material was not made (13). Thus the distinct possibility exists that their plant material was not, in reality, *R. pyramidalis*. Along similar lines, no mention was made in the paper of Sobá *et al.* (3) that they deposited a voucher specimen representative of their investigational material for reference purposes.

With regard to chemical variability, the authenticated material gave definite positive tests for alkaloids (*vide supra*), which has been duplicated and confirmed by the studies of Ristić and Thomas (7). The material studied by Sobá *et al.* (3) was devoid of alkaloids, although their test methods were not defined.

SUMMARY

The vine of *R. pyramidalis* (Lam.) Urb. (*Leguminosae*), popularly known as pega palo and used in folkloric medicine as an aphrodisiac, has been the subject of the present investigation. Extracts from this plant were found to be devoid of androgenic activity and did not significantly alter the sexual behavior of normal rats when the following measures were taken: latency to first mount, number of incomplete mounts (no intromission), number of complete mounts (intromission), number of ejaculations, length of refractory periods (time from ejaculation to the next sexual response), and amount of time spent in actual sexual behavior.

In a general biological screening of a defatted ethanol extract of *R. pyramidalis* vine, inhibitory activity was observed against *Mycobacterium avium* and *L. casei* (*in vitro*). The extract was devoid of antitumor activity, and in gross observation studies using mice, central nervous system depression was observed.

The vine was found to contain three alkaloids by means of thin-layer chromatography, comprising 0.19% of total crude bases. Tannins, saponins, and organic acids and phenols were also found to be present, but tests for the presence of flavonoids were negative.

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Trifluoromethyl Analogs of Amphetamine and Norephedrine

By ROGER M. PINDER and ALFRED BURGER

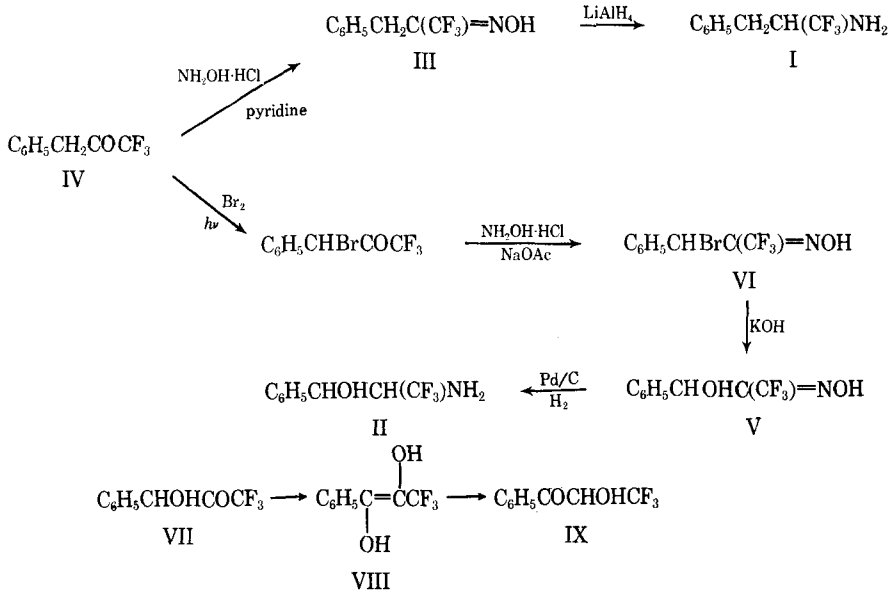
Trifluoromethyl analogs of amphetamine (I) and norephedrine (II) were synthesized for pharmacological evaluation. They showed no activity in profile tests for anorectic activity (I), antiemetic activity (I), CNS activity (I), MAO-inhibitory activity (I, II), and pressor activity (II).

THE SYNTHESIS and pharmacological investigation of organic fluorine compounds has led to the development of such important drugs as the fluorinated inhalation anesthetics (1), the fluorinated corticosteroids (2), the trifluoromethylphenothiazine tranquilizers and the trifluoromethylthiazide diuretics (1, 2). A number of compounds containing the trifluoromethyl group have been found to possess anesthetic, ataractic, and antiemetic (1), diuretic (1, 3), antihistaminic (4), tumor inhibitory (5, 6), and antimicrobial (7, 8), hypotensive (9), and spasmolytic (10) properties.

The trifluoromethyl group is particularly suited to replace the methyl group in known pharmacologically active compounds, both because of the similarity in physical properties of the two classes of compounds and because of the unique chemical and physiological stability of the trifluoromethyl group. The pronounced electron-withdrawing properties of the group will also be expected to play a part in modifying the activity of the prototype compounds.

The authors have now carried out a synthesis of 2-amino-3-phenyl-1,1,1-trifluoropropane (I),

Received February 27, 1967, from the Department of Chemistry, University of Virginia, Charlottesville, VA 22901
Accepted for publication May 5, 1967.
Presented in part to a Medicinal Chemistry Meeting in Miniature, School of Pharmacy, University of North Carolina, Chapel Hill, February 1967.
This investigation was supported by a research grant from Smith Kline & French Laboratories, Philadelphia, Pa., to whom the authors express their appreciation.

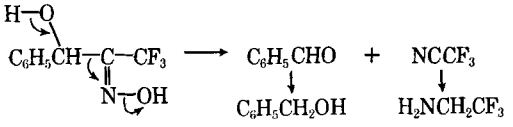


Scheme I

the trifluoromethyl analog of amphetamine (11), by a new sequence in order to make available material for additional pharmacological investigation. Also, the synthesis of the trifluoromethyl analog of norephedrine, *i.e.*, 2-amino-3-hydroxy-3-phenyl-1,1,1-trifluoropropane (II) has been performed.

Compound I was synthesized by reduction of the oxime III with $LiAlH_4$ rather than the previously used method (11) of reductive alkylation of ammonia by the ketone IV. Compound I was also obtained from 2-amino-3-(4-chlorophenyl)-1,1,1-trifluoropropane by dehalogenation (12). The norephedrine analog (II) was obtained by reduction of the oxime of the α-hydroxy ketone (V). The parent ketone, phenyl trifluoroacetyl carbinol (VII), is unstable and undergoes spontaneous enolization to the enediol (VIII), which may further ketonize to the stable benzoyl trifluoromethyl carbinol (IX) (11). The oxime (V) was therefore prepared from the oxime of the bromoketone (VI), by hydrolysis of the bromine atom with ethanolic KOH. Reduction to the amine (II) was effected by catalytic hydrogenation. (Scheme I.)

Reduction with $LiAlH_4$ gave a complex mixture of products, with several runs having varying compositions. Compound II was obtained in a maximum yield of 18%, the other major products being benzylamine, benzyl alcohol, and trifluoroethylamine. Rearrangement and fragmentation of oximes under the conditions of the $LiAlH_4$ reduction are well known (13), and α-hydroxyoximes are particularly susceptible in this respect (14, 15). Benzylamine presumably arises



Scheme II

by a rearrangement of the oxime to an α-hydroxyamide (16), $C_6H_5CHOHNHCOCF_3$, with subsequent reduction and elimination of the trifluoroacetyl group (17). The formation of benzyl alcohol and trifluoroethylamine is somewhat easier to rationalize; a concurrent electron transfer (15) will give benzaldehyde and trifluoroacetonitrile, which will be further reduced to benzyl alcohol and trifluoroethylamine, respectively. (Scheme II.)

The amphetamine analog (I), in standard tests (18),[1] showed no anorectic activity at 25 mg./Kg. (p.o.) in the rat and 10 mg./Kg. in the dog, no antiemetic activity in the dog at 25 mg./Kg., no conditioned escape response blocking action in the rat at 50 and 200 mg./Kg., no tryptamine potentiation in the rat at 100 mg./Kg., and no depletion of catecholamines in the brain and heart of the rat at 100 mg./Kg. (i.p.). The *p*-chloroamphetamine analog showed no anorectic activity in the rat at 29 mg./Kg. (p.o.) and did not deplete heart or brain catecholamines in the rat at 100 mg./Kg. (i.p.). The norephedrine analog (II) showed only 1/300th of the pressor activity of norephedrine itself in the pentobarbitalized rat, and did not deplete brain or heart catecholamines in the rat at 100 mg./Kg. (i.p.).

[1] The authors thank Smith Kline & French Laboratories for the pharmacological data.

EXPERIMENTAL

Benzyl trifluoromethyl ketone, *p*-chlorobenzyl trifluoromethyl ketone, and 3-bromo-3-phenyl-1,1,1-trifluoropropanone were prepared according to Nes and Burger (11).

α-*p*-Chlorophenyltrifluoroacetylacetonitrile had m.p. 79.5–80.5° (benzene).

Anal.—Calcd. for $C_{10}H_5ClF_3NO$: C, 48.50; H, 2.04; N, 5.66. Found: C, 48.42; H, 2.14; N, 5.70.

p-Chlorobenzyl trifluoromethyl ketone had b.p. 65–66° (0.2 mm.).

Anal.—Calcd. for $C_9H_6ClF_3O$: C, 48.55; H, 2.72. Found: C, 48.66; H, 3.09.

The 2,4-dinitrophenylhydrazone, prepared by mixing ethanolic solutions of the ketone and 2,4-dinitrophenylhydrazine with shaking was recrystallized as needles from ethanol, m.p. 111–112°.

Anal.—Calcd. for $C_{15}H_{10}ClF_3N_4O_4$: C, 44.73; H, 2.50; N, 13.91. Found: C, 45.16; H, 2.50; N, 13.90.

The semicarbazone, prepared by refluxing the ketone, sodium acetate, and semicarbazide hydrochloride in ethanol, was recrystallized as plates from dilute ethanol, m.p. 135–136°.

Anal.—Calcd. for $C_{10}H_9ClF_3N_3O$: C, 42.94; H, 3.24; N, 15.03. Found: C, 42.92; H, 3.19; N, 15.28.

The oxime, prepared by refluxing the ketone and $NH_2OH \cdot HCl$ in ethanol and pyridine (1:1), was recrystallized as needles from petroleum ether (b.p. 30–60°), m.p. 60.5–61.5°.

Anal.—Calcd. for $C_9H_7ClF_3NO$: C, 45.57; H, 2.98; N, 5.90. Found: C, 45.56; H, 3.18; N, 5.84.

2-Amino-3-(4-chlorophenyl)-1,1,1-trifluoropropane—To a stirred suspension of $LiAlH_4$ (5.7 Gm., 0.15 mole) in dry ether (100 ml.) was added dropwise a solution of *p*-chlorobenzyl trifluoromethyl ketoxime (23.5 Gm., 0.1 mole) in dry ether (100 ml.). The mixture was heated under reflux for 5 hr., and excess $LiAlH_4$ was destroyed by careful addition of water. Then 10% NaOH (100 ml.) was added, the solid material was filtered off, and the clear yellow filtrate dried ($MgSO_4$). Removal of ether gave a semisolid. The colorless hydrochloride was prepared in ether–petroleum ether, and was purified by sublimation at 150° (1 mm.), m.p. 209–211°, yield 19.0 Gm. (86%).

Anal.—Calcd. for $C_9H_9ClF_3N \cdot HCl$: C, 41.56; H, 3.87; N, 5.39. Found: C, 41.32; H, 3.97; N, 5.42.

The *N*-acetyl derivative, obtained by the Schotten-Baumann method using acetic anhydride, crystallized from dilute ethanol as needles, m.p. 171–172°.

Anal.—Calcd. for $C_{11}H_{11}ClF_3NO$: C, 49.74; H, 4.18; N, 5.27. Found: C, 49.84; H, 4.05; N, 5.41.

2-Amino-3-phenyl-1,1,1-trifluoropropane (11) was prepared in 65% yield from the oxime (III) by a similar method, m.p. of hydrochloride 204–205°. [Lit. (11) m.p. 203–206°.] It was also prepared by the following method.

A mixture of 2-amino-3-(4-chlorophenyl)-1,1,1-trifluoropropane (10 Gm.), methanol (120 ml.), 5% Pd/C (4 Gm.), and KOH (10 Gm.) was shaken at room temperature and 2.8 Kg./cm.^{2} for 5 hr. The catalyst was filtered off and methanol removed under reduced pressure. The residue was taken up in ether, washed with water, and dried ($MgSO_4$). The hydrochloride was identical with that prepared above. Yield, 6.2 Gm. (72%).

3-Bromo-3-phenyl-1,1,1-trifluoropropanone Oxime (VI)—To a solution of hydroxylamine hydrochloride to (40 Gm.) and sodium acetate (40 Gm.) in water (300 ml.) was added all at once 3-bromo-3-phenyl-1,1,1-trifluoropropanone (20 Gm.), and the mixture was shaken vigorously for 10 min. Precipitation of the oxime began immediately and was complete after 30 min. Recrystallization from chloroform gave needles, m.p. 100–102°. Yield, 19 Gm. (85%). $\nu_{max.}^{KBr}$ 3305 (OH), 1695 (C=N, weak) cm.$^{-1}$.

Anal.—Calcd. for $C_9H_7BrF_3NO \cdot H_2O$: C, 36.02; H, 3.09; N, 4.67. Found: C, 36.15; H, 3.02; N, 4.51.

3-Hydroxy-3-phenyl-1,1,1-trifluoropropanone Oxime (V)—To a solution of VI (30 Gm., 0.1 mole) in ethanol (100 ml.) was added dropwise, with stirring and cooling, ethanolic KOH (5.6 Gm. of KOH, 0.1 mole), and the mixture was stirred at room temperature for 2 hr. The precipitated KBr was filtered off and washed thoroughly with ethanol. Most of the ethanol was removed by evaporation under reduced pressure, and water (50 ml.) was added to precipitate the oxime as an oil, which was extracted with ether (2 × 150 ml.) and dried ($MgSO_4$). The ether was removed to yield a yellow oil, which was crystallized from benzene–petroleum ether (b.p. 30–60°), m.p. 90–91.5°, yield, 20 Gm. (90%). $\nu_{max.}^{KBr}$ 3505 (OH), 3250 (OH), 1660 (C=N, weak) cm.$^{-1}$.

Anal.—Calcd. for $C_9H_8F_3NO_2$: C, 49.33; H, 3.68; N, 6.39. Found: C, 49.18; H, 3.70; N, 6.47.

2-Amino-3-hydroxy-3-phenyl-1,1,1-trifluoropropane (II)—A mixture of the oxime (V) (8.8 Gm., 0.04 mole) and 5% Pd/C (4.4 Gm.) in glacial acetic acid (100 ml.) and concentrated H_2SO_4 (8.8 Gm., 0.09 mole) was shaken at room temperature under 2.8 Kg./cm.^{2} of hydrogen. Hydrogen absorption began at once and the theoretical uptake was complete within 2 hr. After the catalyst had been removed by filtration, the clear, colorless filtrate was treated with a solution of NaOH (3.6 Gm., 0.09 mole) in water (15 ml.), with cooling, and the precipitated sodium sulfate was removed by filtration. Acetic acid was removed under reduced pressure, and the residue was made basic with 50% aqueous KOH (cooling). The mixture was extracted with ether (3 × 50 ml.) and dried ($MgSO_4$). Dry HCl was passed into the ethereal solution, and the collected solid was recrystallized from ethanol–petroleum ether (b.p. 30–60°), m.p. 212–214°. Yield, 6.2 Gm. (65%). $\nu_{max.}^{KBr}$ 3445 (OH), 2880 (NH_3^+) cm.$^{-1}$.

Anal.—Calcd. for $C_9H_{10}F_3NO \cdot HCl$: C, 44.74; H, 4.59; N, 5.80. Found: C, 44.49; H, 4.81; N, 5.76.

Hydrogenation in AcOH–anhydrous HCl could not be achieved, a situation also observed in the reduction of 2-indanone oxime (19).

The *N*-acetyl derivative, prepared by boiling the amine with acetic anhydride for 30 min. and then pouring into cold water, was recrystallized from dilute ethanol as needles, m.p. 128.5–130°.

Anal.—Calcd. for $C_{11}H_{12}F_3NO_2$: C, 53.65; H,

4.50; N, 5.69. Found: C, 53.48; H, 4.62; N, 5.80.

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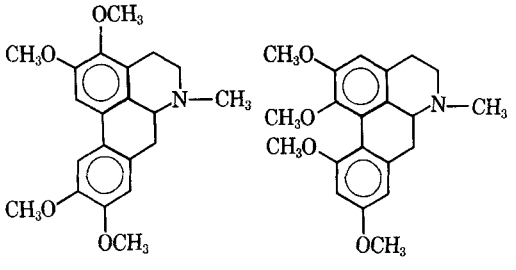
Structure of Argemonine

Identification as (−)-*N*-Methylpavine

By MICHAEL J. MARTELL, JR.*, TAITO O. SOINE, and LEMONT B. KIER†

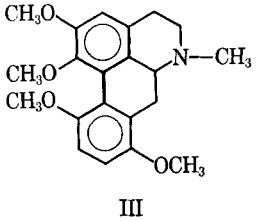
The structure of argemonine has been shown to be (−)-*N*-methylpavine both by chemical evidence and spectral evidence. Racemic *N*-methylpavine has been deracemized as the bitartrates and the base obtained from the D-bitartrate has been shown to be identical with argemonine. The question of whether argemonine is an artifact obtained by cyclization of *N*-methyl-1,2-dihydropapaverine during isolation procedures has been examined, and there appears to be no basis for such conversion.

EARLIER WORK in these laboratories (1, 2) had led to a tentative aporphine-type structural assignment (I) for the alkaloid, argemonine (3). The proposed structure admittedly was biogenetically unfeasible, and Shamma (4), basing his reasoning on the lower than expected intensity of the ultraviolet absorption maxima, suggested alternate formulations (II and III) imposing a 1:11 methoxyl interaction to accentuate the known twist of the biphenyl moiety in aporphines. The resultant reduction in coplanarity would, of necessity, reduce absorption.

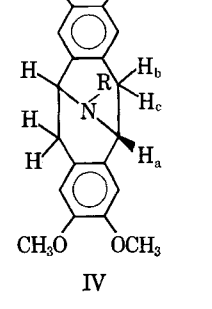


I

II



III



IV

To examine the structural problem further and, initially, to determine the validity of structures I, II, or III, an oxidation of norargemonine ethyl

Received March 8, 1967, from the Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455
Accepted for publication May 4, 1967.
Presented to the Scientific Section, A.PH.A., Miami Beach meeting, May 1963.
A previous communication presenting a portion of this work has appeared in *J. Am. Chem. Soc.*, **85**, 1022(1963). [See also Stermitz, F. R., Lwo, S.-Y., and Kallos, G., *ibid.*, **85**, 1551(1963).]
The authors are grateful to Dr. V. J. Bauer (Lederle Laboratories) for helpful discussions, Mr. W. Fulmor and staff (Lederle Laboratories) for the many absorption spectra, Mr. A. Struck and staff (Central Research Division, American Cyanamid Co., Stamford, Conn.) for the mass spectra, and Dr. J. H. Boothe (Lederle Laboratories) for encouragement. Microanalyses were performed by the Microanalytical Laboratory, School of Chemistry, University of Minnesota, Minneapolis.
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