Chem. Pharm. Bull. 27(8)1771—1779(1979)

UDC 547.779.1.04.09 : 615.217.34.011.5.076.9

Synthesis of Pyrazolone Derivatives. XXXVI.[1] Synthetic and Pharmacological Studies on (4*S*,7*R*)-4,7-Methano-1*H*(or 2*H*)-indazoles and indazolium Compounds[2]

Shin-ichi Nagai, Noriichi Oda, Isoo Ito,[3] and Yoshihisa Kudo[3a]

Faculty of Pharmaceutical Sciences, Nagoya City University[3]

(Received December 11, 1978)

(4*S*,7*R*)-1 and 2-substituted-4,7-methanoindazoles were synthesized. The nucleophilic reaction of substituted hydrazines with (1*R*,4*S*)-3-hydroxymethylenebornane-2-one (**1**) gave corresponding (4*S*,7*R*)-1-substituted-4,7-methano-1*H*-indazoles (**3**). Attempts to synthesize 2-substituted-4,7-methanoindazoles starting from (1*R*,4*S*)-3-acetoxymethylenebornane-2-one (**5a**) were unsuccessful. Quarternization of (4*S*,7*R*)-4,7-methanoindazole (**3a**) afforded (4*S*,7*R*)-4,7-methano-1*H*-indazolium compounds (**8**, **9** and **10a**, **b**). (4*S*,7*R*)-2-Substituted-4,7-methanoindazoles (**11** and **12**) were successfully obtained by the reaction of **3a** with acetic anhydride and hydroxylamine-O-sulfonic acid. The structure assignments of the 1 and 2-substituted compounds were made on the basis of their NMR spectra. Pharmacological profiles of newly synthesized compounds were studied *in vivo* and *in vitro*. The behavioral symptoms of mice treated with compounds **10a** and **10b** were serious abnormal gait and catalepsy. The *in vitro* studies on isolated ileum preparation and isolated heart preparation suggested that compound **10b** has effective anticholinergic and antihistaminergic actions.

Keywords——(4*S*,7*R*)-1-substituted-4,7-methanoindazoles; (4*S*,7*R*)-2-substituted-4,7-methanoindazoles; (4*S*,7*R*)-4,7-methanoindazolium compounds; nucleophilic reaction; catalepsy; abnormal gait; anticholinergic action; antihistaminergic action

In the previous paper of this series, we reported the synthesis of (4*S*,7*R*)-1-substituted-4,7-methano-1*H*-indazole-3-carboxylic acids and described the marked stimulatory actions of some (4*S*,7*R*)-*N*-substituted-4,7-methanoindazole-3-carboxamides on nerve-muscle preparations of bullfrog.

The high reactivity of α-hydroxymethyleneketones has been widely recognized and exploited in syntheses of various hetero ring systems.[4] As an extension of a program aimed at the development of new pharmacologically effective (4*S*,7*R*)-4,7-methanoindazoles, we now wish to report the synthesis of (4*S*,7*R*)-1 or 2-substituted-4,7-methano-1*H* or 2*H*-indazoles (**3**, **11** and **12**) and indazolium compounds (**8**, **9** and **10**) from (1*R*,4*S*)-3-hydroxymethylenebornane-2-one (**1**). In addition, the pharmacological profiles of the newly synthesized compounds *in vivo* and *in vitro* are described.

Synthesis

(1*R*,4*S*)-3-Hydroxymethylenebornane-2-one (**1**) was obtained *via* a condensation of (1*R*,4*S*)-bornane-2-one with isoamyl formate. On treatment with hydrazine hydrate, compound **1** gave (1*R*,4*S*)-2-hydrazono-3-hydroxymethylenebornane (**2**) in 81% yield. Assignment of the structure **2** was based on the infrared (IR) spectrum and nuclear magnetic resonance (NMR) spectrum, which showed disappearance of the carbonyl absorption band and the

1) Part XXXV: S. Nagai, N. Oda, I. Ito, and Y. Kudo, *Chem. Pharm. Bull.* (Tokyo), **27**, 1764 (1979).
2) A part of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *3-1 Tanabe-dori, Mizuho-ku, Nagoya 467, Japan*; *a*) Present address: *Laboratory of Pharmacology, Mitsubishi Kasei Institute of Life Sciences, 11 Minamiooya, Machida 194, Japan.*
4) A. Fravolini, G. Grandolini, and A. Martani, *Gazz. Chim. Ital.*, **103**, 755 (1973), and references cited therein.

presence of a methylene proton signal at δ 6.56. Cyclization of **2** with a few drops of sulfuric acid in methanol proceeded in excellent yield to provide (4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*(2*H*)-indazole (**3a**).

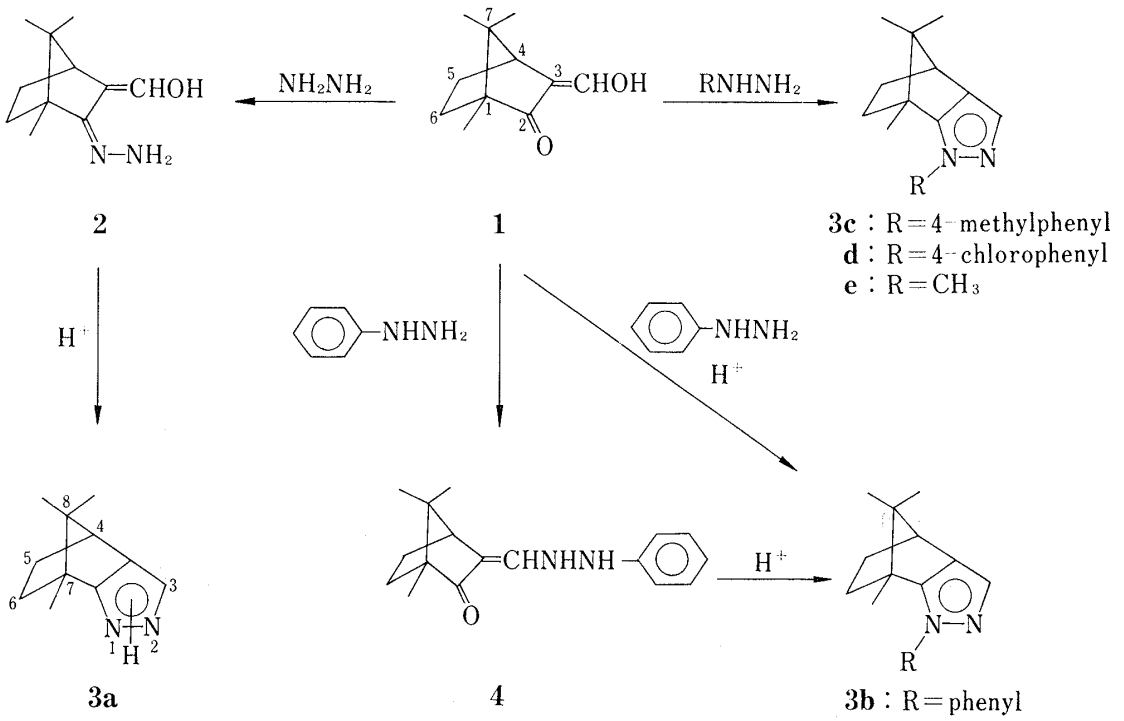


Chart 1

Condensation of **1** with phenylhydrazine resulted in the formation of (1*R*,4*S*)-3-(3-phenylhydrazo)methylenebornane-2-one (**4**). The IR spectrum showed carbonyl absorption at 1745 cm^{-1} and secondary amine absorption at 3290 cm^{-1}. The preparation of (4*S*,7*R*)-7,8,8-trimethyl-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (**3b**) was readily carried out by treatment of **4** with a catalytic amount of sulfuric acid or hydrobromic acid, whereas direct cyclization from **1** to **3b** by acidic treatment resulted in the formation of **3b** in low yield. However, (4*S*,7*R*)-7,8,8-trimethyl-1-(4-methylphenyl)-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (**3c**) and (4*S*,7*R*)-1-(4-chlorophenyl)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (**3d**) were obtained in excellent yield from compound **1**. As the methyl-substituted nitrogen of methylhydrazine is considered to be more nucleophilic, we expected to obtain 2-methyl-4,7-methanoindazole as well as 1-methyl-4,7-methanoindazole by condensation of **1** with methylhydrazine. Unexpectedly, only a single isomer corresponding to (4*S*,7*R*)-1,7,8,8-tetramethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (**3e**) was isolated in quantitative yield; the structure was assigned on the basis of the NMR spectrum as follows. It has been reported that irradiation of the N-methyl resonance in 2,7-dimethyl-4,5-dihydropyrazolo[4,3-*g*]benzothiazole results in narrowing of the pyrazole proton signal.[4] No such coupling, however, could be detected in compound **3e**. Thus, it appeared that the hydroxymethylene showed high reactivity, resulting in the formation of (4*S*,7*R*)-1-substituted-4,7-methanoindazoles (**3**).

For the synthesis for 2-substituted-4,7-methanoindazole, protection of the hydroxymethylene group of **1** is necessary in order to bring about a selective nucleophilic attack on the ketone group. Consequently, (1*R*,4*S*)-3-acetoxymethylenebornane-2-one (**5**) seemed to be a useful precursor. Acetylation of **1** with acetyl chloride in the presence of sodium methoxide yielded compound **5a** as a colorless liquid, boiling at 115—120° (3 mmHg). Treatment of **5a** with a mixture of acetic anhydride and sulfuric acid resulted in the quan-

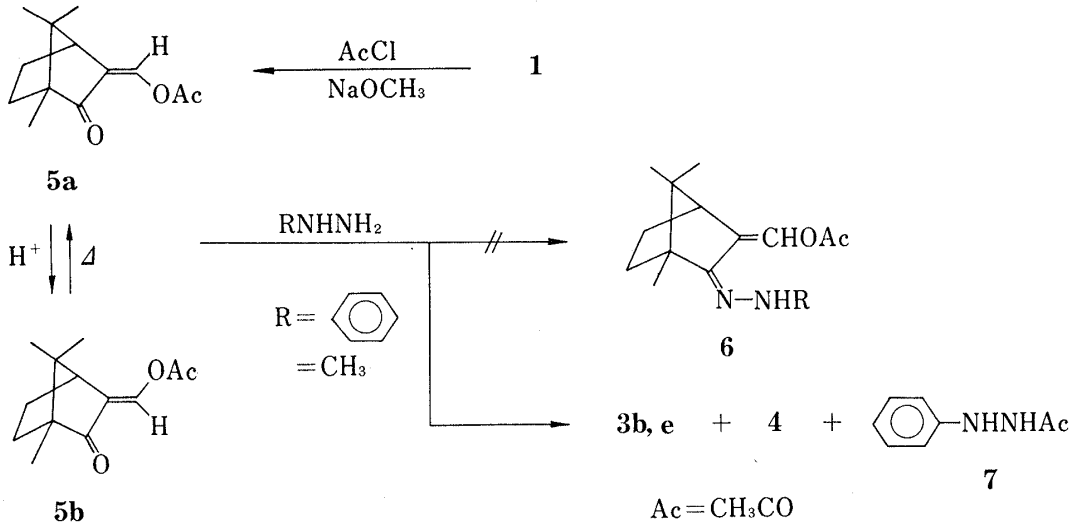
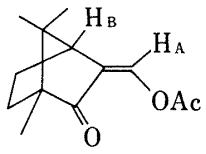
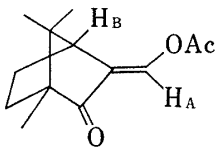


Chart 2

titative formation of the colorless crystalline isomer (**5b**), mp 63—65°, which could be readily converted to the original liquid isomer (**5a**) upon heating. Structure assignment of the two isomers was accomplished by NMR. NMR spectral data of crystalline **5b**, shown in Table I, provide evidence for the *E*-form, in which the H_A proton occupies a position closer to the carbonyl group, resulting in a moderate downfield shift compared with the H_A proton of the *Z*-form (**5a**).

Table I. NMR Spectra of **5a** and **5b**

Compound		Form	H_A	H_B
5a		*Z*	7.14 (s)	2.54 (d, J=4 Hz)
5b		*E*	7.92 (s)	2.88 (d, J=4 Hz)

Unexpected results were obtained when compound **5a** was treated with phenylhydrazine in methanol. Separation of the reaction products by chromatography through a silica gel column gave three compounds, but not the desired pyrazole (**6**). The three compounds were confirmed to be **3b**, **4** and 1-acetyl-2-phenylhydrazine (IR and mixed melting point determination with authentic samples). Similar condensation of **5a** with methylhydrazine gave only compound **3e**, and no 2-methyl-4,7-methanoindazole could be detected.

Further efforts were directed toward the introduction of a methyl group into the N-2 position of the pyrazole ring. Reaction of **3a** with dimethyl sulfate yielded (4*S*,7*R*)-1,7,8,8-tetramethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazolium methylsulfate (**8**), the structure of which was confirmed by transformation of **8** to **3e** with lithium aluminum hydride.

Methylation of **3a** with methyl iodide in a sealed tube gave two substances, (4*S*,7*R*)-1,1,7,8,8-pentamethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazolium iodide (**9**) and **3e**, which

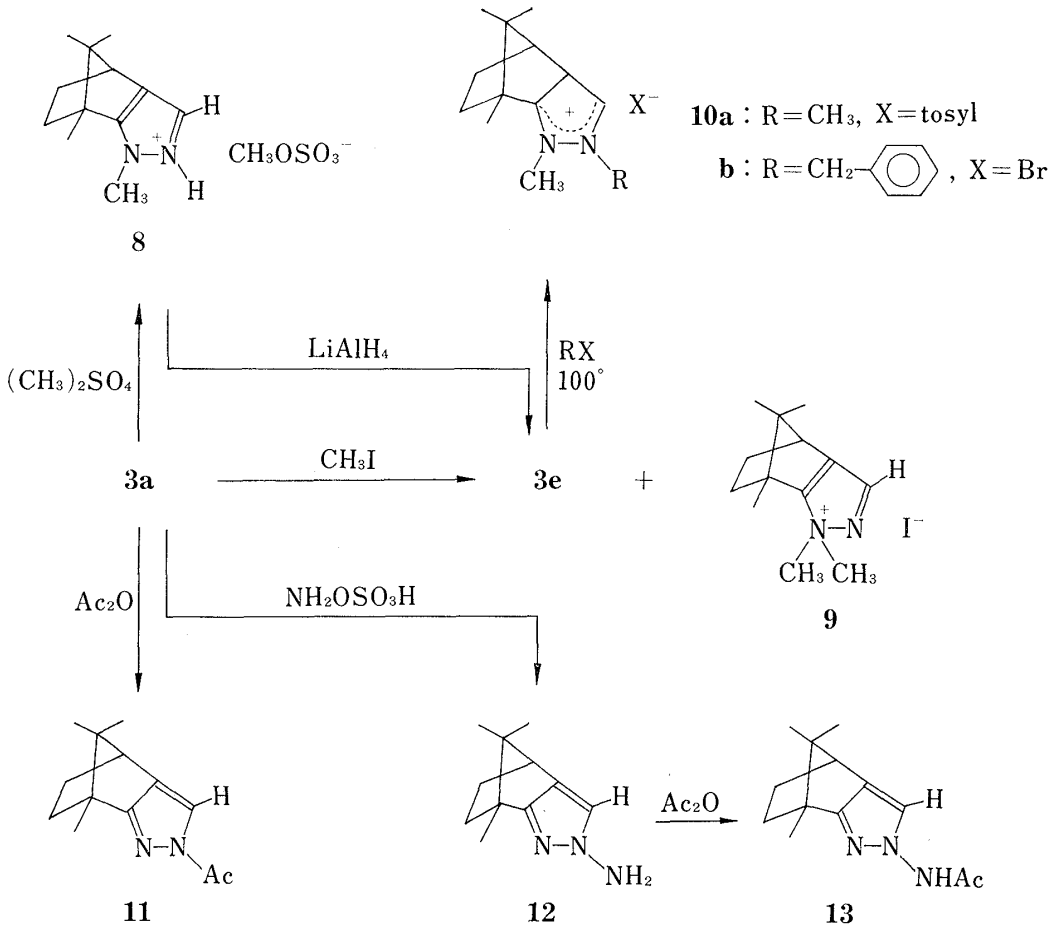


Chart 3

were separated by silica gel chromatography. The structure assignment of **9** was based on the NMR spectrum, which showed two methyl signals with very similar chemical shifts.

Anticipating that quarternization of 4,7-methanoindazole might increase the reactivity of the carbon atoms of the pyrazole toward nucleophilic reagents and also might introduce some biological activity owing to increased solubility in water, we synthesized (4*S*,7*R*)-1,2,7,8,8-pentamethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazolium tosylate (**10a**) and (4*S*,7*R*)-2-benzyl-1,7,8,8-tetramethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazolium bromide (**10b**) by heating **3e** with methyl tosylate and benzyl bromide at 100°. Attempted reactions between **10a**, **b** and nucleophilic reagents, however, were unsuccessful.

N-2 Substitution reactions were achieved in the following cases. Prolonged heating of **3a** with acetic anhydride in the presence of sodium acetate resulted in the formation of (4*S*,7*R*)-2-acetyl-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (**11**) in 85%yield. In the NMR spectrum of **11**, an aromatic proton appeared downfield by 0.65 ppm relative to that of **3a** on account of the deshielding effect of the acetyl carbonyl. This means that the acetyl group is adjacent to an aromatic proton.

Compound **3a** and hydroxylamine-O-sulfonic acid were allowed to react in the presence of potassium hydroxide to afford a light yellow oil as a sole product in 83% yield. Although the formation of the 1-amino isomer was considered possible, the structure of the product was confirmed to be (4*S*,7*R*)-2-amino-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (**12**) on the basis of spectral data; in particular, the NMR spectrum showed a chemical shift of aromatic proton upfield by 0.32 ppm relative to that of **3a**. This result suggests that the aromatic proton is adjacent to the amino group and consequently within the shielding zone of the nitrogen. Further evidence for the assigned structure was provided by the NMR spectrum of (4*S*,7*R*)-2-acetylamino-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-inda-

zole (**13**), which showed a downfield shift of the aromatic proton by 0.12 ppm relative to that of **12** due to the anisotropy of the acetyl carbonyl group.

Pharmacological Results and Discussion

Pharmacological profiles of newly synthesized compounds were studied *in vivo* and *in vitro*. In the present study, the general pharmacological properties of these compounds were examined by means of Irwin's test, and their anticholinergic and antihistaminergic actions were studied further.

Methods

1) **Irwin's Test**——The behavior of a mouse treated with the new compounds was observed according to Irwin's description. Compounds were dissolved in 0.5% CMC solution and were injected intraperitoneally.

2) **Isolated Ileum Preparations of Mice and Guinea Pigs**——Ileum was isolated from a mouse or a guinea pig, and suspended in a 20 ml organ bath filled with Tyrode's solution (pH 7.8±0.1; temperature, 20—24°). Compounds dissolved in Tyrode's solution were applied to the organ bath. Tension developed in the ileum was detected by means of an isotonic transducer and recorded on a DC-recorder (Toa Electronics EPR-2T). Acetylcholine (Ovisot, Daiichi), histamine-2HCl (Wako Pure Chem.) and barium chloride (Wako Pure Chem.) were used as spasmogenics.

3) **Isolated Perfused Heart Preparation of Bullfrog**——Isolated bullfrog (*Rana catesbeiana*) heart was perfused with Ringer's solution according to Yagi's method. The activity of the heart was recorded with an isometric transducer and a DC-recorder (Toa Electronics EPR-2T). Drugs were dissolved in Ringer's solution and applied to a venous reservoir (volume, 3 ml).

Results

1) Irwin's Test

Obvious behavioral disturbance could be observed after the intraperitoneal administration of compound **10a** (60—100 mg/kg). Hypothermia, loss of pinna reflex, serious abnormal gait and catalepsy were the main behavioral changes observed within 60 min after the injection. When 100 mg/kg was injected intraperitoneally, convulsion and respiratory arrest could be observed after 60 min, and the mouse died about 80 min after the administration. At a dose of 50 mg/kg (*i.p.*), the compound did not have any apparent behavioral effect. The effects of compound **10b** were even more pronounced than those of compound **10a**. Tremor, twitches, serious abnormal gait, catalepsy, loss of pinna reflex could be seen within 10 min after intraperitoneal administration of the drug (70 mg/kg). The animal died 15 min after the injection with serious convulsions. Rapid death occurred at a dose of 100 mg/kg (*i.p.*) after almost the same symptoms as those observed in mice treated with 70 mg/kg (*i.p.*). When 50 mg/kg was injected, the animal showed an obvious catalepsy, but recovered completely within 60 min. At a dose as low as 40 mg/kg (*i.p.*), the compound caused no apparent behavioral disturbance.

Other newly synthesized compounds showed no obvious behavioral disturbance.

2) Effects on Ileum Isolated from the Mouse and Guinea Pig

Compound **10b** ($1.0—5.0\times10^{-4}$ M) was found to have effective relaxant action on the ACh (10^{-7} M)-induced contracture of mouse ileum, whereas compound **10a** (upto 5.0×10^{-4} M) showed only slight action on the isolated mouse ileum. When the preparation was pretreated with compound **10b** (5×10^{-4} M), ACh (10^{-7} M) had no effect on the tension of the ileum.

Compound **10b** showed relaxing action on guinea pig ileum stimulated by histamine (10^{-6} M). Compound **10a**, however, had almost no effect on the histamine-induced contraction. Compound **10b** ($1—2\times10^{-4}$ M) showed a weak relaxing action on ileum treated with barium chloride (10^{-4} M).

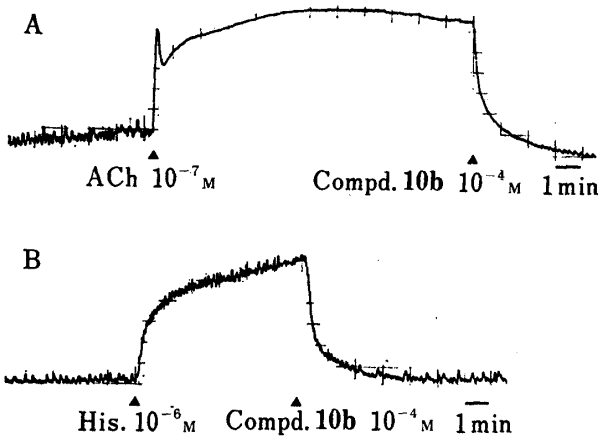


Fig. 1. Effects of Compound **10b** on the Histamine- or Acetylcholine-induced Contraction of the Isolated Ileum Preparation

A: antagonistic action of compound **10b** (10^{-4} M) on the acetylcholine (10^{-7} M)-induced contraction of mouse ileum. B: antagonistic action of compound **10b** (10^{-4} M) on the histamine (10^{-6} M)-induced contraction of guinea pig ileum.

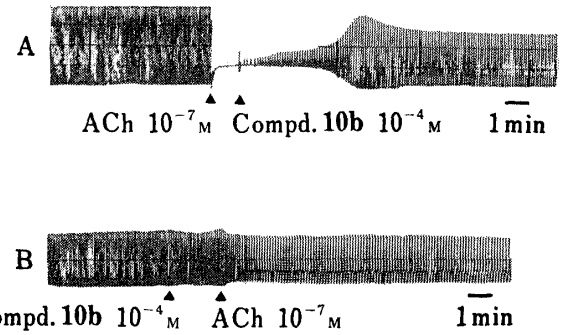


Fig. 2. Antagonistic Actions of Compound **10b** to Acetylcholine on the Frog Isolated Perfused Heart

A: treatment with compound **10b** after the cardiac arrest induced by acetylcholine (10^{-7} M). B: effect of pretreated compound **10b** (10^{-4} M) on the acetylcholine (10^{-7} M)-action.

3) Effects on the Isolated Perfused Heart of Bullfrog

Compound **10b** (10^{-4} M) alone showed no effect on the contractility and heart rate of the isolated heart. However, the compound had a marked antagonistic action on the ACh (10^{-7} M)-induced negative inotropic action. On the other hand, negative chromotropic action of ACh remained unchanged after treatment with the compound.

Discussion

The most obvious symptoms induced by the tested compounds were serious abnormal gait and catalepsy. Rapid death seemed to be due to respiratory arrest. The *in vitro* studies on the isolated ileum preparation and isolated heart preparation suggested that compound **10b** has effective anticholinergic and antihistaminergic action. We have no data to indicate whether these anticholinergic and antihistaminergic actions participate in the observed behavioral changes induced by the compound. In the present study only a limited pharmacological profile was examined, but these new compounds may well be valuable as experimental tools.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL-JNM-100 spectrometer using tetramethylsilane as an internal standard with deuteriochloroform as a solvent unless otherwise indicated, and chemical shifts (δ) are given in ppm relative to tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Mass spectra were measured on a Hitachi M-52 mass spectrometer. Optical rotations were measured with a Yanagimoto OR-10 photomagnetic direct reading polarimeter. IR spectra were measured with an IRA-2 unit (Nihon Bunko Spectroscopic Co.), and recorded as Nujol mulls unless otherwise indicated. Gas liquid chromatography (GLC) was carried out on a JEOL JGC 1100 gas liquid chromatograph using a stainless steel column (3 mm × 2 m) packed with 3% SE-30 on 80—100 mesh Chromosorb-W with N_2 carrier gas. Detection was by FID.

(1*R*,4*S*)-2-Hydrazono-3-hydroxymethylenebornane (2)——A solution of 1 g of **1** and 0.33 g of hydrazine hydrate in 10 ml of MeOH was refluxed for 4 hr then evaporated down under reduced pressure. After trituration with petroleum ether, the residue was recrystallized from *n*-hexane to give colorless needles, mp 88—90°. Yield 81%. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 68.25; H, 9.56; N, 14.23. IR ν_{max} cm^{-1}: 3460 and 3300 (NH_2). NMR δ: 6.56 (1H, s, CHOH), 5.76 (2H, br s, NH_2). $[\alpha]_D^{25}$ +135.3° (c=0.266, EtOH).

(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*(2*H*)-indazole (3a)——A mixture of 7 g of **2**, 5 drops of sulfuric acid and 20 ml of MeOH was refluxed for 5 hr, then evaporated down. The residual oil was washed with $NaHCO_3$ solution and extracted with $CHCl_3$. Removal of the solvent yielded crystals. Analytical and physical data are summarized in Table II.

(4*S*,7*R*)-7,8,8-Trimethyl-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (3b)——A mixture of 0.2 g of **4**, 10 ml of AcOH and 2 ml of 48% HBr was refluxed for 3 hr then evaporated down. Water was added to the residue, and precipitated crystals were filtered, washed with $NaHCO_3$ solution and dried. Analytical and physical data are summarized in Table II.

General Procedure for (4*S*,7*R*)-1-Substituted-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazoles (3c—e)——A solution of **1** (0.01 mol) and N-substituted hydrazine (or hydrochloride) (0.01 mol) in 20 ml of MeOH was refluxed for 3—6 hr. After removal of MeOH by evaporation, the residue was recrystallized. Analytical and physical data are summarized in Table II.

(1*R*,4*S*)-3-(3-Phenylhydrazo)methylenebornane-2-one (4)——A solution of 1 g of **1** and 0.5 g of phenylhydrazine in 20 ml of MeOH was refluxed for 3.5 hr then evaporated down. The residual oil was chromatographed on silica gel. Elution with $CHCl_3$ gave a light yellow viscous oil. Yield 0.39 g (52%). GLC showed one peak at 100°, t_R=13.7 (N_2 1.6 kg/cm², H_2 0.5 kg/cm², air 2 kg/cm²). *Anal.* Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.73; H, 8.31; N, 10.31. IR ν_{max} cm^{-1}: 3290 (NH), 1745 (CO).

Table II. (4*S*,7*R*)-1-Substituted-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazoles (3)

Compd. No.	R	mp (°C) (Rec. solv.) and appearance	$[\alpha]_D^{25}$ in EtOH (*c*)	Yield (%)	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	H	N	NMR C(3)–H	NMR Substituent
3a[a]	H	153—155 (petr. ether) Colorless plates	+42.7° (0.234)	89	176	$C_{11}H_{16}N_2$	74.96 (74.87	9.15 9.05	15.89 15.93)	7.08 (s)	10.66 (br s, NH)
3b		126—128 (ether) Colorless plates	+21.1° (0.294)	79	252	$C_{17}H_{20}N_2$	80.91 (80.98	7.99 7.74	11.10 10.83)	7.30 (s)	7.40 (s)
3c	CH_3– 	159—161 (ether) Light yellow plates	+18.6° (0.42)	80	266	$C_{18}H_{22}N_2$	81.16 (80.93	8.32 8.46	10.52 10.47)	7.24 (s)	2.38 (s)
3d	Cl– 	168—170 (ether) Colorless plates	+12.9° (0.232)	75	286	$C_{17}H_{19}ClN_2$	71.19 (71.21	6.68 6.51	9.77 9.93)	7.33 (s)	7.40 (s)
3e	CH_3	97— 98 (petr. ether) Light yellow plates	+11.0° (0.364)	83	190	$C_{12}H_{18}N_2$	75.74 (75.57	9.53 9.78	14.72 14.79)	7.08 (s)	3.81 (s)

a) IR ν_{max} cm^{-1}: 3180 (NH).

(*Z*)-(1*R*,4*S*)-3-Acetoxymethylenebornane-2-one (5a)——A solution of 5 g of **1** in 30 ml of dry ether was added dropwise to a suspension of 1.6 g of sodium methoxide in 30 ml of dry ether at room temperature. After stirring overnight, a solution of 2.1 ml of acetyl chloride in 10 ml of dry benzene was added to the resulting suspension, and the mixture was stirred for 24 hr then evaporated down under reduced pressure. The residue was fractionally distilled to give a colorless oil, bp 115—120° (3 mmHg) (lit.[5] bp 110° (0.4 mmHg). Yield 4.1 g (67%). NMR δ: 2.21 (3H, s, CH_3CO).

(*E*)-(1*R*,4*S*)-3-Acetoxymethylenebornane-2-one (5b)——A solution of 1 g of **5a** in a mixture of 0.8 ml of Ac_2O and 0.3 ml of sulfuric acid was allowed to stand at room temperature for 2 days, then poured onto ice-water. The white solids that separated were filtered off and recrystallized from petroleum ether to give

5) W. Roza, Z. Jozef, and A. Wieslaw Z, *Rocz. Chem.*, **43**, 833 (1969).

colorless needles, mp 63—65°. Yield 0.62 g (62%). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.99; H, 8.14. $[\alpha]_D^{23}$ +123.3° (c=1.088, EtOH). NMR data are summarized in Table I.

Reaction of 5a with Phenylhydrazine——A solution of 0.5 g of **5a** and 0.25 g of phenylhydrazine in 10 ml of MeOH was refluxed for 1 hr. The solution was evaporated down and the residual oil was triturated with ether to give white solids. Recrystallization from ether afforded 1-acetyl-2-phenylhydrazine (**7**), mp 128—129°. Yield 0.06 g. *Anal.* Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.21; H, 6.56; N, 18.63. The mother liquor was evaporated down and chromatographed on silica gel. Elution with $CHCl_3$ gave 0.08 g of **4** and 0.07 g of **3b**. IR spectra of **4** and **3b** were identical with those of authentic **4** and **3b**, respectively.

Reaction of 5a with Methylhydrazine——A mixture of 0.5 ml of AcOH and 5 ml of 1,2-dimethoxyethane was added to a stirred solution of 0.5 g of **5a** and 0.1 g of methylhydrazine. After reflux for 1 hr, the mixture was evaporated down under reduced pressure. The residual oil was chromatographed on Al_2O_3. Elution with $CHCl_3$ gave crude material. Recrystallization from ether gave colorless needles, mp 97—98°. Yield 0.35 g (85%). This compound was identical with **3e** (IR spectrum and mixed melting point determination).

(4*S*,7*R*)-1,7,8,8-Tetramethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazolium Methylsulfate (8)——A suspension of 0.5 g of **3a** in 1.5 ml of dimethyl sulfate was heated with stirring at 110°. After cooling, the mixture was washed with $NaHCO_3$ solution and extracted with $CHCl_3$. Removal of $CHCl_3$ gave an oil which solidified on trituration with ether. The resulting powder was recrystallized from benzene to give colorless plates, mp 110—113°. Yield 0.32 g (37.2%). *Anal.* Calcd. for $C_{13}H_{22}N_2O_4S$: C, 51.64; H, 7.33; N, 9.26. Found: C, 51.57; H, 7.51; N, 9.20. NMR δ: 3.76 (3H, s, N(1)-CH_3), 4.22 (3H, s, $CH_3SO_4^-$), 7.63 (1H, s, C(3)-H).

Reduction of 8 with Lithium Aluminum Hydride——A suspension of 0.1 g of **8** and 0.1 g of $LiAlH_4$ in 5 ml of THF was stirred at room temperature for 4 hr. After usual work-up, colorless plates were obtained quantitatively on recrystallization from petroleum ether, mp 97—98°. This material was identical with **3e** (IR and mixed melting point).

(4*S*,7*R*)-1,1,7,8,8-Pentamethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazolium Iodide (9)——A solution of **3a** in 5 ml of methyl iodide was placed in a sealed tube and heated at 110—120° for 3 hr. After cooling, the mixture was evaporated down under reduced pressure. The residual needles were washed with $NaHCO_3$ solution and extracted with $CHCl_3$. Solids obtained after removal of $CHCl_3$ were chromatographed on silica gel. Elution with $CHCl_3$ gave 0.12 g (44%) of **3e** as colorless plates, mp 97—98°. Elution with $CHCl_3$–EtOH (9: 1) gave colorless crystals (**9**), mp 217—220° after recrystallization from ether–MeOH. Yield 0.21 g (45%). *Anal.* Calcd. for $C_{13}H_{21}IN_2$: C, 47.00; H, 6.37; N, 8.43. Found: C, 47.51; H, 6.65; N, 8.60. NMR ($CDCl_3$–CD_3OD) δ: 4.24 (3H, s, N–CH_3), 4.29 (3H, s, N–CH_3), 7.94 (1H, s, C(3)–H).

(4*S*,7*R*)-1,2,7,8,8-Pentamethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazolium Tosylate (10a)——A mixture of 1 g of **3e** and 1.1 g of methyl tosylate was stirred at 100° for 3 hr. After cooling, the residue was washed repeatedly with dry ether and recrystallized from ether–MeOH to give hygroscopic colorless crystals, mp 143—146° (in a sealed tube). Yield 1.6 g (81%). *Anal.* Calcd. for $C_{20}H_{28}N_2O_3S$: C, 63.80; H, 5.35; N, 7.44. Found: C, 64.21; H, 5.59; N, 7.53. NMR ($CDCl_3$–CD_3OD) δ: 2.35 (3H, s, $C_6H_4CH_3$), 4.00 (6H, s, 2×N^+–CH_3), 7.70 (1H, s, C(3)–H). MS m/e: 190 (M^+−$TsCH_3$). $[\alpha]_D^{23}$ +14.0° (c=0.3, EtOH).

(4*S*,7*R*)-2-Benzyl-1,7,8,8-tetramethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazolium Bromide (10b)——A mixture of 0.45 g of **3e** and 0.49 g of benzyl bromide was stirred at 100° for 3 hr. After cooling, the mixture was washed with dry ether and dried over P_2O_5 under reduced pressure. Recrystallization from ether–EtOAc gave hygroscopic light yellow crystals, mp 164—167° (foaming) (in a sealed tube). Yield 0.73 g (86%). *Anal.* Calcd. for $C_{19}H_{25}BrN_2$: C, 63.16; H, 6.97; N, 7.75. Found: C, 63.41; H, 6.73; N, 7.56. NMR (D_2O) δ: 4.00 (3H, s, N–CH_3), 5.67 (2H, s, $CH_2C_6H_5$), 7.90 (1H, s, C(3)–H). MS m/e: 190 (M^+−$C_6H_5CH_2Br$). $[\alpha]_D^{23}$ +16.4° (c=0.44, EtOH).

(4*S*,7*R*)-2-Acetyl-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (11)——A solution of 0.2 g of **3a** and 0.1 g of AcONa in 3 ml of Ac_2O was refluxed for 1 hr. After cooling, the mixture was poured onto ice-water and allowed to stand in a refrigerator overnight. The precipitates were filtered off, washed with water and dried. Recrystallization from ether gave colorless prisms, mp 48—50°. Yield 0.21 g (85%). *Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.42; H, 8.54; N, 12.76. IR ν_{max} cm^{-1}: 1733 ($COCH_3$). NMR δ: 2.61 (3H, s, $COCH_3$), 7.73 (1H, s, C(3)–H). GLC showed one peak at t_R=6.3 (100—200°, 10°/min, N_2 1.6 kg/cm^2, H_2 0.5 kg/cm^2, air 2 kg/cm^2). $[\alpha]_D^{23}$ +59° (c=0.322, EtOH).

(4*S*,7*R*)-2-Amino-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (12)——Hydroxylamine-O-sulfonic acid (3.8 g) was added portionwise to a stirred suspension of 2 g of **3a** and 10.2 g of powdered KOH in 30 ml of dry DMF at 20—30°. The mixture was stirred for 10 min, poured onto cracked ice and extracted with benzene. Removal of benzene and DMF under reduced pressure, followed by distillation gave a light yellow liquid, bp 123—125° (3 mmHg). Yield 1.8 g (83%). *Anal.* Calcd. for $C_{11}H_{17}N_3$: C, 69.07; H, 8.96; N, 21.97. Found: C, 68.89; H, 8.73; N, 21.77. IR ν_{max} cm^{-1}: 3320 and 3220 (NH_2), 1640 (NH). NMR δ: 5.32 (2H, br s, NH_2), 6.76 (1H, s, C(3)–H). MS m/e: 191 (M^+), 176 (M^+−CH_3). UV λ_{max}^{EtOH} nm (log ε): 236 (3.90). $[\alpha]_D^{25}$ +21.9° (c=1.91, EtOH). GLC showed one peak at t_R=13.0 (100—200°, 4°/min, N_2 1.6 kg/cm^2, H_2 0.5 kg/cm^2, air 2 kg/cm^2).

(4*S*,7*R*)-2-Acetylamino-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (13)——A solution of 0.1 g of **12** in 3 ml of Ac_2O and 3 ml of pyridine was refluxed for 2 hr, then evaporated down under reduced

pressure. The residual oil was triturated with petroleum ether–ether to give a powder. Recrystallization from ether gave colorless prisms, mp 73—75°. Yield 0.09 g (75%). *Anal.* Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.80; H, 8.23; N, 18.13. NMR δ: 2.00 (3H, s, $COCH_3$), 6.88 (1H, s, C(3)-H). MS *m/e*: 233 (M^+), 190 ($M^+ - COCH_3$).

Acknowledgement The authors are grateful to Prof. M. Watanabe of this Faculty for his valuable advice. They are also indebted to the members of the Microanalytical Center of this Faculty for elemental analyses and NMR spectral measurements.