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SYNTHESIS OF THE 8H-ISOQUINO[2,1-b][2]BENZAZOCINE SYSTEM VIA 1,3-DIPOLAR CYCLOADDITION OF 8-METHOXYBERBERINEPHENOLBETAINE

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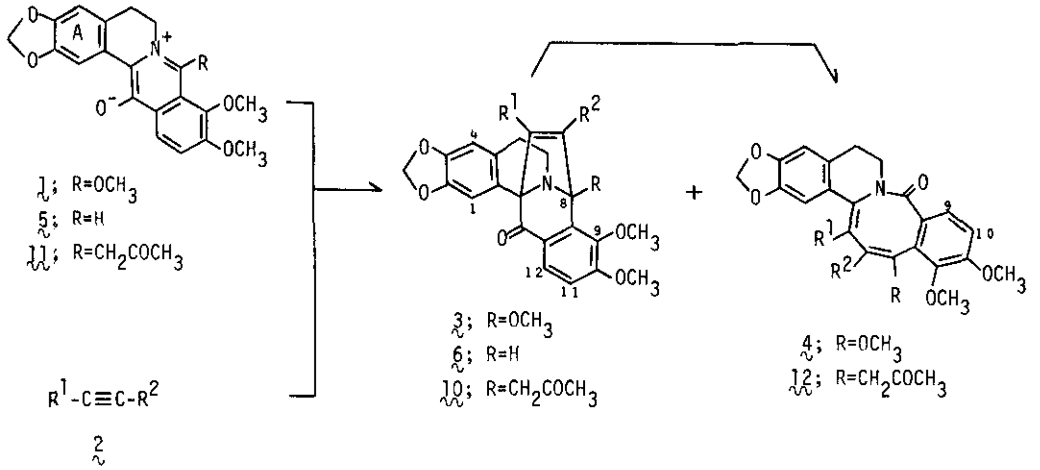
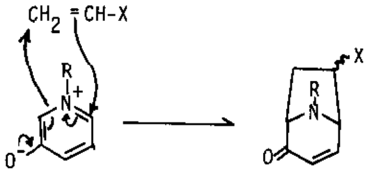
Abstract — Reaction of 8-methoxyberberinephenolbetaine with various acetylenic compounds afforded the 1,3-dipolar cycloadducts, which were heated subsequently in ethanol to provide the 8H-isoquino[2,1-b][2]benzazocines in excellent yields.

1,3-Dipolar cycloaddition of six-membered heteroaromatic betaines has been recently demonstrated to be a useful reaction for synthesis of heterocyclic compounds.[1] We now report a simple synthesis of a new ring system, 8H-isoquino[2,1-b][2]benzazocine, via 1,3-dipolar cycloaddition of 8-methoxyberberinephenolbetaine (1)[2] derived from berberine.

Treatment of 1 with dimethyl acetylenedicarboxylate (2a) in tetrahydrofuran (THF) under reflux for 10 min afforded the cycloadduct (3a)[57%, mp 247-249°, m/e 523 (M^+), ν ($CHCl_3$) 1735sh, 1730 and 1690 cm^{-1}, δ ($CDCl_3$) 7.74 (1H, d, H-12), 6.85 (1H, d, H-11), 6.83 (1H, s, H-1), 6.57 (1H, s, H-4), 5.90 (2H, s, OCH_2O), 3.87 (3H, s, OCH_3), 3.83 (6H, s, $OCH_3 \times 2$), 3.73 and 3.51 (each 3H, s, OCH_3)] along with the azocine (4a)[22%, mp 252-253°, m/e 523 (M^+), ν 1720, 1715 and 1638 cm^{-1}, δ 6.91 (2H, s, H-9 and H-10), 6.57 (1H, s, H-4), 6.17 (1H, s, H-1), 5.85 (2H, s, OCH_2O), 3.97, 3.90, 3.70, 3.60 and 3.55 (each 3H, s, OCH_3)]. Heating of 3a in ethanol effected smooth isomerization leading to the azocine (4a)(93%). The azocine (4a) was also obtained conveniently in 91% yield in one-pot by treatment of 1 with 2a in THF followed by heating in ethanol without isolation of the cycloadduct (3a). The reaction of 1 with several other acetylenes (2) gave the similar results which were summarized in the Table.

In the reaction of 1 with unsymmetrical acetylenes (2c and 2d), the cycloadducts





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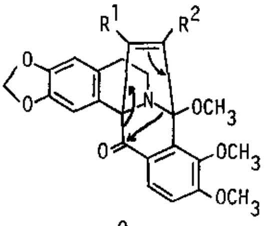

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a ; $R^1=R^2=CO_2CH_3$
b ; $R^1=R^2=COC_6H_5$
c ; $R^1=CO_2CH_3$, $R^2=H$
c'; $R^1=H$, $R^2=CO_2CH_3$
d ; $R^1=COCH_3$, $R^2=H$
d'; $R^1=H$, $R^2=COCH_3$

Table. 1,3-Dipolar cycloaddition of the betaine (1) with dipolarophiles (2)

Dipolarophile	Adduct	Yield(%)	Azocine	Yield(%)		
2a	3a	57	4a	22	91^a	93^b
2b	3b	78	4b	4	89^a	90^b
2c	3c	63	4c	2	50^a	79^b
	3c'	19	4c'	3	27^a	89^b
2d	3d	45	4d	3	43^a	72^b
	3d'	12	4d'	4	32^a	71^b

a; One-pot reaction of 1 with 2. b; Isomerization of 3.

(3c)(63%) and (3d)(45%) were obtained predominantly in comparison with the regioisomers (3c')(19%) and (3d')(12%), respectively. The structures of 3c, 3c', 3d, and 3d' were established from the comparison of the chemical shift of the olefinic hydrogen in the ^{1}H-NMR spectra of the corresponding azocines (4c, 4c', 4d, and 4d'): δ ($CDCl_3$) 4c 5.41, 4c' ≥6.38,[3] 4d 5.24, and 4d' ≥6.40.[3] The lower field shift of the olefinic hydrogen in 4c' and 4d' is due to the effect of anisotropy of the aromatic ring A. Contrary to the general regiospecificity of the cycloaddition 7 → 8,[1,4] where X is an electron withdrawing substituent, the above results offer the first examples which exhibited the reverse regioselectivity. Similarly the reaction of berberinephenolbetaine (5)[5] with 2c or 2d gave the cycloadducts [6c (62%) and 6c' (18%)] or [6d (64%) and 6d' (12%)]: δ ($CDCl_3$, H-8) 6c 4.97 (d, J=2.5 Hz), 6c' 5.30 (s), 6d 4.95 (d, J=3 Hz), 6d' 5.34 (s). The present regioselectivity would be rationalized mainely by secondary orbital overlap[4] between the ring A of 1 or 5 and the substituent of 2c or 2d in the transition state.

The isomerization of the cycloadducts (3) to the azocines (4) would proceed by electrocyclic reaction as depicted in 9 similar to those reported by Padwa[6] and Katritzky.[7] Because the 8-acetonyl adduct (10a) derived from the betaine (11)[8] also isomerized easily to the corresponding azocine (12a) while the 8-hydrogen adducts (6) did not produce the azocines under the same reaction conditions mentioned above, the 8-methoxyl group in 3 may play an important role in the isomerization as a steric releasing effect[9] rather than an electron donating one. Further mechanistic study on the isomerization is now in progress.

REFERENCES AND FOOTNOTES

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3. The signal of the olefinic hydrogen in 4c' and 4d' could not be distinguished from the singlets due to aromatic protons. This value showed the highest-field signal in this region.
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9. A severe steric interaction between the 8- and 9-methoxyl groups in **3** diminishes by isomerization to **4**.

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