TOTAL SYNTHESIS OF PSEUDO TYPE OF PROTOPINE ALKALOIDS

Kazuhiko Orito,* Shigekazu Kudoh, Kinji Yamada and Mitsuomi Itoh
Department of Chemical Process Engineering, Hokkaido University,
Sapporo, Hokkaido, 060 Japan

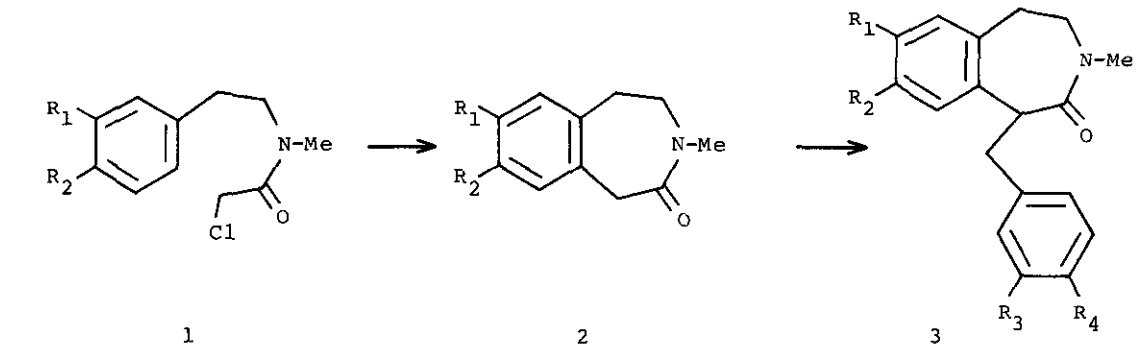
Photolysis of the chloroacetamides (1) gave the benzazepinones (2), whose benzyl derivatives (3) were cyclized to the benz[d]-indeno[1,2-b]azepines (4) by treatment with phosphoryl chloride. Dye-sensitized photo-oxygenation of 4, followed by lithium aluminum hydride reduction and manganese dioxide oxidation of the products 5, led to a total synthesis of pseudoprotopine (7a) and fagarine II (7b) as well as their analogs 7c and 7d.

The synthesis of protopine alkaloids has been performed owing to chemical[1] or photochemical[2] transformation reactions of protoberberine alkaloids. The present communication describes the total synthesis of pseudo type of protopine alkaloids by a common route, consisting of the photo-oxygenative ring enlargement reaction[3] of a tetrahydrobenz[d]indeno[1,2-b]azepine moiety and further elaboration of a resultant dibenzazecinedione product, and leading to pseudoprotopine (7a) and fagarine II (7b) as well as the preconceived alkaloids 7c and 7d.

Base-induced photocyclization[4] of N-chloroacetyl-N-methylphenethylamines 1a and 1b (irradiated with high pressure mercury lamp, two equivalents of sodium hydroxide) provided the 3-benzazepin-2-ones 2a and 2b (>50 %), which were heated with 3,4-methylenedioxy or 3,4-dimethoxybenzyl bromide in a mixture of dry tetrahydrofuran and N,N-dimethyl formamide (10:1 volume %) in the presence of sodium hydride.[5] The resultant 1-benzylazepinone 3a (83 %), mp 182-184 °C, [ν_{max}^{Nujol} 1645 cm^{-1}; δ ($CDCl_3$) 2.92 (s, 3H, N-CH_3), 2.8-4.1 (m, 6H), 4.33 (dd, 1H, J = 6, 9 Hz, C_1-H), 5.93 (s, 4H, 2×OCH_2O), 6.66, 6.75 (ds, 2H, C_6- or C_9-H), 6.79, 6.84 (ds, 3H, $C_{2',5',6'}$-H's)] was treated with phosphoryl chloride in toluene (reflux, 5 h) to give 4a (70 %), mp 150-151 °C, which was spectrally identical with 2,3,9,10-bismethylenedioxy-7-methyl-5,6,7,12-tetrahydrobenz[d]indeno[1,2-b]azepine reported

previously by Kametani and his co-workers.[6a] Similar cyclization of 3b, mp 112-115 °C, 3c, mp 169-170 °C, and 3d, mp 157-158 °C, proceeded smoothly to yield the known enamines, 4b (80 %), mp 187-188 °C (lit.[6a] mp 189-191 °C), 4c (85 %), mp 176-179 °C (lit.[6a] mp 175-177 °C) and 4d (79 %), mp 182-183 °C (lit.[6b] mp 187-188 °C), respectively. Thus, the scheme [1 → 2 → 3 → 4] constitutes the convenient alternative route to the benz[d]indeno[1,2-b]azepine ring system.

Photo-oxygenation of 4a was carried out (methylene blue, 650 W-tungsten-iodine lamp, 18-20 °C, 10 min) on the basis of the preliminary experiments.[3] The ir spectrum of the product 5a displayed absorption maxima at 1688 and 1618 cm^{-1} due to desoxybenzoin function and amide group, suggesting the presence of the ten-membered amido-ketone ring system, as shown in the figure. Successive reduction of this



1,2: a. $R_1+R_2=$<O>; b. $R_3=R_4=OMe$

3~7: a. $R_1+R_2=R_3+R_4=$<O>; b. $R_1+R_2=$<O>, $R_3=R_4=OMe$;
c. $R_1=R_2=OMe$, $R_3+R_4=$<O>; d. $R_1=R_2=R_3=R_4=OMe$

dibenzazecinedione 5a with lithium aluminum hydride in tetrahydrofuran (reflux, 3 h) produced an amino alcohol 6a (79 % from 4a) [ν_{max}^{Nujol} 3545 cm^{-1}; δ ($CDCl_3$) 2.12 (s, 3H, N-CH_3), 2.2-3.1 (m, 5H, C_5-H_2, C_6-H_2 and C_{13}-H), 3.23 (d, 1H, J ≈ 15 Hz, C_8-H), 3.32 (dd, 1H, J = 2, 16 Hz, C_{13}-H), 3.95 (d, 1H, J = 15 Hz, C_8-H), 5.38 (dd, J = 2, 8 Hz, C_{14}-H), 6.63, 6.67, 6.83, 7.14 (each s, 4H, aromatic H's). Treatment of 6a with activated manganese dioxide[7] in chloroform (room temperature, 1 h) led to the mild oxidation of the hydroxyl function to ketone carbonyl to give pseudoprotopine (7a) (85 %), mp 201-202 °C (lit.[8] mp 200-202 °C, lit.[1d] mp 200-201 °C), whose spectral data (ir, uv and ^1H nmr) were identical with those of the natural product.[1d,8] In the same manner as described above, 4b, c, d gave the corresponding crystalline amino-alcohols, 6b (74 %), mp 174-175 °C, 6c (72 %), mp 161-170 °C, and 6d (83 %), mp 157-158 °C, through the amido-ketones 5b, c, d of the dibenzazecine type.

Application of the aforementioned oxidation to 6b afforded the alkaloid, fagarine II (7b) (86 %), mp 200-202 °C (lit.[1b,9] mp 200-201 °C), whose ir and uv spectra were identical with those of the authentic specimen.[1b] Further, the ^1H nmr spectrum of 7b displayed peaks at δ ($CDCl_3$) 1.90 (s, 3H, N-CH_3), 2.51 (m, 2H, C_6-H), 2.90 (m, 2H, C_5-H), 3.54 (s, 2H, C_8-H), 3.78 (s, 2H, C_{13}-H), 3.89, 3.92 (each s, 4H, 2×OCH_3), 5.98 (s, 2H, OCH_2O), 6.67, 6.70 (each s, 2H, C_4-H and C_9- or C_{12}-H), 6.80 (s, 1H, C_{12}- or C_9-H), 6.99 (s, 1H, C_1-H), in good accordance with the data reported for protopine alkaloids.[10]

Similarly, 7c (90 %), mp 160-162 °C (ether), [ν_{max}^{Nujol} 1670 cm^{-1}; $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}; λ_{max}^{EtOH} 288 mμ (ε 9,800); δ ($CDCl_3$) 1.83 (s, 3H, N-CH_3), 2.56 (m, 2H, C_6-H), 3.00 (m, 2H, C_5-H), 3.56 (s, 2H, C_8-H), 3.72 (s, 2H, C_{13}-H), 3.93 (s, 6H, 2×OCH_3), 5.99 (s, 2H, OCH_2O), 6.71, 6.73 (each s, 2H, C_4-H and C_9- or C_{12}-H), 6.80 (s, 1H, C_{12}- or C_9-H), 7.10 (s, 1H, C_1-H)] and 7d (amorphous, 92 %, methiodide mp 173 °C) [free base, ν_{max}^{Nujol} 1660 cm^{-1}; $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}; λ_{max}^{EtOH} 282 mμ (ε 9,500); δ ($CDCl_3$) 1.84 (s, 3H, N-CH_3), 2.56 (m, 2H, C_6-H), 3.00 (m, 2H, C_5-H), 3.58 (s, 2H, C_8-H), 3.76 (s, 2H, C_{13}-H), 3.89 (s, 3H, OCH_3), 3.93 (s, 9H, 3×OCH_3), 6.76 (s, 2H, C_4-H and C_9- or C_{12}-H), 6.85 (s, 1H, C_{12}- or C_9-H), 7.12 (s, 1H, C_1-H) were readily obtained in this method.

Thus, the new method offers a total synthesis of four kinds of pseudo type of protopine alkaloids, although any report on the isolation of the latter two 7c and 7d has not yet been presented.

References

1. a) R. D. Haworth and W. H. Perkin, Jr., J. Chem. Soc., 1926, 445; ibid., 1926, 1796; R. D. Haworth, J. B. Koepfli and W. H. Perkin, Jr., ibid., 1927, 2261; K. W. Bentley and A. W. Murray, ibid., 1963, 2497; b) D. Giacopello, V. Deulofeu and J. Comin, Tetrahedron, 1964, 20, 2971; c) D. Giacopello and V. Deulofeu. Tetrahedron Letters, 1966, 2859; Tetrahedron, 1967, 23, 3265; d) R. M. Sotelo and D. Giacopello, Austral. J. Chem., 1972, 25, 385.
2. M. Hanaoka, C. Mukai and Y. Arata, Heterocycles, 1976, 4, 1685.
3. K. Orito and M. Itoh, J. Chem. Soc., Chem. Comm., 1978, 812.
4. K. Orito and S. Kudoh, unpublished method, which will be detailed elsewhere.
5. K. Orito and T. Matsuzaki, Tetrahedron, in press.
6. a) T. Kametani, M. S. Premila, S. Hirata, H. Seto, H. Nemoto and K. Fukumoto, Can. J. Chem., 1975, 53, 3824; b) T. Kametani, S. Hirata, F. Satoh, and K. Fukumoto, J. Chem. Soc., Perkin I, 1974, 2509; T. Kametani, S. Hirata, H. Nemoto, M. Ihara, S. Hibino and K. Fukumoto, J. Chem. Soc., Perkin I, 1975, 2029.
7. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, J. Chem. Soc., 1952, 1094.
8. S. R. Johns, J. A. Lamberton, H. J. Tweeddale and R. I. Willing, Austral. J. Chem., 1969, 22, 2233.
9. G. V. Stuckert, 'Investigations del Laboratorio de Quimica Biólogica,' Vol. I, Córdoba, Argentina, 1933, p. 109; V. Deulofeu and J. Comin, Farmaco, 1954, 9, 340.
10. N. S. Bhacca, L. F. Johnson and J. N. Shoolery, 'NMR Spectra Catalog,' Vol. I, Spectrum No. 339, Varrian Associates, 1962; C. J. Pouchert and J. R. Camphell, 'The Aldrich Library of NMR Spectra,' Vol. 10, Aldrich Chem. Company, Inc., 1962, p. 122; A. D. Cross, L. Dolejs, V. Hanuš, M. Maturová and F. Šantavý, Coll. Czech. Chem. Comm., 1965, 1335; F. R. Stermitz, L. Chen and J. I. White, Tetrahedron, 1966, 22, 1095 and see ref. 1c, 1d and 7 also.

Received, 1st October, 1979