The Syntheses of Homoproaporphines by Phenolic Oxidative Coupling. II.[1] Separation of Two Isomeric Dienones of Homoproaporphines

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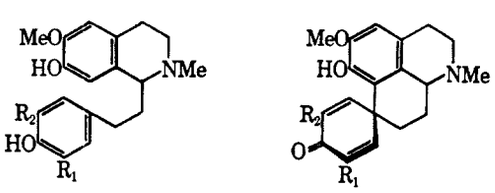
Oxidation of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (**3**) with potassium ferricyanide or ferric chloride gave a mixture of two isomeric dienones (**5a** and **5b**) which were separated. The methoxy analog of phenethylisoquinoline (**4**) also gave the dienone **6** by phenolic oxidative coupling reaction.

We have reported biogenetic type syntheses of some isoquinoline alkaloids by phenolic oxidative coupling[2-4] including the synthesis of homoproaporphine-type compound **2** from phenethylisoquinoline (**1**).[1] Barton and Cohen[5] suggested that the biogenesis of certain aporphine alkaloids involved the initial formation of dienones, followed by dienone–phenol rearrangement, and Battersby[6] postulated that dienol–benzene rearrangement may also be involved. The evidence for these hypotheses has been reinforced by the isolation of dienones, proaporphines, such as crotonosine, glaziovine, pronuciferine, and stepharine,[7] and also from feeding experiments by Barton.[8] On the other hand, Battersby gave a laboratory analogy by synthesis of isothebaine from orientaline by way of orientalinone through the phenolic oxidation and reduction, followed by dienol–benzene rearrangement.[9]

Since the proaporphines have an important role in the biosyntheses mentioned above, "homoproaporphines" also might be thought to play a similar role in the biosyntheses of "homoaporphines" [10] which as we shall see later have been found in nature. We, therefore, set out to prepare 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)- (**3**) and 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenethyl)-6-methoxy-2-methylisoquinoline (**4**) as the most promising precursors to homoproaporphines.



1, $R_1 = R_2 = H$
3, R_1 = OMe; $R_2 = H$
4, $R_1 = R_2$ = OMe

2, $R_1 = R_2 = H$
5a, R_1 = OMe; $R_2 = H$ or *vice versa*
b, $R_1 = H$; R_2 = OMe or *vice versa*
6, $R_1 = R_2$ = OMe

The former phenethylisoquinoline derivative **3** corresponds to orientaline which is the most popular intermediate in phenolic oxidation to the various isoquinoline alkaloids, and the latter, **4**, is based on the reason that androcymbine has three methoxy groups in the phenethyl moiety. During our experiments, Battersby certified the correctness of part of our speculation by the isolation of homoaporphine alkaloids such as kreysigine, floramultine, and multifloramine.[10] We now report our independent syntheses of homoproaporphines **5** and **6**.

The diphenolic phenethylisoquinolines **3** and **4** were prepared as in the following explanation which is outlined in Scheme I. Benzyloxycinnamic acids **7a** and **7b** were reduced with nickel aluminum alloy and 10% sodium hydroxide aqueous solution according to our method,[11] and reaction of the resulting hydroxyphenylpropionic acids, **8a** and **8b**, with 4-benzyloxy-3-methoxyphenethylamine afforded the amides **9a** and **9b**, whose phenolic hydroxyl group was protected by ethoxycarbonylation to give the amides **10a** and **10b**. Bischler–Napieralski reaction of these amides afforded the corresponding 3,4-dihydroisoquinoline derivatives, **11a** and **11b**, which were methylated with methyl iodide to give the methiodides **12a** and **12b**, respectively.

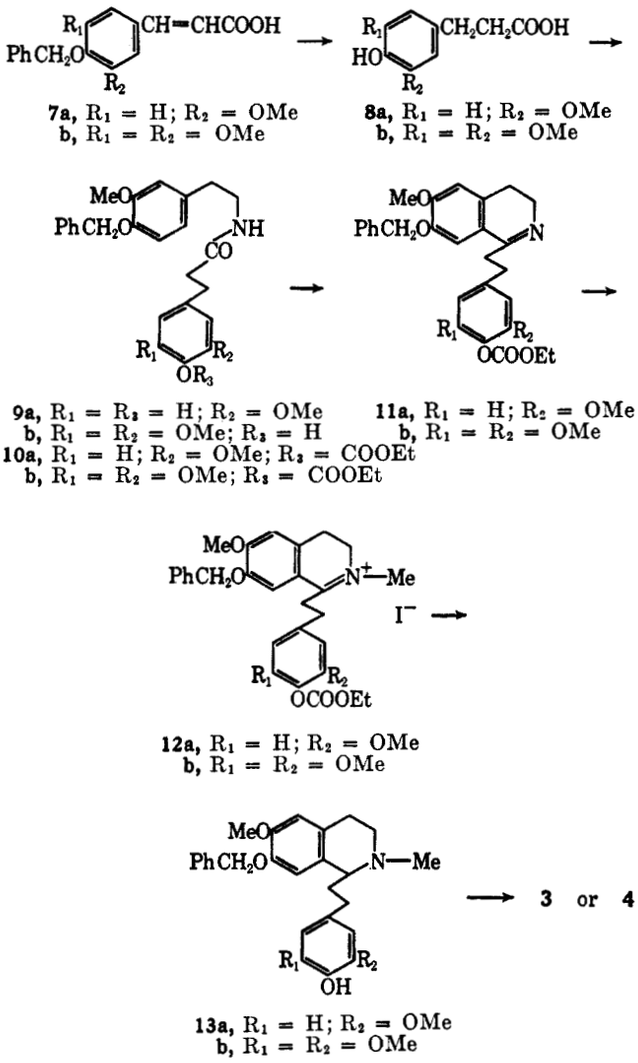
Reduction of **12a** and **12b** with sodium borohydride gave 1,2,3,4-tetrahydro-2-methylisoquinolines **13a** and **13b**, whose debenzylation with concentrated hydrochloric acid afforded the diphenolic phenethylisoquinolines **3** and **4**.

The oxidation of phenethylisoquinoline **3** to the dienone **5** was investigated under various conditions, the best procedure being the one in which 1 molar equiv of isoquinoline hydrochloride was treated with 6 moles of ferric chloride in water at 20° for 3 hr in a current of nitrogen. By this method the desired dienone **5** was obtained regularly in crystalline form in 46.0% yield. That the yield of dienone obtained by this method was much higher than that of our previous results[1] is probably due to the greater reactivity of isoquinoline **3** in phenol oxidation than of isoquinoline **1** reported previously, since the former, **3**, has one extra oxygen function in the phenethyl ring. However, by use of a two-phase system of potassium ferricyanide buffered with 8% ammonium acetate and chloroform, the dienone **5** was obtained in 16% yield. On the other hand, the oxidation with manganese dioxide gave only a tar.

In spite of showing one spot on its thin layer chromatogram under various solvent systems, this

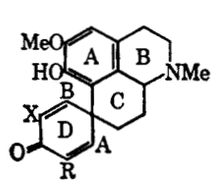
(1) Part I: T. Kametani, H. Yagi, F. Satoh, and K. Fukumoto, *J. Chem. Soc., Sect. C*, in press.
(2) T. Kametani and I. Noguchi, *ibid.*, 1440 (1967).
(3) T. Kametani and H. Yagi, *Chem. Commun.*, 366 (1967).
(4) T. Kametani, T. Kikuchi, and K. Fukumoto, *ibid.*, 546 (1967); *Chem. Pharm. Bull.* (Tokyo), in press.
(5) D. H. R. Barton and T. Cohen, *Festschr. Arthur Stoll*, 117 (1957).
(6) A. R. Battersby, *Proc. Chem. Soc.*, 189 (1963).
(7) L. J. Haynes and K. L. Stuart, *J. Chem. Soc.*, 1784, 1789 (1963); K. Bernauer, *Helv. Chim. Acta*, **46**, 1783 (1963); **47**, 2119, 2122 (1964); B. Gilbert, M. E. A. Gilbert, M. M. De Oliveira, O. Riveiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 694 (1964); M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Rauffauf, and J. A. Weisbach, *Chem. Ind.* (London), 282 (1964).
(8) D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *Chem. Commun.*, 259 (1966); L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby, *ibid.*, 141 (1965).
(9) A. R. Battersby, T. H. Brown, and J. H. Clemment, *J. Chem. Soc.*, 4550 (1965).
(10) A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 450 (1967).
(11) T. Kametani and Y. Nomura, *Yakugaku Zasshi*, **74**, 413 889 (1954).

SCHEME I



dienone was a mixture of two isomers: dienone A (19.1% yield with $FeCl_3$, 3.5–4.5% yield with $K_3Fe(CN)_6$), colorless prisms, mp 156–158° dec (**5a**), and dienone B (17.5% yield with $FeCl_3$, 4.8% yield with $K_3Fe(CN)_6$), colorless prisms, mp 193–195° (**5b**). Both compounds were separated by recrystallization from benzene. Since one of them has the methoxyl group of ring D below the general plane of rings A, B, and C and the other has the methoxyl group at the reverse side, namely, above this plane, it is necessary to decide which is which.

The structure of dienone **5a** as one of the oxidation products was assigned as follows; the molecular formula of $C_{20}H_{23}O_4N$ was supported by microanalysis and mass spectrometry (M^+ 341), and the infrared spectrum showed the typical dienone absorption at 1657, 1619, and 1600 cm^{-1}; the ultraviolet spectrum at 243 and 286 mμ (log ε 4.41, 4.24) also supported this system. Furthermore, the nmr data

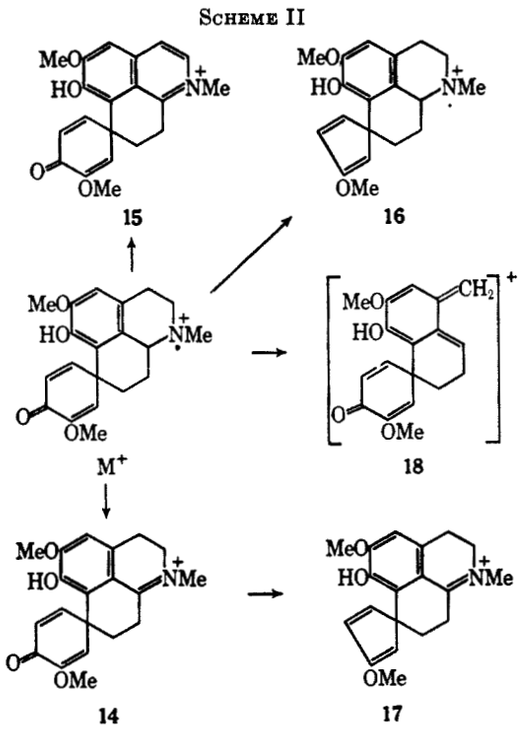


5a, R = OMe

support the structure of the dienone A as is shown in the Experimental Section.

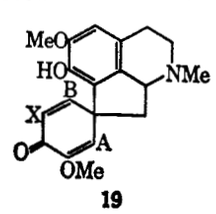
Moreover, the mass spectrum showed strong peaks at 341 (M^+), 340 ($M^+ - 1$) (**14**), 324 ($M^+ - 17$) (**15**), 313 ($M^+ - 28$) (**16**), 312 ($M^+ - 29$) (**17**), and 298 ($M^+ - 43$) (**18**). These peaks were assigned to the following ion because they were shifted just 30 mass units ($M^+ - OMe$) compared with those of the dienone **2**.[1] The formation of the radical ion **16** and ion **17** from the molecular ion and ion **14**, respectively, reveals that the oxidation product has a keto group (see Scheme II).

SCHEME II



The dienone **5b** was similar to dienone **5a** in the ultraviolet (λ_{max} 244, 289 mμ (log ε 4.12, 3.80)), infrared (ν_{max} 1658, 1636, 1608 cm^{-1}), and mass (M^+, $M^+ - 1$, $M^+ - 28$, $M^+ - 29$, $M^+ - 43$) spectra, but there was a small difference in the nmr spectrum.

Battersby and co-workers[9] and Shamma and Slusarchyk[12] reported nmr data for orientalinone (**19**).



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There is a difference between their assignment of chemical shift in the dienone system; thus Battersby assigned H_A at τ 4.08 as doublet, H_B at 3.21 as quartet, and H_X at 3.67 as doublet. On the other hand, Shamma assigned H_A at τ 3.98, H_B at 3.40 as quartet, and H_X at τ 3.05 as doublet. The nmr data of our crude dienones, a mixture of dienone A and dienone B, showed signals which were compatible with Shamma's data. However, after separation of both dienones A and B, the nmr data of each dienone were

(12) M. Shamma and W. A. Slusarchyk, *Chem. Commun.*, 528 (1965).

in good agreement with Battersby's assignment mentioned above.

The second diphenolic phenethylisoquinoline (**4**) was also oxidized with ferric chloride to give the dienone (**6**) in analytical pure state in 18% yield. This structure was supported by microanalysis and spectrometry: the infrared spectrum showed 1656 and 1618 cm^{-1}; the ultraviolet spectrum showed λ_{max} 232 and 278 mμ (log ϵ 4.04, 4.03). The nmr spectrum showed τ 7.65 (N-methyl), 6.44 and 6.37 (olefinic O-methyl), 6.22 (aromatic O-methyl), 4.14 and 4.0 (a pair of doublets, olefinic protons, J = 2.5 cps), and 3.57 (aromatic proton). These nmr data were in close agreement with the data of Battersby's dienone.[10]

By comparing the chemical shifts of olefinic protons and olefinic O-methyl group in dienones A and B (**5a** and **5b**) with those of dienone **6**, it was possible to come to the conclusion that one of the two isomeric dienones **5a** or **5b** has the O-methyl group above the general plane of rings A, B, and C and that the methoxyl group of the other lies below this plane. The precise determination of the configurations of **5a** and **5b** will be reported elsewhere.

Experimental Section

Melting points are uncorrected. The infrared spectra were taken in chloroform solution unless otherwise noted with a Hitachi EPI-S_2 spectrophotometer. Ultraviolet spectra were taken in methanol solution on a Hitachi EPS-3 recording spectrophotometer. Mass spectra were measured on a Hitachi RMU-6D mass spectrometer. Nmr spectra were measured on a Hitachi H-60 in deuteriochloroform solution using tetramethylsilane as an internal standard unless otherwise noted. As usual, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.[13]

4-Hydroxy-3-methoxyphenylpropionic Acid (8a).—To a suspension of 11.7 g of **7a** in 550 ml of 10% sodium hydroxide solution was added portionwise 19 g of Raney Ni at 80° within 1.5 hr with stirring and the stirring was continued at 100° for 1 hr more. After cooling, the metallic precipitate was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid. The crystals separated were extracted with 500 ml of ether. The extract was washed with saturated sodium chloride solution, dried over Na_2SO_4, and evaporated to give 7 g of colorless needles which were recrystallized from water to give colorless needles, mp 89–90° (lit.[14] mp 89–90°).

N-(4-Benzyloxy-3-methoxyphenethyl)-4-hydroxy-3-methoxyphenylpropionamide (9a).—A mixture of 9.5 g of β-(4-benzyloxy-3-methoxyphenyl)ethylamine and 7.3 g of **8a** was heated at 180–190° for 1 hr in a current of nitrogen. After cooling, the reaction mixture was taken in chloroform. The extract was washed with 10% hydrochloric acid solution, 5% sodium bicarbonate solution, and water, dried over K_2CO_3, and evaporated to give 13.4 g of **9a** as a brownish solid which was recrystallized from ethanol to give colorless prisms, mp 148–149°, ν_{max} 3495 (OH), 3355 (NH), 1658 cm^{-1} (amide C=O).

Anal. Calcd for $C_{26}H_{29}O_5N$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.41; H, 6.84; N, 3.58.

N-(4-Benzyloxy-3-methoxyphenethyl)-4-ethoxycarbonyloxy-3-methoxyphenylpropionamide (10a).—To a stirred solution of 10 g of **9a** and 2.8 g of triethylamine in 100 ml of chloroform was added dropwise 2.6 g of ethyl chlorocarbonate under cooling within 30 min. The reaction mixture was allowed to stand at room temperature for 30 min. After the reaction, the mixture was washed with 5% hydrochloric acid solution and water and dried over Na_2SO_4. Evaporation of the solvent gave a pale brownish solid which was recrystallized from benzene–hexane to give 11.5 g of **10a** as colorless needles, mp 101–102°, ν_{max} 3355 (NH), 1750 (ethoxycarbonyl C=O), 1658 cm^{-1} (amide C=O).

Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.76. Found: C, 68.36; H, 6.48; N, 2.54.

7-Benzyloxy-1-(4-ethoxycarbonyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (11a).—A mixture of 11.25 g of **10a**, 25 ml of phosphoryl chloride, and 250 ml of dry benzene was heated under reflux on a water bath for 1 hr and concentrated *in vacuo* to leave a yellowish viscous syrup which was taken in 200 ml of chloroform.

The chloroform extract was made basic with 10% aqueous ammonia, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave a brownish solid which was recrystallized from benzene–hexane to give 10.2 g of **11a** as colorless prisms, mp 126–127°, ν_{max} 1754 (ethoxycarbonyl C=O), 1620 cm^{-1} (—C=N—).

Anal. Calcd for $C_{29}H_{31}NO_6$: C, 71.14; H, 6.38; N, 2.86. Found: C, 70.75; H, 6.52; N, 2.51.

7-Benzyloxy-1-(4-ethoxycarbonyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (12a).—**11a**, 10.2 g, 15 ml of methyl iodide, and 20 ml of methanol were refluxed on a water bath for 2 hr. The reaction mixture was concentrated *in vacuo* to leave a yellowish caramel which was recrystallized from methanol to give 11.4 g of **12a** as yellowish needles, mp 87–88°.

Anal. Calcd for $C_{30}H_{34}NO_6 \cdot {}^3/_2H_2O$: C, 54.87; H, 5.91; N, 2.13. Found: C, 55.32; H, 6.16; N, 2.16.

7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (13a).—To 11.4 g of **12a** in 50 ml of methanol was added portionwise 5.0 g of sodium borohydride with stirring at 0° during 1.5 hr, and the stirring was continued for 30 min at room temperature. Then, after 8 ml of water had been added to the above solution, the resultant mixture was heated under reflux on a water bath for 1 hr. After removal of the solvent, the resultant residue was treated with 100 ml of water and extracted with chloroform. The extract was washed with water, dried over K_2CO_3, and evaporated to give 7.9 g of **13a** as a brownish viscous syrup. Recrystallization of the hydrochloride from methanol–ether gave colorless prisms, mp 245–246° dec, ν_{max} 3510 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{32}NO_4Cl$: C, 68.99; H, 6.86; N, 2.99. Found: C, 69.40; H, 7.09; N, 2.85.

1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (3).—A mixture of 7.1 g of the hydrochloride of **13a**, 80 ml of ethanol, and 80 ml of concentrated hydrochloric acid was heated on a water bath for 4 hr. Evaporation of the solvent gave 4.8 g of the hydrochloride of **3** as a yellowish syrup. The free base showed ν_{max} 3510 (OH), 2780 cm^{-1} (N–CH_3); nmr signals appeared at τ 7.60 (N–CH_3, 3 H, s), 6.27, 6.29 (O–CH_3, 3 H, s), 4.12 (OH, 2 H, br).

Phenol Oxidation of 3. A.—A solution of 5.2 g of the above hydrochloride of **3** in 200 ml of water was added to a solution of 28 g of ferric chloride in 200 ml of water at room temperature during 10 min in a current of nitrogen. After the stirring had been continued for 3 hr more, no starting material was detected on the thin layer chromatogram. The reaction mixture was made basic with 28% ammonia and extracted with 1 l. of chloroform. The chloroform extract was washed with water, dried over Na_2SO_4, and evaporated to leave 4 g of a brownish gum which was chromatographed on 60 g of silica gel using chloroform containing 2% methanol as the eluent for inspection by thin layer chromatography.

Evaporation of appropriate fractions gave 3.55 g of a colorless gum which was triturated with benzene to give the dienone A as colorless crystals, mp 145–149°. Recrystallization from benzene afforded 910 mg of **5a** as colorless prisms: mp 156–158° dec; ν_{max} 3459 (OH), 1658 (C=O), 1634 and 1608 cm^{-1} (C=C); λ_{max} 234 (log ϵ 4.41), 286 mμ (log ϵ 4.24).

The nmr spectrum[15] showed expected N-methyl (τ 7.56, 3 H), aromatic O-methyl (τ 6.26, 3 H), and olefinic O-methyl resonances (τ 6.46, 3 H) as singlets. Furthermore, a singlet at τ 3.47 due to one aromatic proton of ring A and nine protons in the range of τ 6.55–8.50 as a complicated pattern were observed. In addition, the spectrum also showed a doublet

(13) We have designated as triplet and quartet coupled protons whose apparent patterns fit these designations. It should therefore be understood that these coupling patterns have not been completely analyzed and the constants presented are done to permit the reader to construct the general pattern of the curve.

(14) F. Tiemann and N. Nagai, *Ber.*, **11**, 650 (1890).

(15) In this case the ABX system of olefinic proton is shown as **5c** described before for the sake of convenience.

corresponding to one proton at τ 4.02, which was assigned to H_A of the dienone system and showed the transannular coupling (J_{AB} = 2.5 cps) with H_B. Another doublet with J_{BX} = 10 cps, at τ 3.74, equivalent to one proton, corresponds to H_X, and a quartet centered at τ 3.12, equivalent to one proton, is assigned to H_B. These chemical shifts are similar to those of orientalinone.[9] The mass spectrum showed the peaks at *m/e* 341 (M^+), 340 ($M^+ - 1$), 324 ($M^+ - 17$), 313 ($M^+ - 28$), 312 ($M^+ - 29$), and 298 ($M^+ - 43$).

Anal. Calcd for $C_{20}H_{23}NO_4 \cdot {}^1/_2C_6H_6$:[16] C, 72.60; H, 6.89; N, 3.66. Found: C, 72.89; H, 7.24; N, 3.60.

On the other hand, addition of hexane to the mother liquor, from which the dienone A was removed, afforded the dienone **5b** as colorless prisms, mp 190–193°. Recrystallization from benzene–hexane gave 769 mg of colorless prisms: mp 193–195°; ν_{max} 3495 (OH), 1658 (C=O), 1636 and 1608 cm^{-1} (C=C); λ_{max} 244 (log ϵ 4.12), 289 mμ (log ϵ 3.80).

The τ values showed the methyl resonances at τ 7.58 (N-methyl, 3 H), 6.26 (aromatic O-methyl, 3 H), and 6.40 (olefinic O-methyl, 3 H), an aromatic proton at 3.48, and the olefinic protons at 4.20 (H_A, doublet, 1 H, J_{AB} = 2.5 cps), 3.81 (H_X, doublet, 1 H, J_{BX} = 10 cps), and 3.0 (H_B, quartet, 1 H, coupled with H_A and H_X). The mass spectrum showed peaks at *m/e* 341 (M^+), 340 ($M^+ - 1$), 324 ($M^+ - 17$), 313 ($M^+ - 28$), 312 ($M^+ - 29$), and 298 ($M^+ - 43$).

Anal. Calcd for $C_{20}H_{23}NO_4 \cdot {}^1/_6C_6H_6$:[17] C, 71.30; H, 6.78; N, 3.96. Found: C, 71.29; H, 7.00; N, 3.70.

B. To a solution of 15 g of potassium ferricyanide in 250 ml of 8% aqueous ammonium acetate was added dropwise a solution of 0.71 g of **3** in 100 ml of chloroform with vigorous stirring at room temperature for 2 hr in a current of nitrogen. The stirring was continued for 3 hr more, and the chloroform layer was separated and treated as in procedure A to afford 55 mg of dienone A and 46 mg of dienone B.

4-Benzyloxy-3,5-dimethoxycinnamic Acid (7b).—A mixture of 20 g of 4-benzyloxy-3,5-dimethoxybenzaldehyde,[18] 15.6 g of malonic acid, 60 ml of pyridine, and 3.5 ml of piperidine was heated on a water bath at 100° for 2 hr and then refluxed for 15 min. After cooling, the reaction mixture was poured into 20% hydrochloric acid solution, and a white-brown syrup that separated was extracted with ether. The extract was washed with saturated sodium chloride solution and dried over Na_2SO_4. Evaporation of the solvent gave a pale brown viscous syrup: ν_{max} 1685 (carboxylic C=O), 1633 cm^{-1} (C=C); nmr τ 6.30 (2 OCH_3, 6 H, s), 5.08 (-CH_2Ph, 2 H, s), 3.75 and 2.45 (two AB-type doublets with *trans* coupling, 2 H, J = 16 cps), −0.8 (carboxylic OH, 1 H, br).

4-Hydroxy-3,5-dimethoxyphenylpropionic Acid (8b).—To a suspension of 23.8 g of **7b** in 1 l. of 10% sodium hydroxide solution was added portionwise 40 g of Raney Ni at 80° within 1 hr with stirring and the stirring was continued at 100° for 1 hr more. After cooling, the metallic precipitate was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid. The crystals separated were extracted with 3.5 l. of ether. The extract was washed with saturated sodium chloride solution and dried over Na_2SO_4. Evaporation of the solvent gave a pale yellow solid, which was recrystallized from ether–hexane to give **8b** as colorless needles: mp 102–104°; ν_{max} 3505 (OH), 1710 cm^{-1} (carboxylic C=O); nmr τ 7.29 (-CH_2-CH_2-, 4 H, A_2B_2 type, m), 6.24 (2 OCH_3, 6 H, s), 3.59 (aromatic proton, 2 H, s), 1.87 (carboxylic and phenolic OH, 2 H, br).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.61; H, 6.63.

N-(4-Benzyloxy-3-methoxyphenethyl)-4-hydroxy-3,5-dimethoxyphenylpropionamide (9b).—A mixture of 7.1 g of β-(4-benzyloxy-3-methoxyphenyl)ethylamine and 6.3 g of **8b** was heated at 190° for 2 hr in a current of nitrogen. After cooling, the reaction mixture was extracted with chloroform, and the extract was washed with 10% hydrochloric acid solution and with 5% sodium bicarbonate solution and water, dried over K_2CO_3, and evaporated to give 12.7 g of **9b** as a reddish solid which was recrystallized from benzene–hexane to give colorless needles: mp 116–117°, ν_{max} 3500 (OH), 3300 (NH), 1658 cm^{-1} (amide C=O).

Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.98; H, 6.81; N, 2.63.

N-(4-Benzyloxy-3-methoxyphenethyl)-4-ethoxycarbonyloxy-3,5-dimethoxyphenylpropionamide (10b).—To a stirred solution of 12 g of **9b** and 2.54 g of triethylamine in 100 ml of chloroform was added dropwise 2.76 g of ethyl chlorocarbonate under cooling within 10 min. The reaction mixture was allowed to stand at room temperature for 1.5 hr. After the reaction, the mixture was washed with 5% hydrochloric acid solution and water and dried over K_2CO_3. Evaporation of the solvent gave 9.7 g of **10b** as a reddish viscous syrup: ν_{max} 3300 (NH), 1760 (ethoxycarbonyl C=O), 1660 cm^{-1} (amide C=O); nmr τ 8.68 (-CH_2-CH_3, 3 H, t, J = 7 cps), 6.21 (O-CH_3, 3 H, s), 6.28 (2 OCH_3, 6 H, s), 5.77 (-CH_2-CH_3, 2 H, q, J = 7 cps), 4.95 (-CH_2Ph, 2 H, s), 4.20 (NH, 1 H, br).

7-Benzyloxy-1-(4-ethoxycarbonyloxy-3,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (11b).—A mixture of 9.5 g of **10b**, 11.0 g of phosphoryl chloride, and 100 ml of benzene was heated under reflux on a water bath for 2 hr and concentrated *in vacuo* to leave a yellowish viscous syrup which was taken in 150 ml of chloroform. The chloroform extract was made basic with 10% aqueous ammonia, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave a brownish solid which was recrystallized from methanol and then chloroform–ethanol to give 7.8 g of **11b** as colorless prisms, mp 171–173°.

Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.39; N, 2.70. Found: C, 69.84; H, 6.70; N, 2.79.

7-Benzyloxy-1-(4-ethoxycarbonyloxy-3,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (12b).—**11b**, 6.8 g, 25 ml of methyl iodide, and 50 ml of chloroform were refluxed on a water bath for 3 hr. The reaction mixture was concentrated *in vacuo* to leave a yellowish powder which was recrystallized from methanol–ether to give 7.2 g of **12b** as pale yellow needles, mp 171–172° dec.

Anal. Calcd for $C_{31}H_{36}NO_7I \cdot H_2O$: C, 54.79; H, 5.63. Found: C, 54.69; H, 5.72.

7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxy-3,4-dimethoxyphenethyl)-6-methoxy-2-methylisoquinoline (13b).—To 7.0 g of **12b** in 200 ml of methanol was added portionwise 3.5 g of sodium borohydride with stirring at 0° during 30 min, and the mixture was allowed to stir for 30 min at room temperature. Then, 20 ml of 10% potassium hydroxide solution was added to the above reaction mixture which was heated under reflux for 30 min. After removal of the solvent, a solution of the resultant residue in 100 ml of water was then acidified with diluted hydrochloric acid, basified with 10% aqueous ammonia, and extracted with chloroform. The chloroform extract was washed with water, dried over K_2CO_3, and evaporated to give 4.0 g of **13b** as a brownish viscous syrup: ν_{max} 3500 (OH), 2750 cm^{-1} (N-CH_3); nmr τ 3.58 (N-CH_3, 3 H, s), 6.20 (3 OCH_3, 9 H, s), 4.96 (-CH_2Ph, 2 H, s). Recrystallization of the hydrochloride from methanol–ether gave pale yellow needles, mp 212–213°.

Anal. Calcd for $C_{28}H_{34}NO_5Cl \cdot {}^1/_2H_2O$: C, 66.07; H, 6.93. Found: C, 65.96; H, 6.99.

1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenethyl)-6-methoxy-2-methylisoquinoline (4).—A mixture of 4.15 g of the hydrochloride of **13b**, 100 ml of ethanol, and 100 ml of concentrated hydrochloric acid was heated on a water bath for 5 hr. Evaporation of the solvent gave 2.78 g of the hydrochloride of **4** as a pale brown caramel: ν_{max} 3503 (OH), 2775 cm^{-1} (N-CH_3); nmr τ 7.58 (N-CH_3, 3 H, s), 6.20 (3 OCH_3, 9 H, s), 5.30 (2 OH, 2 H, br).

Phenol Oxidation of 4.—A suspension of 2.63 g of the above hydrochloride of **4** in 200 ml of water was added at room temperature to a solution of 10 g of ferric chloride in 300 ml of water during 10 min in a current of nitrogen. The stirring was continued for 3 hr more, and in the final stage no starting material was detected on the thin layer chromatogram. The reaction mixture was then basified with 10% aqueous ammonia and extracted with 600 ml of chloroform. The extract was washed with water and dried over Na_2SO_4 and evaporated to leave 1.5 g of a pale brown caramel which was chromatographed

(16) The presence of benzene was confirmed by the following evidence: δ_{max}^{KBr} 690 cm^{-1} (benzene); nmr τ 2.68 ($^1/_2C_6H_6$, 3 H, s); and mass spectrum *m/e* 78.

(17) The presence of benzene was confirmed by the following evidence: δ_{max}^{KBr} 690 cm^{-1} (benzene); nmr τ 2.68 ($^1/_6C_6H_6$, 1 H, s); and mass spectrum *m/e* 78.

(18) (a) T. Kametani, S. Kano, and T. Kikuchi, *Yakugaku Zasshi*, **86**, 423 (1966); (b) K. Kratze, T. Horezschi, and G. Billek, *Monatsch.*, **85**, 1154 (1954).

on 25 g of silica gel using chlofoform containing 2% methanol as the eluent for inspection by thin layer chromatography.

Evaporation of appropriate fractions gave 870 mg of yellow-orange crystals which were recrystallized from chloroform–benzene to give 671 mg of **6** as colorless needles: mp 176–178° dec; ν_{max} 3500 (OH), 1656 (C=O), 1618 cm^{-1} (C=C); λ_{max} 232 (log ϵ 4.04), 278 mμ (log ϵ 4.03); nmr τ 7.65 (N–CH_3, 3 H, s), 6.44 and 6.37 (olefinic O–CH_3, 3 H, s), 4.16 and 4.0 (olefinic protons, 2 H, a pair of d), 3.57 (aromatic proton, 1 H, s). The mass spectrum showed the molecular ion at m/e 371.

Anal. Calcd for $C_{21}H_{25}NO_5 \cdot {}^1/_2C_6H_6$:[19] C, 70.21; H, 6.87. Found: C, 69.90; H, 7.26.

(19) The presence of benzene was confirmed by the peak at τ 2.68 ($^1/_2$ C_6H_6, 3 H, s) in the nmr spectrum and the ion at m/e 78 in the mass spectrum.

Registry No.—**3** hydrochloride, 14897-72-4; **4** hydrochloride, 14897-73-5; **6**, 14897-76-8; **7b**, 14897-77-9; **8a**, 1135-23-5; **8b**, 14897-78-0; **9a**, 14897-79-1; **9b**, 14897-80-4; **10a**, 15038-85-4; **10b**, 15038-86-5; **11a**, 14897-81-5; **11b**, 14897-82-6; **12a**, 14924-44-8; **12b**, 15038-87-6; **13a** hydrochloride, 14924-45-9; **13b** hydrochloride, 14924-46-0.

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The Preparation and Study of Some 1-Norbornenyl and Norbornenyl-1-carbinyl Derivatives[1,2]

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As part of a general program to investigate the inductive effect of the vinyl group apart from its resonance effect, the synthesis and properties of a fair number of 1-norbornenyl and norbornenyl-1-carbinyl derivatives are described. It is felt that these compounds, by their structure, have the resonance effect of the double bond effectively cancelled and by their reactivity exhibit the true inductive effect of the linkage. The syntheses of these substances proceeded principally from norbornene-1-carboxylic acid (**5**). The preparation of **5** is described in detail from *exo*-2-bromonorbornane-1-carboxylic acid (**6**). As the process can lead to norbornene-2-carboxylic acid (**7**) instead, conditions leading to either acid are delineated. Among the other compounds prepared and characterized were the amine salt (**12**), the acetate (**23**), the chloride (**27**), the phenyl ketone (**34**), the aldehyde (**35**), the carbinol (**37**), and the acetic acid (**40**). Several mechanistic studies were performed. First, the bridgehead chloride **27** exhibited no displacement reactivity even though it is formally an allylic chloride. Second, the hydrolysis of norbornenyl-1-carbinyl tosylate (**38**) in aqueous acetone was about 16 times slower at 25° than the saturated analog **42**, a direct experimental confirmation of the heretofore calculated inductive effect of the homoallylic double bond. When *sym*-collidine was present in the solvent, the composition of the hydrolysate was unrearranged **37** (42%), and a new alcohol, bicyclo[3.2.1]oct-6-en-1-ol (**44**, 58%), was isolable in high yield. Only the latter alcohol was obtained in the absence of collidine because **37** underwent decomposition. Lastly, generation and decomposition of the norbornenyl-1-carbinyl diazonium ion from the tosylhydrazone **36** *via* an alkaline treatment of it in N-methylpyrrolidone again gave a product composed of **44** (47%), but, in addition, bicyclo[2.2.2]oct-2-en-1-ol (**43**, 44%) was also formed. This reaction is yet another example of alcohol formation in tosylhydrazone decompositions. The relative tendencies of the methano and ethano bridges to migrate in these reactions is discussed, with emphasis on the strain relieved and the delocalization possible in the transitional species. No evidence for etheno bridge migration was found in either reaction.

Considerable activity has centered in norbornene chemistry for some time.[3] The fixed geometry[4] of the ring has allowed the study of mechanistic items of interest such as π participation in the solvolysis of the *anti*-**7** and *exo*-**5** brosylates[5] and chlorides,[6] as well as in several norbornenylcarbinyl substrates.[7] Oddly enough, with all the work done in the area, only a few examples of 1-norbornenyl or norbornenyl-1-carbinyl derivatives exist in the literature. Most significantly, Bly and co-workers[8] have independently also investigated the norbornenyl-1-carbinyl system in solvolysis and deamination reactions. In addition, 1-methylnorbornene (**1**) is known,[9a] but only recently has some of its chemistry been reported.[9b] And lastly, 1-norbornenol (**2**) was prepared some years ago[10] and

(1) Taken from the dissertations of C. A. S. (June 1964) and W. J. W. (June 1967).

(2) (a) *Cf.* J. W. Wilt and C. A. Schneider, *Chem. Ind.* (London), 951 (1963), for a preliminary account of some of this material. (b) Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, Abstracts, Paper 79S.

(3) Much carbonium ion chemistry of norbornene may be found in J. A. Berson, "Molecular Rearrangements," Part I, P. deMayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 111 ff.

(4) The geometry is apparently not known definitely. The data applied to norbornene have been determined on other, more or less related compounds. *Cf.* K. Tori, R. Muneyuki, and H. Tanida, *Can. J. Chem.*, **41**, 3142 (1963).

(5) S. Winstein, H. M. Walborsky, and K. C. Schreiber, *J. Am. Chem. Soc.*, **72**, 5795 (1950); S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955); see also, H. Tanida, T. Tsuji, and T. Irie, *J. Org. Chem.*, **31**, 3941 (1966).

(6) J. D. Roberts and W. Bennett, *J. Am. Chem. Soc.*, **76**, 4623 (1954); W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

(7) For the *syn*- and *anti*-7-carbinyl brosylates, see R. K. Bly and R. S. Bly, *J. Org. Chem.*, **31**, 1577 (1966); for the *exo*- and *endo*-2-carbinyl brosylates and carbinylamines, see R. R. Sauers, R. A. Parent, and H. M. How, *Tetrahedron*, 2907 (1965).

(8) (a) R. S. Bly and Q. E. Cooke, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, Abstracts, Paper 80S; (b) R. S. Bly and E. K. Quinn, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, Paper 91O. We appreciate the details of these comprehensive studies from Professor Bly and the several discussions with him throughout the course of this study.

(9) (a) M. Blanchard, *Bull. Soc. Chim. France*, 1264 (1961). It should be mentioned that the isomeric 2-methylnorbornene is misnamed the 1 isomer in various parts of a recent paper by W. F. Erman, *J. Org. Chem.*, **32**, 765 (1967). (b) Oxymercuration–demercuration: H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Am. Chem. Soc.*, **89**, 1525 (1967). Hydrochlorination; H. C. Brown and K.-T. Liu, *ibid.*, **89**, 3898 (1967). Protonic acid additions: P. von R. Schleyer, *ibid.*, **89**, 3901 (1967).

(10) C. J. Norton, Dissertation, Harvard University, 1955.