Some 2-Substituted Derivatives of 2-Dimethylamino-1,2,3,4-tetrahydronaphthalene

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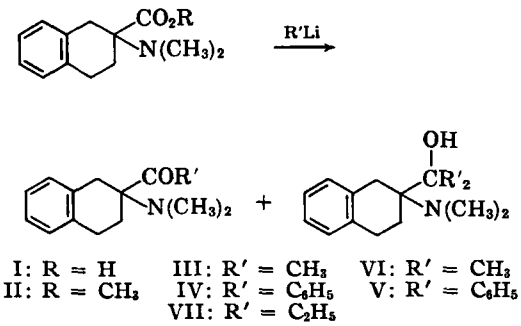
The synthesis and pharmacological examination of several 2-dimethylamino-1,2,3,4-tetrahydronaphthalene 2-alcohols, 2-esters, and 2-ketones is described.

IT HAS BEEN postulated that potent morphine-type analgetics must contain a rigid structure in which the position of the basic nitrogen relative to an aromatic ring is fixed within narrow limits (1). In morphinan the 1,3-fused ring system serves to hold the nitrogen in the axial conformation. Since morphinan contains the 2-amino-1,2,3,4-tetrahydronaphthalene moiety, properly designed derivatives of this structural segment could be candidates for analgetic tests. In simple derivatives of 2-amino-1,2,3,4- tetrahydronaphthalene, the nitrogen will tend to assume the more stable equatorial position, and means other than ring fusion have now been considered to produce axial amino derivatives. Bulky groups in the 2-position with some degree of polarity, whose solvation may further increase their bulk, may cause a dimethylamino group at position 2 to assume an axial conformation. This article describes the synthesis of such compounds. Because bulky groups, on the other hand, may interfere with receptor fit, several compounds containing smaller ester and keto groups in position 2 were also prepared for pharmacological evaluation.

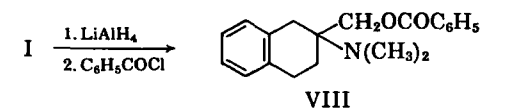
Starting with 2-amino-2-carboxy-1,2,3,4-tetrahydronaphthalene (2), the amino group was methylated by an adaptation of the method of Clarke, *et al.* (3), and the carboxyl function was esterified. The synthesis of alkyl and aryl ketones proceeded from 2-carboxy-2-dimethylamino-1,2,3,4-tetrahydronaphthalene (I), or better from its methyl ester (II). Treatment of I with methyllithium at 25° gave small yields of 2-acetyl-2-dimethylamino-1,2,3,4-tetrahydronaphthalene (III) besides nonbasic decomposition products. Phenyllithium led to a mixture from which 2-benzoyl-2-dimethylamino- (IV) and 2-dimethylamino-2-(α-hydroxybenzhydryl)-1,2,3,4-tetrahydronaphthalene (V) could be separated. Compound V was also obtained from the reaction of phenyllithium and II at 25°, no ketone being isolated in this case. By contrast, the action of methyllithium on II furnished a mixture which on chromatography yielded 55% of 2-acetyl-2-dimethylamino-1,2,3,4-tetrahydronaphthalene (III) and 22% of 2-dimethylamino-2-(2-hydroxy-2-propyl)-1,2,3,4-tetrahydronaphthalene (VI). Reaction of II with ethyllithium furnished a mixture from which only a small amount of 2-dimethylamino-2-propionyl-1,2,3,4-tetrahydronaphthalene (VII) could be elaborated.

Reduction of I with lithium aluminum hydride gave 2-dimethylamino-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene whose benzoate ester (VIII) was prepared for pharmacological tests.

Compounds II, III, V, and VIII were screened pharmacologically.[1] None of them exhibited analgetic properties in mice at doses up to 200 mg./Kg.; the substances gave no indication of central nervous system depression or excitation, and did not produce hypoglycemia three hours after oral administration of 100 mg./Kg. to 18-hour fasted guinea pigs.



I: R = H III: R′ = CH_3 VI: R′ = CH_3
II: R = CH_3 IV: R′ = C_6H_5 V: R′ = C_6H_5
VII: R′ = C_2H_5



VIII

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EXPERIMENTAL[2]

2 - Carboxy - 2 - dimethylamino - 1,2,3,4 - tetrahydronaphthalene (I).—A mixture of 2-amino-2-carboxy-1,2,3,4-tetrahydronaphthalene(2)(140 Gm., 0.73 mole), formaldehyde solution U.S.P. (1 L.), and 98% formic acid (1 L.) was refluxed for 10 hours; 100 ml. of concentrated hydrochloric acid was added, and volatile materials were removed by distillation. To the oily residue was added ethanol (750 ml.), and the solid which separated was filtered and washed with ether. Yield, 110 Gm. (70%). Recrystallization from ethanol gave a colorless material, m.p. 223–227° (decompn.). The infrared spectrum was compatible with an amino acid hydrochloride.

Anal.—Calcd. for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.29; H, 7.12. Found: C, 61.19; H, 6.94.

2 - Carbomethoxy - 2 - dimethylamino - 1,2,3,4-tetrahydronaphthalene (II).—A solution of I (50 Gm., 0.2 mole) in methanol (300 ml.) was treated slowly with a solution of diazomethane, prepared from 110 Gm. of N-methyl-N-nitrosourea, in 2 L. of ether at 0°. After standing overnight, most of the solvents were distilled off, the residue was taken up in ether, washed with potassium hydroxide solution, dried over sodium sulfate, and the ether was evaporated. The residual oil (34 Gm., 71%; b.p. 137°/0.3 mm.; n_D^{25} 1.5310) gave a hydrobromide salt which was recrystallized from isopropyl alcohol-isopropyl ether, m.p. 180°. The infrared spectrum had bands at 3.4, 3.6, 5.8, 6.3, 6.7, 6.9, 7.3, 8–8.5, 9.0, 9.3, 9.7, 9.9, 10.1, 11.0, 11.5, 12.0, 12.6, 12.8, 13.4, 14.2, and 14.8μ.

Anal.—Calcd. for $C_{14}H_{19}NO_2 \cdot HBr$: C, 53.34; H, 6.40. Found: C, 53.54; H, 6.54.

A small yield of the same methyl ester was obtained by refluxing I with equal weights of methanol and sulfuric acid.

2 - Carbethoxy - 2 - diethylamino - 1,2,3,4 -tetrahydronaphthalene.—Prepared in the same manner as the methyl ester, using diazoethane or ethanol and sulfuric acid. Yield 50%, based on weight of oil. Infrared bands of the base were at 3.4, 3.6, 5.8, 6.7, 6.9, 7.3, 8.3, 9.0, 9.75, 10.1, 11.0, 11.4, 12.4, 13.5, and 14.1μ. The hydrobromide, prepared in ether solution, was recrystallized from isopropyl alcohol-isopropyl ether, m.p. 160°.

Anal.—Calcd. for $C_{15}H_{21}NO_2 \cdot HBr$: C, 54.71; H, 6.74. Found: C, 54.44; H, 6.65.

Reaction of I with Phenyllithium.—To a stirred solution of 0.3 mole of phenyllithium in 300 ml. of ether was added, under nitrogen, 10 Gm. (0.04 mole) of I-hydrochloride in quantities of about 0.5 Gm., with sufficient time between additions to allow vigorous refluxing to cease. After 3 hours at 25° the mixture was poured on ice and the ether layer washed with dilute hydrochloric acid to dissolve all basic materials. The acid extracts were made basic with potassium hydroxide solution and extracted with ether. The combined ether extracts were dried and evaporated. The solid residue was crystallized fractionally from ethanol. The more soluble product (18%) melted at 82–83°; its infrared spectrum showed bands at 5.95μ (C=O), and 13.3 and 13.9μ (monosubstituted phenyl); there was no OH band. It represented the phenyl ketone IV.

Anal.—Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57. Found: C, 81.75; H, 7.25.

The colorless hydrobromide crystallized from isopropyl alcohol-isopropyl ether, m.p. 175–176°.

Anal.—Calcd. for $C_{19}H_{21}NO \cdot HBr$: C, 63.33; H, 6.16. Found: C, 63.37; H, 6.28.

The less soluble compound (28%), m.p. 155–157°, was identical with V and obtained in better yield as described in the next experiment.

2 - Dimethylamino - 2 - (α - hydroxybenzhydryl)-1,2,3,4-tetrahydronaphthalene (V).—To 0.3 mole of phenyllithium in 300 ml. of ether was added 10 Gm. (0.04 mole) of II. The mixture was stirred under nitrogen at 25° for 6 hours, decomposed with ice, and the ether layer was dried over sodium sulfate and evaporated. The solid residue (60% yield) was recrystallized from ethanol, m.p. 155–157°. The material was identical (mixture m.p. and infrared spectra) with the less soluble substance described in the preceding experiment.

Anal.—Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.58; H, 7.59.

Reaction of 2-Carbomethoxy-2-dimethylamino-1,2,3,4-tetrahydronaphthalene (II) with Methyllithium.—A mixture of 0.3 mole of methyllithium and 10 Gm. of II in 300 ml. of ether was stirred for 3 hours, poured on ice, and the ether layer was extracted well with dilute hydrochloric acid The acid solution was made alkaline and re-extracted with ether. The oily residue from the dried ether extracts exhibited a large C=O band in the infrared, and a small OH band, and the latter did not increase when, in another experiment, the reaction time was extended to 9 hours. Chromatography in ether on Alcoa F-20 alumina furnished 5 Gm. (55%) of a solid, m.p. 52–53°; infrared peaks at 3.4, 3.6, 5.8, 6.75, 6.85, 7.4, 7.9, 8.4, 8.7, 8.9, 9.3, 9.5, 9.9, 10.75, 11.2, 11.9, and 13.3μ. This material represented 2-acetyl-2-dimethylamino-1,2,3,4-tetrahydronaphthalene (III) and was identical with a substance obtained in low yield from I and methyllithium.

Anal.—Calcd. for $C_{14}H_{19}NO$: C, 77.37; H, 8.81. Found: C, 77.04; H, 8.71.

The hydrobromide crystallized from isopropyl alcohol-isopropyl ether, m.p. 173–175°.

Anal.—Calcd. for $C_{14}H_{19}NO \cdot HBr$: C, 56.37; H, 6.75. Found: C, 55.91; H, 6.72.

A second, oily, fraction from the alumina column weighed 2 Gm. (22%) and represented the alcohol VI; infrared bands at 2.8, 3.4, 3.6, 6.3, 6.7, 6.9, 7.3, 7.7, 7.9, 8.1, 8.4, 9.0, 9.3, 9.6, 10.0, 10.6, 10.9, 11.1, 11.5, 11.8, 12.1, 12.4, 13.4, and 14.8 μ.

2 - Dimethylamino - 2 - propionyl - 1,2,3,4 - tetrahydronaphthalene (VIII).—This ethyl ketone was prepared as described for the lower homolog (III), using ethyllithium. The oily reaction product (6 Gm., 58%) exhibited both carbonyl and hydroxyl peaks in the infrared; only after chromatography could a solid salt be obtained from the ketonic fraction. The hydrobromide crystallized from isopropyl alcohol-isopropyl ether, m.p. 161–164°.

Anal.—Calcd. for $C_{15}H_{21}NO \cdot HBr$: C, 57.69; H, 7.10. Found: C, 57.90; H, 6.90.

2 - Benzoyloxymethyl - 2 - dimethylamino - 1,2,3,4-tetrahydronaphthalene (VIII).—To a filtered and stirred solution of 10 Gm. (1.25 moles) of lithium aluminum hydride was added, under nitrogen and in

[2] All melting points are corrected, boiling points uncorrected. Microanalyses by Mrs. Margaret Logan and Mrs. Dorothy Ellis.

small portions, 10 Gm. (0.04 mole) of I-hydrochloride. The mixture was refluxed for 2 hours, allowed to stand at 26° for 6 hours, decomposed with water and worked up as usual. The oily yellow material (6.5 Gm., 82%) had a strong OH peak in its infrared spectrum. It was benzoylated directly with 20 ml. of benzoyl chloride and 150 ml. of 10% sodium hydroxide solution for 15 minutes, the mixture was decomposed with ice, extracted with dilute hydrochloric acid, the acid solutions were made alkaline and re-extracted with ether. The oily product from the dried ether extract weighed 5 Gm. (50%) and exhibited an ester band in its infrared spectrum. Its hydrobromide crystallized from ethyl formate-isopropyl ether, m.p. 194–197°.

Anal.—Calcd. for $C_{20}H_{23}NO_2 \cdot HBr$: C, 61.54; H, 5.94. Found: C, 61.00; H, 6.10.

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Analysis of the Volatile Components of Ylang-Ylang Oil by Gas Chromatography

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Five samples of commercially available ylang-ylang oil were analyzed by gas chromatography. Of the various stationary liquid phases used, a 20% Ucon on Chromosorb P(w/w) gave consistently the best separation. The composition of extra, first, second, and third quality fractions and pure oil No. 123 was determined on the basis of relative retention times.

Most essential oils are complex mixtures of individual organic compounds that contain varied functional groups which make complete and detailed analysis relatively difficult or at times impossible using conventional procedures.

Thus, prior to the advent of gas chromatography, the analyses of essential oils were tedious and time consuming. Furthermore, in certain instances in which other methods were used, the analyses were not considered complete (1). The availability and development of gas chromatography as an analytical tool has not only greatly facilitated the separation, and at times the identification, of the constituents of a number of essential oils, but also reduced the time required for analyses (2, 3).

One of the important ingredients in a number of perfumes and other cosmetic products is ylang-ylang oil. This is obtained from the flowers of the ylang-ylang tree (*Cananga odorata*, Hook *f et* Thomson), which is probably a native of the Philippines (1). The important commercial sources of this oil for use in the United States today are the Nossi-Be and Comoro Islands. The oil is available in four different quality fractions, based on the respective boiling points, and is classified commercially as extra, first, second, and third quality fractions. The extra fraction exhibited the highest specific gravity and the lowest refractive index when compared to the other fractions. The samples labeled extra and first quality possess the strongest and finest odors.

That the chemical composition of the oil may be related to the manner in which the oil is extracted from the flowers has been shown by Glitchitch and Naves (4). They found that when the flowers were initially extracted with petroleum ether and the extract concentrated and distilled, the product was almost free of sesquiterpenes (5). On the other hand, if the flowers were steam distilled, a relatively high concentration of sesquiterpenes was found. This was interpreted by some authors to mean that the sesquiterpenes are formed during distillation from compounds insoluble in petroleum ether and should not be considered true natural products in the strict sense (1).

The chemical composition of ylang-ylang oil was cursorily investigated as early as 1873 working with samples obtained in the Philippines (6–8). In 1932, Glitchitch and Naves (4) using a classical separation identified certain constituents of the extra oil and reported a semiquantita-

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