

Syntheses of Analgesics. Part XXX (1). Conformational Studies of Diastereoisomeric Quaternary Ammonium Salts of 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines (2)

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The configuration of the quaternary ammonium salts (Va and Vb) from 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II) and 3-methyl-2-butenyl bromide was determined spectroscopically. Moreover, configurational studies on 3-benzyl (VIa and VIb) and 3-(3-methyl-2-butenyl)benzazocinium bromides (VIIa and VIIb) were also achieved.

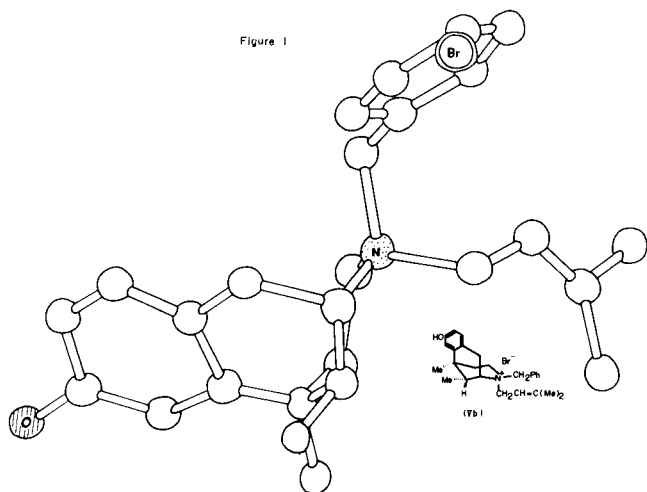
There are many reports (4-12) on configurational studies of the stereoisomers of quaternary ammonium salts by chemical and spectroscopic methods. We have also studied the stereochemistry of the quaternary ammonium salts obtained from the intermediate to pentazocine (I), and the results of this study are herein reported.

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine (II), in which the methyl group at the C-11 position was in the *cis*-configuration to the aromatic ring, was treated with an equimolar amount of 3-methyl-2-butenyl bromide to give a stereoisomeric mixture of quaternary ammonium salts in 75% yield. This was separated into 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (Va), m.p. 164-166° dec. and its epimer (Vb), m.p. 210-212° dec. in

a ratio of 1:3 by fractional crystallization. It is well known that in a quaternization of a cyclic amine, axial attack by the electrophile occurs in preference to equatorial attack when the substituent on the nitrogen atom is bulkier than the electrophile (11,12). Moreover, the stereochemistry of the piperidine part of the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines was studied by kinetics and spectroscopic methods and also by X-ray analysis of *cis*-3-allyl (III) and *cis*-3-cyclopropylmethyl derivatives (IV), and the results indicated that the chair form was assumed and the substituent on the nitrogen had the equatorial orientation (13,14). Therefore, the benzyl group on nitrogen in the main product should have the equatorial orientation (Vb) as shown in Scheme 1. This fact was proved by the following reaction. Quaternization of pentazocine (I) by benzyl bromide gave a mixture (80%) which was separated by crystallization into Va and Vb (Va:Vb = 6:1). The former compound (Va) was obtained as the main product, which proved the above conclusion to be correct.

Furthermore, the nmr spectral studies on 1,2,3,4,5,6-hexahydro-8-hydroxy-3,3,6,11-tetramethyl-2,6-methano-3-benzazocinium iodide (VIII) and its deuterium compound (IX) indicated that the equatorial quaternary *N*-methyl group resonated at a higher field than the axial one due to the effect of the benzene ring (15). In our samples (Va and Vb) the chemical shift (δ 4.80 ppm) of the methylene group in the quaternary *N*-benzyl residue of Vb was observed at a higher field than that (δ 4.92 ppm) of Va. In the latter case the methylene group resonated at δ 5.17 and 4.67 as two doublets ($J = 14.5$ Hz) and the chemical shift of this group was calculated at

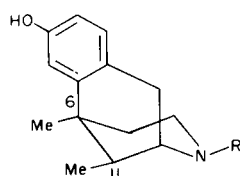
Figure 1



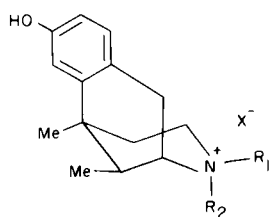
a mean value. This fact also supported that the main product in the first reaction should be formulated as Vb and the minor product as Va.

1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocine was treated with benzyl bromide or 3-methyl-2-butenyl bromide to give the benzazocinium bromides (VIa and VIIa) as a single product, and the isomers VIb and VIIIb were obtained from the reaction of methyl bromide with II and I. The chemical shifts of methyl group in the compounds (VIb and VIIIb) formed by a reaction with methyl bromide were observed at a lower field than those of the corresponding isomers (VIa and VIIa) and the benzyl methylene in VIb resonated at a higher field than that of VIa as shown in Table I. Thus, the methyl group on the nitrogen atom in the compounds VIa and VIIa occupied equatorial orientation and the methyl group in VIb and VIIIb was found to be situated axial. This fact showed that the electrophile assumed the axial position as reported by McKenna and his co-workers (11) and Casy and his co-workers (12).

SCHEME 1



- I, R = CH₂CH=C(Me)₂
 II, R = CH₂Ph
 III, R = CH₂CH=CH₂
 IV, R = CH₂⊠



- Va, R₁ = CH₂CH=C(Me)₂, R₂ = CH₂Ph, X = Br
 b, R₁ = CH₂Ph, R₂ = CH₂CH=C(Me)₂, X = Br
 VIa, R₁ = Me, R₂ = CH₂Ph, X = Br
 b, R₁ = CH₂Ph, R₂ = Me, X = Br
 VIIa, R₁ = Me, R₂ = CH₂CH=C(Me)₂, X = Br
 b, R₁ = CH₂CH=C(Me)₂, R₂ = Me, X = Br
 VIII, R₁ = R₂ = Me, X = I
 IX, R₁ = Me, R₂ = CD₃, X = I

Catalytic reduction (16) or treatment with the thio-phenol (17) of Va, Vb or a mixture of Va and Vb gave pentazocine (I), which was identical in all aspects with

TABLE I

The Nmr Spectra of Quaternary Ammonium Salts, δ (CF₃COOH).

	$\geq N^+CH_2Ph$	$\geq N^+Me$
5a	4.92 (a)	
5b	4.80	
6a	4.97 (a)	3.21
6b	4.84 (a)	3.32
7a		3.20
7b		3.32

(a) The chemical shift of this was calculated as a central value because this showed a typical AB type doublet.

the authentic sample (18). Furthermore, the structure of Vb suggested by the above spectroscopic studies was supported by X-ray crystallographic study of this base. Thus compound (Vb) was found to be structure X and its mirror image as shown in Figure 1 (19).

EXPERIMENTAL (20)

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium Bromides (Va and Vb).

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

To a suspension of 3.07 g. of the benzazocine (II) in 15 ml. of dry acetone was added 1.50 g. of 3-methyl-2-butenyl bromide, and the mixture was allowed to stand for 65-70 hours at 20-30° in the absence of moisture. After evaporation of acetone, the residue was triturated with ether to give 4.6 g. of a colorless solid, which was recrystallized from ethanol to afford 0.8 g. of Va as colorless prisms, m.p. 164-166° dec.; ν max (potassium bromide) cm⁻¹: 3150 (OH), 1660 (C=C); nmr δ (trifluoroacetic acid) ppm: 7.63 (5H, singlet, NCH₂C₆H₅), 7.05-7.60 (3H, multiplet, aromatic H), 5.80 br (1H, -CH=C<), 4.67 and 5.17 (each 1H, doublet, $J = 14.5$ Hz, $\geq N^+CH_2C_6H_5$), 1.82 and 2.06 (each 3H, singlet, C=C(CH₃)₂), 1.67 (3H, singlet, 6-CH₃), and 1.18 (3H, doublet, $J = 7$ Hz, 11-CH₃). This was characterized as half mole of ethanol adduct by nmr analysis (21) [nmr δ (trifluoroacetic acid) ppm: 4.61 (1H, quartet, $J = 7$ Hz, CH₃CH₂-OCOCF₃), 4.06 (1H, quartet, $J = 7$ Hz, CH₃CH₂OH), 1.51 (3/2H, triplet, $J = 7$ Hz, CH₃CH₂OCOCF₃), and 1.49 (3/2H, triplet, $J = 7$ Hz, CH₃CH₂OH).

Anal. Calcd. for C₂₆H₃₄BrNO·½C₂H₅OH: C, 67.63; H, 7.78; N, 2.92. Found: C, 67.63; H, 8.13; N, 3.18.

To the mother liquor from Va was added an excess of ether and the separated crystals were recrystallized from ethanol to give 2.2 g. of Vb as colorless prisms, m.p. 210-212° dec.; ν max (potassium bromide) cm⁻¹: 3150 (OH), 1660 (C=C); nmr δ (trifluoroacetic acid) ppm: 7.63 (5H, singlet, NCH₂C₆H₅), 7.00-7.50 (3H, multiplet, aromatic H), 5.75 br (1H, -CH=C), 4.80 (2H, singlet, $\geq N^+CH_2C_6H_5$), 1.93 and 2.05 (each 3H, singlet, C=C(CH₃)₂), 1.60 (3H, singlet, 6-CH₃), and 1.10 (3H, doublet, $J = 7$ Hz, 11-CH₃).

Anal. Calcd. for $C_{26}H_{34}BrNO$: C, 68.41; H, 7.51; N, 3.07. Found: C, 68.37; H, 7.43; N, 3.19.

(b) From Pentazocine (I).

A mixture of 2.85 g. of pentazocine (I), 1.71 g. of benzyl bromide and 15 ml. of dry acetone was allowed to stand at 20-30° for 65 hours and worked up by method (a) to give 3.1 g. of Va and Vb which were identical with the samples obtained by method (a) in ir and nmr spectral comparisons, respectively.

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocinium Bromides (VIa and VIb).

(a) The Preparation of VIa.

A mixture of 462 mg. of 1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocine, 342 mg. of benzyl bromide, and 6 ml. of dry acetone was set aside at 20-25° for 24 hours and the crystals which separated were collected by filtration and recrystallized from ethanol to give 723 mg. of VIa as colorless prisms, m.p. 181-183° dec.; nmr δ (trifluoroacetic acid) ppm: 7.70 (5H, singlet, $CH_2C_6H_5$), 6.96-7.35 (3H, multiplet, aromatic H), 5.16 and 4.78 (each 1H, each doublet, $J = 14.5$ Hz, $\geq \overset{\dagger}{N}-CH_2C_6H_5$), 3.21 (3H, singlet, $\geq \overset{\dagger}{N}-CH_3$), 1.72 (3H, singlet, 6- CH_3) and 1.19 (3H, doublet, $J = 7$ Hz, 11- CH_3).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.66; H, 7.01; N, 3.48. Found: C, 65.45; H, 7.25; N, 3.35.

(b) The Preparation of VIb.

To a suspension of 1.5 g. of II in 10 ml. of acetone was added an excess of methyl bromide, and the mixture was allowed to stand at 20-25° for 17 hours and the separated crystals were collected and recrystallized from ethanol to give 1.76 g. of VIb as colorless prisms, m.p. 239-240° dec.; nmr δ (trifluoroacetic acid) ppm: 7.71 (5H, singlet, $CH_2C_6H_5$), 7.06-7.55 (3H, multiplet, aromatic H), 4.98 and 4.70 (each 1H, each doublet (distorted), $J = 14.5$ Hz, $\geq \overset{\dagger}{N}-CH_2C_6H_5$), 3.32 (3H, singlet, $\geq \overset{\dagger}{N}-CH_3$), 1.60 (3H, singlet, 6- CH_3), and 1.11 (3H, doublet, $J = 7$ Hz, 11- CH_3).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.66; H, 7.01; N, 3.48. Found: C, 65.75; H, 7.10; N, 3.60.

1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium Bromides (VIIa and VIIb).

(a) The Preparation of VIIa.

A mixture of 1.0 g. of 1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocine, 0.7 g. of 3-methyl-2-butenyl bromide, and 5 ml. of dry acetone was set aside for 17 hours at 10-20°, and the solvent was distilled to leave a solid, which was recrystallized from ethanol to give 1.32 g. of VIIa as colorless prisms, m.p. 107-109° dec.; ν max (potassium bromide) cm^{-1} : 1662 (C=C); nmr δ (trifluoroacetic acid) ppm: 6.95-7.35 (3H, multiplet, aromatic H), 5.53 br (1H, $-CH=C<$), 3.20 (3H, singlet, $\geq \overset{\dagger}{N}-CH_3$), 2.03 and 1.97 (each 3H, each singlet, $C=C(CH_3)_2$), 1.61 (3H, singlet, 6- CH_3), and 1.12 (3H, doublet, $J = 7$ Hz, 11- CH_3).

Anal. Calcd. for $C_{20}H_{30}BrNO$: C, 63.15; H, 7.95; N, 3.68. Found: C, 63.00; H, 8.05; N, 3.80.

The crystals (160 mg.) obtained from the mother liquor were identical with the above sample.

(b) The Preparation of VIIb.

To a suspension of 1.0 g. of pentazocine (I) in 5 ml. of dry acetone was added an excess of methyl bromide and the mixture was allowed to stand at 15° for 2.5 hours. After evaporation of the solvent, the residue was recrystallized from 2-propanol to give 1.06 g. of VIIb as colorless prisms, m.p. 102-104° dec.;

ν max (potassium bromide) cm^{-1} : 1662 (C=C); nmr δ (trifluoroacetic acid) ppm: 6.95-7.35 (3H, multiplet, aromatic H), 5.55 br (1H, $-CH=C<$), 3.32 (3H, singlet, $\geq \overset{\dagger}{N}-CH_3$), 2.00 and 1.93 (each 3H, each singlet, $>C=C(CH_3)_2$), 1.56 (3H, singlet, 6- CH_3) and 1.07 (3H, doublet, $J = 7$ Hz, 11- CH_3).

Anal. Calcd. for $C_{20}H_{30}BrNO$: C, 63.15; H, 7.95; N, 3.68. Found: C, 63.05; H, 8.10; N, 3.40.

The crystals (140 mg.) obtained from the mother liquor were identical with the above sample.

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- (20) Melting points are not corrected. Infrared spectra were determined with a Hitachi 215 spectrometer. Nmr spectra were taken with a JNM-MH-60 spectrometer with tetramethylsilane as an internal reference.
- (21) A part of trifluoroacetic acid as solvent was esterified with the solvated ethanol during nmr determination.