A NOVEL PHTHALIDEISOQUINOLINE SYNTHESIS FROM THE BENZ[d]INDENO[1,2-b]AZEPINE

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Permanganate oxidation of 12-chloro-5,6,7,7a-tetrahydro-2,3,9,10-tetramethoxy-7-methylbenz[d]indeno[1,2-b]azepine (17) in the presence of piperidine, followed by reduction with sodium borohydride gave the phthalideisoquinoline (19).

Biogenetically, the phthalideisoquinoline (14)[1] and protopine (4) type alkaloids[2] are formed in nature by oxidative modification of tetrahydroprotoberberines (5).[3] Moreover, the rhoeadan alkaloids (11) could be biosynthesised from protoberberines (5) by oxidation.[4] Although the biogenesis of the spirobenzylisoquinolines (8) still remains to be established by in vivo experiment, this type of alkaloid may be derived in plants from the protoberberine alkaloids.[5] As described above, the protoberberines play an important role in the biogenesis of some isoquinoline alkaloids and recently there have been reports on the biomimetic synthesis of the isoquinoline alkaloids from protoberberines.[6]

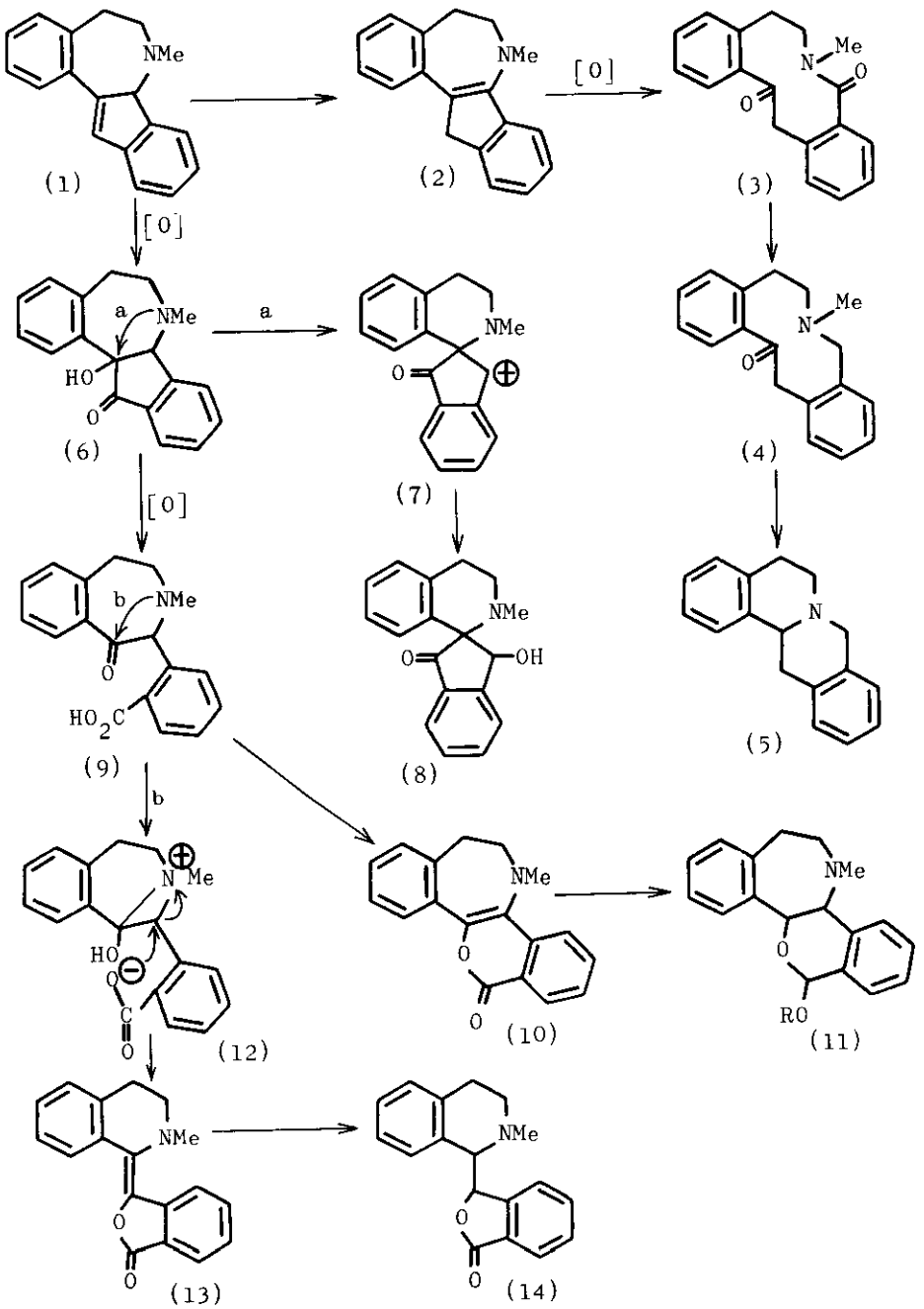
On the other hand, the benz[d]indenoazepines (1,2)[7,8,9,10] occupy chemically an important position; thus, this type of compounds has been obtained from the spirobenzylisoquinoline (8),[7] protoberberines (5),[10] and 1-benzoylisoquinoline[9]

and converted into the rhoeadan (11)[7,8] and spirobenzylisoquinoline (8) alkaloids.[11]

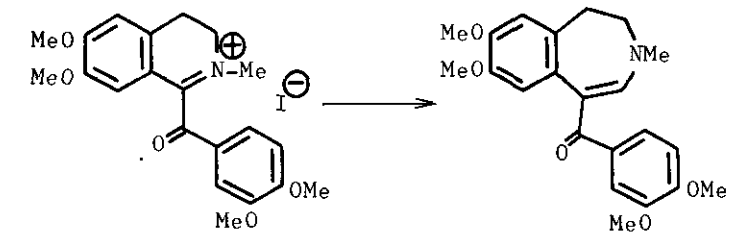
We also expected the benz[d]indeno[1,2-b]azepine (1) to be converted into the protopine (4)-tetrahydroprotoberberine (5), spirobenzylisoquinoline (8), rhoeadan (11) and phthalideiosquinoline (14) type bases by oxidation as shown in Scheme 1. Thus, if oxidation of 1 would proceed after isomerisation of 1 to 2, the amido ketone (3) would be formed, which is a precursor for protopine (4) or tetrahydroprotoberberine (5). Mild oxidation of 1 gives the keto alcohol (6), whose ring contraction (as shown in route a), followed by hydroxylation of 7, would furnish a spirobenzylisoquinoline (8). Further oxidation of 6 gives the ring-opening keto-carboxylic acid (9), whose recyclisation by formation of enol lactone affords 10, a key precursor or rhoeadan (11). On the other hand, aziridine formation of 9, followed by ring opening of the resulting 12, yields 13 which is easily converted into the phthalideisoquinoline (14) by reduction. On the ground of this analysis, we examined an oxidation of the benz[d]indeno[1,2-b]azepine type of compound (1).

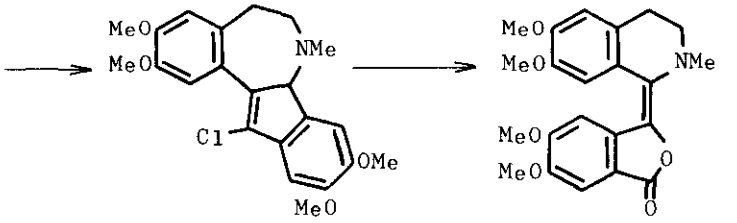
Treatment of 5-benzoyl-2,3-dihydro-3-methyl-1H-3-benzazepine (16)[9] (prepared by reaction of 3,4-dihydropapaveraldine methiodide (15) with diazomethane) with phosphoryl chloride in boiling toluene gave 12-chloro-5,6,7,7a-tetrahydro-2,3,9,10-tetramethoxy-7-methylbenz[d]indeno[1,2-b]azepine (17) (90 %)[12] in addition to a small amount of 5-formyl-4-phenylbenzazepine (21). The latter (21) was obtained as a major product (80 %) by treatment of 16 with phosphorous pentoxide in boiling toluene. This product has a formula $C_{22}H_{25}NO_5$ [microanalysis and mass spectrum, m/e 383 (M^+)] and a formyl group [δ($CDCl_3$) 8.91 (1H, s) and m/e 354 (M^+ - CHO)]. The u.v. spectrum (MeOH) showed λ_{max} at 350, 323^{sh}, 293^{sh}, 266, and 229 nm, and was similar to that of the same system of compounds.[8,9] The n.m.r. spectrum [δ ($CDCl_3$) 3.86 (3H, s, OMe), 3.90 (9H, s, 3 x OMe), 6.61 (1H, s, ArH), 6.84 (1H, s, ArH), 6.92 (2H, s, ArH) and 7.20 (1H, s, ArH)] revealed the presence of an enamine system by the resonance of N-methylene group at 2.9 - 3.2 (2H, m) and 3.6 - 3.9

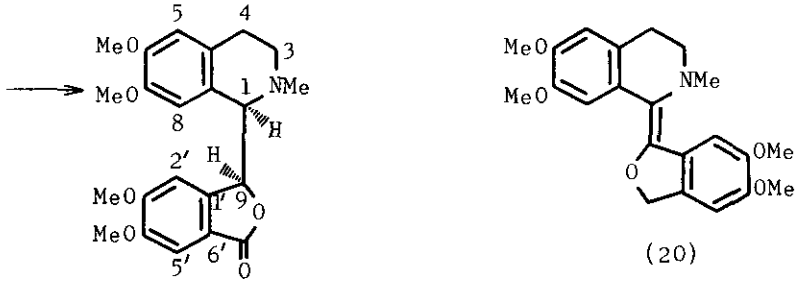
Scheme 1

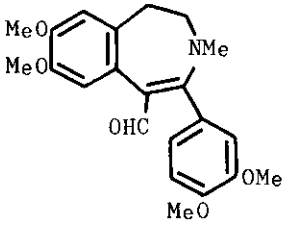


Scheme 2


MeO
MeO
N-Me
I
O
OMe
MeO
NMe
(15)
(16)


MeO
MeO
NMe
Cl
OMe
MeO
O
(17)
(18)


5
4
3
MeO
MeO
1
NMe
8
H
2'
H
1'
9
O
6'
5'
OMe
(19)
(20)


MeO
MeO
NMe
OHC
OMe
MeO
(21)

(2H, m)[8] and the chemical shift of N-methyl at 2.63 indicated a phenyl group located a at the α-position of the enamine system.

The oxidation of 17 with potassium permanganate in acetone in the presence of piperidine and acetic acid at 0° for 0.5 hr[13] gave the lactone (18) [$C_{22}H_{23}NO_6$, m/e 397 (M^+)] in 15 % yield in addition to many unpurified products.

The reduction of (18) with sodium borohydride in methanol afforded the phthalide-isoquinoline (19), ν_{max} ($CHCl_3$) 1755 - 1750 (five membered aromatic lactone), λ_{max} (MeOH) 303^{sh}, 291, and 257 nm. The mass spectrum showed a base peak at m/e 206 together with a weak molecular ion (m/e 399) which suggested this product to be a phthalideisoquinoline.[14] Moreover, the n.m.r. spectrum (δ in $CDCl_3$) showed two methine protons coupled each other at 4.07 (d, J 4 Hz, C_1 - H) and 5.56 (d, J 4 Hz, C_9 - H) in addition to N-methyl at 2.58, four O-methyl at 3.73, 3.78, 3.86 and 3.92, and four aromatic protons at 6.18 (C_8 - H), 6.48 ($C_{2'}$ - H), 6.62 (C_5 - H) and 7.25 ($C_{5'}$ - H) as each singlet. These data revealed that the product has the structure 19, belonging to the erythro series and our spectral data are in good accordance with the data published by Shamma.[15]

The stereochemistry of 18 could be assigned to the Z - rather than the E - form by consideration of the n.m.r. spectrum. Thus the presences of an O-methyl group (δ 3.53) resonating at abnormally high field and two aromatic protons (7.57 and 7.73) shifted to downfied are similar to those of 1,2,9,10-tetramethoxyaporphine.[16]

A transformation of the benzylisoquinoline into the phthalideisoquinoline through benzindenoazepine provides the third synthetic method for the phthalideiosquinolines.[15]

REFERENCES

1 A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, J. Chem. Soc. (C), 1968, 2163; A. R. Battersby, R. J. Francis, M. Hirst, R.

Southgate, and J. Staunton, Chem. Comm., 1967, 602.

2 D. H. R. Barton, R. H. Hesse, and G. W. Kirby, Proc. Chem. Soc., 1963, 267.

3 H. R. Schütte, "Biosynthese der Alkaloide", ed. by K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 367.

4 H. Rönsch, European J. Biochem., 1972, 28, 123.

5 M. Shamma and C. D. Jones, J. Amer. Chem. Soc., 1969, 91, 4009; 1970, 92, 4943; M. Shamma and J. F. Nugent, Tetrahedron, 1973, 29, 1265; H. L. Holland, M. Castillo, D. B. MacLean, and I. D. Spenser, Canad. J. Chem., 1974, 52, 2818.

6 T. Kametani, K. Fukumoto, and F. Satoh, Bioorg. Chem., 1974, 3, 430, and refs. cited herein.

7 H. Irie, S. Tani, and H. Yamane, Chem. Comm., 1970, 1713; J. C. S. Perkin I, 1972, 2986.

8 K. Orito, R. H. F. Manske, and R. Rodrigo, J. Amer. Chem. Soc., 1974, 96, 1944.

9 T. Kametani, S. Hirata, F. Satoh, and K. Fukumoto, J. C. S. Perkin I, 1974, 2509.

10 B. Nalliah, R. H. Manske, and R. Rodrigo, Tetrahedron Letters, 1974, 2853.

11 S. O. Desilva, K. Orito, R. H. F. Manske, and R. Rodrigo, Tetrahedron Letters, 1974, 3243.

12 T. Kametani, S. Hirata, H. Nemoto, M. Ihara, S. Hibino, and K. Fukumoto, J. C. S. Perkin I, to be submitted.

13 R. Tull, R. E. Jones, S. A. Robinson, and M. Tishler, J. Am. Chem. Soc., 1955, 77, 196.

14 M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, J. Amer. Chem. Soc., 1963, 85, 2807.

15 M. Shamma and V. St. Georgiev, Tetrahedron Letters, 1974, 2339.

16 M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p. 220.

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