361. Found: 240.1375. NMR: 1.92, 2.10, 2.30 (s, 9H, Me×3), 5.92 (m, 1H, CH), 7.30—7.72, 8.20—8.60 (m, 5H, aromatic H), 10.30 (b, 1H, NH).

The mother liquor of the above crystals was evaporated and the residue was chromatographed through a column of silicagel, which was eluted with (a) benzene–$CHCl_3$ (1: 1), (b) benzene–$CHCl_3$ (2: 3) and (c) benzene–$CHCl_3$–MeOH (8: 15: 0.5). The eluate of fraction (a) after crystallization from ether gave a mixture of **4a** and its isomer **4b** (**4b**: **4a**=85: 15), mp 80—86°. Pure **4b** has not been obtained. *Anal.* Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.24; H, 6.73; N, 23.40. Mass M$^+$: Calcd. 240.1361. Found: 240.1358. NMR: 1.92, 2.10, 2.30 (s, 9H, Me×3), 6.62 (m, 1H, CH), 7.30—7.72, 8.20—8.60 (m, 5H, aromatic H), 10.30 (b, 1H, NH).

3-Methyl-*s*-triazolo[3,4-*a*]phthalazine——(**4c**; 15 mg) was obtained from fraction (b), which was crystallized from AcOEt, mp 170.5—172.5°. *Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.21; H, 4.38; N, 30.80. UV λ_{max}^{MeOH} (ε): 234 (3.1×10^4), 240 (4.2×10^4), 248 (3.4×10^4). Mass M$^+$: Calcd. 184.0748. Found: 184.0746. NMR: 2.85 (s, 3H, Me), 7.70—8.70 (m, 5H, aromatic H).

The eluate of fraction (c) was submitted to preparative TLC and developed with $CHCl_3$–AcOEt (20: 2). Two bands appeared at *Rf* 0.11 and 0.16. Extraction of the *Rf* 0.11 band and crystallization of the extract from ether gave **4d** (70 mg) mp 112—114°, identical with an authentic sample of 1-[2-(1-methyl-ethylidene)-hydrazino]phthalazine prepared from acetone and **1**. *Anal.* Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 66.24; H, 6.08; N, 28.17. UV λ_{max}^{MeOH} (ε): 229 (6.8×10^3), 269 (1.3×10^4), 278 (1.9×10^4), 345 (9.6×10^3). Mass M$^+$: Calcd. 200.1061. Found: 200.1069. NMR: 2.05, 2.15 (s, 6H, Me×2), 7.20—8.40 (m, 5H, aromatic H).

Crystallization of the compound from the *Rf* 0.16 band gave 3,5,5-trimethyl-4,5-dihydro-1,2,4-triazepino-[3,4-*a*]phthalazine (**4e**, 15 mg), mp 82—83°. *Anal.* Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found:

C, 69.95; H, 6.71; N, 23.53. UV λ_{max}^{MeOH} (ε): shoulder 240 (9.5×10^3), shoulder 267 (8.5×10^3), shoulder 278 (5.5×10^3), 341 (1.5×10^4). Mass M^+: Calcd. 240.1361. Found: 240.1358. NMR: 1.83, 2.14 (s, 9H, Me×3), 2.73 (s, 2H, CH_2), 7.65—7.85, 8.80—9.10 (m, 5H, aromatic H).

b) A solution of 1-hydrazinophthalazine hydrochloride (3.93 g) and mesityl oxide (1.96 g) in MeOH (60 ml) was refluxed for 3 hr and neutralized with $NaHCO_3$ (1.85 g). The solvent was removed *in vacuo* (50 ml) and the crystalline residue was separated from the solution by filtration, which after recrystallization from isopropyl ether gave **4a** (2.92 g), mp 132—133°.

1-[1-Methyl-2-(1-methyl-ethylidene)hydrazino]phthalazine (VII)——A solution of 1-methyl-1-(1-phthalazinyl)hydrazine[6] hydrochloride (211 mg) and acetone (1 ml) in MeOH was refluxed for 3 hr under N_2, cooled and neutralized with $NaHCO_3$ (84 mg). The solvent was removed *in vacuo* and the residue was chromatographed on alumina. Elution with benzene gave 149 mg of VII, oil. *Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.01; H, 6.50; N, 25.96. NMR: 1.51 (s, 6H, Me×2), 2.83 (s, 3H, N–Me), 7.30—7.95 (m, 5H, aromatic H).

1-[2-(1,2-Dimethyl-butylidene)hydrazino]phthalazine (IX)——A solution of 3-methylpentane-2 one (2.6 g) and **1** (3.9 g) in MeOH was refluxed for 4 hr, cooled and concentrated. The residue was chromatographed on alumina. Elution with benzene $CHCl_3$ (1: 1) gave 2.9 g of IX, oil. *Anal.* Calcd. for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.50; H, 7.41; N, 23.32. NMR: 0.90 (t, 3H, CH_2CH_3), 1.14 (d, 3H, $CHCH_3$), 1.30—1.85 (m, 2H, CH_2), 2.10 (s, 3H, Me), 2.39 (m, 1H, CH), 7.30—7.65, 7.68, 8.20—8.40 (m, 5H, aromatic H).

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6) K.T. Potts and C. Lovelette, *J. Org. Chem.*, **34**, 3221 (1969).

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Synthesis of N-Methyl-2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro-[4,5]decan-8-yl]ethylamine

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For the studies on modification of mesembrine (II), N-methyl-2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylamine (I) was synthesized from 1,4-dioxaspiro[4,5]decan-8-one (III): the Cope reaction of III with ethyl cyanoacetate gave 1,4-dioxaspiro[4,5]decan-8-ylidene cyanoacetate (IV), whose Grignard reaction with 4-halogeno-1,2-dimethoxybenzene afforded ethyl 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro-[4,5]decane-8-cyanoacetate (V). Hydrolysis of V followed by decarboxylation gave 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-acetonitrile (VIII), which was reduced with $LiAlH_4$ to obtain 2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]-ethylamine (IX). Treatment of IX with ethyl chloroformate followed by reduction with $LiAlH_4$ furnished I.

It is said that *Sceletium expansum* L. Bol. and *Sceletium tortuosum* N.E. Brown, which are used as a stimulant by the natives of South Africa, exert a strong narcotic action,[2] and these species consist of a mixture of alkaloids closely related to the major alkaloid mesembrine[3] (II).

The title compound (I), whose structure is the modification of mesembrine (II), was synthesized in an object of its pharmacological investigation.

1) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
2) R.R. Arndt and P.E.J. Kruger, *Tetrahedron Letters*, **37**, 3237 (1970).
3) K. Bodendorf and W. Krieger, *Arch. Pharm.*, **290**, 441 (1957).