[CONTRIBUTION FROM THE LABORATORIES OF GORDON A. ALLES, PH.D.]

SYNTHESIS OF CERTAIN COMPOUNDS RELATED TO α-FAGARINE[1]

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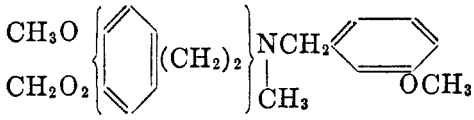
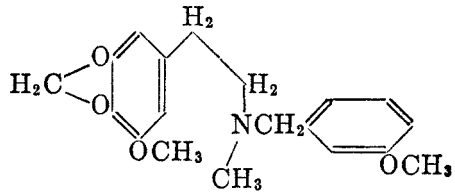
Deulofeu and co-workers (1, 2, 3) have proposed (I) as a provisional structure for α-fagarine, the position of the methoxyl, methylenedioxyl, and methylene groups being unestablished. Because α-fagarine has been reported as effective in arresting cardiac arrythmias (1), especially in some cases where quinidine had failed, it was of interest to synthesize one of the possible compounds of the general structure (I) in order to compare its chemical and pharmacological properties with those of α-fagarine.

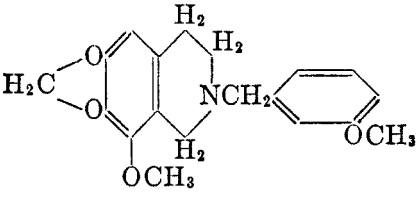


(I)

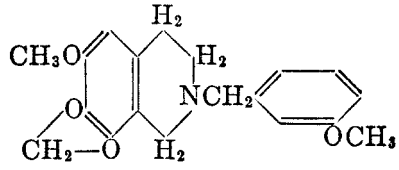


(II)

The distribution of the methoxyl, methylenedioxyl, and methylene groups selected in (II) was that considered most probable, namely the 3,4-methylenedioxy-5-methoxyphenethylamine arrangement. This was thought to be the most probable arrangement since it is that found in numerous alkaloids, *e.g.* cotarnine, gnoscopine, narceine, narcotine, and many others. For comparison of their chemical and pharmacological properties with that of the open-chain compound (II) there were also prepared the tetrahydroisoquinolines (III) and (IV).



(III)



(IV)

For the synthesis of (II), N-(*m*-methoxybenzyl)homomyristicylamine was first synthesized by catalytic reduction of the Schiff base from *m*-methoxybenzaldehyde and homomyristicylamine. The resulting secondary amine was then methylated with methyl sulfate to give the desired tertiary N-methyl amine (II). The required homomyristicylamine has previously been prepared

[1] Surry [*J. Am. Chem. Soc.*, **70**, 2887 (1948)] reported the synthesis of N-(3-methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine after the present manuscript had been submitted for publication. Our conclusions support their findings.

by several methods (8, 10, 11, 12, 13), but it was thought that the facile rhodanine synthesis of Gränacher (4, 5) might be used to advantage in the synthesis of the amine from myristicinaldehyde. Homomyristicylamine was prepared from myristicinaldehyde in an over-all yield of 51% using this method.

The tetrahydroisoquinolines (III) and (IV) were prepared from N-(*m*-methoxybenzyl)homomyristicylamine by ring closure with formaldehyde and hydrochloric acid following the method of Späth (6). While only one tetrahydroisoquinoline was possible with the compound of Späth, two are possible here and both were obtained. These were separated by the difference in solubility of their hydrochlorides. Too little material was available to determine the absolute position of the methoxyl and methylenedioxyl groups in these two isoquinolines. However, upon the basis of the work of Salway (14) on the synthesis of cotarnine in which corresponding 1-benzyltetrahydroisoquinolines were synthesized and identified, the structures tentatively assigned are 2-(*m*-methoxybenzyl)-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III) for the isomer having the higher-melting hydrochloride and 2-(*m*-methoxybenzyl)-6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV) for the isomer having the lower-melting hydrochloride. Further work is needed to establish these structures with certainty.

α-Fagarine is reported (2) to melt at 169–170°, its hydrochloride melts at 192° and the base gives a red-violet color with concentrated sulfuric acid which changes to purple and finally, upon long standing, to a dark brown. The N-methyl-N-(*m*-methoxybenzyl)homomyristicylamine (II) is a liquid which could not be crystallized, its hydrochloride melts at 165–167° and with concentrated sulfuric acid it gives a clear yellow color which becomes green-yellow on standing. Both of the tetrahydroisoquinolines give a yellow color with sulfuric acid, showing they too differ from α-fagarine. Hence it may be concluded that none of these substances is identical with α-fagarine.

The data on the pharmacological trial of these compounds in our laboratories will be published elsewhere by Gordon A. Alles and Charles H. Ellis.

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EXPERIMENTAL

All melting points are uncorrected.

Myristicinaldehyde. Fractional distillation of 700 g. of Dodge and Olcott heavy nutmeg oil gave 436 g. of myristicin, b.p. 152–155°/18 mm. This was isomerized to isomyristicin by boiling under reflux for 24 hrs. with 1.4 l. of 3 *N* ethanolic potassium hydroxide. From this mixture was isolated 352 g. of isomyristicin, b.p. 162–163°/15 mm., which after recrystallization from methanol gave isomyristicin as white needle-crystals, m.p. 43–44°; Power (7) gives 44°. The isomyristicin was oxidized in 96-g. batches according to Salway (8). The aldehyde was obtained as a white crystalline powder, m.p. 131–132°, in 41% yield.

The aldehyde gave a 2,4-dinitrophenylhydrazone, dark brown-red needles, m.p. 232°, identical with that described by Baker (9).

5-Myristicinalrhodanine. A mixture of 118 g. of myristicinaldehyde, 90 g. of rhodanine,

165 g. of anhydrous sodium acetate, and 500 ml. of glacial acetic acid was gently boiled for 1 hr. After cooling, the mixture was poured into 5 l. of cold water. The orange-yellow solid was washed with alcohol and ether, and dried; yield 165 g. (85%). A sample recrystallized from "Cellosolve" melted at 254–255°.

Anal. Calc'd for $C_{12}H_9NO_4S_2$: C, 48.80; H, 3.07.
Found: C, 48.95; H, 3.10.

α-Thiono-β-(3,4-methylenedioxy-5-methoxyphenyl) propionic acid. A suspension of 104 g. of myristicinalrhodanine in 420 ml. of 4 *N* sodium hydroxide was heated with stirring in a boiling water-bath until practically all the solid had dissolved. The filtered solution was cooled to 10° and 420 ml. of an ice-cold solution of 4 *N* hydrochloric acid was rapidly added with vigorous stirring. The thiono acid separated as a granular yellow solid. The yield was nearly theoretical, but it proved to be wise to use this product directly in the following step without drying or further purification.

A sample was recrystallized from aqueous methanol for analysis; yellow crystalline powder, m.p. 153–154° dec.

Anal. Calc'd for $C_{11}H_{10}O_5S$: C, 51.96; H, 3.97.
Found: C, 51.4; H, 4.14.

α-Oximino-β-(3,4-methylenedioxy-5-methoxyphenyl)propionic acid. The thiono acid from 165 g. of myristicinalrhodanine was dissolved in a solution prepared by dissolving 38.5 g. sodium in 1100 ml. of ethanol and adding a solution of 115 g. of hydroxylammonium chloride in 100 ml. of water. This solution was heated to boiling for 30 minutes, filtered to remove sodium chloride and any insoluble material, and evaporated to dryness under reduced pressure. The residue was dissolved in dilute sodium hydroxide, filtered, and well cooled, after which it was made acid to Congo Red while stirring with a mechanical stirrer. The crystalline product was filtered off, washed with water, and dried; weight 131 g. (93% yield, based upon the myristicinalrhodanine, 2 steps).

A sample was recrystallized from 20% methanol-water for analysis; microscopic, colorless needles, m.p. 150–151°.

Anal. Calc'd for $C_{11}H_{11}NO_6$: C, 52.2; H, 4.38.
Found: C, 52.17; H, 4.62.

3,4-Methylenedioxy-5-methoxyphenylacetonitrile. To 400 ml. of acetic anhydride at 45° was added, in small portions, 131 g. of the oximino acid. The spontaneous reaction caused the temperature to rise to 90°, with the evolution of carbon dioxide. After boiling for 10 min. the solution was evaporated to dryness under reduced pressure, the cooled residue was taken up in benzene, washed with water and then dilute sodium hydroxide, dried over magnesium sulfate, and distilled under reduced pressure. The fraction boiling at 160–165°/2 mm. weighed 68.5 g. (70% yield). After recrystallizing from methanol a product melting at 89–90° was obtained. Hahn (13) gives m.p. 90°.

Homomyristicylamine. A mixture of 36.2 g. of 3,4-methylenedioxy-5-methoxyphenylacetonitrile, 100 ml. of methanol, 200 ml. of a saturated solution of ammonia in methanol, and 4 ml. of Raney nickel catalyst sludge was reduced at 100° for 2 hrs. at an initial pressure of 420 lbs./sq. in. The catalyst was filtered off, the ammonia and methanol distilled, and then the residue, giving 33.6 g., b.p. 145–147°/3 mm. (91% yield). The hydrochloride melted at 163–164° in agreement with Decker and Becker (10).

N-(m-methoxybenzyl)homomyristicylamine hydrochloride. A mixture of 9.8 g. of homomyristicylamine and 6.8 g. of *m*-methoxybenzaldehyde was allowed to stand for 10 min., during which time it became warm and turbid from the separation of water. The mixture was then dissolved in 50 ml. of ethanol, 100 mg. of Adams platinic oxide catalyst was added followed by hydrogenation at 3 atmospheres pressure for 2 hrs. at ambient temperature. The catalyst was removed and the solution was acidified with ethanolic hydrogen chloride. The amine hydrochloride crystallized out. Upon reworking the filtrate, additional amine salt was isolated; in all, 12.7 g. (72% yield) of crystalline salt, m.p. 142–143° was obtained.

Anal. Calc'd for $C_{18}H_{21}NO_4 \cdot HCl$: C, 61.44; H, 6.30; Cl, 10.08.
Found: C, 61.80; H, 6.32; Cl, 10.02.

N-methyl-N-(m-methoxybenzyl)homomyristicylamine. A solution of 6.5 g. of N-(*m*-methoxybenzyl)homomyristicylamine, obtained from the hydrochloride by treatment with alkali, in 50 ml. of ethyl ether was treated with 2.6 g. of methyl sulfate. The solution was refluxed for 5 min., water was added, the solution made strongly basic with sodium hydroxide, and the ether and aqueous phases were separated. The ether phase was treated with 4 *N* hydrochloric acid and sodium nitrite to convert any secondary amine into the nitroso derivative, insoluble in dilute acid. The ether layer was discarded and the aqueous layer was made basic with sodium hydroxide. The amine which separated was extracted with ether and the ether layer was dried over potassium carbonate. After removing the drying agent, the ether was distilled leaving a thick oily residue (3.3 g.) which would not crystallize.

The base was dissolved in ethanol, treated with a slight excess of ethanolic hydrogen chloride, ether was added just to turbidity, and the solution was cooled in the refrigerator, giving 3.4 g. of white crystals which after recrystallizing from ethanol-ether melted at 165–167°.

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HCl$: C, 62.37; H, 6.61; Cl, 9.69; N, 3.83.
Found: C, 62.58; H, 6.74; Cl, 9.68; N, 3.84.

Cyclization of N-(m-methoxybenzyl)homomyristicylamine. A mixture of 11.5 g. of N-(*m*-methoxybenzyl)homomyristicylamine, 5 ml. of 40% formaldehyde, and 10 ml. of water was heated for 30 min. on a boiling water-bath. The aqueous layer was decanted from the gummy material and the latter was warmed with 150 ml. of 2 *N* hydrochloric acid. After adding 30 ml. of ethanol the solution was allowed to cool. The crystals which separated were washed with ethanol, the ethanol washings being kept separate from the aqueous filtrate; 1.8 g. of crystals, m.p. 115°, was obtained. From the aqueous filtrate 1.8 g. of crystals, m.p. 190–192°, separated upon prolonged standing. By reworking the filtrate a total of 2.8 g. of the higher-melting fraction was obtained. The lower-melting isomer was obtained from the filtrate by a procedure described below.

2-(m-Methoxybenzyl)-6,7-methylendioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (*III*). The free isoquinoline obtained from 3.8 g. of the higher-melting hydrochloride was heated for 30 min. with 3 ml. of acetic anhydride. The excess acetic anhydride was destroyed with water, the solution was acidified with an excess of 1 *N* hydrochloric acid and the non-basic organic material was extracted with ether and discarded. The aqueous layer was evaporated to dryness and the residue was crystallized from ethanol-ether; weight 3.0 g., m.p. 189–191°.

Anal. Calc'd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.71; H, 6.10; Cl, 9.73.
Found: C, 62.84; H, 6.10; Cl, 9.62.

2-(m-Methoxybenzyl)-6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (*IV*). The base from the combined aqueous filtrates of several cyclizations was liberated with sodium hydroxide, extracted with ether, dried, and the ether evaporated. The residue was heated on a boiling water-bath for 30 min. with an excess of acetic anhydride, the excess anhydride was destroyed with water, the solution was cooled and acidified with 50 ml. of 1 *N* hydrochloric acid. The solution was evaporated to dryness and the residue was crystallized from ethanol-ether, giving 2.7 g. of material melting at 120–125°. Recrystallization from ethanol-ether failed to change the melting point.

Anal. Calc'd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.71; H, 6.10; Cl, 9.73.
Found: C, 62.0, 62.0; H, 5.92, 6.17; Cl, 9.76.

SUMMARY

N-(*m*-methoxybenzyl)-N-methylhomomyristicylamine and its hydrochloride have been synthesized as one of the possible structures for α-fagarine. Likewise the two isomeric 1,2,3,4-tetrahydroisoquinolines, 2-(*m*-methoxybenzyl)-6,7-methylenedioxy-7-methoxy- and 2-(*m*-methoxybenzyl)-6-methoxy-7,8-methyl-

enedioxy-, were prepared and compared with α-fagarine. None of these structures is identical with α-fagarine.

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