

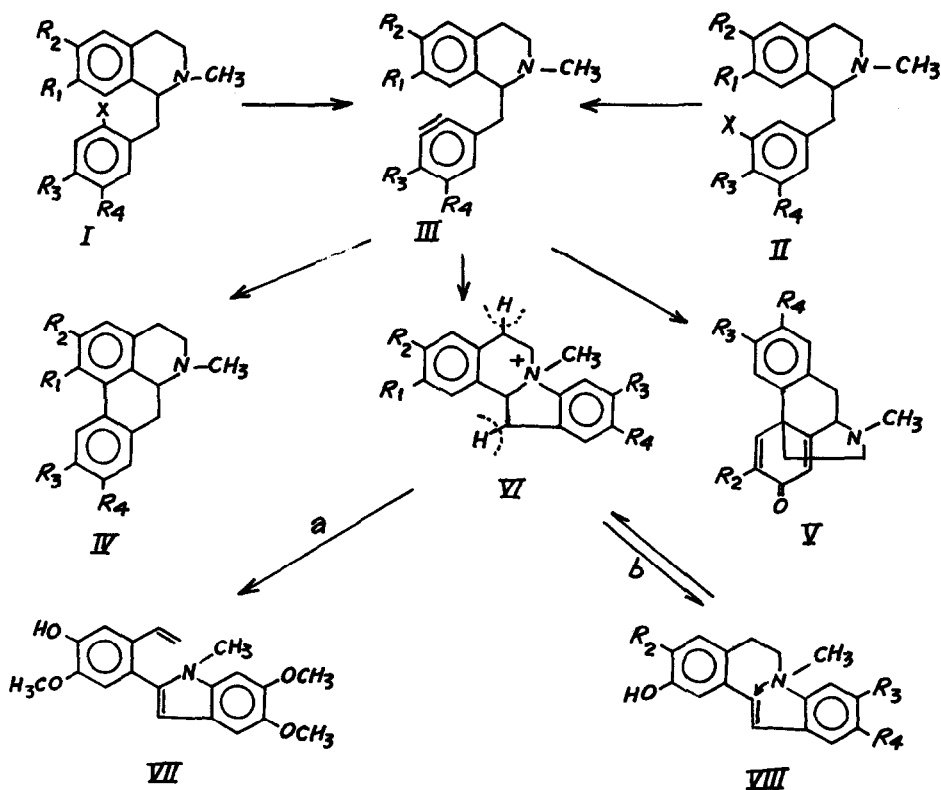
SYNTHESIS OF APORPHINE, MORPHINANDIENONE AND DIBENZINDOLIZINIUM
ALKALOIDS THROUGH BENZYNE CYCLISATION

S.V. Kessar, (Miss) Rajwant Randhawa and S.S. Gandhi

(Department of Chemistry, Panjab University, Chandigarh-14, India)

(Received in UK 14 June 1973; accepted for publication 20 June 1973)

Subsequent to our publication² on synthesis of aporphines through reaction of phenolic 1-benzyltetrahydroisoquinolines (I, R₁ = OH, X = Cl or Br) with metal amides in liquid ammonia, two groups have independently reported work on similar lines. While the results of Kametani³ correspond with ours, Gibson et al. found no evidence for aporphine formation on reaction of II (R₁ = OH, R₂ = R₃ = OCH₃, R₄ = H, X = Br) under these conditions.⁴



The latter result cast some doubt on our assumed mechanism of cyclisation (I \rightarrow III \rightarrow IV), since benzyne formation from 2'-halogenated (I) and 3'-halogenated (II) substrates should proceed at comparable rates and afford the same intermediate (III). It became necessary to examine the alternate possibility that in case of I cyclisation occurred through intramolecular halogen displacement by the nucleophilic ortho carbon atom of the phenoxide ion (I, $R_1=O^-$) formed in the basic reaction medium. However, even prolonged treatment of Ia ($R_1=OH$, $R_2=OCH_3$, R_3 , $R_4=O-CH_2-O$, $X=Br$) with excess potassium hydroxide in liquid ammonia, conditions ensuring generation of the anion but not of benzyne, was found to result in no loss of halogen. Further, a reinvestigation of the reaction of IIa ($R_1=OH$, $R_2=R_3=OCH_3$, $R_4=H$, $X=Br$) with potassium amide in liquid ammonia (10 moles potassium amide, 3 hrs) gave, in our hands, the aporphine IVd ($R_1=OH$, $R_2=R_3=OCH_3$, $R_4=H$; m.p. 181-82°; m/e, 311 (M^+), 310 ($M-1$), 296 ($M-15$), 280 ($M-31$), 268 ($M-43$); UV λ_{max}^{EtOH} 266 (log ϵ 4.03), 274 (log ϵ 4.05), 305 (log ϵ 3.8) nm] in 20 % yield. Thus intermediacy of benzyne in these cyclisations seems well established. It is interesting to note that in III ($R_1=O^-$) attack of benzyne at the para carbon atom also occurred, albeit to a limited extent, to give the morphinandienone skeleton V [from Ia amurine (Va, $R_2=OCH_3$, R_3 , $R_4=O-CH_2-O$) was isolated in 2 % yield and identified by comparison with the natural alkaloid⁵].

Dibenzindolizine compounds⁶ [VIa, $R_1=OH$, $R_2=OCH_3$, R_3 , $R_4=O-CH_2-O$, m.p. 173-74°, 15 %; VIb, $R_1=OH$, $R_2=R_3=R_4=OCH_3$, m.p. 101-103°, 30 %; VIc, $R_1=OH$, $R_2=OCH_3$, $R_3=R_4=H$, m.p. 212-214°, 25 %; VIId, $R_1=OH$, $R_2=R_3=OCH_3$, $R_4=H$, m.p. 207-209°, 10 %] constitute the third product isolated from reaction of I and II with potassium amide in liquid ammonia⁷. These salts could be readily converted into the corresponding alkaloids e.g. treatment of VIa with aq. potassium iodide afforded Cryptowoline iodide (m.p. 242-43°; lit⁸ m.p. 245-46°). Besides its synthetic utility, isolation of substantial quantities of VI is intriguing because of two reasons (a) propensity of benzyne for intramolecular reaction with a tertiary nitrogen even in presence of

excess of strongly nucleophilic amide ions and abundant ammonia molecules, (b) stability of VI under conditions expected to result in a Hofmann elimination⁹ (path a or b). In fact in reaction of Ie ($R_1=R_3=R_4=OCH_3, R_2=OH, X=Br$) the latter process did occur and only the styrene VII ($C_{20}H_{21}NO_4, m.p. 180-181^\circ; NMR^{10} (CDCl_3), \delta 5.0 (dd, J=10.2, 1.0 \text{ Hz}; 1H), \delta 5.6 (dd, J=17.5, 1.5 \text{ Hz}; 1H) \delta 6.2-6.5 (1H, \text{multiplet})$) could be isolated (30 %). It seems that in VI a-d the presence of the negative charge on the oxygen atom¹¹ sufficiently decreases, by mesomeric effect, the acidity of para benzylic hydrogens so as to suppress reaction through path a. Elimination through path b may not be proceeding due to strain associated with the dihydroazone¹² system (VIII). However, it is likely¹³ that VIII is formed in the highly basic reaction medium but undergoes a transannular cyclisation (VIII \rightarrow VI) subsequently¹⁴. Treatment of If ($R_1=R_2=OCH_3, R_3, R_4=O-CH_2-O, X=Br$) with KNH_2/K (2:1) in liquid ammonia gave (40 %) the corresponding dihydro derivative of VIII [$C_{20}H_{23}NO_4, m.p. 169-70^\circ; NMR (CDCl_3) \delta 3.95 (2 \times OCH_3, 6H), \delta 2.55 (N-CH_3, 3H), \delta 4.0 (O-CH_2-O, 2H), \delta 2.8 - 3.2 (Complex, 4 \times CH_2, 8H), \delta 6.6 - 6.9 (Aromatic, 4H); m/e 341 (M^+), 326 (M-CH_3); UV \lambda_{max}^{EtOH} 290 (\log \epsilon 3.9) \text{ nm}$], presumably through in situ reduction of the initially formed VI or VIII. This seems a promising route to dibenzoazonines which are of interest for aromaticity studies.

REFERENCES AND FOOT-NOTES

1. Part XI of the series 'New routes to condensed polynuclear compounds', Part X, S.V.Kessar, N. Parkash and G.S. Joshi, Tetrahedron Ms 4910.
2. S.V. Kessar, S. Batra and S.S. Gandhi, Ind. J. Chem., 8, 468-69 (1970). Besides Domesticine (25 %), Thalimidine (25 %) and N-Methylcaaverine (20 %) have also been synthesised by us through this route.
3. T. Kametani, S. Shibuya, K. Kigasawa, M. Hiragi and O. Kusama. J. Chem. Soc.(c) 2712 (1971); T. Kametani, K. Fukumoto and T. Nakano, Tetrahedron, 28, 4667 (1972).

4. M.S. Gibson, G.W. Prenton and J.M. Walthew, J. Chem. Soc.(c) 2234 (1970). Only partial reaction, resulting in recovery of a diminished quantity of the starting material, was observed.
5. We are indebted to Prof. W. Dopke for a sample of amurine.
6. Structures VIa-d have been confirmed through mass ($M-HX$, $M-CH_2X$, $M-CH_2X-1$) and NMR (DMSO) δ 3.65 ($N^+ - Me$), δ 5.5 (t, $J=8.0$ Hz, 12a-H) spectroscopy⁸.
7. Results presented at the convention of Indian Chemical Society, Allahabad 1972, see abstract page 79.
8. T. Kametani and K. Ogasawara, J. Chem. Soc.(c) 2208 (1967).
9. A.C. Cope and E.R. Trumbull, organic reactions, Vol. 11, John Wiley and Sons, New York, 1960. p. 373.
10. G.K. Hamer and W.F. Reynolds, Can. J. Chem. 46, 3813 (1968). The formed dihydroindole gets aromatised during work-up.
11. In reaction of IIb ($R_1, R_2 = O-CH_2-O$, $R_3 = OCH_3$, $R_4 = H$, $X = Br$), another substrate without the protective phenolic function, formation of a Hofmann elimination product, of unassigned structure, was observed, See ref. 4.
12. No particular geometry at the double bond is implied.
13. G. Wittig, Angew. Chem. 63, 15 (1951).
14. On addition of ammonium chloride or during work-up. Such transannular cyclisations in medium sized aza rings are known; R.H.F. Manske, The Alkaloids, Vol. IV, Academic Press Inc, New York, 1954. p. 151; D.D.O' Rell, F.G.H. Lee and V. Boekelheide, J. Am. Chem. Soc. 94, 3205 (1972).