effect to be much more pronounced than additive effect. Refrigeration dramatically slows the rate of decomposition.

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Synthesis of (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine

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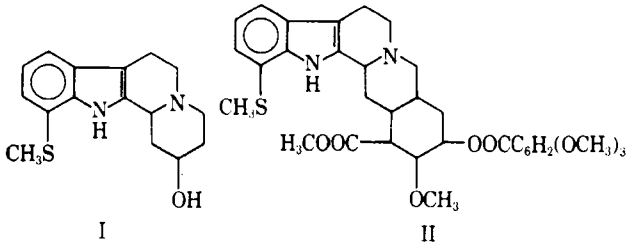
Abstract □ (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine was synthesized as a cardiovascular agent. Biological evaluation of the title compound and several precursors (7-methylthiotryptamine formate, 7-methylthiotryptamine formamide, 8-methylthio-3,4-dihydro-β-carboline, *trans*-11-methylthio - 1,2,3,4,6,7,12,12b - octahydro - 2 - oxoindolo[2,3 - *a*] quinolizine) showed no activity.

Keyphrases □ (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine—synthesis, pharmacological evaluation □ Thioindole derivatives—synthesis and pharmacological evaluation of (±)-*trans*-11-methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine

The title compound, (±)-*trans*-11-methylthio-1,2,3,4,-6,7,12,12b - octahydrohydroxyindolo[2,3 - *a*]quinolizine (I), was prepared as an extension of the authors' interest in thioindole derivatives and the reported (1) activity of methiopidine (II). Unsubstituted octahydroindolo[2,3-*a*]-quinolizine has been synthesized (2) and reported to be a hypotensive agent. Synthesis (Scheme I) of I was achieved by first preparing 7-methylthiotryptamine through a sequence described by Abramovitch and Shapiro (3). Preparation of the phenylhydrazone (III) was carried out *via* the Japp-Klingemann reaction of S-methyl - 2 - aminobenzenethiol and 3 - carbethoxy - 2-piperidone. Cyclization of III into the β-carboline (IV) was smooth in hot acetic acid–hydrogen chloride gas. Hydrolysis of the β-carboline (IV) to the amino acid (V) was quantitative in 5% alcoholic potassium hydroxide. Decarboxylation to 7-methylthiotryptamine (VI) was accomplished with difficulty in refluxing 2 *N* hydrochloric acid–acetic acid. Synthesis of the octahydroindolo[2,3-*a*]quinolizine (X) followed a procedure described previously (4–6). Addition of ethyl acetate–90% formic acid (1:1) to an ethyl acetate solution of 7-methylthiotryptamine afforded the formate salt (VII) which, upon heating, was converted to the formyl derivative (VIII). The *N*-formyl derivative was treated under Bischler–Napieralski conditions to form the Schiff base (IX), which was converterted to the *trans*-indolo[2,3-*a*]-quinolizine (X) by warming with methyl vinyl ketone and a catalytic amount of ethanol saturated with hydrogen chloride gas. Assignment of the *trans*-configuration was based on the presence of a Bohlman band between 2700 and 2800 cm.$^{-1}$ (KBr) on the IR spectrum (7). Reduction of X with lithium aluminum hydride afforded the title compound, I.



I II

PHARMACOLOGICAL RESULTS

The compounds were tested[1] in a variety of *in vitro* and *in vivo* assays: antibacterial, antifungal, antiparasitic, and antiviral assays. In some cases they were checked for activities of potential interest in the cardiovascular and behavioral fields. A total of 114 individual bioassays was run.

The compounds were tested in chicks (8) for possible anticoccidal activity and for *in vitro* anthelmintic activity against larvae or eggs of trichostrongyle nematodes (9). Antiviral screening (10) was conducted at sample concentrations up to 400 mcg./ml. in cell cultures.

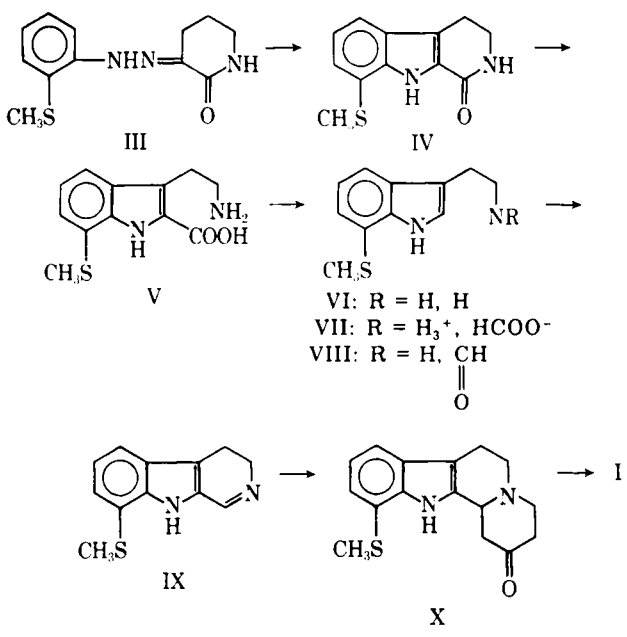
Activity was demonstrated only by Compound VII in any of the screening procedures. Compound VII was active in a concentration of 400 p.p.m. against the organism *Bacillus megaterium* (ATCC 7056). The compound was tested by the medicated agar dilution technique, in which the compound is added to the agar and the test organism is inoculated (about 3 × 10^5 cells) on the surface. The end-point is the level of compound that prevents emergence of visible growth. Since Compound VII was active against only a single organism, lower dose levels were not run.

EXPERIMENTAL[2]

7-Methylthiotryptamine Formate (VII)—To a vigorously stirred solution of 19.4 g. (0.094 mole) of crude VI (11) in ethyl acetate (100 ml.) was slowly added a solution of 1:1 ethyl acetate–90% formic

[1] In the Merck Sharp & Dohme Research Laboratories.

[2] All melting points were determined in open glass capillaries on a Thomas–Hoover apparatus and are corrected.



Scheme I

acid. The solid was collected and recrystallized from ethanol to give 19.5 g. (82%) of white crystals, m.p. 152–153°.

Anal.—Calc. for $C_{12}H_{16}N_2O_2S$: C, 57.10; H, 6.39; N, 11.11; S, 12.69. Found: C, 56.80; H, 5.21; N, 11.43; S, 12.71.

***N*-Formyl-7-methylthiotryptamine (VIII)**—A test tube containing 7 g. (0.038 mole) of the formate salt VII was heated in an oil bath at 185° for 45 min. After cooling, a small portion of ethanol was added to the thick gummy residue. Vigorous stirring of the mixture yielded white crystals; 5.35 g. (82%) was collected and recrystallized from a minimal amount of hot water, m.p. 109–110°.

Anal.—Calc. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.95; S, 13.68. Found: C, 61.51; H, 6.14; N, 11.97; S, 13.45.

8-Methylthio-3,4-dihydro-β-carboline (IX)—A mixture of 7 g. (0.03 mole) of VIII and of anhydrous benzene (126 ml.) was heated until solution was nearly complete. The solution was allowed to cool slightly and then 21 g. (0.137 mole) of freshly distilled phosphorus oxychloride was added dropwise. When spontaneous boiling ceased, the solution was heated for 30 min. on an oil bath. Upon cooling, the hydrochloride salt of the desired product precipitated. The hydrochloride, 6.8 g. (90.5%), m.p. 242–243°, upon neutralization yielded the free amine as white crystals, m.p. 87–88°.

Anal.—Calc. for $C_{12}H_{11}N_2S \cdot HCl$: C, 57.02; H, 5.18; N, 11.08; S, 12.86. Found: C, 56.72; H, 5.33; N, 10.84; S, 12.68.

***trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo-[2,3-*a*]quinolizine (X)**—To a warmed solution of 34 g. (0.136 mole) of IX in absolute ethanol (75 ml.) were added 38 g. (0.544 mole) of methyl vinyl ketone and a catalytic amount of absolute ethanol saturated with hydrogen chloride. The solution was allowed to reflux for 6 hr. and then to cool overnight, and the solvent was removed *in vacuo*. The residue, on crystallization from ethanol, gave 4.5 g. (9.9%) of the crude ketone X. A pure sample of the ketone X, m.p. 164–166°, was obtained *via* preparative TLC using chloroform–methanol (1:9) as the solvent. The 2,4-dinitrophenylhydrazone derivative had a melting point of 148–150°.

Anal.—Calc. for $C_{22}H_{22}N_6O_4S$: C, 56.64; H, 4.75; N, 18.01; S, 6.87. Found: C, 56.75; H, 4.91; N, 17.78; S, 6.93.

(±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydro-2-hydroxyindolo[2,3-*a*]quinolizine (I)—A solution of 0.9 g. (0.003 mole) of crude X in 100 ml. of anhydrous dioxane–anhydrous ether (1:1) was slowly added to 0.12 g. (0.003 mole) of lithium aluminum hydride in 100 ml. of the same solvent. After the addition was completed, the solution was allowed to reflux overnight and then to cool, and the solvent was removed *in vacuo*. The residue, on crystallization from chloroform–acetone, yielded 0.4 g. (43%) of the crude I, m.p. 250–252° dec. Preparative TLC using chloroform–acetic acid (95:5) as solvent afforded an analytical sample of the alcohol IX, m.p. 262–264°.

Anal.—Calc. for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.72. Found: C, 66.48; H, 7.24; N, 9.51.

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