A NEW SYNTHETIC ROUTE TO BENZAZOCINES INCLUDING THE FIRST EXAMPLE OF 2-BENZAZOCINES

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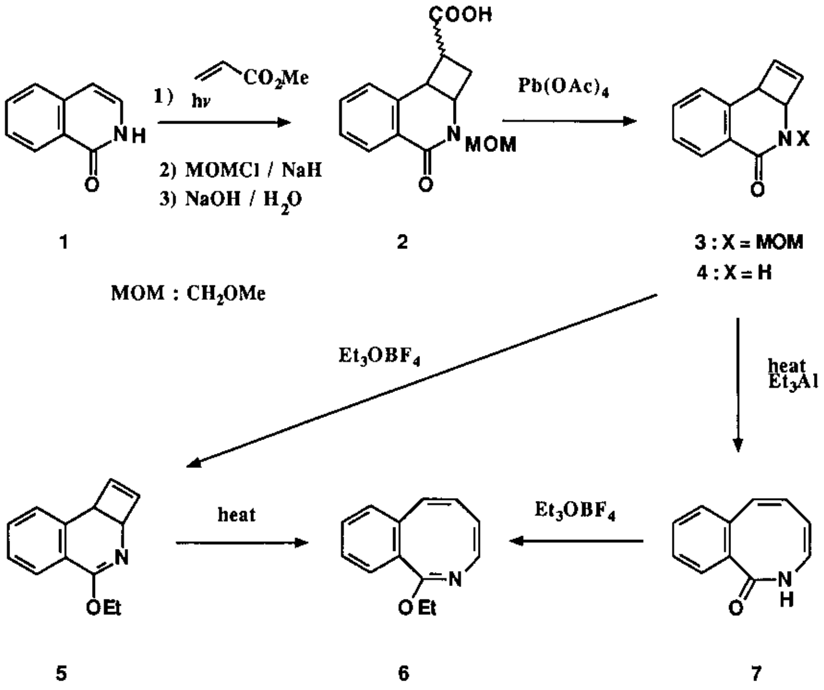
Abstract —— 1-Ethoxy-2-benzazocine (6), the first example of 2-benzazocines, was prepared from 1-isoquinolone (1) via 2a,8b-dihydrocyclobut[c]isoquinolone (4). Similarly, 2-alkoxy-1-benzazocines (12a,b) were obtained from 2-quinolone (10) via the cyclobuta[c]quinolone (11).

A variety of fully unsaturated 1,4-diheterocines containing oxygen, nitrogen, and/or sulfur atoms have been prepared[1,2] as relatively stable ten-π-electron systems, isoelectronic with the cyclooctatetraene dianion. On the contrary, azocines are typical π-equivalent heterocyclic analogs of non-aromatic cyclooctatetraene, therefore, only several examples are known.[3-5] With regard to fused azocines, 2-methoxy-1-benzazocine and 4-methoxy-3-benzazocine are obtained by Bechmann rearrangement of benzotropone oximes,[4] and 2,3,4,5,6-pentaphenyl-1-benzazocine is synthesized by Diels-Alder addition of tetraphenylcyclopentadienone with 2-phenylbenzazete.[5] We report here a new synthetic route to benzazocines and the synthesis of the first example of 2-benzazocines.

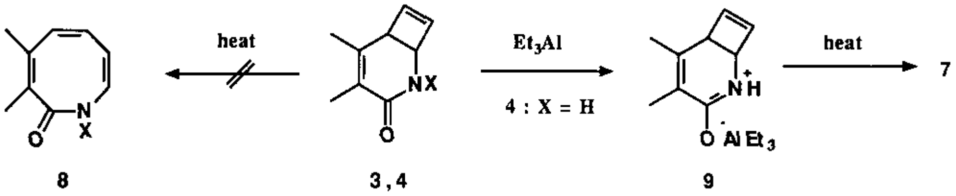
1-Isoquinolone (1) was photo-cycloadded with methyl acrylate and the resulting adduct[6] was protected as its N-methoxymethyl (MOM) derivative then hydrolyzed to give the tricyclic acid (2) (mp 158-160 °C) in ca. 60% yield from 1. The acid (2) was oxidatively decarboxylated on treatment with lead tetraacetate to afford 3-methoxymethyl-2a,8b-dihydrocyclobut[c]isoquinolone (3) (mp 75-77 °C: 90% yield), which was treated with conc. sulfuric acid in 60% acetic acid to give the N-unsubstituted cyclobut[c]isoquinolone (4) (mp 156-158 °C)[7] quantitatively. Treatment of 4 with triethyloxonium tetrafluoroborate (Meerwein reagent) gave the iminoether derivative (5) (mp 21-23 °C; 65% yield), which was heated in toluene at 100 °C for 8 h giving rise to the desired 1-ethoxy-2-benzazocine (6) as an oil in 95% yield.[8] This azocine (6) is the first example of 2-benzazocines and was also obtained by the following different route from 4.



Scheme 1

Although the cyclobutisoquinolone (4) was heated in toluene at 100 °C for 20 h, no reaction occurred. However, heating 4 in benzene containing triethylaluminum at 80 °C for 10 h resulted in ring-expansion to give the benzazocine (7) (mp 149-151 °C) in 80% yield. Treatment of 7 with Meerwein reagent gave the 2-benzazocine (6) in 90% yield. In addition, even when the N-MOM derivative (3) was heated in xylene at 180 °C for 15 h, no reaction occurred, in analogy with 4. These results indicate that the cyclobutene ring in 3 and 4 does not undergo thermal electrocyclic ring cleavage. Therefore, the ring-expansion of the cyclobutisoquinoline (5) into the azocine (6) may proceed only by Cope rearrangement of the aza-cyclohexadiene moiety. In the case used triethylaluminum, the reagent may assist the tautomerization of the lactam form (4) to the iminoether form (9); the latter may undergo Cope rearrangement to give 7.

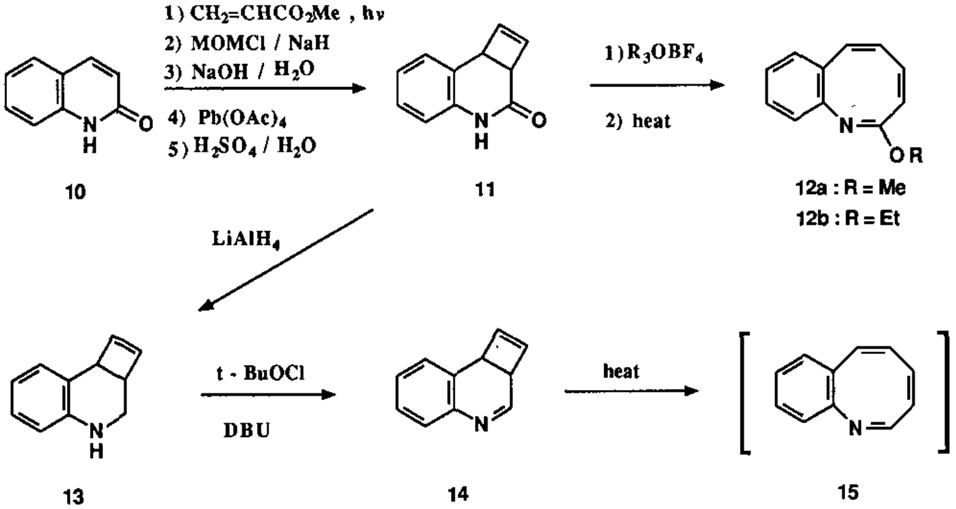
Similarly, 2-methoxy- (12a) (oil)[4] and 2-ethoxy-1-benzazocine (12b) (mp 57-58 °C)



Scheme 2

were obtained from 2-quinolone (10) in ca. 30% yields via the cyclobuta[c]quinolone (11) (mp 202-203 °C) by the similar route to the preparation of 6 from 1 (Scheme 3).[9]

In order to obtain unsubstituted parent 1-benzazocine (15), the dihydrocyclobuta[c]quinoline (14) was prepared. $LiAlH_4$ reduction of the lactam (11) gave the amino compound (13) (mp 97-98.5 °C; 90% yield), which was dehydrogenated on treatment with t-butyl hypochlorite and diazabicyclo[5.4.0]undecene (DBU) to afford the cyclobuta[c]quinoline (14) (oil) in 60% yield. On heating at 70 °C in benzene, the compound (14) gradually decomposed to give a complex mixture and no characterizable products could be isolated, except for quinoline (ca. 15% yield).



Scheme 3

It is known that azocines are thermally unstable and unsubstituted monolyclic parent azocine can exist only at -50 °C,[10] however, α-alkoxy groups stabilize the azocine rings.[3,4] Therefore, in the present cases, the unsubstituted benzazocine (15), probably initially formed, may decompose under the thermal reaction condition, whereas α -alkoxy compounds (6) and (12) can be isolated as stable compounds.

REFERENCES AND NOTES

1. E. Vogel, H.-J. Altenbach, and D. Cremer, Angew. Chem., Int. Ed. Engl., 1972. 11, 935; H.-J. Altenbach and E. Vogel, ibid., 1972, 11, 937; H.-J. Altenbach, H. Stegelmeier, M. Wilhelm, B. Voss, J. Lex, and E. Vogel, ibid., 1979, 18, 962; A. G. Anastassiou, H. S. Kasmai, and D. Hauer, ibid., 1982, 21, 971; B. Z. Zipperer, D. Hunkler, H. Fritz, G. Rihs, and H. Prinzbach, ibid., 1984, 23, 309; H. J. Eggelte and F. Bickelhaupt, Tetrahedron, 1977, 33, 2151; H. J. Eggelte, F. Bickelhaupt, and B. O. Loopstra, ibid., 1978, 34, 3631.
2. J. Kurita, S. Yamada, H. Sakai, and T. Tsuchiya, J. Chem. Soc., Chem. Commun., 1985, 1254.
3. L. A. Paquette and T. Kakihana, J. Am. Chem. Soc., 1968, 90, 3897; L. A. Paquette, Angew. Chem., Int. Ed. Engl., 1971, 10, 11.
4. L. A. Paquette, L. B. Anderson, J. F. Hansen, S. A. Lang, Jr., and H. Berk, J. Am. Chem. Soc., 1972, 94, 4907.
5. B. M. Adger, C. W. Rees, and R. C. Storr, J. Chem. Soc., Perkin Trans. 1, 1975, 45.
6. The photocycloaddition gave a mixture of two head-to-tail adducts (75% and 5%) and two head-to-head adducts (5% and 3%). Recrystallization of the mixture from benzene without isolation by chromatography afforded almost purely one head-to-tail adduct (65%), which was used in the next reaction and is tentatively assigned as the exo-isomer, although the stereochemistry of these adducts is not clear at present. (cf. G. R. Evanea and D. Fabiry, Tetrahedron Lett., 1971, 1749).
7. Satisfactory elemental analyses and spectral data were obtained for all new compounds reported. 4: Ir (KBr): 1658 (C=O) cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ : 4.32 (1H, d, J=4.6 Hz, 8b-H), 4.71 (1H, d, J=4.6 Hz, 2a-H), 6.22 and 6.35 (each 1H, d, J=3 Hz, 1- and 2-H), 7.36 (1H, br, NH), 7.1-7.6 (3H, m, 6-, 7-, and 8-H), 8.21 (1H, dd, J=8 and 1 Hz, 5-H).
8. 6: ^{1}H-Nmr (CDCl$_3$) δ : 1.33 and 4.29 (3H, t, and 2H, q, J=7 Hz, 1-OEt), 5.13 (1H, dd, J=8.8 and 4 Hz, 4-H), 5.95 (1H, dd, J=10.4 and 4 Hz, 5-H), 6.58 (1H, d, J=8.8 Hz, 3-H), 6.62 (1H, d, J=10.4 Hz, 6-H), 6.9-7.5 (4H, m, Ph-H). 7: Ir (KBr): 1670 (C=O) cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ : 5.73 (1H, dd, J=8.8 and 3.7 Hz, 4-H), 6.04 (1H, d, J=8.8 Hz, 3-H), 6.09 (1H, dd, J=11.5 and 3.7 Hz, 5-H), 6.78 (1H, d, J=11.5 Hz, 6-H), 7.2-7.5 (4H, m, Ph-H), 7.61 (1H, br, NH).
9. 12b: ^{1}H-Nmr (CDCl$_3$) δ : 1.35 and 4.28 (3H, t, and 2H, q, J=7 Hz, 2-OEt), 5.97 (1H, d, J=11.4 Hz, 3-H), 6.1-6.2 (2H, m, 4- and 5-H), 6.63 (1H, d, J=11 Hz, 6-H), 6.8-7.2 (4H, m, Ph-H).
10. D. W. McNeil, M. E. Kent, E. Hedaya, P. F. D'Angelo, and P. O. Schissel, J. Am. Chem. Soc., 1971, 93, 3817.

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