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STEREOSPECIFIC INTRODUCTION OF 3α-METHOXY GROUP TO THE VERSATILE INTERMEDIATE OF 11-OXYGENATED ETHANOPHENANTHRIDINE ALKALOIDS. TOTAL SYNTHESES OF (±)-CRINAMINE, (±)-6-HYDROXYCRINAMINE, (±)-CRIWELLINE, AND (±)-MACRONINE.

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In previous paper[1] we have introduced 3β-methoxy group (cis to aryl group) in highly stereoselective manner to the bicyclic compound (1) which was lead to various 11-oxygenated ethanophenanthridine and related alkaloids such as haemanthamine[1], haemanthidine[2], and tazettine[2]. We describe here stereospecific introduction of 3α-methoxy group (trans to aryl group) which appeared in the title alkaloids occurring in Amaryllidaceae plants.

Previous report[1] on bromohydrination of the bicyclic compound (1) showed that the attack of bromonium ion exclusively took place from the convex-face (cis to aryl group) and that the reaction proceeded mainly through the conformation A ($R^1+R^2=O$) thus giving the bromoacetal (2) predominantly. This implies that the stereochemistry of the transition state where anion is introduced also plays an important role in the ionic addition reaction to the double bond. This was hold for methoxybromination of 1, where 4, m.p.185-190°, and 5, m.p.228-230°, were produced in ratio of 2:1 on treatment with N-bromoacetamide (NBA) in methanol.

Steric course of anion attack to the intermediate bromonium ion will be changed by introduction of a bulky substituent in the α-side of the molecule, which will block introduction of anions via conformation A (R^1=OAc, R^2=H) thus forcing the reaction to proceed through the conformation B (R^1=OAc, R^2=H) and thus will completely reverse the product ratio. This was proved to be true. Reaction of MeOBr (prepared from NBA and MeOH in presence of $HClO_4$)

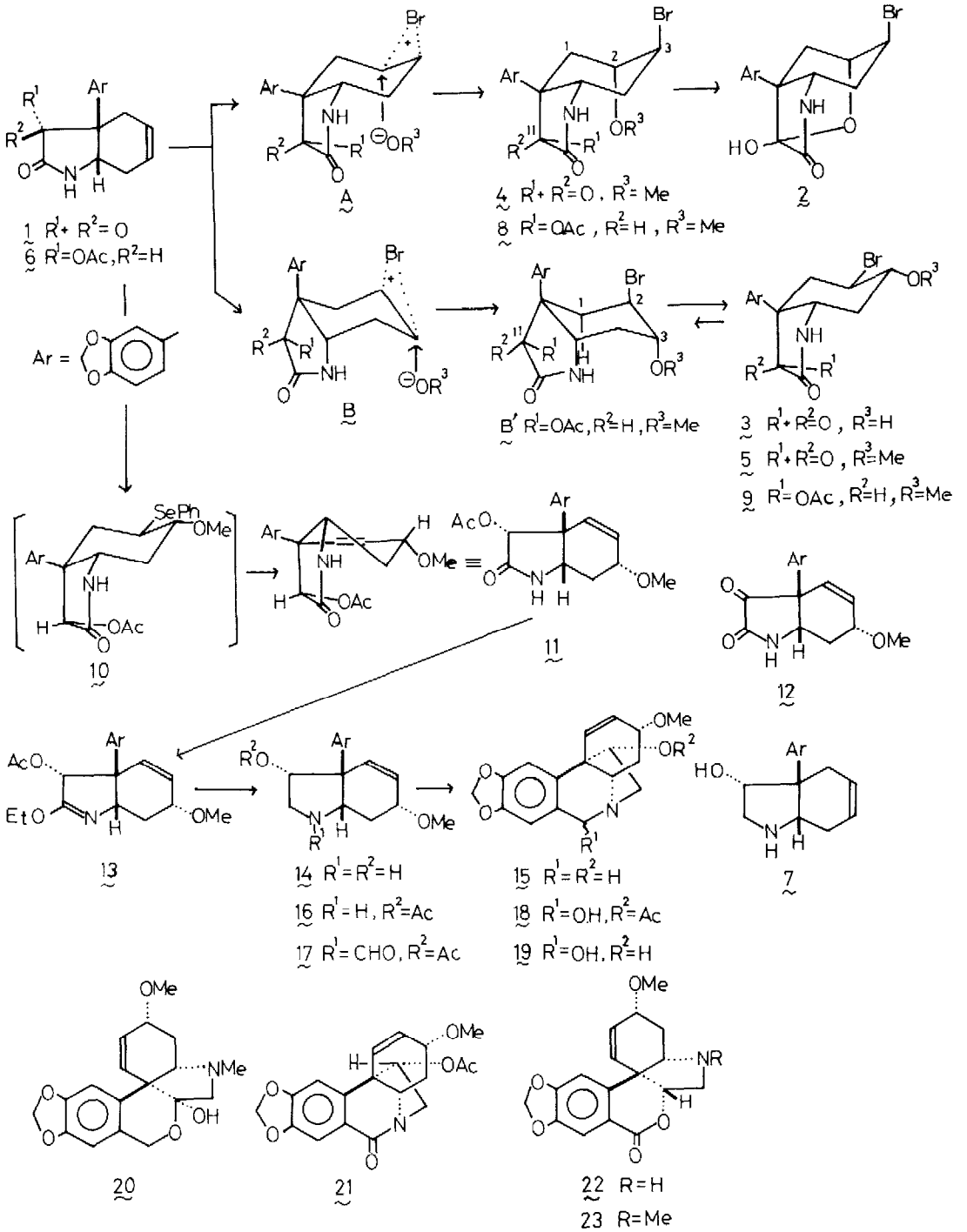
on the acetoxy-lactam (6)[3] at 0° gave the methoxy-bromo-compounds (85%) (8), gum, and (9), m.p.166-169°, in ratio of 1:5 together with a minute amount of unidenfified compound (~10%)[4]. Stereochemistries of 8 and 9 were determined by correlating them with 4 and 5 respectively. Short hydrolysis (NaOH-MeOH) of 9 and Jones' oxidation of the resulting alcohol gave 5, the minor product in methoxybromination of 1, while 4 was converted to 8 by reduction ($NaBH_4$-MeOH) and acetylation.

The addition of PhSeOMe worked similarly. Treatment of 6 with $(PhSe)_2$ and NBA (in place of Br_2 as originally reported[5]) in MeOH at room temp followed by oxidation of the resulting methoxy-selenide (10) with 3% H_2O_2 in THF at room temp gave, with concomitant elimination of phenylselenoxide, the allyl-methyl-ether (11), m.p.193-195°, IR: 1750, 1725cm^{-1}, NMRδ(ppm): 2.10($OCOCH_3$) 3.37(OCH_3), 5.91(1H,d, J=10 Hz) and 6.33(1H, dd, J=4 and 10 Hz)(olefinic protons), 6.07(1H, s,)(>CH-OAc), as a sole product (35%). The stereochemistry of 11 was established as follows. Dehydrobromination of 5[6] with DBU in toluene yielded 12, which on reduction with $Zn(BH_4)_2$ in ether followed by acetylation afforded 11, identical with the compound obtained above.

Stereospecific introduction of 3α-methoxy group to the bicyclic compound (1) was thus achieved and the title natural alkaloids[7] were synthesised from 11 as follows.

Crinamine. The compound 11 was reduced with $LiAlH_4$ in THF to the amine (14), whose hydrochloride was heated with 30% HCHO for 8 hr to furnish (±)-crinamine (15), m.p.215-220°.

6-Hydroxycrinamine. The compound 11 was converted on treatment with triethyl-oxoniumfluoroborate to the imino-ether (13) which on reduction with $NaBH_4$-$SnCl_4$ $2Et_2O$ complex[8] in dimethoxyethane gave the amine (16). Formylation of 16 with HCOOAc-pyridine yielded the formate(17)(60% from 11), gum, IR: 1740, 1670cm^{-1},. Treatment of 17 with $POCl_3$ in toluene at 120° for 2 hr followed by basification with dilute NH_4OH as described in the synthesis of haemanthidine[2] afforded the acetate (18)(35%), m.p.249-250°, which on short hydrolysis (K_2CO_3-MeOH) furnished (±)-6-hydroxycrinamine (19) m.p.223-225°.


1 R¹+R²=O
6 R¹=OAc, R²=H
Ar =
A
B
4 R¹+R²=O, R³=Me
8 R¹=OAc, R²=H, R³=Me
2
B' R¹=OAc, R²=H, R³=Me
3 R¹+R²=O, R³=H
5 R¹+R²=O, R³=Me
9 R¹=OAc, R²=H, R³=Me
10
11
12
13
14 R¹=R²=H
16 R¹=H, R²=Ac
17 R¹=CHO, R²=Ac
15 R¹=R²=H
18 R¹=OH, R²=Ac
19 R¹=OH, R²=H
7
20
21
22 R=H
23 R=Me

Criwelline. Methylation of the acetate (18) with CH_3I in MeOH followed by treatment with 5% KOH (room temp, 1 hr) gave after purification through the picrate (m.p.231-233°), (±)-criwelline (20), m.p.154-157° in almost quantitative yield.

Macronine. The acetate (18) was oxidized (MnO_2 in CH_2Cl_2, 2 hr, room temp) to the lactam (21)(70%), m.p.222-228°, IR: 1745, 1695, 1610cm^{-1}. Short hydrolysis (K_2CO_3, 1 hr, room temp) of 21 and acid treatment of the hydrolysate yielded the lactone (22) which on methylation with HCHO-$NaBH_4$ furnished (±)-macronine (23), m.p.183-187°, in 60% yield.

The racemic alkaloids above synthesised were identified respectively by comparisons of TLC and/or of their spectral data (IR in $CHCl_3$, and NMR in $CDCl_3$) with the natural specimens.

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References and Footnotes

1. Y.Tsuda, K.Isobe, and A.Ukai, Chem. Comm., 1971, 1555.
2. Y.Tsuda, A.Ukai, and K.Isobe, Tetrahedron Letters, 1972, 3153.
3. The compound (6), m.p.204-205°, was obtained from 1 as a sole product by $NaBH_4$ reduction followed by acetylation, whereby convex-face attack of the hydride took place. The stereochemistry was proved by correlation with the known compound
4. The ratio was dtermined from the intensity ratio of OMe peaks in the NMR spectrum of the raw product. (δ3.40 for 9, 3.44 for 8, and 3.09 for unidentified compound).
5. K.B.Sharpless and R.F.Lauer, J.Org.Chem., 39, 427 (1974).
6. Dehydrobromination of 9 did not give satisfactory result probably due to the steric hindrance by 11α-OAc group on approaching the base to 1α-H in the conformation B'(R^1=OAc, R^2=H).
7. W.C.Wildman, The Amaryllidaceae alkaloids, R.H.F.Manske, "The Alkaloids" Vol XI. p. 307, (1968). Academic Press.
8. Y.Tsuda, T.Sano, and H.Watanabe, Synthesis, to be published.