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REVISED STEREOCHEMISTRY OF 3-AZA-3-METHYL-6-CYCLOALKYLAMINO-BICYCLO[3.3.1]NONAN-9-OLS

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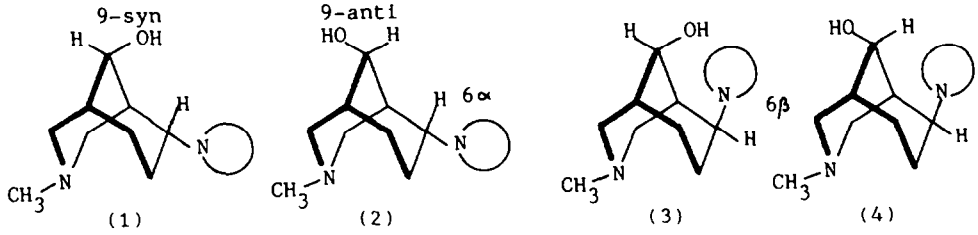
Abstract - The re-examination of stereochemistry of the title compounds is reported. The present results suggest a more reasonable configuration assignments than previously described.

Several years ago Britten and O'Sullivan[1,2] described the synthesis and stereochemistry of 3-aza-3-methyl-6-cycloalkylamino-bicyclo[3.3.1]nonan-9-ones and -9-ols. In this paper we have re-examined this system, our studies resulting in a revision of the earlier work.

Britten and O'Sullivan applied the method of selective acylation, first used by House et al.[3] for both separating and defining the stereochemistry of certain bicyclic amino-alcohols. In the work of Britten and O'Sullivan this method was applied to ascertain the stereochemistry of the more complicated bicyclic amino-alcohols (1) (2) (3) and (4) obtained by reduction of an isomeric mixture of the 9-keto compounds. The full stereochemistry of all the four isomers was given; however, according to our own results, the assignments for the C(6) and C(9) configurations in isomers (2) and (3) were erroneous.



Scheme 1.

This is due to neglect of considering the obvious participation of the cycloalkylamino nitrogen atom in the intramolecular acyl transfer. Britten and O'Sullivan supposed that only isomers (2) and (4) were capable of undergoing acylation reaction with 4-nitrobenzoyl chloride in chloroform. However, when taking the similar effect of both nitrogens into account, the acylation can take place in the case of (3), as well. It is the isomer (1) alone, formed in the largest amount during the reduction, which cannot react in such a way.

Britten and O'Sullivan found that only one isomer of a mixture of

(2) and (3) was acylated, whereas the other precipitated as the hydrochloride salt. As an erroneous conclusion, the acylated isomer was characterized by the steric formula (2), and the non-acylated by (3). Contrary to these findings, we have found that both components of the mixture of (2) and (3) were acylated, one of them undergoing esterification more quickly than the other. Meanwhile, the slightly soluble dihydrochloride salt of the latter was formed partially, thus such a single treatment yielded a mixture of the 4-nitrobenzoyl derivatives. The hydrolysis of this ester mixture gave the amino-alcohols (2) and (3) again, containing now one of the isomers in a greater proportion. On repeating the acylation process, the practically isomer free ester derivative and the dihydrochloride salt derivative, respectively, of the two amino-alcohols could be separated. According to our NMR and IR studies of the separated isomers and on the basis of independent chemical evidence for the nitrogen participation (see below), we assign the steric structure (3) to the ester-forming isomer; therefore, the isomer precipitating as salt during the acylation treatment must have the structure (2).

In order to determine the C(6) and C(9) configurations in (2) and (3) by NMR spectroscopy, the technique of shift reagents was applied. The europium atom of $Eu(fod)_3$ is complexed with the hydroxyl oxigen since not considering the O-H proton, it is the C(9)-H which shows the greatest shift in both cases. As the lanthanide induced shift (LIS) of the different protons depend on the distances measured from the Eu atom, the location of the N-methyl group having an easily assignable signal can be surely ascertained. If the LIS values of the N-methyl group were plotted versus those of the C(9)-H proton in the cases of both isomers (Fig. 1.), two straight lines of considerably different slope were obtained. The salt-forming isomer shows the steeper, and the ester-forming one the less steep slope.

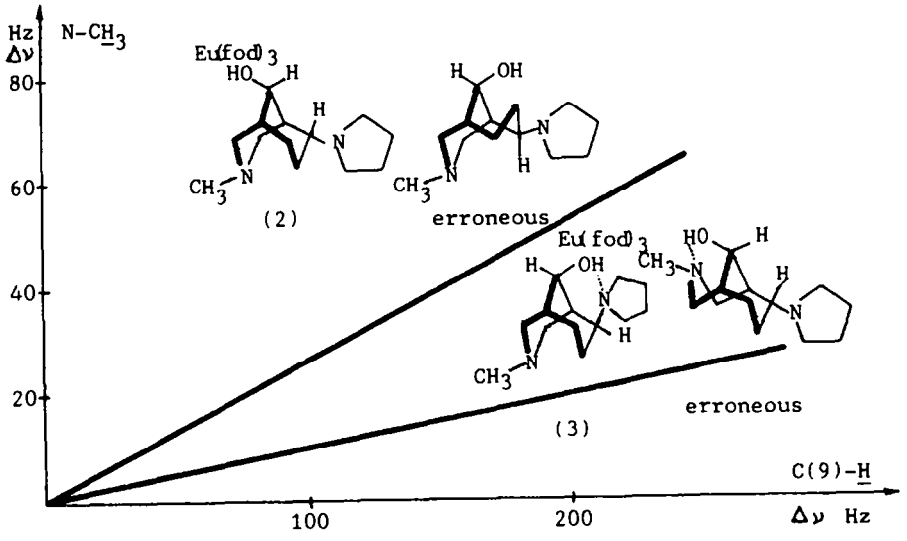


Figure 1.
LIS data of isomers (2) and (3)

From these facts it can be concluded that the N-methyl group is closer to the O(H) atom in the salt forming-isomer, than in the ester-forming one. Consequently, the former has the structure (2), and the latter (3).

The IR spectrum of a strongly diluted carbon disulfide solution (0.0025 M) of (3) shows an intense absorption at 3190 cm^{-1} in the OH region, which is due to a strong intramolecular association. Considering the NMR arguments detailed above, this hydrogen bonding can be formed only with the pyrrolidine nitrogen and not the

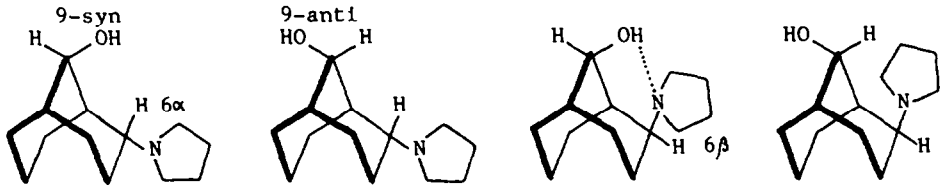
piperidine nitrogen as stated by Britten and O'Sullivan.

As the above-mentioned authors have mistaken the structure of (2) and (3) for each other, the conformations proposed (see Fig. 1.) and the interpretation of the mass spectra[6] should be considered erroneous.

The pure isomers (2) and (3) were also subjected separately to acylation reaction with 4-nitrobenzoyl chloride in chloroform solution. The reaction of (2) gave 78.3 % of the ester product, and 18.9 % of unchanged amino-alcohol in the dihydrochloride salt form, whereas in the case of (3) 98.2 % of 4-nitrobenzoate ester was produced. Upon the same treatment no acylated derivative of (1) was detected by TLC. These observations prove the possible assistance of both the pyrrolidine and piperidine nitrogen atoms in the intramolecular N to O acyl transfer, provided the steric conditions for such a process are favourable.

The separation of the mixture of (2) and (3) was also accomplished by distillation, a simpler method than selective acylation in this case.

The participation of the cycloalkylamino nitrogen in the intramolecular acyl transfer was independently verified in a similar bicyclic compound. In an attempt to acylate a mixture of all four possible isomers (5) (6) (7) and (8) of 2-pyrrolidinyl-bicyclo[3.3.1]nonan-9-ol by the same method, there was obtained only one ester product.



(5) (6) (7) (8)

Scheme 2.

The IR spectrum in carbon disulfide solution (0.0025 M) of the pure amino-alcohol obtained from this ester by hydrolysis showed an absorption at 3210 cm^{-1}, which is indicative of an intramolecularly bonded OH group. It is only isomer (7) which contains the functional groups in positions suitable to allow both N to O acyl transfer and hydrogen bonding.

EXPERIMENTAL

M.p.'s were determined on a Büchi SMP-20 apparatus and are uncorrected. ^1H NMR spectra were obtained on a Tesla BS 487/A spectrometer at 80 MHz, in $CDCl_3$ solutions containing hexamethyl-disiloxane as internal standard.

6α- and 6β-(N-Pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-ones. The method of Britten and O'Sullivan was followed. To the enamine obtained from 1-methyl-4-piperidone and pyrrolidine, acrylaldehyde was added to yield 65.5 % of the aminoketone, b.p. 117-122°C/9 Pa (0.07 Hgmm). Lit.[2] b.p. 124-126°C/0.75 mm. Spectroscopical data (IR, NMR) were identical with those described in the literature[2].

6α-(N-Pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-syn-ol (1)[7] and 6α-(N-pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-anti-ol (2). Compound (1) was prepared by reduction of the mixture of the aminoketones described above with $NaBH_4$/iPrOH, followed by crystallization from ether - ethyl acetate mixture[2]. M.p. 168-169°C, lit.[2] m.p. 169-170°C. Spectroscopical data (IR, NMR) were identical with those reported[2].

The mother liquor of recrystallization was concentrated and treated with 4-nitrobenzoyl chloride in chloroform. The precipitated hydrochloride of (2) was isolated and made alkaline with potassium hydroxide to yield (2) as the free base, m.p. 132°C. Melting point and spectroscopical data were identical with those described for (3) in the literature[2].

6β-(N-Pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-syn-ol (3). A mixture of the isomeric amino-alcohols (from which (1) had been separated by crystallization

containing (2) and (3) chiefly) was distilled under reduced pressure through a 30-cm column filled with metal packing. The pure (3) distilled at 146-150°C/25 Pa (0.2 mm) and solidified shortly, m.p. 55-57°C. Melting point and spectroscopical data (IR, NMR) were identical with those described for (2) in the literature[2].

6α-(N-Pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-anti-yl 4-nitrobenzoate. To a solution of 1.0 g (4.46 mmole) of (2) in 15 ml of chloroform there was added 0.83 g (4.47 mmole) of 4-nitrobenzoyl chloride, with cooling. The reaction mixture was allowed to stand for 12 hours at room temperature. The precipitated material was filtered off, washed with chloroform and dried. It was the dihydrochloride of (2), 0.25 g (18.9 %), m.p. 223-225°C (crude). The mother liquor and the chloroform solution used for washing were combined and concentrated under reduced pressure. The viscous residue was dissolved in a small amount of water, acidified with conc. HCl (pH 3), and extracted with ether to remove the non-basic products. The aqueous part was made alkaline with potassium carbonate, extracted with chloroform and the extract dried over magnesium sulfate. After concentration 1.30 g (78.3 %) of yellow crystalline material was obtained, m.p. 154-155°C (from ethanol). ^{1}H NMR 8.25 (4 H, s, broad , Ar-H); 4.90 (1 H, broad, C(9)-H); 2.12 (3 H, s, N-CH_3). IR (KBr) 2770 (N-CH_3); 1705 (C=O); 1520, 1340 (NO_2). Calc. for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.28; N, 11.25 %; Found: C, 64.32; H, 7.42; N, 11.17 %.

The substance thus obtained proved to the 4-nitrobenzoate ester derivative of the amino-alcohol (2) which was reported by Britten and O'Sullivan[2] to fail to undergo acylation and to which, erroneously, structure (3) was attributed.

6β-(N-Pyrrolidinyl)-3-aza-3-methyl-bicyclo[3.3.1]nonan-9-syn-yl 4-nitrobenzoate. To a solution of 3.0 g (13.4 mmole) of (3) in 20 ml of chloroform there was added 2.5 g (13.5 mmole) of 4-nitrobenzoyl chloride with cooling. The mixture was allowed to stand at room temperature for 12 hours. The formation of any crystalline material was not observed. Application of the isolation procedure described above afforded 4.90 g of a yellow crystalline substance (98.2 %) which melted at 150°C (from ethanol). Melting point and spectroscopical data were identical with those of compound described as the 4-nitrobenzoate derivative of (2) in the literature[2].

2β-(N-Pyrrolidinyl)-bicyclo[3.3.1]nonan-9-syn-yl 4-nitrobenzoate. To a solution of 16.7 g (0.08 mole) of (5) (6) (7) and (8) isomeric mixture[4,5] in 80 ml of chloroform there was added 14.84 g (0.08 mole) of 4-nitrobenzoyl chloride in 20 ml of chloroform, in one portion, at room temperature. The reaction mixture was allowed to stand for 24 hours. Only one 4-nitrobenzoate ester derivative formed, and three amino-alcohols remained unchanged as shown by TLC. The solvent was removed under reduced pressure and the residue dissolved in a small quantity of water, acidified with conc. HCl to pH 3 and extracted with ether removing the non-basic materials. The aqueous layer was made weakly alkaline (pH 8) with solid potassium carbonate and extracted with chloroform. Practically, the extract contained only the ester. (The extraction carried out at pH 10 gave all basic compounds and was not suitable to separate the ester product.) The organic phase was dried over magnesium sulfate and concentrated. A solution of the crude ester in ethanol was treated with ethereal hydrogen chloride to yield 1.6 g of the crystalline hydrochloride salt, m.p. 254-256°C (dec.). IR (KBr) 1710 (C=O); 1515,1340 (NO_2). Calc. for $C_{20}H_{26}N_2O_4$.HCl: C, 60.82; H, 6.89; N, 6.49; Cl, 8.97 %; Found: C, 60.62; H, 6.85; N, 6.72; Cl,8.98%. The ester base liberated from its hydrochloride had m.p. 94-95°C (from heptane). ^{1}H NMR 8.22 (4 H, s, Ar-H); 4.96 (1 H, broad, C(9)-H).

2β-(N-Pyrrolidinyl)-bicyclo[3.3.1]nonan-9-syn-ol (7). A solution of 1.0 g (2.79 mmole) of 2β-(N-pyrrolidinyl)-bicyclo[3.3.1]nonan-9-syn-yl 4-nitrobenzoate in 10 ml of ethanol was treated with 0.56 g (10 mmole) of potassium hydroxide in 5 ml of water at room temperature. Within an hour the hydrolysis was complete (TLC). The mixture was concentrated under reduced pressure, diluted with 5 ml of water and extracted with methylene chloride. The organic extract was dried over magnesium sulfate and concentrated to give 0.55 g(94 %) of a colourless viscous oil. ^{1}H NMR 3.59 (1 H, broad, C(9)-H). This chemical shift is in a fearly good agreement with the corresponding band of (3) (3.56), but differs from the C(9)-H signal of (2) (3.44). IR (CS_2, 0.0025 M) 3210 (OH, intramolecularly H-bonded).

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[7] Several melting points and spectroscopical data are essentially identical with those found by Britten and O'Sullivan[2]. These data are, however, assigned to the correct structures in this paper.