Tetrahedron Letters No. 51, pp 4867 - 4870, 1971. Pergamon Press. Printed in Great Britain.

PHOTOCHEMICAL SYNTHESIS OF ISOINDOLO[1,2-b][3]BENZAZEPINE DERIVATIVES. PREPARATION OF SCHÖPF-SCHWEICKERT AMINE VI [1].

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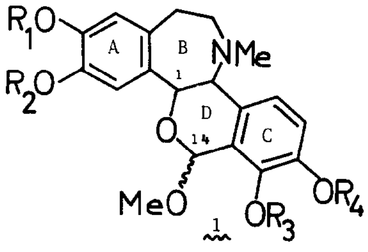
(Received in USA 26 October 1971; received in UK for publication 16 November 1971)

In 1965, outstanding efforts by Šantavý and coworkers culminated in the structural elucidation of rhoeadine (**1a**) which proved to be the first member of the significant and biosynthetically intriguing [3] Rhoeadine group of alkaloids belonging to the benzylisoquinoline family [4]. Until recently, the state of the synthetic art in this area appeared to lie in dormancy. In view of the abrupt awakening of interest [5,6,7], we wish to report our different approach [8] to this group of alkaloids which involves a new and apparently general type of photocyclization reaction (**6** → **7**) and which so far has led to the efficient and facile synthesis of Schöpf-Schweickert amine VI (**8b**) [9], a compound which occupies a position of some historical importance in benzylisoquinoline alkaloid chemistry [4a,10].



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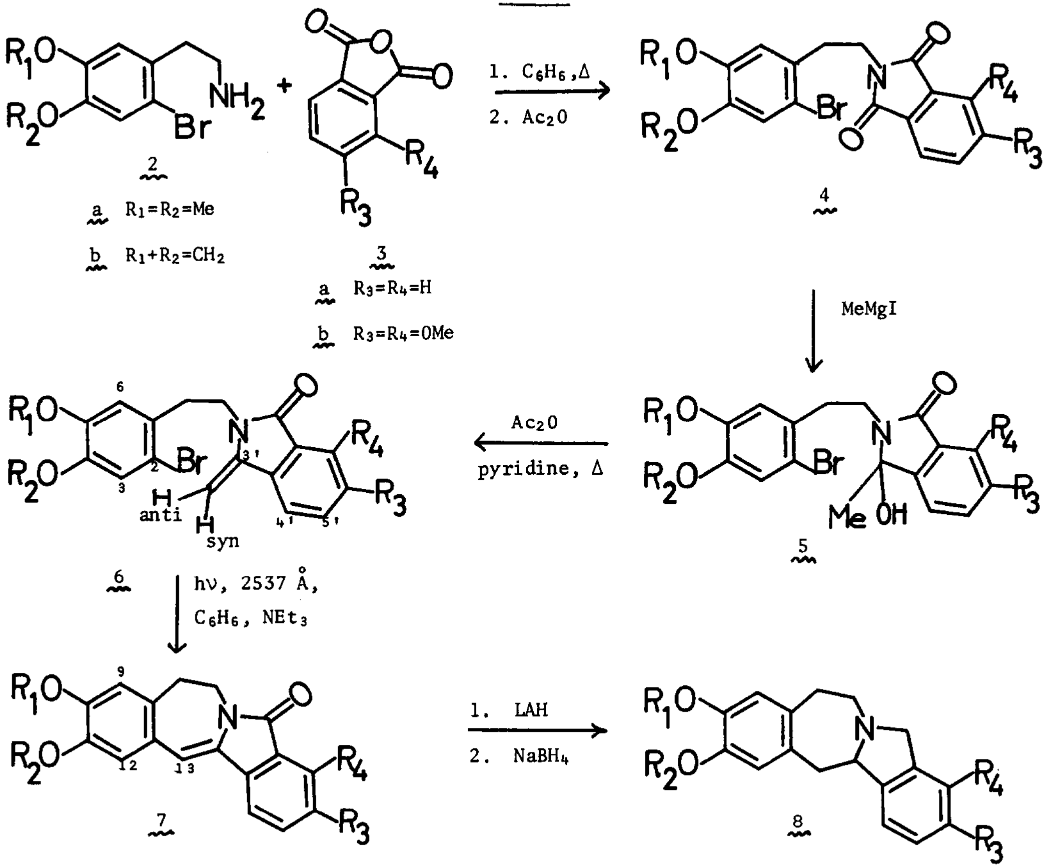
a $R_1+R_2=R_3+R_4=CH_2$, B/D cis, C_1- and C_{14}-H's cis;

b $R_1=R_2=R_3=R_4=Me$, B/D trans, C_1- and C_{14}-H's trans.

In a model study, the phthalimidine [12] derivative **6a** [mp 140-141°; m/e (% rel. intensity) 389 (M^+, 3), 387 (M^+, 3), 308 (100), 244 (70), 242 (70), 158 (75); ir ($CHCl_3$) 1705 (C=O), 1650 (C=C) cm^{-1}; uv max (MeOH) 308 (6650), 293 (6900), 260 (sh, 11,000), 251 (13,000), 235 (15,000) mμ; nmr ($CDCl_3$) τ 2.1-2.6 (m, 4H, aromatics), 3.00 (s, 1H, H_3), 3.30 (s, 1H, H_6), 4.85 (d, 1H, J 2Hz, H_{syn}), 5.05 (d, 1H, J 2Hz, H_{anti}), 6.00 (t, 2H, J 7Hz, $-CH_2N$), 6.17 and 6.33 (2s, 6H, 2 x OMe), 6.98 (t, 2H, J 7Hz, $-C\underline{H}_2CH_2N$)] was obtained from **2a** and phthalic anhydride (**3a**) in four unexceptional and high yield steps (SCHEME) [13]. Photolysis of **6a** gave the isoindolo[1,2-b][3]benzazepine derivative **7a** in 20% yield: mp 195-196°; m/e (% rel. intensity) 307 (M^+, 100), 292 (58), 193 (26), 164 (58); ir ($CHCl_3$) 1695 (C=O), 1650 (C=C) cm^{-1};

SCHEME



4-8: a $R_1=R_2=Me$, $R_3=R_4=H$; b $R_1+R_2=CH_2$, $R_3=R_4=OMe$; c $R_1=R_2=Me$, $R_3=R_4=OMe$.

uv max (MeOH) 368 (21,000), 257 (9200), 237 (sh, 6400), 224 (14,000) mμ; nmr ($CDCl_3$) τ 2.1-2.6 (m, 4H, aromatics), 3.10 (s, 1H, H_{12}), 3.22 (s, 1H, H_9), 3.43 (s, 1H, H_{13}), 5.83 (t, 2H, J 4Hz, $-CH_2N$), 6.05 (s, 6H, 2 x OMe), 6.87 (t, 2H, J 4Hz, $-CH_2CH_2N$) . Although photocyclizations involving bromo aromatics [14] and N-acyl enamines [15] have been previously used in benzylisoquinoline alkaloid synthesis, to the best of our knowledge the photoreaction 6a → 7a represents the first time that these two functions have been used in concert for the formation of a new C-C bond [16].

The phthalimidine 6b, required for the elaboration of Schöpf-Schweickert amine VI (8b), was prepared by identical synthetic operations to those used for 6a but starting with 2b and hemipinic anhydride (3b) [17] (SCHEME). It may be noted that the crucial step in this sequence, addition of Grignard reagent to the phthalimide 4b, occurred exclusively at the less hindered carbonyl to give, after dehydration, compound 6b [mp 181-182°; m/e (% rel. intensity) 352 (M^+, 100), 228 (20), 226 (20), 218 (99); ir ($CHCl_3$) 1700 (C=O), 1640 (C=C) cm^{-1}; uv max (MeOH) 320 (6600), 295 (sh, 6600), 267 (10,000), 239 (15,000) mμ; nmr ($CDCl_3$) τ 2.41 (d, 1H, J 8Hz, $H_{4'}$), 2.97 (d, 1H, J 8Hz, $H_{5'}$), 2.59 (s, 1H, H_3), 3.22 (s, 1H, H_6), 4.03 (s, 2H, $-OCH_2O$), 4.30 (d, 1H, J 2Hz, H_{syn}), 4.67 (d, 1H, J 2Hz, H_{anti}), 6.02 (s, 6H, 2 x OMe), 6.06 (t, 2H, J 8Hz, $-CH_2N$), 6.97 (t, 2H, J 8Hz, $-C\underline{H_2}CH_2N$)]. This result was both reasonably predicted and amply precedented [18]. Photocyclization of 6b as before afforded the expected product 7b in 21.5% yield [13]. Successive reduction using lithium aluminum hydride and sodium borohydride gave Schöpf-Schweickert amine VI (8b) in 85% yield [19]. The synthetic material was shown to be identical by spectral, mp and mixture mp comparison with an authentic sample [9].

Since no Rhoeadine alkaloids corresponding to the oxygen alkylation pattern of 8b have been isolated to this date [4], we have also prepared the tetramethoxy analogue 8c according to the route described in the SCHEME [13]. In our view, compound 8c may serve as a precursor for the alkaloid alpinine (1b) and experiments directed towards achieving this transformation are in progress.

Acknowledgements

The financial support of the National Research Council of Canada is gratefully acknowledged. We are deeply indebted to Professor G. Habermehl who was able to provide the authentic sample of Schöpf-Schweickert amine VI from the late Professor Schöpf's laboratories, Technische Hochschule, Darmstadt. We warmly thank Professor D. B. MacLean for some of the mass spectra, Professor G. L. Lange for the use of the Rayonet Preparative Photochemical Reactor, Dr. R.H.F. Manske for advice and encouragement, and Mr. F. Grail of Chemical Abstracts Service for solving our nomenclature problems. Mr. B. M. Clarke, Jr. very ably carried out some large scale preparations.

References and Footnotes

1. Abstracted from the Ph.D. Thesis of H.O.B., University of Waterloo, 1971.
2. National Research Council of Canada Scholar, 1970-71.
3. For preliminary incorporation results, see H. Böhm and H. Rönsch, Z. Naturforsch., 23B, 1553 (1968).
4. (a) F. Šantavý in "The Alkaloids," R.H.F. Manske, ed., Academic Press, New York, 1970, Vol. XII, p. 398; (b) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Elsevier, Amsterdam, 1969, p. 144.
5. H. Irie, S. Tani, and H. Yamane, Chem. Commun., 1713 (1970).
6. T. Kametani, S. Hirata, S. Shibuya, and K. Fukumoto, J. Chem. Soc., C, 1927 (1971).
7. W. Klötzer, S. Teitel, J. F. Blout, and A. Brossi, J. Amer. Chem. Soc., 93, 4321 (1971).
8. For our earlier efforts in this field, see H. O. Bernhard and V. Snieckus, Tetrahedron, 27, 2091 (1971).
9. C. Schöpf and M. Schweickert, Chem. Ber., 98, 2566 (1965).
10. Compounds possessing this skeleton have not yet been isolated from natural sources but are obtained when papaverrubines (1, NH for NMe) are treated with mineral acid [4a,11].
11. D. Walterová and F. Šantavý, Coll. Czech. Chem. Commun., 33, 1623 (1968).
12. For a review on this class of compounds, see J. D. White and M. E. Mann, Advan. Heterocyclic Chem., 10, 113 (1969).
13. All new compounds exhibit spectral and analytical data in full accord with their structures.
14. M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, J. Org. Chem. 35, 175 (1970); A. Mondon and K. Krohn, Chem. Ber., 103, 2729 (1970).
15. I. Ninomiya, T. Naito, and T. Kiguchi, Chem. Commun., 1669 (1970).
16. For a photocyclization reaction of a phthalimidine (6, no Ar ring oxygenation, $C_{3'}$=C(Br)C_6H_5, no C_2-Br) which produced the same skeleton (7), see A. Marsili and V. Scartoni, Tetrahedron Lett., 887 (1969). In our series, attempts to prepare an analogous compound (6a-c, $C_{3'}$=CHBr, no C_2-Br) by bromination led only to an angularly substituted isoquinoline derivative resulting from a rapid Pictet-Spengler cyclization of the brominated intermediate.
17. E. H. White and M. M. Bursey, J. Org. Chem., 31, 1914 (1966).
18. S. Graebe, Ann., 247, 288 (1888); M. R. Henze and W. J. Leanza, J. Org. Chem., 17, 7, (1952).
19. The enamine obtained from LAH reduction of 7b was highly unstable to air oxidation and could not be characterized; LAH reduction products of 7a and 7c exhibited similar behavior, cf. also ref. 11.