Studies on the Syntheses of Analgesics. Part XXXII (1). An Alternative Synthesis of 1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine [Studies on the Syntheses of Heterocyclic Compounds. Part CDLXXX (2)]

Tetsuji Kametani (3), Kazuo Kigasawa, Mineharu Hiiragi, Fumio Satoh, Hideo Sugi and Tsuneo Uryu

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan and
Research Laboratories, Grelan Pharmaceutical Co. Ltd., Sakurashinmachi, Setagayaku, Tokyo, Japan

Received April 17, 1972

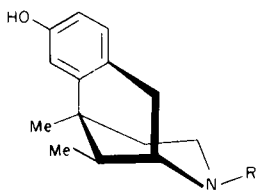
Bischler-Napieralski reaction of the amides (VIII and IX), derived from the 3-methyl-3-pentenylamine (III) with the phenylacetic acid derivatives (V ~ VII), gave the 5,6-dihydropyridines (XII and XIII), which were reduced, followed by *N*-benzylation, to afford the 1,2,5,6-tetrahydropyridines (XIX ~ XXI). Grewe-type cyclization of these compounds gave 3-benzyl-3-benzazocine (II), which was already converted into pentazocine (Ic). Moreover, the 1,2,5,6-tetrahydropyridines (XIX ~ XXI) were also obtained from the 2-benzylidene-1,2,5,6-tetrahydropyridine (XVII ~ XVIII) from the *N*-benzylamine (IV) of III *via* the amides (X and XI).

There are many reports on the synthesis of the benzazocine derivatives involving cyclazocine (Ia), phenazocine (Ib), and pentazocine (Ic) as effective analgesics (4,5). The pentazocine, 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine (Ic) has been applied widely in many countries as a non-addicting and strong analgesic. This pentazocine was synthesized from 3,4-lutidine (5-8) or from ethyl methyl ketone and cyanoacetic acid (9,10), but these methods had some defects from the industrial points of view such as Grignard reaction and use of an expensive palladium.

As a result of our study to find a method of synthesis of pentazocine which does not have the above disadvantages, the synthesis of a useful intermediate, 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II), and the selective conversion of the quaternary ammonium salt XXII into pentazocine (Ic) in good yield is reported.

The fusion of a mixture of 3-methyl-3-pentenylamine (III) and 3-methylpentylamine with 4-benzyloxyphenylacetic acid (V) gave the amide VIII and its saturated amide, *N*-(3-methylpentyl)-4-benzyloxyphenylacetamide, respecitvely, which were also obtained from 4-benzyloxyphenacetyl chloride (VI). The amide IX was obtained from a mixture of amines and 4-ethoxycarbonyloxyphenacetyl chloride (VII). The products showed the amide-carbonyl bond in the ir spectrum, and in the nmr spectrum two types of methyl groups on the olefinic

SCHEME 1



(Ia) R = CH_2-cyclopropyl
(Ib) R = CH_2CH_2Ph
(Ic) R = $CH_2CH{=}C(Me)_2$
(II) R = CH_2Ph

double bond and on the saturated carbon atom resonated at 1.55 and 0.7-1.0 ppm, thus suggesting the products to be a mixture of the expected amides VIII and IX and its saturated amides, *N*-(3-methylpentyl)-4-substituted phenylacetamides. The cyclization of these products without separation of Bischler-Napieralski type reaction (11,12) with phosphoryl chloride gave the dihydropyridine XII and XIII hydrochlorides after separation of the *N*-(3-methylpentyl)-4-substituted phenylacetamides by extraction. The products showed the C=N function in the ir spectra, and in the nmr spectra the two methyl groups on the pyridine ring resonated at 1.78 ppm in XII and at 1.75 ppm in XIII as a broad signal equivalent to six protons, and methylene protons on benzyl group were observed at 3.75 ppm in XII and 3.74 ppm in XIII as a

singlet equivalent to two protons. Reduction of the cyclized products XII and XIII with sodium borohydride gave the corresponding tetrahydropyridines XIV and XV. Moreover, hydrolysis of the reduction products XV without isolation gave 1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)pyridine (XVI). The structure of the reduction products XIV, XV, and XVI were proved by the disappearance of the C=N function in the ir spectra and by nmr spectra described in the experimental section. Treatment of the tetrahydropyridines XIV, XV, and XVI with benzyl chloride gave the *N*-benzylated products XIX, XX, and XXI. The compound XXI was also obtained quantitatively by acidic or alkaline hydrolysis of XIX and XX, and was identical with the authentic sample prepared by the standard method (8).

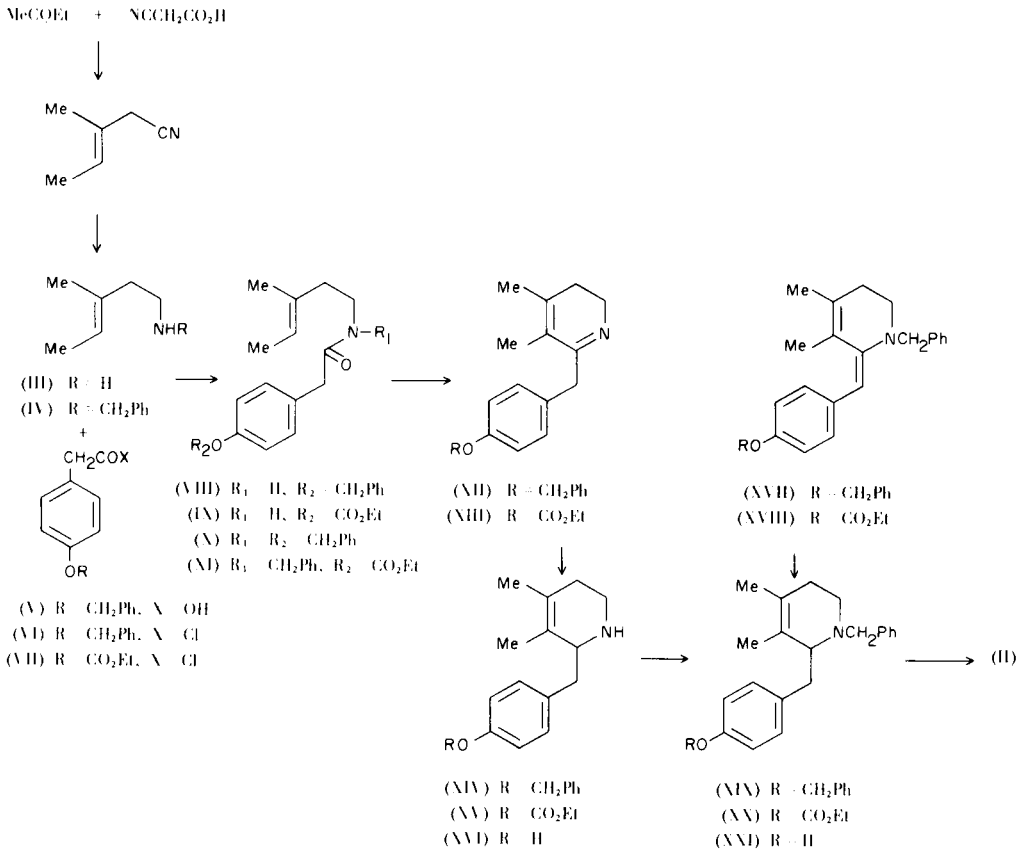
The reaction of 4-substituted phenacetyl chlorides VI and VII with a mixture of *N*-benzyl-3-methyl-3-pentenylamine (VII) and *N*-benzyl-3-methylpentylamine (10) gave a mixture of the amides X and XI and their saturated amides, which were cyclized with phosphoryl chloride by Bischler-Napieralski type reaction without purification and separation to give the expected 2-benzylidenetetrahydropyridines XVII and XVIII after separation of the saturated amides. The ir spectra of these products lacked the amide-carbonyl band and the signal of olefinic proton observed in the starting materials was absent in the cyclized products. Sodium borohydride reduction of XVII and XVIII afforded the tetrahydropyridine derivatives XIX, XX, and XXI, which were identical with the products from the secondary amines XIV, XV, and XVI.

Cyclization of 1-benzyl-1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethylpyridine (XXI) with 47% hydrobromic acid for 7 hours gave, in 90% yield, 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II).

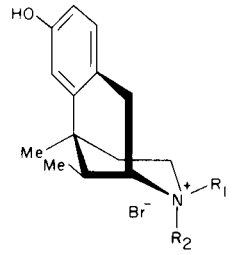
Quaterization of II with 3-methyl-2-butenyl bromide gave two kinds of stereoisomers (XXIIα and XXIIβ) (13), which, after separation, were reduced on Raney Cobalt in ethanol in the presence of ammonia to give the pentazocine (Ic) in 87-93% yield.

Thus, a modified synthesis of pentazocine applicable in the industrial field has been achieved.

SCHEME 2



SCHEME 3



(XVIIα) R_1 CH_2CH-C(Me)(Me), R_2 CH_2Ph

(XVIIβ) R_1 CH_2Ph, R_2 CH_2CH C(Me)(Me)

EXPERIMENTAL (14)

N-(3-Methyl-3-pentenyl)-4-benzyloxyphenylacetamide (VIII).

(a) To a stirred solution of 15 g. of a mixture of 3-methyl-3-pentenylamide (III) and 3-methylpentylamine (10) in 100 ml. of benzene in the presence of 60 ml. of 1*N* sodium hydroxide solution was added dropwise 4-benzyloxyphenacetyl chloride [prepared from 20 g. of 4-benzyloxyphenylacetic acid] in 150 ml. of benzene under ice-cooling during 30 minutes and the mixture was stirred for 1 hour at room temperature. The organic layer was separated and washed with water, 10% hydrochloric acid, and water, dried over sodium sulfate, and evaporated to give 25 g. (90%) of the amide (15) and its saturated amide as colorless needles, m.p. 85-89° (from ether-*n*-hexane), ν max (potassium bromide) cm^{-1}: 1635 (-NH-C=O); nmr δ (deuteriochloroform) ppm: 2.11 (2H, triplet, J = 7 Hz, CH_2-C=C), 3.40 (2H, triplet, J = 7 Hz, CH_2N), 3.56 (2H, singlet, CH_2CO), 5.17 (2H, singlet, -$OCH_2C_6H_5$), 5.24 (1H, broad, -CH=C), 7.01 and 7.26 (each 2H, A_2B_2 type quartet, J = 9 Hz, -OC_6H_4-), and 7.48 (5H, singlet, $CH_2C_6H_5$).

(b) A mixture of 12.1 g. of 4-benzyloxyphenylacetic acid (V) with 8 g. of a mixture of 3-methyl-3-pentenylamine (III) and 3-methylpentylamine (10) was heated for 8 hours at 110-130°, and this was dissolved in 100 ml. of benzene. The benzene solution was washed with 5% sodium hydroxide, water, 10% hydrochloric acid, and water, dried over sodium sulfate, and the benzene was distilled to give 9.8 g. (60.5%) of the amide (VIII) and its saturated amide as colorless needles, m.p. 85-89° (from ether-*n*-hexane); the spectroscopic data of this product were identical with those of the sample prepared by the method (a).

2-(4-Benzyloxybenzyl)-5,6-dihydro-3,4-dimethylpyridine (XII).

A mixture of 19 g. of the amide (VIII) and its saturated amide was refluxed with 15 g. of phosphoryl chloride in 200 ml. of benzene for 2 hours. After distillation of benzene and the excess of phosphoryl chloride, the residue was dissolved in water and washed with ether. Evaporation of water *in vacuo* gave 7.5 g. (75%) (15) of the dihydropyridine (XII) hydrochloride as colorless needles, m.p. 139-140° (from water-2-propanol); ν max (potassium bromide) cm^{-1}: 1660 (C=N); nmr (free base) δ (deuteriochloroform) ppm: 1.78 (6H, singlet, 3-CH_3 and 4-CH_3), 2.00 (2H, triplet, J = 7.5 Hz, CH_2-C=C), 3.57 (2H, triplet, J = 7.5 Hz, N-CH_2), 3.75 (2H, singlet, N=C-CH_2-C_6H_4-), 5.14 (2H, singlet, $OCH_2C_6H_5$), 7.05 and 7.32 (each 2H, A_2B_2 type quartet, J = 9 Hz, $CH_2C_6H_4$-), and 7.51 (5H, singlet, $CH_2C_6H_5$).

Anal. Calcd. for $C_{21}H_{23}NO$·HCl·0.5 H_2O: C, 71.88; H, 6.89; H, 3.99. Found: C, 72.03; H, 7.11; N, 3.73.

2-(4-Benzyloxybenzyl)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XIV).

To a stirred solution of 7.5 g. of the dihydropyridine (XII) hydrochloride in 100 ml. of methanol was added in small portions 2 g. of sodium borohydride under cooling, and the mixture was refluxed for 30 minutes. After the methanol had been distilled off, the resulting pale brown syrup was decomposed with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give XIV as a pale brown syrup, which was converted into the corresponding hydrochloride in the usual manner. The hydrochloride was recrystallized from methanol-ether to give 6 g. (80%) of the tetrahydropyridine XIV hydrochloride as colorless needles, m.p. 208-210°; nmr (free base) δ (deuteriochloroform) ppm: 1.68 (6H, singlet, 3-CH_3 and 4-CH_3), 5.11 (2H, singlet, $OCH_2C_6H_5$), 7.02 and 7.28 (each 2H, A_2B_2 type quartet, J = 9 Hz, -$CH_2C_6H_4$-), and 7.50 (5H, singlet, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{21}H_{25}NO$·HCl: C, 73.35; H, 7.62; N, 4.07. Found: C, 72.87; H, 7.82; N, 3.84.

N-Benzyl-*N*-(3-methyl-3-pentenyl)-4-benzyloxyphenylacetamide (X).

A mixture (10 g.) of *N*-benzyl-3-methyl-3-pentenylamide (IV) and *N*-benzyl-3-methylpentylamine in 100 ml. of benzene was treated with 4-benzyloxyphenylacetyl chloride [prepared from 10 g. of 4-benzyloxphenylacetic acid] in 150 ml. of benzene in the presence of 100 ml. of 1*N* sodium hydroxide solution in the same manner as the case of VIII to give 17 g. of the amide (X) and its saturated amide as a pale yellow oil; ν max (liquid) cm^{-1}: 1640 (NH-CO); nmr δ (deuteriochloroform) ppm: 1.59 (6H, broad singlet, CH_3-C=C-CH_3), 5.08 (2H, singlet, $OCH_2C_6H_5$), 5.18 (1H, broad signal, CH=C), 7.33 (5H, singlet, $NCH_2C_6H_5$), and 7.48 (5H, singlet, $OCH_2C_6H_5$). This product was used in the following reaction without separation.

1-Benzyl-2-(4-benzyloxybenzylidene)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XVII).

A mixture of 17 g. of the above amides (X and its saturated amide), 10 g. of phosphoryl chloride, and 100 ml. of benzene was heated under reflux for 5 hours, and the excess of reagent and the solvent was distilled to leave a residue, which was dissolved in water and washed with ether. The aqueous layer was made basic with 28% ammonia and extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated to give 3 g. of XVII as a pale brown syrup; nmr δ (deuteriochloroform) ppm: 1.84 (6H, singlet, 3-CH_3 and 4-CH_3), 3.58 and 4.07 (each 1H, a pair of doublet, J = 13 Hz, $NCH_2C_6H_5$), 5.14 (2H, singlet, $OCH_2C_6H_5$), 7.40 (5H, singlet, $NCH_2C_6H_5$), and 7.51 (5H, singlet, $OCH_2C_6H_5$). This product was used immediately in the following reaction due to its instability.

1-Benzyl-2-(4-benzyloxybenzyl)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XIX).

(a) A mixture of 5.8 g. of the above tetrahydropyridine (XIV) hydrochloride, 5 g. of sodium hydrogen carbonate, 120 ml. of ethanol, and 2.2 g. of benzyl chloride was refluxed for 5 hours, and the mixture was filtered to remove separated inorganic material. The filtrate was evaporated to leave a residue, which was dissolved in ether. The extract was washed with water, dried over sodium sulfate, and evaporated to leave XIX as a pale brown oil, the hydrochloride of which was recrystallized from ethanol-ether to give 6.77 g. (81%) of the hydrochloride of XIX as colorless needles, m.p. 171-173°; nmr (free base) δ (deuteriochloroform) ppm: 1.68 (6H, singlet, 3-CH_3 and 4-CH_3), 3.70 (2H, singlet,

$NCH_2C_6H_5$), 5.18 (2H, singlet, $OCH_2C_6H_5$), 7.00 and 7.27 (each 2H, A_2B_2 type quartet, J = 9 Hz, OC_6H_4), 7.27 (5H, singlet, $NCH_2C_6H_5$), and 7.55 (5H, singlet, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{28}H_{31}NO\cdot HCl$: C, 77.48; H, 7.43; N, 3.23. Found: C, 77.09; H, 7.34; N, 3.17.

The oxalate of XIX gave colorless prisms from 2-propanol-ether, m.p. 144-145°.

Anal. Calcd. for $C_{28}H_{31}NO\cdot C_2H_2O_4$: C, 73.90; H, 6.82; N, 2.87. Found: C, 74.09; H, 7.00; N, 2.67.

(b) The above tetrahydropyridine (XVII) hydrochloride (3 g.) in 50 ml. of methanol was treated with 1 g. of sodium borohydride under the same condition as well as XIV to give brown oil, the hydrochloride of which was recrystallized from methanol-ether to give 0.9 g. of colorless needles, m.p. 171-173°. Melting point and spectral data of this product were identical with those of the sample prepared by method a.

N-(3-Methyl-3-pentenyl)-4-ethoxycarbonyloxyphenylacetamide (IX).

To a stirred solution of 12 g. of a mixture of 3-methyl-3-pentenylamine (III) and 3-methylpentylamine (10) in 100 ml. of benzene was added dropwise 4-ethoxycarbonyloxyphenacetyl chloride [prepared from 22.4 g. of 4-ethoxycarbonyloxyphenylacetic acid (16)] in the same way as the case of VIII to give 31 g. of a mixture of the amide (IX) and its saturated amide as a colorless oil; ν max (liquid) cm^{-1}: 1750 (OCO_2Et), 1635 (NHCO); nmr δ (deuteriochloroform) ppm: 1.35 (3H, triplet, J = 7 Hz, OCH_2CH_3), 1.50 (6H, broad singlet, $CH_3C{=}CCH_3$), 3.37 (2H, singlet, $O{=}C\text{-}CH_2$), 4.27 (2H, quartet, J = 7 Hz, OCH_2CH_3) and 5.17 (1H, broad signal, $CH{=}C$).

2-(4-Ethoxycarbonyloxybenzyl)-5,6-dihydro-3,4-dimethylpyridine (XIII).

A mixture of 15 g. of the above amide (IX) and its saturated amide, 15 g. of phosphoryl chloride and 100 ml. of benzene was refluxed for 2 hours, and the same treatment as the case of XVII gave 6.4 g. of XIII as a yellow oil; nmr δ (deuteriochloroform) ppm: 1.35 (3H, triplet, J = 7 Hz, OCH_2CH_3), 1.75 (6H, singlet, 3-CH_3 and 4-CH_3), 3.74 (2H, singlet, $N{=}C\text{-}CH_2$-), 4.33 (2H quartet, J = 7 Hz, OCH_2CH_3), and 7.25 (4H, broad singlet, OC_6H_4-).

1,2,5,6-Tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethylpyridine (XVI).

To a solution of 6 g. of the dihydropyridine (XIII) in 80 ml. of methanol was added in small portions 2 g. of sodium borohydride, and then 25 ml. of 20% sodium hydroxide solution was added to the above mixture. After reflux for 30 minutes, the solvent was removed by distillation and the residue was digested in water and treated with an excess of crystalline ammonium chloride. This solution was extracted with ether, and the extract was washed with water, dried over sodium sulfate, and evaporated to give 4 g. of XVI as a pale brown viscous oil; nmr δ (deuteriochloroform) ppm: 1.70 (6H, singlet, 3-CH_3 and 4-CH_3), 6.58 (2H, singlet, NH and OH) and 6.78 and 7.12 (each 2H, A_2B_2 type quartet, J = 9.5 Hz, OC_6H_4-).

N-Benzyl-*N*-(3-methyl-3-pentenyl)-4-ethoxycarbonyloxyphenylacetamide (XI).

4-Ethoxycarbonyloxyphenacetyl chloride [prepared from 15.7 g. of 4-ethoxycarbonyloxyphenylacetic acid (16)] in 150 ml. of benzene was treated with 16 g. of a mixture of *N*-benzyl-3-methyl-3-pentenylamine (IV) and *N*-benzyl-3-methylpentylamine (10) in 100 ml. of benzene in the presence of 140 ml. of 1*N* sodium hydroxide solution under the same condition as VIII to give 27 g. (95%) of XI and its saturated amide as a colorless oil; ν max (chloroform) cm^{-1}: 1630 (NHCO), 1755 (OCO_2Et); nmr δ (deuteriochloroform) ppm: 1.39 (3H, triplet, J = 7 Hz, OCH_2CH_3), 1.60 (6H, singlet, $CH_3C{=}CCH_3$), 4.38 (2H, quartet, J = 7 Hz, OCH_2CH_3), and 7.40 (5H, singlet, $NCH_2C_6H_5$). This was used in the following reaction without separation because of difficulty for separation.

1-Benzyl-2-(4-ethoxycarbonyloxybenzylidene)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XVIII).

A solution of 27 g. of the amide (XI) and its saturated amide and 17 g. of phosphoryl chloride in 50 ml. of benzene was refluxed for 2 hours to give 11 g. of XVIII as a brown syrup, which was used immediately in the following reaction, since it was unstable.

1-Benzyl-1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethylpyridine (XXI).

(a) A mixture of 4 g. of the above tetrahydropyridine (XVI), 1.9 g. of sodium hydrogen carbonate, 80 ml. of ethanol and 2.5 g. of benzyl chloride was refluxed for 2.5 hours, and the same treatment as XIX afforded 6.5 g. of a pale brown viscous syrup, the hydrochloride of which was recrystallized from ethanol-ether to give 2.5 g. of the hydrochloride of XXI as colorless needles, m.p. 216-217°; nmr (free base) δ (deuteriochloroform) ppm: 1.68 (6H, singlet, 3-CH_3 and 4-CH_3), 3.71 (2H, singlet, $NCH_2C_6H_5$), 6.83 and 7.14 (each 2H, A_2B_2 type quartet, J = 9 Hz, $CH_2C_6H_4O$-), and 7.28 (5H, singlet, $NCH_2C_6H_5$). The free base forms the corresponding hydrobromide, m.p. 211-212°.

Anal. Calcd. for $C_{21}H_{25}NO\cdot HBr$: C, 64.94; H, 6.75; N, 3.61. Found: C, 65.18; H, 7.04; N, 3.70.

(b) The above tetrahydropyridine XVIII (11 g.) in 150 ml. of methanol was treated with 2.7 g. of sodium borohydride and 50 ml. of 20% sodium hydroxide in the same way as XVI to give 5 g. of a pale pink caramel, the hydrochloride of which was recrystallized from ethanol-ether to give 2.5 g. of colorless needles, m.p. 216-217°. This was identical with the sample prepared by method (a) in melting point and spectral comparisons.

(c) A mixture of 2.17 g. of the tetrahydropyridine XIX hydrochloride, 20 ml. of 35% hydrochloric acid, and 20 ml. of ethanol was refluxed for 2 hours, and then the solvent and reagent were distilled to leave a residue, which was washed with ether and recrystallized from ethanol-ether to give 1.6 g. (90%) of the hydrochloride of XXI as colorless needles, m.p. 216-217°. This was identical with the specimen prepared by method (a) in melting point and spectral comparisons.

(d) A mixture of 360 mg. of the tetrahydropyridine XX and 100 ml. of 5% methanolic potassium hydroxide solution was refluxed for 1 hour, and the solvent was then distilled off. The residue was digested in water and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to leave 290 mg. of a pale brown viscous syrup, the hydrochloride of which gave 250 mg. of colorless needles, m.p. 216-217° (from ethanol-ether). The melting point and spectral data of this product were identical with those of the sample prepared by method (a).

2-(4-Ethoxycarbonyloxybenzyl)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XV).

The above dihydropyridine XIII hydrochloride (7 g.) in 300 ml. of water was treated with 2 g. of sodium borohydride and worked up as usual to give 5.8 g. of XV as a colorless oil; ν max (chloroform) cm^{-1}: 1760 (-OCO_2Et); nmr δ (deuteriochloroform) ppm: 1.32 (3H, triplet, J = 7 Hz, OCH_2CH_3), 1.62 (6H,

(6H, singlet, 3-CH_3 and 4-CH_3), 4.24 (2H, quartet, J = 7 Hz, OCH_2CH$_3$), 5.85 (1H, broad signal, -NH), and 7.10 and 7.36 (each 2H, A_2B_2 type quartet, J = 9 Hz, -CH$_2$C$_6H_4$O-).

1-Benzyl-2-(4-ethoxycarbonyloxybenzyl)-1,2,5,6-tetrahydro-3,4-dimethylpyridine (XX).

A mixture of 400 mg. of the tetrahydropyridine (XV), 20 ml. of ethanol, 200 mg. of benzyl chloride, and 150 mg. of sodium hydrogen carbonate was refluxed for 3 hours to give 520 mg. of a pale yellow caramel, which was purified on silica gel column chromatography by elution with chloroform. The first eluate gave 350 mg. (70%) of XX as a colorless caramel; nmr δ (deuteriochloroform) ppm: 1.37 (3H, triplet, J = 7 Hz, -OCH$_2$CH_3), 1.66 (6H, singlet, 3-CH_3 and 4-CH_3), 3.69 (2H, singlet, NCH_2C$_6$-H$_5$), 4.42 (2H, quartet, J = 7 Hz, OCH_2CH$_3$), and 7.28 (5H, singlet, NCH$_2$C$_6H_5$).

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II).

A mixture of 550 mg. of the above tetrahydropyridine (XXI) hydrochloride and 10 ml. of 47% hydrobromic acid was heated at 130-140° for 7 hours. The mixture was made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to leave 650 mg. of a pale brown caramel, the hydrochloride of which was recrsytallized from ethanol-ether to give 495 mg. (90%) of the hydrochloride of II as colorless prisms. The spectroscopic data were superimposable on those of the authentic sample.

1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine (Ic).

(a) A solution of 1.07 g. of XXIIβ in 25 ml. of ethanol containing 250 mg. of ammonia was hydrogenated in the presence of 2.5 ml. of Raney Cobalt (W-7) at room temperature and atmospheric pressure. After absorption of the calculated amount of hydrogen (53 ml.) within 8 hours, the solvent was evaporated off to leave 620 mg. (92.7%) of a pale brown caramel, which contained 87.3% of Ic by gas chromatographical determination (17). Purification by silica gel column chromatography with chloroform-methanol (98:2) as an eluant gave 537 mg. (80.3%) of Ic as colorless prisms, the melting point and spectral data of which were identical with those of the authentic sample.

(b) A solution of 1.10 g. of XXIIα in 40 ml. of ethanol containing 200 mg. of ammonia was hydrogenated with 2 ml. of Raney Cobalt (W-7) at room temperature and atmospheric pressure. After 7 hours, 54 ml. of hydrogen were absorbed, and the mixture was worked up as usual to give 670 mg. (97.4%) of a pale brown caramel, which contained 93.3% of Ic by gas chromatographical determination (17). This was subjected to silica gel chromatography by elution with chloroform-methanol (98:2) to give 575 mg. of Ic as colorless prisms. This product was identical with the authentic sample in spectral and melting point comparison.

Acknowledgments.

We are indebted to Dr. K. Fukumoto, Pharmaceutical Institute, Tohoku University for his kind suggestion. We are grateful to President A. Yanagisawa and Director O. Takagi, Grelan Pharmaceutical Co. Ltd., and thank them for their encouragement. We also thank Miss A. Kawakami, Miss C. Yoshida, Miss T. Yoshida, and Miss R. Kato for microanalyses and spectral determinations.

REFERENCES

(1) Part XXXI, T. Kametani, K. Kigasawa, M. Hiiragi, and T. Aoyama, *J. Heterocyclic Chem.*, **9**, 1061 (1972).

(2) Part CDLXXIX, T. Kametani, *et al.*, the preceding paper; this paper forms Part IV of "Benzomorphan and Related Compounds," Part III, *J. Med. Chem.*, **13**, 1064 (1970).

(3) Communications concerning this paper should be directed to Professor Tetsuji Kametani.

(4) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294, 1432 (1959).

(5) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pieson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

(6) N. F. Albertson and W. F. Wetterau, *J. Med. Chem.*, **13**, 302 (1970); Belgian Patent, 719,408.

(7) H. Moriyama, H. Yamamoto, H. Nagata, and T. Tamaki, Japanese Patent, 45-31664 and 45-40285.

(8) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, N. Wagatsuma, and K. Wakisaka, *J. Heterocyclic Chem.*, **6**, 43 (1969).

(9) Japanese Patent, 43-11895 and 43-20186.

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

(11) O. Schnider and J. Hellerback, *Helv. Chim. Acta*, **33**, 1437 (1950).

(12) S. Sugasawa and S. Saito, *Chem. Pharm. Bull. (Tokyo)*, **4**, 237 (1956).

(13) T. Kametani, K. Kigasawa, M. Hiiragi, F. Satoh, S. Saito, H. Sugi, and T. Uryu, *J. Heterocyclic Chem.*, **9**, in press (1972).

(14) All melting points are uncorrected. Ir and nmr spectra were measured on a type Hitachi-215-recording photometer and JNM-MH-60 (60Mc) with tetramethylsilane as internal standard, respectively. Gas chromatography was determined with Hitachi K-23.

(15) The yield of this product was calculated on the recovery of the saturated amide.

(16) J. Finkelstein, *J. Am. Chem. Soc.*, **73**, 550 (1951).

(17) 10% SE-30 on Chromosorb W (1m) was used as a column, and the temperature of column was 210°. Nitrogen (40 ml./min.) was used as a carrier gas.