Studies on the Syntheses of Heterocyclic Compounds. Part DV (1). Cyclization Products of 1-Substituted 2-Benzyl-1,2,5,6-tetrahydropyridines [Syntheses of Analgesics. Part XXXV (2)]

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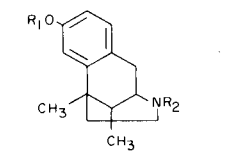
Treatment of 1,2,5,6-tetrahydro-2-(4-hydroxy- and/or 4-methoxybenzyl)-3,4-dimethyl-1-(3-methyl-2-butenyl)pyridines (IV and V) and 2-(4-methoxybenzyl)-3,4-dimethyl-1-(3-methyl-2-butenyl)-4-piperidinol (X) with acid afforded 9-(4-hydroxy- and/or 4-methoxybenzyl)-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (XIII and XIV). In contrast, the corresponding 1-allyl-substituted derivatives VI, VII, and XI were converted into the expected 3-allyl-1,2,3,4,5,6-hexahydro-8-hydroxy- and/or 8-methoxy-6,11-dimethyl-2,6-methano-3-benzazocine (II and III).

Previously we reported the synthesis of pentazocine (I) (4-8) and the Sumitomo group investigated the cyclization of 1-allyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (VII) (9). In attempting to extend this method to the preparation of related 2,6-methano-3-methano-3-benzazocines, we investigated the acid treatment of the 1,2,5,6-tetrahydropyridines IV-VII and 4-piperidinols X and XI, obtained by alkylation of compounds VIII, IX, and XII (6,7,8,10) with allyl bromide and 3-methyl-2-butenyl bromide. In contrast to the 1-allyl-substituted pyridines VI and VII and piperidinol XI which were cyclized with either 47% hydrobromic acid or polyphosphoric acid to give the allyl benzazocines (II and III) in low yield, the corresponding 1-(3-methyl-2-butenyl) derivatives (IV, V, and X) behaved abnormally and gave instead the substituted 1-azabicyclo[3,3,1]non-6-enes (XIII and XIV).

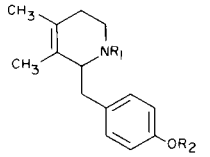
Treatment of the tetrahydropyridines IV and V and the piperidinol X with 47% hydrobromic acid afforded in 65-70% yield 9-(4-hydroxybenzyl)-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (XIII) whose nmr spectrum exhibited characteristic signals for three methyl groups on a saturated carbon, one methyl group on an olefinic carbon, one olefinic proton and four aromatic protons. Moreover, the fragment ion at m/e 178 indicated the presence of 4-hydroxybenzyl group. Similarly, reaction of IV, V and X with polyphosphoric acid also formed XIII but in 5-10% yield and in addition 9-(4-methoxybenzyl)-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (XIV) was isolated from V and X in 2-3% yield.

The difference in reactivity between the 3-methyl-2-butenyl compounds IV, V, and X and the corresponding allyl derivatives VI, VII, and XI may be attributable to the position of protonation of the olefinic system. While the latter compounds VI, VII, and XI are protonated at the olefinic bond in the tetrahydropyridine ring (6,8), it is likely that the 3-methyl-butenyl derivative IV, V and X are protonated at the allylic bond due to hyperoconjugation of the two methyl groups.

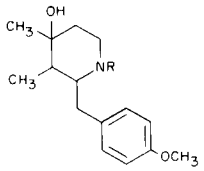
SCHEME I



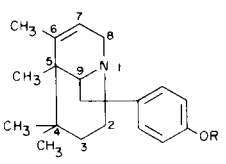
I: R_1 H, R_2 $CH_2CH{=}C(CH_3)_2$
II: R_1 H, R_2 $CH_2CH{=}CH_2$
III: R_1 CH_3, R_2 $CH_2CH{=}CH_2$



IV: R_1 $CH_2CH{=}C(CH_3)_2$, R_2 H
V: R_1 $CH_2CH{=}C(CH_3)_2$, R_2 CH_3
VI: R_1 $CH_2CH{=}CH_2$, R_2 H
VII: R_1 $CH_2CH{=}CH_2$, R_2 CH_3
VIII: R_1 R_2 H
IX: R_1 H, R_2 CH_3



X: R $CH_2CH{=}C(CH_3)_2$
XI: R $CH_2CH{=}CH_2$
XII: R H



XIII: R H
XIV: R CH_3

TABLE I

Starting Material	Products from Method A	Products from Method B
IV	XIII (a) (70%)	XIII (10%)
V	XIII (65%)	XIII (8 %) XIV (b) (3%)
X	XIII (5 %)	XIII (5 %) XIV (2%)
VI	II (c) (5 %)	II (5 %)
VIII	II (3 %)	II (3 %) III (d) (2%)
XI	II	II (5 %) III (2%)

(a) 9-(4-Hydroxybenzyl)-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (XIII): m.p. 165-166° (from acetone), δ (deuteriochloroform) 0.93, 1.05, and 1.09 (each 3H, each s, 2 x C_4- and C_5-CH_3), 1.81 (3H, s, C_6-CH_3), 5.76 (1H, broad signal, C_7-*H*), 6.32 and 6.95 (each 2H, A_2B_2 type q, J = 9 Hz, -C_6H_4O-), 8.37 (1H, s, O*H*), *m/e* 285 (M^+), 178 (M^+ - 107).

Anal. Calcd. for $C_{19}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.87; H, 9.69; N, 4.79.

(b) 9-(4-Methoxybenzyl)-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (XIV): colorless caramel, δ (deuteriochloroform) 0.90, 1.00 and 1.05 (each 3H, each s, 2 x C_4- and C_5-CH_3), 1.76 (3H, s, C_6-CH_3), 3.85 (3H, s, OCH_3), 5.78 (1H, broad signal, C_7-*H*), 6.97 and 7.34 (each 2H, A_2B_2 type q, J = 9 Hz, C_6H_4O). Picrate; m.p. 210-212°.

Anal. Calcd. for $C_{20}H_{29}NO{\cdot}C_6H_3N_3O_7$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.73; H, 6.06; N, 10.47.

(c) 3-Allyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II): m.p. 141-142° [lit. (11), m.p. 141-144°], the spectral data of which were identical with those of the authentic sample.

(d) 3-Allyl-1,2,3,4,5-hexahydro-8-methoxy-6,11-dimethyl-2,6-methano-3-benzazocine (III): m.p. 215-216° (hydrochloride) [lit. (11), m.p. 216-218°], δ (deuteriochloroform) (free base) 0.82 (3H, d, J = 7 Hz, C_{11}-CH_3), 1.35 (3H, s, C_6-CH_3), 3.15 (2H, d, J = 7.5 Hz, NCH_2CH=), 3.79 (3H, s, OCH_3), 5.08 and 5.19 (each 1H, m, $NCH_2CH{=}CH_2$), 5.90 (1H, m, NCH_2CH=).

EXPERIMENTAL

Melting points are uncorrected. The mass and nmr spectra were measured with Hitachi RMU-7 and JNM-MH-60 spectrometers with tetramethylsilane as an internal standard, respectively.

1,2,5,6-Tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethyl-1-(3-methyl-2-butenyl)pyridine (IV).

A mixture of 4.5 g. of tetrahydropyridine VIII hydrochloride (8), 2.5 g. of sodium bicarbonate, 3.7 g. of 3-methyl-2-butenyl bromide, and 80 ml. of dimethylformamide was heated at 135° for 3 hours. The reaction mixture was poured into 100 ml. of ice-water and extracted with 100 ml. of ether. The extract was washed with water, dried over magnesium sulfate and evaporated to give a pale brown solid, which was recrystallized from acetone to give 2.5 g. of 3,4-dimethylpyridine IV as colorless prisms, m.p. 108-109°, δ (deuteriochloroform) 1.65 [12 H, broad s, C_3-CH_3, C_4-CH_3, and $CH{=}C(CH_3)_2$], 3.22 (2H, d, J = 9 Hz, N-CH_2-CH=), 5.35 (1H, broad signal, N-CH_2-CH=), 6.57 and 7.17 (each 2H, A_2B_2 type q, J = 9 Hz, -C_6H_4O), 7.64 (1H, s, O*H*).

Anal. Calcd. for $C_{29}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 80.14; H, 9.65; N, 4.96.

1,2,5,6-Tetrahydro-2-(4-methoxybenzyl)-3,4-dimethyl-1-(3-methyl-2-butenyl)pyridine (V).

A mixture of 2 g. of tetrahydropyridine IX hydrochloride (8), 1.6 g. of sodium bicarbonate, 1.35 g. of 3-methyl-2-butenyl bromide, and 50 ml. of dimethylformamide was heated at 135° for 4 hours and worked up as above to give 2.5 g. of 3,4-dimethylpyridine V as a pale yellow caramel, δ (deuteriochloroform) 1.64 [12H, broad s, C_3-CH_3, C_4-CH_3, and -$CH{=}C(CH_3)_2$], 3.09 (2H, d, J = 9 Hz, N-CH_2CH=), 3.80 (3H, s, OCH_3), 5.14 (1H, broad signal, N-CH_2-CH=), 6.86 and 7.25 (each 2 H, A_2B_2 type q, J = 9 Hz, -C_6H_4O-).

2-(4-Methoxybenzyl)-3,4-dimethyl-1-(3-methyl-2-butenyl)-4-piperidinol (X).

A mixture of 2.2 g. of piperidinol XII hydrochloride (6), 2.7 g. of potassium carbonate, 1.4 g. of 3-methyl-2-butenyl bromide, and 30 ml. of dimethylformamide was heated at 135° for 3 hours and treated as above to give a caramel, the hydrochloride of which was recrystallized from ethanol to give 2.9 g. of 1-(3-methyl-2-butenyl)-4-piperidinol (X) hydrochloride as colorless prisms, m.p. 229-230° dec., δ (deuteriochloroform) (free base) 0.91 (3H, d, J = 7 Hz, C_3-CH_3), 1.03 (3H, s, C_4-CH_3), 1.63 and 1.73 (each 3H, each s, -$CH{=}C(CH_3)_2$), 3.80 (3H, s, OCH_3), 5.42 (1H, broad signal, -CH=), 6.86 and 7.18 (each 2H, A_2B_2 type q, J = 9 Hz, -C_6H_4O-).

Anal. Calcd. for $C_{20}H_{31}NO_2{\cdot}HCl$: C, 67.87; H, 9.11; N, 3.96. Found: C, 67.90; H, 9.07; N, 4.12.

1-Allyl-1,2,5,6-tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethylpyridine (VI).

A mixture of 2 g. of tetrahydropyridine VIII hydrochloride (8), 1.7 g. of sodium bicarbonate, 1.15 g. of allyl bromide, and 50 ml. of dimethylformamide was heated at 130-135° for 3 hours and worked up as above to give a caramel, the hydrochloride of which was recrystallized from acetone to give 1.5 g. of the 1-allyl-3,4-dimethylpyridine VI hydrochloride as colorless prisms, m.p. 177-180°, δ (deuteriochloroform) (free base) 1.61 and 1.71 (each 3H, each s, C_3- and C_4-CH_3), 3.30 (2H, d, J = 9 Hz, NCH_2-CH=), 5.10 and 5.34 (each 1H, m, $CH{=}CH_2$), 5.90 (1H, m, $CH{=}CH_2$), 6.81 and 7.23 (each 2H, A_2B_2 type q, J = 9 Hz, -C_6H_4O), 7.03 (1H, s, O*H*).

Anal. Calcd. for $C_{17}H_{23}NO{\cdot}HCl$: C, 69.50; H, 8.23; N, 4.76. Found: C, 69.67; H, 8.52; N, 4.72.

1-Allyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpryidine (VII).

A mixture of 2 g. of tetrahydropyridine IX hydrochloride (8), 1.5 g. of sodium bicarbonate, 1.1 g. of allyl bromide and 30 ml. of dimethylformamide was heated at 135-145° for 3 hours and worked up as above to give an oily substance, the oxalate of

which was recrystallized from acetone to give 1.3 g. of the oxalate of VII as colorless prisms, m.p. 109-111°, δ (deuteriochloroform) (free base) 1.63 (6H, s, C_3- and C_4-CH_3), 3.16 (2H, d, J = 9 Hz, NCH_2CH), 3.84 (3H, s, OCH_3), 4.95 and 5.19 (each 1H, m, $CH=CH_2$), 5.75 (1H, m, $CH=CH_2$), 6.89 and 7.27 (each 2H, A_2B_2 type q, J = 9 Hz, $-C_6H_4O-$).

Anal. Calcd. for $C_{18}H_{25}NO \cdot C_2H_2O_4 \cdot 0.25\ H_2O$: C, 65.64; H, 7.58; N, 3.83. Found: C, 65.71; H, 7.49; N, 3.81.

1-Allyl-2-(4-methoxybenzyl)-3,4-dimethyl-4-piperidinol (XI).

A mixture of 3 g. of piperidinol XII hydrochloride (6), 2.2 g. of sodium bicarbonate, 1.52 g. of allyl bromide and 30 ml. of dimethylformamide was heated at 125-135° for 3 hours and worked up as above to give a caramel, the hydrochloride of which was recrystallized from acetone to gvie 3 g. of 4-piperidinol XI hydrochloride as colorless prisms, m.p. 198-200° dec., δ (deuteriochloroform) (free base) 0.95 (3H, d, J = 7 Hz, C_3-CH_3), 1.10 (3H, s, C_4-CH_3), 3.24 (2H, d, J = 9 Hz, NCH_2CH), 3.82 (3H, s, OCH_3), 5.12 and 5.35 (each 1H, m, $CH=CH_2$), 5.95 (1H, m, $CH=CH_2$), 6.87 and 7.20 (each 2H, A_2B_2 type q, J = 9 Hz, $-C_6H_4O-$).

Anal. Calcd. for $C_{18}H_{27}NO_2 \cdot HCl$: C, 66.34; H, 8.68; N, 4.31. Found: C, 66.35; H, 8.72; N, 4.21.

The Treatment of 1,2,5,6-Tetrahydro-3,4-dimethylpyridines (IV-VII) and 3,4-Dimethyl-4-piperidinols (X and XI) with Acid.

All the reactions were carried out under the conditions as follows and products are shown in Table I.

Method A. Treatment with 47% Hydrobromic Acid.

A mixture of 0.5 g. of pyridines (IV-VII) or piperidinols (X and XI) and 10 ml. of 47% hydrobromic acid was heated at 130-140° for 7 hours. The reaction mixture was made basic with ammonia and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and evaporated to give a crude product, which was purified by silica gel chromatography.

Method B. Treatment with Polyphosphoric Acid.

A mixture of pyridines (IV-VII) or piperidinols (X and XI) and polyphosphoric acid [prepared from 2.5 g. of phosphorus pentoxide and 3.3 g. of 85% phosphoric acid] was heated at 130-135° for 7 hours, to a mixture of which 15 ml. of 3 *N* hydrochloric acid was added at 100°. Furthermore, after the resulting mixture had been refluxed for 1 hour, it was made basic with ammonia and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated to give a crude product which was purified by silica gel chromatography.

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