of quercetin with at least one methoxy group at the 3-position.

An attempt was made to hydrolyze the quercetin dimethyl ether isolated from tobacco flowers by heating it in 7% sulfuric acid solution for 12 hr. on a steam bath. No sugar was found on paper chromatograms of the reaction mixture, nor was there any significant change observed in the unknown compound, although a trace of some nonflavonol material could be located on the chromatogram by observing the chromatogram under ultraviolet light. These tests indicated that the unknown compound was not a flavone nor a glycoside of quercetin.

When an ethanol solution of the tobacco quercetin dimethyl ether was shaken with sodium amalgam, and then acidified with hydrochloric acid, a salmon pink color was obtained. Thus, substitution of the 3-position of the quercetin was again indicated.[6]

Mixtures of quercetin-3-methyl ether and quercetin-3,7-dimethyl ether, which were synthesized and purified in our laboratory as described in later paragraphs, could be readily separated by paper chromatography, using the solvent system nitromethane-benzene-water (2:3:5 v./v., upper layer), with R_f values of 0.13 and 0.85, respectively. The naturally occurring compound had a R_f value of 0.83 in this solvent system, thus indicating the likelihood of its being a dimethyl, and not a monomethyl quercetin 3-methyl ether.

The fluorescence was quenched by the addition of acetic anhydride to the solid compound,[3] indicating a free 5-hydroxy group on the quercetin. The reaction of the isolated compound with alcoholic ferric chloride solution, and its behavior during methylation, likewise indicated a free phenolic group at the 5-position.

Addition of anhydrous sodium acetate to the solution of the tobacco quercetin dimethyl ether, by the method of Jurd and Horowitz,[7] caused a shift in the short wave-length band of its ultraviolet absorption spectrum from 254 to 275 mμ. This indicates that the 7-hydroxy position of the tobacco quercetin dimethyl ether is open.

The long wave-length band of the ultraviolet absorption spectrum of the tobacco unknown did not shift in absolute ethanol saturated with boric acid and anhydrous sodium acetate, by the spectral method of Jurd.[8] Thus, at least one hydroxyl of the *o*-dihydroxy group (3′,4′) of quercetin was blocked in the tobacco unknown in question.

Degradation of the isolated tobacco quercetin dimethyl ether was carried out by dissolving 1 mg. of the unknown in 30 ml. of a 2*N* solution of sodium hydroxide in a mixture of 50% ethanol and 50% water, and evaporating the solution to dryness in an oven at 120°. The residue was dissolved in water, acidified with hydrochloric acid to a *p*H of 2, and extracted four times with 20-ml. portions of ether. The ether solution was concentrated to 1 ml. and studied by paper chromatography. The acid obtained after degradation proved to be vanillic acid (4-hydroxy-3-methoxybenzoic acid) by the identification procedure of Hergert and Goldschmid.[9] Thus, the 4′-position of the tobacco quercetin dimethyl ether has a free phenolic group, whereas the 3′-position has a methoxy group on it. The structure of the isolated tobacco compound is, therefore, quercetin-3,3′-dimethyl ether.

Studies on both tobacco leaves and flowers obtained from a 1955 field-grown crop at Argonne indicated the presence in each of a quercetin dimethyl ether (which may have been quercetin-3,3′-dimethyl ether instead of the reported quercetin-3,7-dimethyl ether), plus a compound giving color tests similar to and co-chromatographing with authentic quercetin-3-methyl ether.[10] A third compound appeared to be kaempferol-3-methyl ether by preliminary tests. Kaempferol is 3,4′,5,7-tetrahydroxyflavone. The spectral tests of Jurd and Horowitz[7] and of Jurd[8] were not run on these 1955 samples, and their identifications were only tentative. On the 1958 greenhouse-grown tobacco flowers, the quercetin-3,3′-dimethyl ether was present in relatively larger amount, but the compounds which might have been flavonol monomethyl ethers were not present in sufficient amount to undertake the studies needed for unequivocal confirmation of their structures.

Preparation of pure quercetin-3-methyl ether and quercetin-3,7-dimethyl ether. Both of these compounds were synthesized by the method reported by Jain and co-workers[4] for quercetin-3,7-dimethyl ether. On paper chromatographic examination, the resulting methylated quercetin precipitate appeared to be a complicated mixture containing five or more different derivatives of quercetin. Using methanol as the suspending medium, the precipitate was adsorbed onto Magnesol (Food Machinery and Chemical Corp., New York). The column was developed with a solvent system containing two parts of water-saturated ethyl acetate and one part nitromethane. Brown-fluorescing material, with some traces of blue-fluorescing impurities, moved rapidly off the column, leaving the major portion of the blue-fluorescing substances on the column. The eluates containing the brown-fluorescing mixture were then further purified by extended paper chromatography, using in order the solvent systems 60% acetic acid–water, 15% acetic acid–water, and nitromethane–benzene–water (2:3:5 v./v. upper layer) for purification of the quercetin-3-methyl ether. For obtaining pure quercetin-3,7-dimethyl ether, the 60% acetic acid–water, nitromethane-benzene–water, and finally 60% acetic acid–water systems were used. R_f values in the 15% acetic acid and 60% acetic acid systems were respectively: quercetin-3-methyl ether, 0.17 and 0.63 and quercetin-3,7-dimethyl ether, 0.19 and 0.72. Each of these compounds was eluted from its final chromatogram with 50% methanol–water. The purified quercetin-3-methyl ether checked in every respect (fluorescence, R_f values, color tests, and spectral studies) with authentic quercetin-3-methyl ether kindly furnished by Dr. R. M. Horowitz, USDA Fruit and Vegetable Laboratory, Pasadena, Calif. The identity of the purified, synthetic quercetin-3,7-dimethyl quercetin was checked by procedures similar to those described above for the determination of the structure of the tobacco quercetin-3,3′-dimethyl ether isolated from tobacco.

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Fluoro Analogs of Prostigmine

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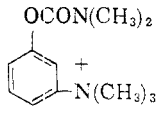
The useful physiological properties of prostigmine,[1] I, and its analogs suggested exploration of

(1) A. Stempel and J. A. Aeschlimann, *Medicinal Chemistry*, Vol. III, John Wiley & Sons, New York, N. Y., 1956. p. 239 (see pp. 270–274).

trifluoromethylphenyl carbamates, and related compounds, II.



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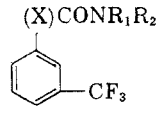


II

X = O, NH
R_1R_2 = H, alkyl, aryl

In particular, employment of a strongly *meta* orienting trifluoromethyl group[2] evaluated replacement of the electronically similar trimethylammonium group[3,4] of I. The steric effects of the trifluoromethyl group[5] and its incorporation into biologically active agents[6] have been recently described. The *meta* relationship of the oxy function in II was indicated on pharmacological[7] and chemical[2,8–12] bases.

The compounds were conveniently prepared by reaction of the appropriate isocyanate ester with *m*-trifluoromethylphenol or *m*-trifluoromethylaniline and are described in Table I.

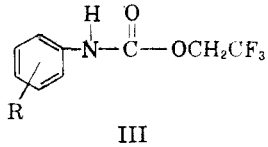
TABLE I

m-TRIFLUOROMETHYLPHENYL CARBAMATES AND UREAS, II

No.	R_1[a]	M.P.[b,c]	Formula	Nitrogen,[d] % Calcd.	Found
		X = —O—			
1	CH_3—[e]	[f]	$C_{10}H_{10}F_3NO_2$	[g]	
2	C_2H_5—	52–53	$C_{10}H_{10}F_3NO_2$	6.0	6.1
3	*n*-C_4H_9—	43–44	$C_{12}H_{14}F_3NO_2$	5.4	5.0
4[h]	C_6H_5—	142[c1]	$C_{14}H_{10}F_3NO_2$	5.0	5.0
5	*p*-$C_2H_5OC_6H_4$—	137–138	$C_{16}H_{14}F_3NO_3$	4.3	4.7
		X = —NH—			
6	C_2H_5—	119–120[c2]	$C_{10}H_{11}F_3N_2O$	12.1	12.0
7	C_4H_9—	[i]	$C_{12}H_{15}F_3N_2O$	10.8	10.5
8	$C_2H_5OOCH_2$—	112–114	$C_{12}H_{13}F_3N_2O_3$	9.7	9.8

[a] R_2 is hydrogen unless otherwise indicated. [b] Melting points are not corrected (capillary). [c] Recrystallizing solvent is hexane unless otherwise shown; [c1]ethanol;[c2]acetonitrile. [d] Analyses by Weiler and Strauss, Oxford, England. [e] R_2 is methyl. [f] B.p. 84–86° (0.2 mm.). [g] *Anal.* Calcd. C, 51.5; H, 4.3. Found: C, 51.7; H, 4.2. [h] Reported by M. T. Leffler and E. J. Matson, *J. Am. Chem. Soc.*, **70**, 3439 (1948), m.p. 138–140°. [i] B.p. 184–192° (2 mm.).

On testing[13] compound 1, the trifluoromethyl analog of I, gave complete ganglionic block at 5 mg./kg., although it was without anticholinesterase activity.[1] Other noted effects were tranquilizing activity with compound 2, anti-tremorine effects with compound 3, and anti-inflammatory activity with compounds 6–8. Compound 6 showed anesthetic activity somewhat better than procaine. The noted tranquilizing activity of compound 2 suggested examination of β,β,β-trifluoroethylcarbanilate analogs, III,[14] which proved to be inactive.



III

R = *p*-CH_3O— (m.p. 81–83°)
R = *p*-Cl— (m.p. 70–71°)

EXPERIMENTAL[15]

N,N-Dimethyl-(m-trifluoromethyl)phenyl carbamate (Compound 1). To a stirred refluxing solution of 8.1 g. (0.05 mole) of *m*-trifluoromethylphenol in 30 ml. of benzene and 10 ml. of triethylamine there was added dropwise 6.0 g. (0.056 mole) of dimethylcarbamyl chloride over 75 min. Stirring and refluxing was continued for 3 hr. When cool, the formed triethylamine hydrochloride was separated and washed with benzene. The filtrate and the benzene washings were combined, the benzene was removed, and the residue distilled to give 8.36 g. (72%) of product, b.p. 84–86° (0.2 mm.).

N-Ethyl-(m-trifluoromethyl)phenyl carbamate (Compound 2). A mixture of 3.24 g. (0.02 mole) of *m*-trifluoromethylphenol, 1.36 g. (0.02 mole) of ethyl isocyanate, and 1 drop of pyridine was warmed under reflux in an oil bath maintained at 100° for 1 hr. When cool, the reaction mixture crystallized and upon trituration with cold hexane gave 2 g. (43%) of product.

Compounds 3–5 were similarly prepared.

N-Ethyl,N'-(m-trifluoromethyl)phenylurea (Compound 6). A mixture of 3.2 g. (0.02 mole) of *m*-aminobenzotrifluoride and 1.36 g. (0.02 mole) of ethyl isocyanate reacted at 20° and solidified. Upon trituration with hexane 2.8 g. (61%) of product was obtained.

Compounds 7 and 8 were similarly prepared.

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(15) Data shown in Table I are not reproduced. Representative examples are shown for the general procedures used.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds, and Dr. I. Rose for the preparation of compound 1.

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Mescaline Analogs. X. 3,4-Dimethyl-, 3,4-Dichloro-, and 3,5-Dimethoxy-4-methyl-β-phenethylamines[1]

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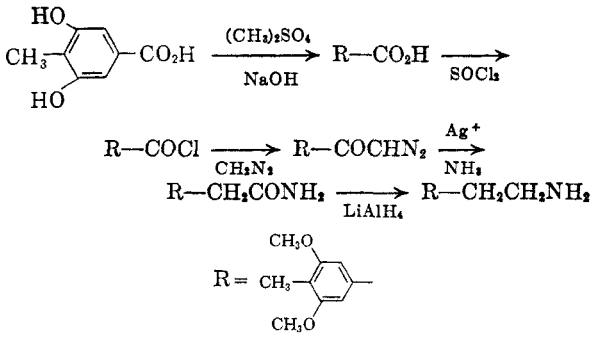
In a continuation of a long-range study of the influence of ring substituents on β-phenethylamines on psychopharmacological activity,[4] three new β-phenethylamines substituted in the 3-, 4-, or 5-positions of the ring were synthesized, and the effect of these compounds on normal cat behavior was examined. The sham rage response[5] induced by 3,4,5-trimethyl-, 4-methyl-, 4-chloro-, and 3,5-dimethyl-4-methoxy-β-phenethylamines[4] prompted investigation of other β-phenethylamines with these ring substituents.

The three new β-phenethylamines described in this communication, 3,4-dimethyl-, 3,4-dichloro-, and 3,5-dimethoxy-4-methyl-, all induced a strong rage response in cats. These findings confirmed previous observations that the substitution of methyl or chloro groups in the 3- and 4-positions of the β-phenethylamine molecule results in compounds which produce a rage syndrome in cats. Replacement of just the 4-methoxy group in mescaline (3,4,5-trimethoxy-β-phenethylamine) with methyl is sufficient to impart rage-producing properties to the compound, whereas mescaline itself does not induce rage.

3,4-Dimethyl-β-phenethylamine was synthesized from 3,4-dimethylbenzyl chloride by conversion to 3,4-dimethylphenylacetonitrile and reduction with lithium aluminum hydride. 3,4-Dichloro-β-phenethylamine was obtained in a similar manner.

3,5-Dimethoxy-4-methyl-β-phenethylamine was synthesized from 3,5-dihydroxy-*p*-toluic acid[6] by the following steps:



Details of the pyschopharmacological properties of these compounds will be published elsewhere.

EXPERIMENTAL[7]

3,4-Dimethylbenzyl chloride. A rapid stream of dry hydrogen chloride gas was passed into a stirred mixture of 106 g. of *o*-xylene, 84 g. of 35% aqueous formaldehyde solution, and 450 ml. of concd. hydrochloric acid kept at 65 ± 5° for 6 hr. The organic layer was separated, the aqueous layer extracted with ether, and the combined organic layer was washed thoroughly with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled through a 12-in. Vigreux column. After removal of unchanged *o*-xylene and a small intermediate fraction, 3,4-dimethylbenzyl chloride was collected as the fraction boiling at 113–116°/22 mm.; yield, 98.4 g. (64%). The structure of this chloromethyl compound has been demonstrated.[8]

3,4-Dimethylphenylacetonitrile. To a stirred solution of 26 g. of sodium cyanide in 30 ml. of water was added a solution of 62 g. of 3,4-dimethylbenzyl chloride in 100 ml. of alcohol, and the resulting mixture was stirred and refluxed for 4 hr. The dark reaction mixture was filtered from inorganic salts, and most of the alcohol was removed from the filtrate by evaporation under reduced pressure. The residue was treated with water, and the crude oily product extracted with ether. The ether solution was washed three times with 50-ml. portions of 1:1 hydrochloric acid to remove foul-smelling isonitrile, then several times with water, and finally dried over anhydrous magnesium sulfate. After removal of ether, the residue was distilled under reduced pressure through a 12 in.-Vigreux column; b.p. 147–150°/22 mm.; yield, 44.6 g. (77%).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.7; H, 7.6. Found: C, 82.4; H, 7.5.

3,4-Dimethyl-β-phenylethylamine. To a stirred solution of 11.7 g. of lithium aluminum hydride in 250 ml. of dry absolute ether was added slowly a solution of 29 g. of 3,4-dimethylphenylacetonitrile at a rate which caused the ether to reflux. The mixture was then stirred and heated under reflux for 0.5 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water until decomposition of the reaction complex was complete. Inorganic matter was removed by filtration, the filtrate was dried (anhydrous magnesium sulfate), filtered again, and treated with alcoholic hydrogen chloride to precipitate the 3,4-dimethyl-β-phenethylamine as its hydrochloride salt; yield, 21 g. (57%); recrystallization from hot alcohol afforded colorless plates, m.p. 222–223°.

Anal. Calcd. for $C_{10}H_{16}ClN$: Cl, 19.1; N, 7.55. Found: Cl, 19.0; N, 7.47.

3,4-Dichlorophenylacetonitrile. A mixture of 100 g. of α,3,4-trichlorotoluene,[9] 130 ml. of ethanol, 33.4 g. of sodium cyanide, and 40 ml. of water was stirred and heated under

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(3) The University of Alabama Medical School.
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