A FACILE SYNTHESIS OF 3-BENZAZEPINE AND DIBENZAZONINE DERIVATIVES ⚲

Hans Bieräugel, Hans-Paul Soetens[1] and Upendra K. Pandit*.
Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

A two-step synthesis of methanodibenzazonine and azepine derivatives starting from readily obtainable isoquinolinium salts is described.

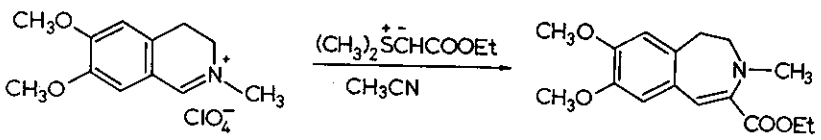
In connection with our studies on the reactivity of carbenes with enamines[2], we have extended the scope of this investigation to include the reaction of ylids with iminium salts. This communication describes a facile synthesis of methanodibenzazonine and 3-benzazepine derivatives via the reaction of sulfuranylidene ylids with suitable isoquinolinium salts. It may be emphasized that the 3-benzazepine system constitutes the nucleus of the rhoeadine and papaverubine alkaloids[3]. The synthesis of benzazepines has been recently reviewed by Kametani and Fukumoto[4].

The reaction of N-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium perchlorate (1) with 2 eq. of ethyl (dimethylsulfuranylidene) acetate[5] (further abbreviated as EDSA) led to a mixture from which only the unstable 1,2-dehydro-2-carboethoxy-3-methyl-7,8-dimethoxy-

⚲ Dedicated to Professor R.B. Woodward on the occasion of his 60th birthday.

-benzazepine (2) was isolated in 10% yield. The structure of 2 followed from its spectroanalytical data: PMR($CDCl_3$) δ=1.33 t (3H, $COOCH_2\underline{CH_3}$), 2.72 s (3H, N-CH_3), 2.80 - 3.18 m (4H, symmetrical pattern for C_4 and C_5 protons), 4.73 q (2H, $COO\underline{CH_2}CH_3$), 6.63 and 6.67 2 × s, (2H, aromatic protons), 6.80 s (1H, C_1-H); IR ($CHCl_3$) 1730 and 1610 cm^{-1}.

The reaction of N-(3',4',5'-trimethoxybenzyl)isoquinolinium perchlorate (3a) with EDSA gave, after reduction with $NaBH_4$, a mixture of benzazepine (4a) and a cyclisation product, which was identified as 1,2,3,10,11-pentamethoxy-14-carboethoxy-13,6-methano[c,f][6]-dibenzazonine (5a). This azonine was isolated as a crystalline product (m.p. 134.5-135°) in 23% yield. The stereochemistry of 5a, especially with respect to the conformation of the 7-membered ring and the relative stereochemistry at C_{13} and C_{14}, deserves comment. The PMR spectrum of 5a is shown in Fig. 1 and the chemical shift assignments are as follows: δ=1.21 t (3H, $COOCH_2\underline{CH_3}$) 1.90 - 2.30 m (1H, C_8-H_A), 3.43 s and 3.05 - 3.60 m (6H, OCH_3, C_7-H, C_8-H_B), 3.76, 3.78, 3.79, 3.93 4 × s, 3.80 AB, q, J_{AB}=18 Hz, (13H, 4 × OCH_3, C_5-H), 4.15 s (1H, C_{13}-H), 4.18 q (2H, $COO\underline{CH_2}CH_3$), 4.44 s (1H, C_{14}-H), 4.50 AB, J_{AB}=18 Hz, (1H, C_5-H), 6.33, 6.43, 7.09 3 × s (3H, aromatic). Particularly revealing are the singlets for the C_{13}- and C_{14}-protons and the high field proton at 1.90 - 2.30 m (C_8-H_A). The singlets for C_{13}-H and C_{14}-H were not affected by temperature, implying thereby a rigid geometrical relationship with a dihedral angle of about 90°. Assignment of C_8-H_A was checked by double resonance; irradiation in the region 1.90 - 2.60 led to simplification of the pattern in the region 3.00 - 3.70, indicating that it is one of the C_7 or C_8 protons. Dreiding molecular models show that the aforementioned results can be only accounted



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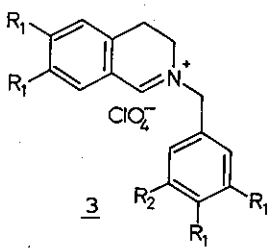
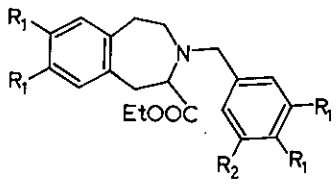


3

	R_1	R_2
a.	OCH_3	OCH_3
b.	OCH_3	H



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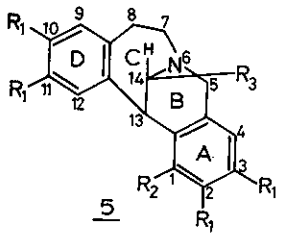
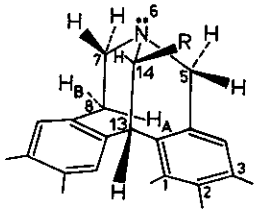
	R_1	R_2
a.	OCH_3	OCH_3
b.	OCH_3	H



5

	R_1	R_2	R_3
a.	OCH_3	OCH_3	COOEt
b	OCH_3	H	COOEt
c.	OCH_3	OCH_3	CH_3



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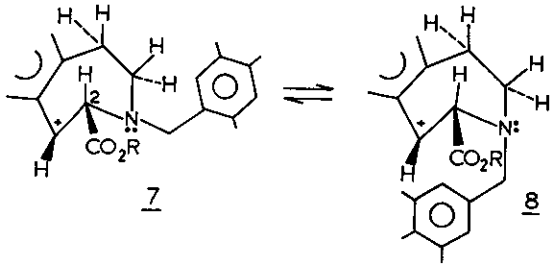
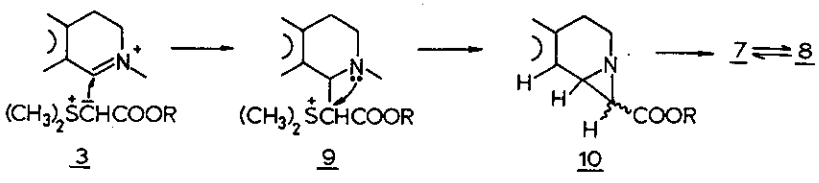


7 ⇌ 8



3 → 9 → 10 → 7 ⇌ 8

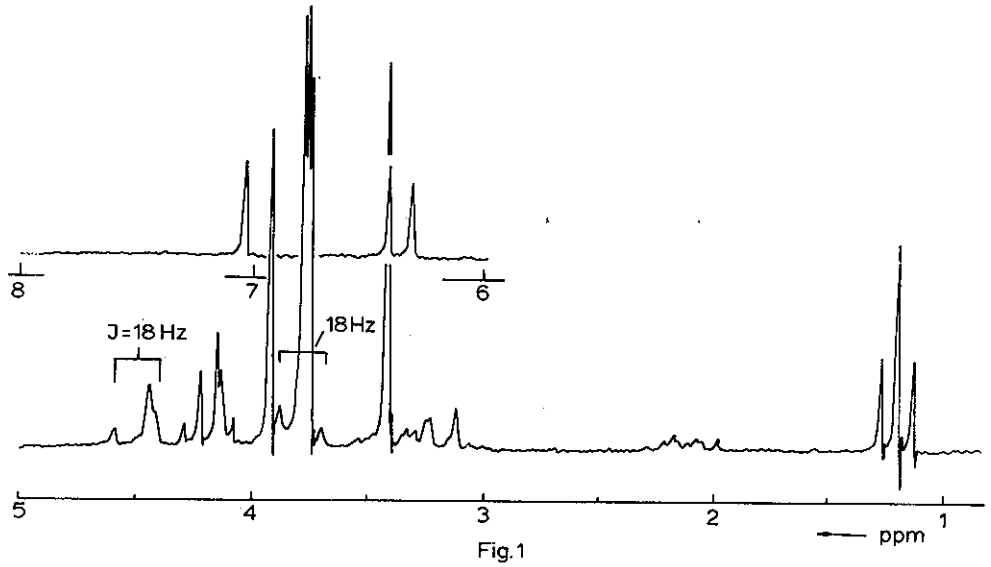


Fig. 1

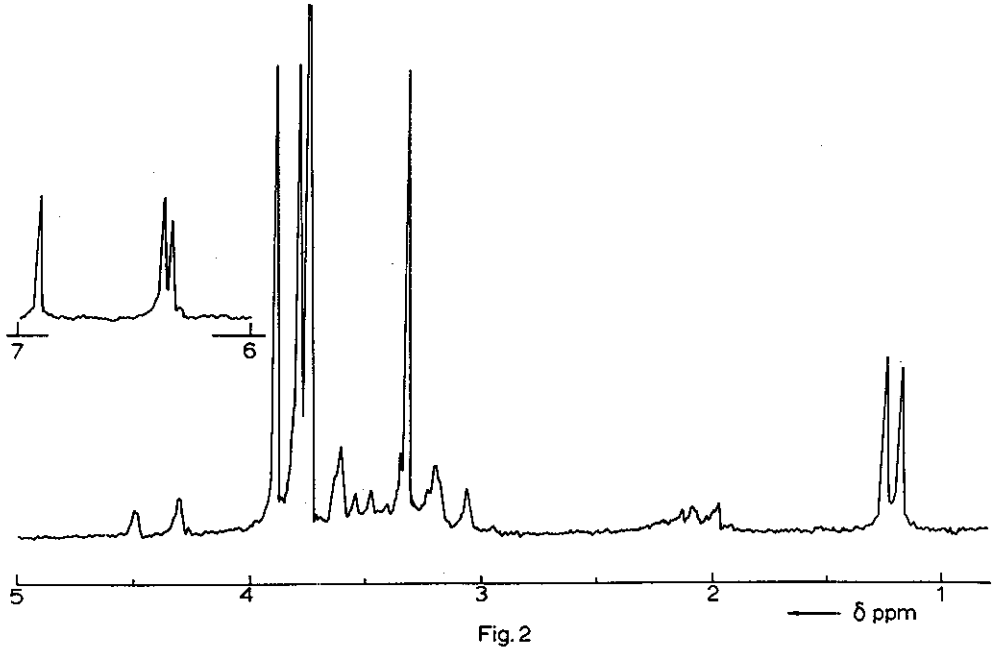


Fig. 2

for by conformation (6) for 5a. The C_{13} and C_{14} protons in 6 are indeed at right angles to each other and the molecule has a distinct rigidity, whereby this geometry is maintained. In 6 the proton C_8-H_A subtends into the shielding zone of the aromatic ring A, a feature which adequately accounts for its high field chemical shift. The mass spectrum of 5a exhibited the molecular ion peak 457(M^+) and a fragmentation pattern consistent with the proposed structure. This pattern is distinctly different from that of an alkaloid containing a berberine skeleton, which is an alternate structure for the cyclization product. The structure of 5a was further supported by its transformation to 5c in three conventional steps: (a) $LiBH_4$, (b) TsCl/pyr. and (c) $LiAlH_4$. The PMR spectrum of 5c (Fig. 2) isolated as a chromatographically pure product, was interpreted as follows: δ=1.2 d (3H, C_{14}-CH_3, J=7.5 Hz), 1.95 - 2.25 m (1H, C_8-H_A), 3.33, 3.75, 3.76, 3.80, 3.90 5 × s, 3.00 - 3.80 m (21H, 5 × OCH_3, C_5-H, C_7-H_2, C_8-H_B, C_{13}-H, C_{14}-H), 4.41 AB, J_{AB}=18 Hz (1H, C_5-H), 6.35, 6.37 and 6.92 3 × s (3H, aromatic).

It should be emphasized that retention of the high field proton (at 1.95 - 2.25 m) in 5c and the general PMR spectral pattern of the latter compound differs significantly from that of the known methyl berberine derivatives.

The reaction of perchlorate (3b) with the aforementioned sulfonium ylid gave, after reduction, the analogous benzazepine and azonine derivatives (4b: 42%) and (5b: 20%), respectively, which were separated by chromatography and isolated as homogeneous products[6].

Concerning the mechanisms of formation of 4 and 5a, it seems reasonable to assume that both the benzazepine and the azonine arise from a common precursor, namely, the stabilized azepine carbonium ion (7 $\rightleftharpoons$ 8). This precursor can be envisaged as arising from the reaction of EDSA with 3a, via the sequence 9 $\longrightarrow$ 10 $\longrightarrow$ 7 $\rightleftharpoons$ 8. While in the intermediate benzazepine carbonium ion a trans diequatorial configuration of the bulky groups (7) will be favoured, this may be expected to exist in equilibrium with relatively smaller amounts of 8, in which the benzyl group occupies an axial orientation. In 7, deprotonation from C_2 results in the benzazepine skeleton which after reduction leads to 4. On the other hand, conformation (8) with the axial benzyl group, can be expected to undergo cyclization to yield the azonine system (6). From Dreiding Models of 8 it can be clearly seen that the latter cyclization process controls the stereochemistry observed for the tetracyclic system.

The synthesis of the azonine system, via a Pomeranz-Fritsch reaction, has been reported for the first time by Sainsbury[7]. The approach described in this communication is a simpler method and in addition, offers the possibility of introducing substituents at the C_{14} position.

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REFERENCES

1 Taken in part from the forthcoming doctorate thesis of H.P. Soetens, University of Amsterdam.

2 (a) S.A.G. de Graaf and U.K. Pandit, Tetrahedron, 1974, 30, 1115.

(b) H.P.M. Thiellier, G.J. Koomen and U.K. Pandit, Heterocycles, 1976, 5, 19.

(c) H. Bieräugel, J.M. Akkerman, J.C. Lapierre Armande and U.K. Pandit, Rec.Trav.Chim., 1976, 95, 266.

3 M. Shamma, "The Isoquinoline Alkaloids", Acad. Press, N.Y. 1972, p. 399.

4 T. Kametani and K. Fukumoto, Heterocycles, 1975, 3, 931.

5 G.P. Payne, J.Org.Chem., 1967, 32, 3351.

6 Spectral data were in agreement with the proposed structures of 4b and 5b.

7 M. Sainsbury, D.W. Brown, S.F. Dyke and G. Hardy, Tetrahedron, 1969, 25, 1881.

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