Anal. Calcd. for $C_{18}H_{22}ClN_3O_4S_2$: C, 48.69; H, 5.00; N, 9.46. Found: C, 48.95; H, 4.98; N, 9.70.

5-Chloro-2,4-bis(dimethylsulfamyl)-N-(p-nitrobenzylidene)-aniline. A mixture of 3.4 g. of 5-chloro-2,4-bis(dimethylsulfamyl)aniline, 3.0 g. of *p*-nitrobenzaldehyde, and 60 ml. of toluene was heated under reflux with a water separator for 20 hr. Upon cooling, the crystalline solid was collected, triturated with 200 ml. of boiling alcohol, and recrystallized from acetonitrile; yield, 3.6 g. (76%), m.p. 221–223°, $\lambda_{max}^{C_2H_5OH}$ 276–281 mμ, ε 25,270.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_6S_2$: C, 42.99; H, 4.03; N, 11.80. Found: C, 43.03; H, 4.26; N, 11.72.

WEST POINT, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

New Alkaloids from *Tiliacora racemosa* (Colebr.). III.[1,2a] Constitution[2b] of Tiliacorine and Tiliarine

K. V. JAGANNADHA RAO AND L. RAMACHANDRA ROW

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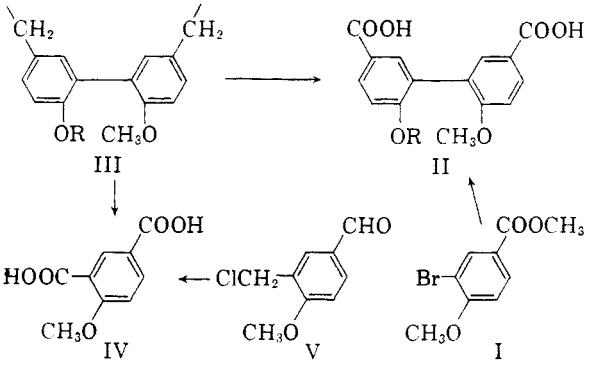
Permanganate oxidation of *O*-methyltiliacorine and *O,N*-dimethyltiliarine gives rise to 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid. Tiliacorine and tiliarine yield, on the other hand, 4-methoxyisophthalic acid and no diphenyldicarboxylic acid. It is, therefore, felt that the free hydroxyl is present in the 2-position of the diphenyl system. This was confirmed by the oxidation of *O*-ethyl ethers of the two alkaloids, which yielded 2′-ethoxy-2-methoxy-diphenyl-5,5′-dicarboxylic acid. On this basis, a structure is suggested for tiliacorine which is derived from two coclaurine units and contains a dibenzo-*p*-dioxin system as in menisarine but with a 2′-hydroxy-2-methoxydiphenyl system in place of 2-methoxydiphenyl oxide group. Tiliacorine and tiliarine are thus the only two bisbenzyl isoquinoline alkaloids isolated from nature with 11,11′-diphenyl link.

In parts I[1] and II[2] of this series, tiliacorine and tiliarine were assigned the molecular formulas $C_{32}H_{23}O_3(OH)(2\text{-}OCH_3)(2\text{-}NCH_3)$ and $C_{32}H_{23}O_3$-$(OH)(2\text{-}OCH_3)(1\text{-}NCH_3, 1\text{-}NH)$ respectively. The hydroxyl is phenolic in character, and may be in a sterically hindered position as it resisted methylation with diazomethane. Both alkaloids exhibit a prominent blue color with sulfur-nitric acid reagent[3] indicating a dibenzo-*p*-dioxin system in the molecule. Furthermore, a study of their ultraviolet absorption spectra[2] suggested a close resemblance with trilobine or menisarine.

Confirmation of the above formulas was sought by a study of the permanganate oxidation of these two alkaloids and their *O*-methyl derivatives. *O*-Methyltiliacorine and *O,N*-dimethyltiliarine furnished the same carboxylic acid (m.p. 338–340°; dimethyl ester 171–173°) during oxidation with 2% permanganate at laboratory temperature. Analysis indicated a dicarboxylic acid with two methoxyls in it and it was identified as 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid (II. R = CH_3) by direct comparison with a synthetic sample obtained by Ullmann's reaction with methyl-3-bromo-4-methoxybenzoate[4] (I).



The oxidation of these alkaloids to diphenyl-5-5′-dicarboxylic acid (II. R = CH_3) is a very significant feature. Diphenyldicarboxylic acids were previously isolated from cocculidine[5] from *Cocculus luarifolius D.C.*, lycorenine[6] from *Lycoris radiata* Herb., Sinomenine[7] from *Sinomenium acutum* and acetyl thebaol[8] after a series of degradative reactions involving Hofmann degradation. These diphenyldicarboxylic acids possess at least one carboxyl group in one of the *ortho* positions of the diphenyl system.

The isolation of the diphenylcarboxylic acid (II. R = CH_3) is thus very significant and indicates

(1) K. V. J. Rao and L. R. Row, *J. Sci. Ind. Research (India)* **16B**, 156 (1957).

(2) (a) K. V. J. Rao and L. R. Row, *J. Sci. Ind. Research (India)* **18B**, 247 (1959).

(2) (b) A recent publication on the same topic by Anjaneyulu *et. al.* (*Chem. & Ind.*, June 6, p. 702, 1959) has prompted us to publish this paper. The information included in this paper has been delayed in publication as the investigation formed part of the D.Sc. thesis of one of us (K. V. J.) which is under preparation.

(3) I. R. C. Bick and A. R. Todd, *J. Chem. Soc.*, 1606 (1950).

(4) G. W. K. Cavill, *J. Soc. Chem. Ind.* **64**, 212 (1945); M. M. Marcel Paty and Raymond Quelet, *Compt. Rend.* **217**, 229 (1943).

(5) S. Yunusov, *J. Gen. Chem. U.S.S.R.*, **20**, 1514 (1950).

(6) H. Kondo and T. Ikeda, *Ber.*, **73**, 867 (1940).

(7) K. Goto, and H. Shishido, *Bull. Chem. Soc., Japan* **16**, 170 (1941).

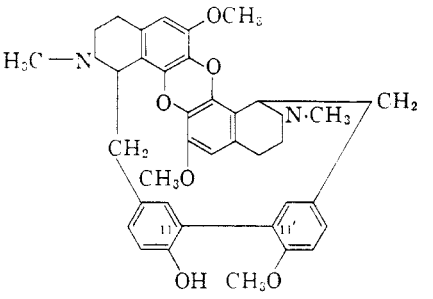
(8) K. W. Bentley and R. Robinson, *Experientia.* **6**, 353 (1950); K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 947 (1952).

the 2,2′-dimethoxydiphenyl system (III. R = CH_3) in *O*-methyltiliacorine and *O,N*-dimethyltiliarine, with a probable attachment of the basic half (which should, of course, contain a dibenzo-*p*-dioxin system) at 5,5′-positions through two methylene groups. The absence of a carboxyl group in the 2- or 3′-positions rules out any phenanthridine structure for them.

Direct oxidation of the two alkaloids with 2% permanganate furnished a dicarboxylic acid different from the diphenyl dicarboxylic acid (II. R = CH_3). It was identified as 4-methoxyisophthalic acid (IV) by direct comparison with a synthetic sample which was secured by permanganate oxidation of 2-chloromethyl-anisaldehyde (V).[9] Obviously, the diphenyl system in the unmethylated alkaloids was getting oxidized. Such an oxidation is possible if the free hydroxyl in both the alkaloids were present in the diphenyl half. Then, on this consideration, tiliacorine and tiliarine may contain the hydroxy diphenyl system (III. R = H).

The position of the hydroxyl in the diphenyl system was further confirmed by ethylation of the alkaloids followed by oxidation. The dicarboxylic acid from *O*-ethyltiliacorine as well as from *O*-ethyl-*N*-methyltiliarine, gave a dimethyl ester different from the dimethyl ester of the carboxylic acid (II. R = CH_3). This confirms the 2′-position of the phenolic hydroxyl in the diphenyl half of tiliacorine and tiliarine, and their *O*-ethyl derivatives should have been oxidized to 2-methoxy-2′-ethoxydiphenyl-5-5′-dicarboxylic acid (II. R = C_2H_5).

Now, to suggest a structure for tiliacorine (or tiliarine) we have to accommodate (a) a 2-methoxy-2′-hydroxydiphenyl system[10] (III. R = H) and (b) a dibenzo-*p*-dioxin system which should also carry two isoquinoline units. Any attachment between the two systems could only be through the two methylene groups in the 5,5′-positions of the diphenyl system. While accommodating these two ring systems in a general structure of biscoclaurine type, it became clear to us that the older molecular formulas[1,2] for tiliacorine and tiliarine required modification. In this context, the methoxyl content could be a guiding factor. Thus in trilobine[11] there is one methoxyl in the dibenzo-*p*-dioxin system and in menisarine[12] two methoxyls. Analytical values for carbon, hydrogen, and nitrogen agree closely with menisarine type, necessitating the change from $C_{36}H_{36}O_6N_2$ to $C_{37}H_{38}O_6N_2$ for tiliacorine (which takes into account the diphenyl system). Anjaneyulu *et al.*[13,14] also suggested this formula for tiliacorine on the basis of oxidative degradation. The only disagreeing factor was the methoxyl content. Our experimental value for methoxyl was only 10.1% for tiliacorine instead of 15.1% on the basis of the new formula. It is well known that low methoxyl values are not unusual. A notable case in this connection, is that of aristolochic acid from *Aristolochia clematitis*.[15] From the foregoing, tiliacorine could be tentatively represented by VI and tiliarine is only a stereo isomer of nor-tiliacorine.



VI

Such a formulation is also supported by the Faltis theory.[16] Tiliacorine and tiliarine are unique examples of the bisbenzylisoquinoline type, having a 2′-hydroxy-2-methoxy diphenyl system in place of the 2-methoxy diphenyl ether system of menisarine.[12] Obviously, this is an intermolecular diphenyl link formed by dehydrogenation at 11 and 11′ positions in two coclaurine units. An intramolecular diphenyl link formation between the 8 and 10 positions is well known to be the basis of biogenetical formation of aporphine alkaloids[17] from a single laudanosine unit.

EXPERIMENTAL

o-Acetyltiliacorine. A 200-mg. sample of tiliacorine was refluxed with 5 ml. of acetic anhydride and 1.0 g. of freshly fused sodium acetate for 2 hr. and then poured into 30 ml. of water. The solution was neutralized with saturated sodium bicarbonate solution and extracted (3 × 20 ml.) with chloroform. *O*-acetyltiliacorine was crystallized three times from benzene–petroleum ether (1:1) when it came out as colorless needles; m.p. 233–236° dec., yield, 150 mg.

Anal. Calcd. for $C_{39}H_{40}O_7N_2$: C, 72.21; H, 6.17; N, 4.32; 1-AcO, 6.64. Found: C, 72.18; H, 6.58; N, 4.43; AcO, 6.74.

O-acetyltiliacorine was deacetylated with methanolic sulfuric acid (5%). The hydrolyzate gave on treatment with

(9) Raymond Quelet and Jean Allard, *Compt. Rend.* **205**, 238 (1937).

(10) It is very interesting to note that Y. Sugii (*J. Pharm. Soc. Japan*, **50**, 183, 1930) isolated a 2,2′-dihydroxy-5,5′-diallyldiphenyl from the bark of *Magnolia officinalis*, Rhed. et Wils and *Magnolia obovata* Thumb. He named it Magnolol. The presence of such a closely related diphenyl in a plant of Magnoliaceae which is also known to give rise to bisbenzylisoquinoline alkaloids, lends support to the structure of tiliacorine proposed in this paper.

(11) M. Tomita and C. Tani, *Chem. Abstr.* **45**, 4728, 4729 (1951).

(12) H. Kondo and M. Tomita, *Chem. Abstr.* **30**, 726 (1936); **33**, 626 (1939).

(13) B. Anjaneyulu, K. W. Gopinath, T. R. Govindachary, and B. R. Pai, *Chem. & Ind. (London)*, 702 (1959).

(14) B. Anjaneyulu, K. W. Gopinath, T. R. Govindachary, and B. R. Pai, *Chem. & Ind. (London)*, 1119 (1959).

(15) M. Pailer, L. Belohlov, and E. Sinomitsch, *Mh. Chemie*, **87**, 17 (1956); **88**, 367 (1957).

(16) F. Faltis, L. Holzinger, P. Ita, and R. Schwartz, *Ber.* **74B**, 79 (1941).

(17) R. Robinson, R. H. Manske and H. L. Holmes, *J. Chem. Soc.* **111**, 876 (1917); *The Alkaloids*, **Vol. IV**, Academic Press, Inc., New York p. 2 (1954).

base and crystallization from chloroform-acetone, rectangular prismatic needles, m.p. 260–261° dec. undepressed by admixture with tiliacorine.

Oxidation of tiliacorine. Isolation of 4-methoxyisophthalic acid (IV). A 2-g. sample of tiliacorine was dissolved in 100 ml. of 4% aqueous sulfuric acid and 500 ml. of 2% potassium permanganate was added dropwise at room temperature with continuous mechanical stirring. After 3 hr., the solution was brownish, turbid, and still purple, when it was saturated with sulfur dioxide. The resulting yellow solution was continuously extracted with ether in a liquid-liquid extractor. The ethereal extract was evaporated and the residue triturated with 25 ml. of 4% sodium bicarbonate solution. Acidification with hydrochloric acid of the bicarbonate extract gave no solid. It was, therefore, continuously extracted with ether for 4 hr. Removal of ether furnished a colorless crystalline solid which came out as colorless needles after three crystallizations from hot water; yield, 220 mg., m.p. 265–266° dec. undepressed by admixture with a synthetic sample of 4-methoxyisophthalic acid. It did not exhibit any blue color with a trace of nitric acid in concd. sulfuric acid.

Anal. Calcd. for $C_9H_8O_5$: C, 55.09; H, 4.08; 1-OCH_3, 15.8. Found: C, 54.65; H, 4.26; OCH_3, 16.32.

A 100-mg. sample of the acid in absolute ethanol was treated with excess diazomethane and kept at 0° for 20 hr. The dimethyl ester crystallized from methanol in the form of prismatic needles; m.p. 94–95°, alone or mixed with a synthetic sample of dimethyl 4-methoxy-isophthalate.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.35; 3-OCH_3, 41.53. Found: C, 58.48; H, 5.29; OCH_3, 42.09.

Oxidation of tiliarine: Isolation of 4-methoxyisophthalic acid (IV). A 3-g. sample of tiliarine was dissolved in 100 ml. of 4% aqueous sulfuric acid and oxidized with 700 ml. of 2% potassium permanganate at room temperature as in the case of tiliacorine and also worked up as before. The carboxylic acid after careful crystallization from hot water, came out as colorless needles, yield, 296 mg., m.p. 266–269°. It did not exhibit any positive dibenzo-*p*-dioxin color reaction.

The dimethyl ester (diazomethane) crystallized from ethanol in the form of prismatic needles, m.p. 93–95° not altered by dimethyl 4-methoxyisophthalate.

4-Methoxyisophthalic acid (IV) was obtained by the permanganate oxidation of 2-chloromethylanisaldehyde according to the method of Quelet and Allard.[9] The isophthalic acid was secured in good yield; but required four crystallizations from aqueous methanol to raise the melting point to 268–269°.

The methyl ester was obtained by esterification with ethereal diazomethane, m.p. 95–96°.

Oxidation of O-methyl tiliacorine dimethiodide. Isolation of 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid (II. R = CH_3). A 2-g. sample of *O*-methyltiliacorine[2] dimethiodide in 300 ml. of water was stirred with freshly prepared silver oxide (from 3 g. of silver nitrate) for 3 hr. and filtered. The light brown filtrate was treated dropwise with 600 ml. of 2% potassium permanganate at room temperature (30°) during a period of 2 hr., until the purple permanganate color was permanent. A strong current of sulfur dioxide was passed through the turbid liquid until it was saturated. There was a considerable amount of pale yellow solid undissolved which was filtered off and the filtrate continuously extracted with ether. On evaporation, the ether extract left a pale yellow solid residue which was crystallized three times from methanol when colorless minute crystals were secured; yield 30 mg., m.p. 328–330°.

The yellow undissolved solid was shaken with 150 ml. of 4% sodium bicarbonate and filtered. On acidification, the filtrate deposited a colorless solid which after three crystallizations from ethanol came out as colorless crystalline material melting indefinitely between 328–332°. Two more crystallizations from methanol acetone (1:1) raised the melting point to 338–340° dec.; yield, 80 mg. identical with the sample obtained above in the filtrate. The carboxylic acid did not exhibit any color with sulfuric–nitric acid reagent.[3]

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63; 2-OCH_3, 20.53. Found: C, 63.81; H, 4.89; OCH_3, 20.21.

The dicarboxylic acid was esterified with ethereal diazomethane. The dimethyl ester came out after two crystallizations from ethanol, as colorless rectangular plates, m.p. 171–173°, alone or mixed with a synthetic sample of dimethyl 2,2 -dimethoxydiphenyl-5,5′-dicarboxylate.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.45; 4-OCH_3, 37.58. Found: C, 65.1; H, 5.58; OCH_3, 36.85.

Oxidation of O,N-dimethyl tiliarine dimethiodide. Isolation of 2,2′-dimethoxy-diphenyl-5,5′-dicarboxylic acid (II. R = Me). A 2-g. sample of *O,N*-dimethyltiliarine dimethiodide[2] was oxidized with 2% potassium permanganate as in the case of *O*-methyltiliacorine dimethiodide. The dicarboxylic acid was similarly isolated and crystallized twice from ethanol (and two more times from acetone) to give minute colorless crystals, m.p. 336–38°; yield, 85 mg., identical with the acid secured above.

The dimethyl ester (diazomethane) came out from ethanol as rectangular plates, m.p. 170–72°, undepressed by the dimethyl ester of 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.46, 4-OCH_3, 37.58. Found: C, 65.58; H, 5.64; OCH_3, 37.05.

Methyl 3-bromo-4-methoxybenzoate (I). A solution of 5 g. of methyl 3-bromo-4-hydroxybenzoate[4] in 150 ml. of anhydrous acetone was refluxed with 3.15 g. of dimethyl sulfate and 7.5 g. of anhydrous potassium carbonate, on a water bath for 8 hr. The inorganic salts were filtered and washed with warm acetone. The residue from evaporation of the acetone filtrate, was shaken with 150 ml. of water and filtered. The solid was crystallized twice from methanol when methyl 3-bromoanisate[4] was secured in the form of colorless crystalline needles, m.p. 99–100°, yield, 5.1 g.

Dimethyl 2,2′-dimethoxydiphenyl-5,5′-dicarboxylate (II. R = CH_3). An intimate mixture of 5 g. of methyl 3-bromo-4-methoxybenzoate and 5 g. of copper bronze was heated at 240–250° in a sealed tube for 4 hr. The material was extracted repeatedly with ether and the extract evaporated. The residue was dissolved in benzene and run over a short column of chromatographic alumina. The colorless benzene eluate was evaporated and the colorless crystalline dimethyl ester crystallized twice from benzene–petroleum ether (b.p. 40–60°); yield, 238 mg., m.p. 171–173°. This agrees with the melting point described by Sugii[18] and by H. Gilman.[19]

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.46; H, 5.45; 4-OCH_3, 37.58. Found: C, 65.1; H, 5.58; OCH_3, 36.85.

A 500-mg. sample of the dimethyl ester was warmed on a water bath with 50 ml. of 4% sodium hydroxide till the solid went into solution. It was cooled and acidified with hydrochloric acid. The 2,2′-dimethoxydiphenyl-5,5′-dicarboxylic acid was crystallized from methanol, m.p. 338–340°, which agrees with the melting point given by Gilman.[19]

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63. Found: C, 63.40; H, 4.80.

Oxidation of O-ethyltiliacorine dimethiodide. An aqueous solution of 3 g. of *O*-ethyltiliacorine dimethiodide[1] in 300 ml. of water was shaken for 2 hr. with silver oxide (freshly prepared from 3 g. of silver nitrate) and filtered. To the filtrate was added 900 ml. of 2% potassium permanganate at laboratory temperature dropwise wih mechanical stirring until the purple color persisted (2 hr.). A brisk current of sulfur dioxide was passed through the turbid solution. After saturation, it was filtered and the filtrate extracted continuously

(18) Y. Sugii, *J. Pharm. Soc. Japan*, **50**, 183 (1930); *Chem. Abstr.* **24**, 3505 (1930).

(19) H. Gilman, J. Swiss, and Lee C. Cheney, *J. Amer. Chem. Soc.* **62**, 1963 (1940).

with ether. Evaporation of the ether extract furnished only a very small residue.

The yellow undissolved solid was shaken with 125 ml. of 4% sodium bicarbonate for 30 min. and filtered. The filtrate was acidified and subjected to continuous extraction with ether. Removal of ether from the extract left a colorless residue which was mixed with the residue obtained above. To the total solid in absolute ethanol, excess diazomethane in ether was added and left at 0° overnight. The methyl ester was purified by two crystallizations from benzene-petroleum ether (1:1) when it came out as colorless prisms melting at 122–125°. Final purification was effected by sublimation at 0.5 mm. and the sublimate crystallized from benzene–petroleum ether (1:1), m.p. 124–125°, yield, 45 mg. The ester did not exhibit any blue color with sulfuric–nitric acid reagent.[3]

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.81; 3-OCH_3 and 1-OC_2H_5 as 4-OCH_3, 36.04. Found: C, 66.71; H, 6.05; OCH_3, 35.77.

Oxidation of O-ethyl-N-methyltiliarine dimethiodide. Two grams of *O*-ethyl-*N*-methyltiliarine dimethiodide[2] was oxidized following the procedure given above. The carboxylic acid was esterified with diazomethane and isolated as the dimethyl ester. The ester was purified by two crystallizations from benzene–petroleum ether (1:1) (solid, m.p. 122–125°) followed by vacuum sublimation at 0.5 mm. The sublimate was crystallized again from benzene–petroleum ether when the methyl ester was secured as colorless prisms, m.p. 123–125°, undepressed by the sample obtained similarly from *O*-ethyltiliacorine dimethiodide.

WALTAIR, INDIA

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XIII.[1] 2-Alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphans and a More Direct Synthesis of the 2-Phenethyl Compound (NIH 7519)

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Starting from *p*-methoxybenzylmagnesium chloride and 1-alkyl-3,4-dimethylpyridinium iodides the 2-alkyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphane IIIb, IIIc, and IIId have been synthesized for neuropharmacological evaluation. Similarly the medically useful IIIf (NIH 7519) results from 3,4-dimethyl-1-phenethylpyridinium bromide or iodide. IIIb, IIId, and IIIe were also prepared from the known compound IIIa by standard reactions. This alternative synthesis confirms the constitution of the 2-alkyl compounds.

The potent (in mice) analgesic 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IIIa)[1] has been found to be effective in blocking a conditioned response in mice and rats, a property not uncommon in morphine and morphine-like analgesics.[2] By varying the nitrogen substituent of III, one could expect to get a wide variation in analgesic activity which would permit to a limited extent a comparison of analgesic and other neuropharmacologic actions. We wish to report a few of the IIIa analogs studied in this connection along with a shorter synthesis for 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (IIIf, NIH 7519.[1,3])

The most convenient route for the preparation of the 2-alkyl compounds was that described previously for IIIa.[4] *p*-Methoxybenzylmagnesium chloride and the appropriate 1-alkyl-(or aralkyl in the case of IIIf) 3,4-dimethylpyridinium iodide (I) were brought to reaction in dry ether. The resultant dihydropyridines (II) in dilute hydrochloric acid were hydrogenated to the corresponding 1,2,5,6-tetrahydro compounds, which were in turn cyclized and *O*-demethylated to III with hydrobromic acid, in 10–30% overall yields based on the starting pyridinium iodides. Because of low water solubility it was necessary to use aqueous alcoholic hydrochloric acid for the hydrogenation step in the preparation of IIIf. It is noteworthy that this synthesis for IIIf is some five steps shorter than that previously reported.[1]

The 2-ethyl (IIIb), 2-butyl (IIId), and 2-amyl (IIIe) compounds have been prepared also from IIIa by a route described earlier[1,3,5] which involves cyanogen bromide *N*-demethylation of the methyl ether of IIIa, acylation of the resultant secondary amine, reduction of the *N*-acyl derivative with ethereal lithium aluminum hydride and *O*-demethylation. This alternative synthesis provided sufficient proof of structure.

The 2-alkyl derivatives IIIb, IIIc, and IIId had no analgesic activity at sub-toxic doses. The *N*-amyl derivative (IIIe), on the other hand, was comparable to morphine in analgesic potency, somewhat more potent than IIIa. This is reasonably consistent with earlier findings[6] in the morphine series where the *N*-ethyl, -propyl, and -butyl homologs have less than one tenth the potency of morphine, and *N*-amylnormorphine is seven-tenths as effective as morphine.

(1) Communication XII, E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

(2) Personal communication from Leonard Cook, Smith, Kline and French Laboratories.

(3) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(4) (a) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (b) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(6) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. Intern. Pharmacodynamie*, **110**, 186 (1957).