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Studies on the Syntheses of Analgesics. XLVI.[1] An Abnormal Hofmann Degradation of N-(4-Hydroxybenzyl)-3-benzazocinium Halides (Studies on the Syntheses of Heterocyclic Compounds. DCLXVIII[2])

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N-(4-Hydroxybenzyl)-3-benzazocine (II) and its similar compounds (I, III, and IV) were prepared by two routes, and selective *N*-debenzylation of the quaternary salts (II and III) of the benzazocines (VIII and IX) was achieved under a Hofmann degradation condition to give pentazocine (V). A normal Hofmann degradation is also described.

Pentazocine, 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine (V),[4] has been used clinically as a non-narcotic analgesic in many countries and attracted the attention of the world. There are many reports on the synthesis of pentazocine,[5] and we also synthesized this compound (V) by debenzylation of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-benzazocinium halide (I) with thiophenoxide or by hydrogenolysis on palladium-charcoal.[6-8]

Recently, one of the present authors reported the formation of the benzyl ether (XII) by an abnormal Hofmann degradation of the phenolic tetrahydroprotoberberine methiodide (XI) with methanolic potassium hydroxide.[9,10] This reaction was applied to 1,2,3,4,5,6-hexahydro-8-hydroxy-3-(4-hydroxybenzyl)-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (II) and similar quaternary salts (III and IV) in order to obtain pentazocine (V) and benzazocine (X),[11] and we wish to report the successful results. In this paper, we also report the normal Hofmann degradation of this salt.[1]

The starting quaternary salts (I—IV) are synthesized as follows; cyanoacetic acid (XIV), prepared from ethyl cyanoacetate (XIII) by treatment with 0.5—1N hydrochloric acid or 26% sodium hydroxide, was condensed with ethyl methyl ketone, and the product was decarboxylated to give a mixture of β,γ-unsaturated nitrile (XV) and α,β-unsaturated one (XVI). The separation of this mixture could be done by washing with aqueous ammonium sulfite

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[1] Part XLV: T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *J. Heterocyclic Chem.*, "in press."
[2] Part DCLXVII: T. Kametani, M· Takeshita, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, "in press."
[3] Location: *a) Aobayama, Sendai; b) Sakurashinmachi-2-chome, Setagaya-ku, Tokyo.*
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[6] T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, and K. Wakisaka, *J. Heterocyclic Chem.*, **6**, 430 (1969).
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[10] T. Kametani, M. Takemura, K. Takahashi, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles*, 2, 653 (1974).
[11] E.L. May and J.H. Ager, *J. Org. Chem.*, 24, 1432 (1959).

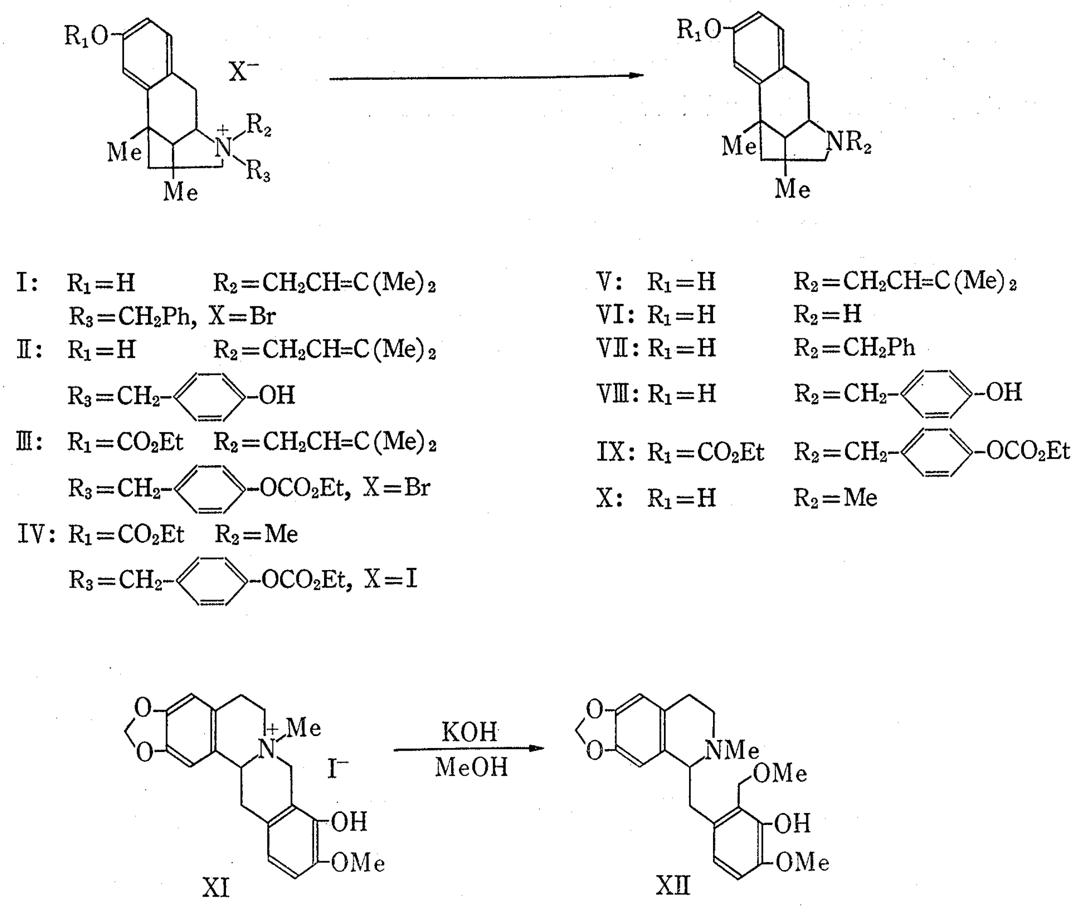

Chart 1

solution which could dissolve the α,β-unsaturated nitrile (XVI). High pressure reduction of pure nitrile (XV) with hydrogen on Raney cobalt in methanol or benzene gave 3-methyl-3-pentenylamine (XVII) together with saturated amine (XVIII). The same reduction of a mixture of both nitriles afforded a mixture of the amines (XVII and XVIII).[12,13]

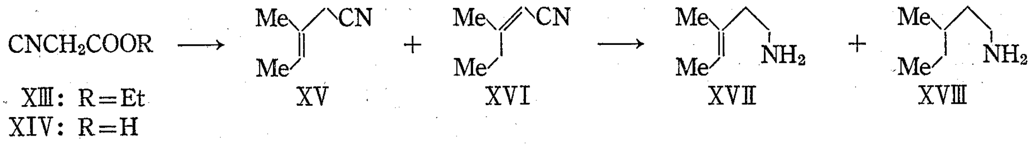

Chart 2

Schotten-Baumann reaction of the amines with 4-methoxyphenylacetyl chloride, followed by Bischler-Napieralski type cyclization of the resulting amide (XIX) with phosphoryl chloride in benzene gave an unstable dihydropyridine derivative (XX), which was without purification reduced with sodium borohydride to afford the tetrahydropyridine (XXI), characterized as an oxalate, mp 162—163°. Treatment of XXI with benzyl bromides in the presence of potassium hydrogen carbonate in ethanol or *N*,*N*-dimethylformamide furnished *N*-benzyl-1,2,5,6-tetrahydropyridines (XXII and XXIII), which were obtained alternatively as follows. The amines (XVII and XVIII) were converted into the corresponding *N*-benzylamines (XXIV and XXV), which on Schotten-Baumann reaction as above gave the

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[12] T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, K. Wakisaka, F. Satoh, T. Aoyama, and H. Ishimaru, *J. Heterocyclic Chem.*, **8**, 769 (1971).

[13] Bayer, Japan Patent 43-11895 (1968).

amides (XXVI and XXVII). Cyclization of these amides with phosphoryl chloride, followed by sodium borohydride reduction of the resulting 2-benzylidene-1,2,5,6-tetrahydropyridine hydrochlorides (XXVIII and XXIX) in the presence of sodium hydroxide afforded the *N*-benzyl-1,2,5,6-tetrahydropyridines (XXII and XXIII).

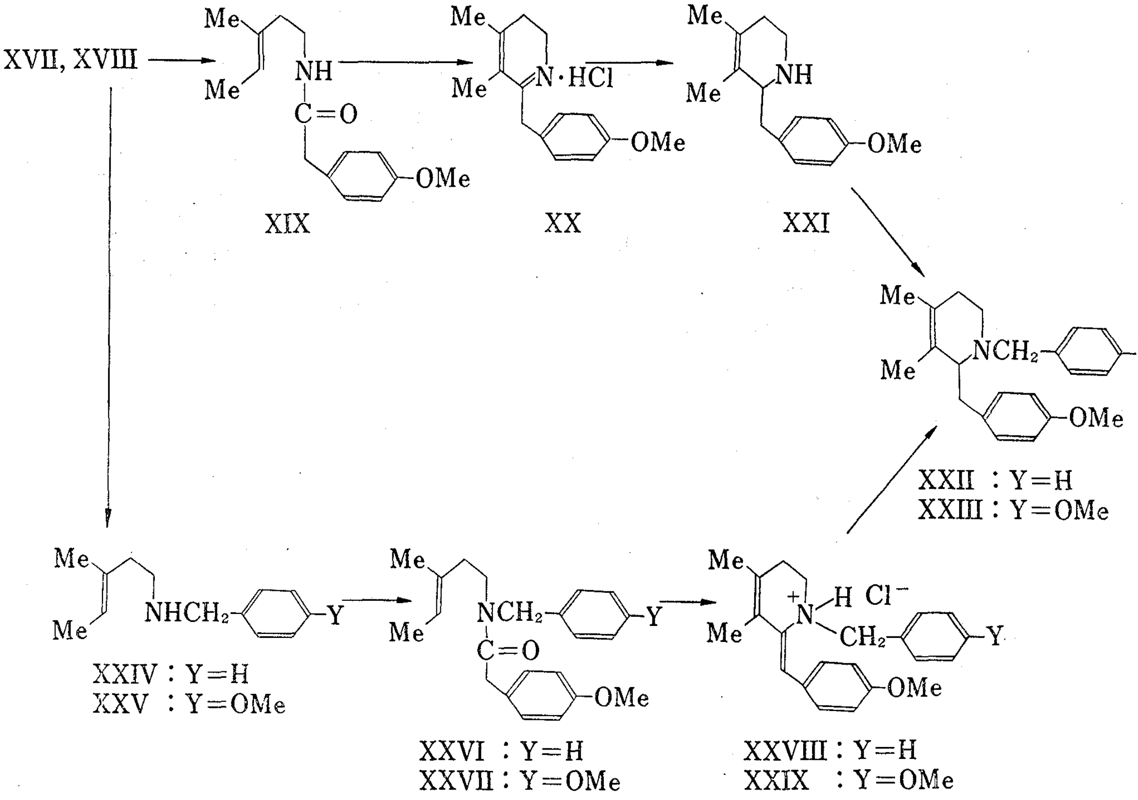

Chart 3

Pictet-Spengler type reaction of the amine (XVII) with methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate at pH 3 gave the piperidinol (XXX)[12,13] but the reaction under pH 1 afforded the tetrahydropyridine (XXI) in addition to the piperidinol (XXX). *N*-Benzylation of the piperidinol (XXX) yielded the tertiary amines (XXXI and XXXII), which were also synthesized by Pictet-Spengler type cyclization of the secondary amines (XXIV and XXV).

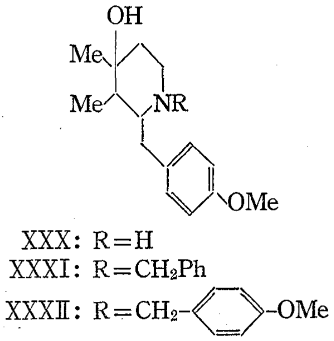

Chart 4

Grewe cyclization of the tetrahydropyridines (XXII and XXIII) or the piperidinols (XXXI and XXXII) with 47% hydrobromic acid gave the corresponding *N*-benzylated 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocines (VII and VIII). *O,O*-Diethoxycarbonyl compound (IX) could be obtained by a reaction of VIII with ethyl chlorocarbonate in the presence of 1N sodium hydroxide solution in chloroform. Treatment of these *N*-benzylated benzazocines (VII—IX) with 1-bromo-3-methyl-2-butene in acetone, ethyl methyl ketone, or acetonitrile and ethyl acetate afforded the corresponding quaternary ammonium salts (I—III), and methylation of IX with methyl iodide gave IV.

Heating the quaternary ammonium salt (IV) with 28% methanolic sodium methoxide solution gave *N*-methylbenzazocine (X) in 47% yield. Similarly the quaternary salts (II and

III) were treated with sodium methoxide at 70—80° to afford pentazocine (V).[14] In these reactions 4-methoxymethylphenol (XXXV) was isolated as a non-basic material. This fact showed that the quinonoid intermediate (XXXIV), which would be derived from XXXIII, was concerned in this reaction. On the other hand, the ammonium salt (I), which has no phenolic hydroxyl group in *N*-benzyl residue, did not give pentazocine (V), but the olefin (XXXVI) [δ (CDCl$_3$) ppm: 5.67 (1H, doublet, J=9.5 Hz) and 6.26 (1H, double doublet, J=9.5 and 5.0 Hz)] by normal Hofmann degradation. The product was hydrogenated in the presence of 30% palladium on carbon to give the tetralin derivative (XXXVII), which showed no ethyl group in nuclear magnetic resonance (NMR) spectrum. Above phenomenon suggests that the phenolic group in *N*-benzyl residue plays an important role in *N*-debenzylation and supports the mechanism proposed in Chart 5.

Thus, we have developed a new synthetic route for pentazocine by an abnormal Hofmann degradation.

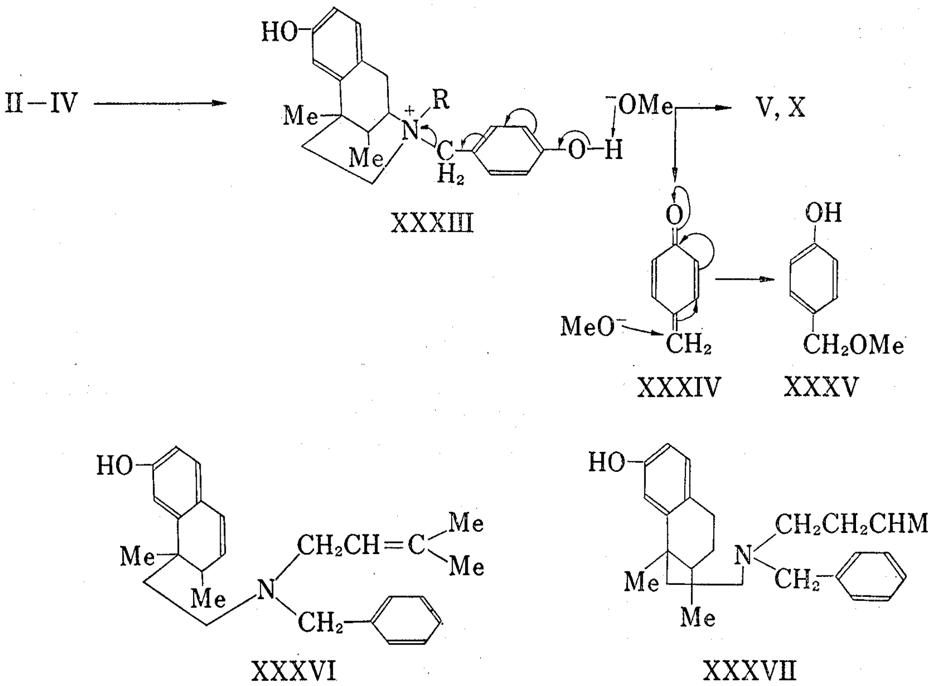

Chart 5

Experimental[15]

3-Methyl-3-pentenenitrile (XV) and 3-Methyl-2-pentenenitrile (XVI)——a) A mixture of 150 g of ethyl cyanoacetate (XIII) and 500 ml of 1 N HCl was heated on a water bath for 1.5 hr, and then water and HCl were removed by distillation *in vacuo* to give (XIV), which was mixed with 113.7 ml of ethyl methyl ketone, 8 g of ammonium acetate, and 200 ml of benzene. The resulting mixture was refluxed for 16 hr using a Dean and Stark apparatus in order to remove 30 ml of water. After decarboxylation by further heating, distillation gave a mixture of 90 g (71.4%) of XV and XVI as a pale yellow oil, bp 156—162°.

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14) This analysis was carried out by a Hitachi 063 equipped with a hydrogen flame ionisation detector and a "silanized" spiral glass column (1 m×3 mm i.d.). The column was packed with 5% SE-3 on chromosorb W (60—80 mesh). Column temperature was 230°. Both detector and flash heater were maintained at 265°. Nitrogen was used as carrier gas as a flow-rate of 40 ml/min and tetracosane was used as an internal standard.

15) All melting points and boiling points are uncorrected. NMR spectra were taken with JNM-MH-60 and JNM-PMX-60 spectrometers (tetramethylsilane as internal reference), and infrared (IR) spectra with a Hitachi-215 recording spectrometer. Gas chromatogram (GC) was measured with a Hitachi-063 type gas chromatographical equipment.

b) To 100 g of ethyl cyanoacetate (XIII) was added slowly 135.4 g of 26% NaOH and the resulting mixture was heated at 70—80° with stirring for 10 min. After cooling, the reaction mixture was made pH 0 by 35% HCl, and this was mixed with 100 ml of benzene. This solution was heated under reflux using a Dean and Stark apparatus. After a calculated amount of water had separated, the reaction mixture was added to 100 ml of ethyl methyl ketone and 4 g of ammonium acetate and treated as above to give a mixture of 65 g (72%) of XV and XVI as a pale yellow oil.

c) A mixture of the nitriles (XV and XVI), 34 g of $(NH_4)_2SO_3 \cdot H_2O$ and 250 ml of water was stirred for 15 hr at 100°. After cooling the organic layer was separated and evaporated to give 20 g of 3-methyl-3-pentenenitrile (XV), NMR (CCl_4) ppm: 1.40—1.99 (3H, multiplet, 4–$C\underline{H}_3$), 1.70 (3H, singlet, 3–$C\underline{H}_3$), 2.98 (2H, broad singlet, $C\underline{H}_2CN$), and 5.23—5.83 (1H, multiplet, –C=C$\underline{H}$–).

Catalytic Hydrogenation of XV——Ten grams of the nitrile (XV) in 20 ml of benzene was hydrogenated at 120—140° and hydrogen pressure of 95 kg/cm^2 in the presence of 1 ml of W-7 Raney cobalt in an autoclave. After absorption of a calculated amount of hydrogen, an inorganic material was filtered off and the filtrate was distilled to give 5.7 g (55%) of the amines (XVII and XVIII) as a pale yellow oil, bp 128—136°, in the ratio of 3: 1, respectively, by NMR spectral analysis.

N-(4-Methoxybenzyl)-3-methyl-3-pentenylamine (XXV)——A mixture of 10 g of the amines (XVII and XVIII), 13.6 g of anisaldehyde and 100 ml of benzene was refluxed for 1 hr and then the solvent was distilled off. The resulting residue was dissolved in 100 ml of methanol, to a cooled solution of which 5.0 g of $NaBH_4$ was added in portions with stirring. After refluxing for 30 min, the methanol was removed by distillation, and the residue was dissolved in chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to leave a brown oil, which was distilled to give 19.2 g (87.4%) of the secondary amine (XXV) as a pale yellow oil, bp 133—136°/3 mmHg, which was used immediately in the synthesis of the amide (XXVII) without separation of XXV.

N-(3-Methyl-3-pentenyl)-4-methoxyphenylacetamide (XIX)——a) A solution of 12.5 g of nitriles (XV and XVI) in 30 ml of benzene was hydrogenated in the presence of 4 ml of W-7 Raney cobalt at 120—140° and hydrogen pressure of 91 kg/cm^2 until the calculated amount of hydrogen had been absorbed. After separation of the catalyst, the filtrate was diluted with benzene to afford 100 ml of total volume and then mixed with 200 ml of 1N NaOH solution. To the above mixture was added dropwise a solution of 4-methoxyphenylacetyl chloride (prepared from 24 g of 4-methoxyphenylacetic acid and 23.5 g of $SOCl_2$) in 80 ml of benzene with stirring and cooling during 1 hr. After stirring for further 2.5 hr, the organic layer was separated and the aqueous layer was extracted with benzene. The organic layers were combined and washed with 5% HCl and water, dried over $MgSO_4$, and evaporated to give 31.7 g (97%) of the amide (XIX) as a powder, IR ν_{max}^{KBr} cm^{-1}: 3260 and 1630, which was used in the following reaction without further purification.

b) A mixture of 20 g of the amines (XVII and XVIII) and 30 g of 4-methoxyphenylacetic acid was heated at 160—170° for 18 hr in a current of nitrogen and extracted with benzene. The benzene extract was washed with 10% NaOH, water, 10% HCl, and water, dried over $MgSO_4$, and evaporated to give 27 g (61%) of the amide (XIX), which was identical with the above sample.

5,6-Dihydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (XX)——A mixture of 10.7 g of the amide (XIX), 10 g of $POCl_3$ and 50 ml of benzene was refluxed for 2 hr, and the excess of reagent and solvent were then distilled off *in vacuo*. The residue was dissolved in water, washed with benzene and extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and evaporated to leave 6.5 g of the 5,6-dihydropyridine (XX) hydrochloride, which was unstable and therefore used immediately in the next reaction, NMR (CD_3OD) ppm: 1.94 (3H, singlet, 3–$C\underline{H}_3$), 2.12 (3H, singlet, 4–$C\underline{H}_3$), 2.66 (2H, triplet, $J=8$ Hz, $C\underline{H}_2C=C$), 3.80 (2H, triplet, $J=8$ Hz, $\rangle NC\underline{H}_2$), 3.83 (3H, singlet, $OC\underline{H}_3$), 4.16 (2H, singlet, $C\underline{H}_2Ar$), 6.98 (2H, doublet, $J=9$ Hz, $Ar\underline{H}$), and 7.03 (2H, doublet, $J=9$ Hz, $Ar\underline{H}$).

1,2,5,6-Tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (XXI)——To a stirred solution of 19 g of the dihydropyridine (XX) hydrochloride in 100 ml of methanol was added slowly 7 g of $NaBH_4$ under cooling during 40 min and the mixture was allowed to stand overnight at room temperature. After evaporation of methanol the residue was dissolved in chloroform, and the extract was washed with water, dried over $MgSO_4$, and evaporated to give 9.03 g (54.0%) of the tetrahydropyridine (XXI) as a syrup, whose oxalate formed needles, mp 162—163° (from 2-propanol), NMR ($CDCl_3$) (free base) ppm: 1.63 (6H, singlet, 3–$C\underline{H}_3$ and 4–$C\underline{H}_3$), (3H, singlet, $OC\underline{H}_3$), 6.70 (2H, doublet, $J=9$ Hz, $Ar\underline{H}$), and 7.02 (2H, doublet, $J=9$ Hz, $Ar\underline{H}$). *Anal.* Calcd. for $C_{15}H_{21}ON \cdot C_2H_2O_4$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.41; H, 7.08; N, 4.30.

Pictet-Spengler Type Cyclization of XVII at pH 1——A suspension of 29.5 g of the amines (XVII and XVIII) in 600 ml of water was adjusted to pH 1 with 35% HCl, to a solution of which was added 15 g of methyl 3-(4-methoxyphenyl)-2,3-expoxypropionate. This mixture was heated at 80—88° for 24 hr with stirring, and then 20 g of methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate was added to the above reaction mixture, which was heated at 80—88° for further 72 hr with stirring. The separated material was removed by decantation and the aqueous layer was made basic with 20% NaOH and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 4.77 g (13%) of the piperidinol (XXXII) as needles, mp 140—141° (lit.,[13] mp 140—141°) (from ether). The mother liquor from (XXXII) was evaporated to leave a residue, which was chromatographed on 250 g of silica gel. Elution with benzene gave 8.18 g

(24%) of the tetrahydropyridine (XXI), whose spectral data were identical with those of the sample described above.

N-Benzyl-N-(3-methyl-3-pentenyl)-4-methoxyphenylacetamide (XXVI)——A solution of 4-methoxyphenylacetyl chloride (prepared from 8.7 g of 4-methoxyphenylacetic acid and 9.7 g of $SOCl_2$) in 30 ml of dry benzene was added dropwise to a stirred mixture of 10 g of the secondary amine (XXIV), 60 ml of benzene and 80 ml of 1 N NaOH under ice-cooling during 1.5 hr. Stirring was continued for 2 hr at room temperature. The benzene layer was separated, washed with water, 5% HCl, and water, dried over Na_2SO_4, and evaporated to leave 16.5 g (92.8%) of the amide (XXVI) as a pale yellow viscous syrup, IR $\nu_{\text{max}}^{\text{liquid}}$ cm^{-1}: 1630; NMR (CCl_4) ppm: 1.58 (6H, singlet, 3–C$\underline{\text{H}}_3$ and 4–C$\underline{\text{H}}_3$), 3.62 (2H, broad singlet, COC$\underline{\text{H}}_2$), 3.75 (3H, singlet, OC$\underline{\text{H}}_3$), 4.00 (2H, broad singlet, NC$\underline{\text{H}}_2$), 6.71 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), 7.23 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), and 7.28 (5H, singlet, Ar–$\underline{\text{H}}$).

N-(4-Methoxybenzyl)-N-(3-methyl-3-pentenyl)-4-methoxyphenylacetamide (XXVII)——Treatment of the secondary amine (XXV) with 4-methoxyphenylacetyl chloride as above gave the amide (XXVII) in 79.9% yield, IR $\nu_{\text{max}}^{\text{liquid}}$ cm^{-1}: 1630; NMR (CCl_4) ppm: 1.52 (6H, broad singlet, 3–C$\underline{\text{H}}_3$ and 4–C$\underline{\text{H}}_3$), 3.40 (2H, singlet, COC$\underline{\text{H}}_2$), 3.55 (6H, singlet, 2×OC$\underline{\text{H}}_3$), and 3.85 (2H, singlet, NC$\underline{\text{H}}_2$Ar).

1-Benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (XXII)——a) A mixture of 2.3 g of the tetrahydropyridine (XXI), 1.4 g of benzyl bromide, 2.0 g of $NaHCO_3$ and 30 ml of ethanol was refluxed for 2 hr and then ethanol was distilled off. The residue was dissolved in ether, whose solution was washed with water and then extracted with 5% HCl. The acidic extract was basified with 10% NaOH and again extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$ and evaporated to leave 2.8 g (87.5%) of XXII as a yellow syrup, whose oxalate formed prisms, mp 159—160° (lit.,⁶⁾ mp 158—160°) (from ethanol-2-propanol), NMR ($CDCl_3$) (free base) ppm: 1.59 (6H, singlet, 3–C$\underline{\text{H}}_3$ and 4–C$\underline{\text{H}}_3$), 3.50 (2H, singlet, NC$\underline{\text{H}}_2$Ar), 3.65 (3H, singlet, OC$\underline{\text{H}}_3$), 6.95 (5H, singlet, Ar$\underline{\text{H}}$), 6.63 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), and 6.95 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$). *Anal.* Calcd. for $C_{22}H_{27}ON \cdot C_2H_2O_4$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.57; H, 7.44; N, 3.31.

b) A mixture of 3.0 g of the amide (XXVI), 3.5 g of $POCl_3$ and 20 ml of chloroform was allowed to stand for 72 hr and the excess of reagent and solvent were distilled off *in vacuo*. The residue was dissolved in 6 ml of methanol, to a solution of which was added a solution of 0.6 g of NaOH in 20 ml of methanol. To the above stirred solution was added in small portions 0.3 g of $NaBH_4$ under ice-cooling and stirring was continued for 30 min at 0°. The resulting mixture was then allowed to stand at room temperature for 1 hr. After evaporation of methanol the residue was taken up in ether, which was extracted with 10% HCl. The acidic aqueous layer was basified with conc. NH_4OH and again extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$, and evaporated to give 0.28 g (20%) of XXII, whose oxalate was identical with the sample prepared by method (a).

1,2,5,6-Tetrahydro-1,2-di(4-methoxybenzyl)-3,4-dimethylpyridine (XXIII)——This compound was synthesized by the method (a) in 57% yield as needles, mp 70—72° (from pet. ether), NMR ($CDCl_3$) ppm: 1.52 (6H, singlet, 3–C$\underline{\text{H}}_3$ and 4–C$\underline{\text{H}}_3$), 2.20 (2H, singlet, NC$\underline{\text{H}}_2$), 3.63 (3H, singlet, OC$\underline{\text{H}}_3$), 3.68 (3H, singlet, OC$\underline{\text{H}}_3$), 6.58 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), 6.88 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), 6.66 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), and 6.98 (2H, doublet, J=9 Hz, Ar$\underline{\text{H}}$). *Anal.* Calcd. for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.97. Found: C, 78.48; H, 7.98; N, 4.05.

4-Hydroxy-1,2-di(4-methoxybenzyl)-3,4-dimethylpiperidine (XXXII)——a) A mixture of 2.49 g of XXX, 2.01 g of 4-methoxybenzyl bromide, 2.0 g of K_2CO_3 and 30 ml of dimethylformamide was refluxed for 6 hr and poured into water. The separated oil was taken in ether, which was extracted with 10% HCl. The aqueous layer was made basic with conc. NH_4OH and extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to afford 3.50 g (94.9%) of XXXII as a syrup, whose hydrochloride gave granules, mp 178—179° (from 2-propanol), NMR ($CDCl_3$) (free base) ppm: 0.97 (3H, doublet, J=7.5 Hz, 3–C$\underline{\text{H}}_3$), 1.15 (3H, singlet, 4–C$\underline{\text{H}}_3$), 3.92 (6H, singlet, 2×OC$\underline{\text{H}}_3$), 3.48 and 4.12 (each 1H, each doublet, J=13.5 Hz, NC$\underline{\text{H}}_2$Ar), 7.01 (4H, doublet, J=9 Hz, Ar$\underline{\text{H}}$), and 7.48 (4H, doublet, J=9 Hz, ArH).

b) A suspension of 2.2 g of the secondary amine (XXV) in 50 ml of water was adjusted to pH 3 with 1 N HCl, to a solution of which was added 2.1 g of methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate. The resulting mixture was heated at 80—90° for 84 hr. The reaction mixture was washed with ether, basified with 5% NaOH and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 2.14 g (58%) of XXXII, which was identical with the authentic sample prepared by method (a).

1,2,3,4,5,6-Hexahydro-8-hydroxy-(4-hydroxybenzyl)-6,11-dimethyl-2,6-methano-3-benzazocine (VIII)——A solution of 22 g of the piperidinol (XXXII) in 220 g of 47% HBr was heated at 125—130° for 3 hr. After cooling, the reaction mixture was made basic with conc. NH_4OH and then extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated to leave a yellow gum, whose hydrobromide (17.7 g, 73.3%) formed needles, mp 240—243° (decomp.) (from 2-propanol), NMR (CD_3SOCD_3) (free base) ppm: 0.94 (3H, doublet, J=7 Hz, 11–C$\underline{\text{H}}_3$), 3.50 (2H, singlet, NC$\underline{\text{H}}_2$Ar), and 6.30—7.32 (3H, multiplet, Ar$\underline{\text{H}}$). *Anal.* Calcd. for $C_{21}H_{25}O_2N \cdot HBr$: C, 62.38; H, 6.48; N, 3.46. Found: C, 62.15; H, 6.51; N, 3.52.

8-Ethoxycarbonyloxy-3-(4-ethoxycarbonyloxybenzyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (IX)——To a mixture of 0.7 g of the benzazocine (VIII), 10 ml of 1 N NaOH and 5 ml of chloroform was added dropwise a solution of 0.5 g of ethyl chloroformate in 5 ml of chloroform within 30 min with stirring under ice-cooling. The mixture was stirred at 0° for 30 min and at room temperature for 1 hr. The organic layer was separated, washed with water, dried over $\mathrm{MgSO_4}$, and evaporated to give 0.95 g (93.9%) of IX as an oil, whose hydrobromide formed crystals, mp 203—204° (from 2-propanol), NMR ($\mathrm{CDCl_3}$) (free base) ppm: 0.82 (3H, doublet, $J=7$ Hz, 11–$\mathrm{C\underline{H}_3}$), 1.32 (3H, singlet, 6–$\mathrm{C\underline{H}_3}$), 1.36 (3H, triplet, $J=7.5$ Hz, $\mathrm{CO_2CH_2}$-$\mathrm{C\underline{H}_3}$), 3.62 (2H, broad singlet, $\mathrm{NC\underline{H}_2Ar}$), 4.26 (2H, quartet, $J=7.5$ Hz, $\mathrm{CO_2C\underline{H}_2CH_3}$), and 7.0—7.45 (multiplet, $\mathrm{Ar\underline{H}}$). *Anal.* Calcd. for $\mathrm{C_{27}H_{33}O_6N\cdot HBr\cdot 1/2H_2O}$: C, 58.17; H, 6.33; N, 2.51. Found: C, 58.32; H, 6.11; N, 2.62.

1, 2, 3, 4, 5, 6-Hexahydro-8-hydroxy-3-(4-hydroxybenzyl)-6, 11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium Bromide (II)——To a solution of 310 mg of the benzazocine (VIII) in 1.5 ml of acetonitrile and 0.5 ml of ethyl acetate was added 300 mg of 1-bromo-3-methyl-2-butene and the mixture was stirred for 20 hr at room temperature. The separated material was filtered off and the solvent was distilled off *in vacuo* to give 235 mg (51.9%) of II as a pale yellow powder, mp 134—138° (decomp.) (from acetone–ether), NMR ($\mathrm{CDCl_3}$) ppm: 0.99 (3H, doublet, $J=6.5$ Hz, 11–$\mathrm{C\underline{H}_3}$), 1.47 (3H, singlet, 6–$\mathrm{C\underline{H}_3}$), 1.80 (3H, singlet, $\rangle$C=C–$\mathrm{C\underline{H}_3}$), 1.89 (3H, singlet, $\rangle$C=C–$\mathrm{C\underline{H}_3}$), 4.87 (2H, singlet, $\mathrm{NC\underline{H}_2Ar}$), and 6.57—7.27 (3H, multiplet, $\mathrm{Ar\underline{H}}$). *Anal.* Calcd. for $\mathrm{C_{26}H_{34}O_2NBr\cdot 1.5H_2O}$: C, 62.51; H, 7.47; N, 2.80. Found: C, 62.37; H, 7.33; N, 3.07.

8-Ethoxycarbonyloxy-3-(4-ethoxycarbonyloxybenzyl)-1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium Bromide (III)——This compound (III) was prepared from IX by the same method as above in 38.9% yield as a pale yellow powder, mp 124—127° (decomp.) (from ether), NMR ($\mathrm{CDCl_3}$) ppm: 0.89 (3H, doublet, $J=6$ Hz, 11–$\mathrm{CH_3}$) 1.39 (3H, singlet, 6–$\mathrm{C\underline{H}_3}$), 1.40 (6H, triplet, $J=6.5$ Hz, $2\times\mathrm{CO_2CH_2C\underline{H}_3}$), 1.65 (3H, singlet, $\rangle$C=C–$\mathrm{C\underline{H}_3}$), 1.73 (3H, singlet, $\rangle$C=C–$\mathrm{C\underline{H}_3}$), 4.30 (4H, quartet, $J=6.5$ Hz, $2\times\mathrm{CO_2C\underline{H}_2CH_3}$), 6.68—8.03 (7H, multiplet, $\mathrm{Ar\underline{H}}$). *Anal.* Calcd. for $\mathrm{C_{32}H_{42}O_6NBr\cdot 1/2H_2O}$: C, 61.43; H, 6.92; N, 2.24. Found: C, 61.22; H, 6.97; N, 2.27.

8-Ethoxycarbonyloxy-3-(4-ethoxycarbonyloxybenzyl)-1, 2, 3, 4, 5, 6-hexahydro-3, 6, 11-trimethyl-2,6-methano-3-benzazocinium Iodide (IV)——A mixture of 115 mg of the benzazocine (X), 3 ml of methyl iodide and 3 ml of methanol was refluxed for 4.5 hr and then the excess of the reagent and methanol were distilled off. The residue was triturated with ether to give a yellow powder, which was recrystallized from 2-propanol-ether to afford 147 mg (94.2%) of IV as yellow crystals, mp 150—152°, NMR ($\mathrm{CDCl_3}$) ppm: 0.91 (3H, doublet, $J=8$ Hz, 11–$\mathrm{C\underline{H}_3}$), 1.38 (6H, triplet, $J=7.2$ Hz, $2\times\mathrm{OCH_2C\underline{H}_3}$), 1.50 (3H, singlet, 6–$\mathrm{C\underline{H}_3}$), 3.35 (3H, singlet, $\mathrm{NC\underline{H}_3}$), 4.32 (4H, quartet, $J=7.2$ Hz, $2\times\mathrm{OC\underline{H}_2CH_3}$), 5.26 (2H, broad singlet, $\mathrm{NC\underline{H}_2Ar}$), and 7.01—7.82 (7H, multiplet, $\mathrm{Ar\underline{H}}$). *Anal.* Calcd. for $\mathrm{C_{28}H_{36}O_6NI}$: C, 55.17; H, 5.95; N, 2.30. Found: C, 54.89; H, 6.07; N, 2.18.

Alkali Treatment of IV——A mixture of 75 mg of IV and 1.5 ml of 28% methanolic sodium methoxide was refluxed for 1 hr, and methanol was then distilled off. The residue was treated with ammonium chloride aqueous solution and extracted with ether. The organic layer was extracted with 5% HCl and the aqueous layer was basified with conc. $\mathrm{NH_4OH}$ and extracted with ether. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to leave a gum which contained the benzazocine (X) in 47.1% yield in gas chromatographic analysis.[14] Recrystallization from ethanol afforded needles, mp 227—231° (lit.,[11] mp 228—233°), whose IR spectrum (KBr) was identical with that of the authentic sample.

The first ethereal extract gave 12 mg of 4-methoxymethylphenol (XXXV) as crystals, mp 81—82° (lit.,[16] 81.5—82.5°) (from benzene–pet. ether), whose NMR spectrum was identical with that of the authentic sample,[16] NMR ($\mathrm{CDCl_3}$) ppm: 3.26 (3H, singlet, $\mathrm{OC\underline{H}_3}$), 4.27 (2H, singlet, $\mathrm{ArC\underline{H}_2}$), 6.57 (2H, doublet, $J=8.0$ Hz, 2–H and 6–H), and 7.04 (2H, doublet, $J=8.0$ Hz, 3–H and 5–H).

Pentazocine (V)——a) A solution of 200 mg of the benzazocinium bromide (III) in 1.5 ml of 28% methanolic sodium methoxide was heated at 72—78° for 2 hr and worked up as above to give a gum which contained pentazocine (V) in 57.8% yield by gas chromatographic analysis.[14] This product was recrystallized from acetone to give pure pentazocine (V) as crystals, mp 146—148°, whose IR spectrum (KBr) was identical with that of the authentic pentazocine. The ethereal extract also gave 4-methoxymethylphenol (XXXV).

b) The same reaction of II afforded pentazocine (V) in 16.1% yield (gas chromatographic analysis).

Hofmann Degradation of I——A solution of 450 mg of I in 3 ml of 28% methanolic sodium methoxide was heated at 80—85° for 2 hr and methanol was removed by distillation. The residue was treated with $\mathrm{NH_4Cl}$ aqueous solution and extracted with ether. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to leave a residue which was chromatographed on 5 g of silica gel. The chloroform eluate gave 320 mg (85.3%) of the naphthylethylamine (XXXVI) as a colorless powder, mp 144—147° (from acetone–ether), NMR ($\mathrm{CDCl_3}$) (free base) ppm: 0.80 (3H, doublet, $J=7.0$ Hz, 2–$\mathrm{C\underline{H}_3}$), 1.04 (3H, singlet, 1–$\mathrm{C\underline{H}_3}$), 1.50 (3H, singlet, $\rangle\mathrm{C{=}CC\underline{H}_3}$), 1.64 (3H, singlet, $\rangle\mathrm{C{=}CC\underline{H}_3}$), 2.80—3.15 (2H, multiplet, $\mathrm{NC\underline{H}_2C}\langle$), 3.53 (2H, broad singlet, $\mathrm{NC\underline{H}_2Ar}$), 5.02—5.35 (1H, multiplet, $\mathrm{-C\underline{H}{=}C(CH_3)_2}$), 5.67 (1H, double doublet, $J=9.5$ and 5.0 Hz, 3–H), 6.26 (1H, doublet, $J=9.5$ Hz, 4–H), 7.23 (5H, singlet, $\mathrm{NCH_2C_6\underline{H}_5}$), and 8.92 (1H, broad singlet, OH). *Anal.* Calcd. for $\mathrm{C_{26}H_{33}ON}$: N, 3.72. Found: N, 3.50.

Hydrogenation of XXXVI——A solution of 375 mg of the 7,8-dihydronaphthalene (XXXVI) in 50 ml of ethanol was shaken in a current of hydrogen on 0.5 g of 30% Pd-C at room temperature and atmospheric

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16) F.H.C. Stewart, *J. Org. Chem.*, **27**, 2662 (1962).

pressure. After absorption of a calculated amount of hydrogen, the catalyst was removed by filtration and then the solvent was evaporated to leave a residue which was basified with 10% NH_4OH and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 370 mg of a pale browm syrup, which was subjected to chromatography on 10 g of silica gel. The eluate with methanol–chloroform (v/v 1 : 99) gave 100 mg of tetralin derivative (XXXVII) as a caramel, which was characterized as hydrochloride to afford prisms, mp 192—194° (from methanol–acetone), IR ν_{max}^{KBr} cm^{-1}: 3190 (OH); NMR ($CDCl_3$) (free base) ppm: 0.82 (9H, doublet, $J=6$ Hz, $\rangle CH{-}C\underline{H}_3$ and $-CH(C\underline{H}_3)_2$), 1.08 (3H, singlet, $\rangle C{-}C\underline{H}_3$), 3.63 (2H, singlet, $NC\underline{H}_2Ar$), and 6.33 (1H, broad singlet, OH). *Anal.* Calcd. for $C_{26}H_{37}ON \cdot HCl$: C, 75.06; H, 9.21; N, 3.37. Found: C, 75.12; H, 9.10; N, 3.36.

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