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Studies on the Chemical Constituents of Rutaceous Plants. LVI.[1] The Development of a Versatile Method for the Synthesis of Antitumor-Active Benzo[*c*]phenanthridine Alkaloids. (6).[1] Limitation of the Dyke Synthetic Pathway for Benzo[*c*]phenanthridine Alkaloids

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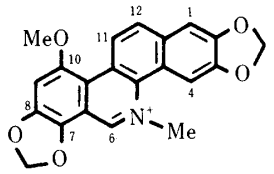
A limitation of the Dyke method for synthesizing benzo[*c*]phenanthridine alkaloids through the 1,2-dihydroisoquinoline derivatives prepared by means of the Pomeranz–Fritsch reaction was clarified; the method is not applicable to such alkaloids having an alkoxy group at the C_{10} position.

Keywords——Dyke method limitation; benzo[*c*]phenanthridine alkaloid synthesis; 5-alkoxy-1,2-dihydroisoquinoline; *peri*-effect

In connection with our studies[2] on the structural establishment of chelirubine[3] (**1**), one of the fully aromatized O_5-benzo[*c*]phenanthridine alkaloids,[4] we attempted to synthesize it through the Dyke method,[5] involving a step of condensation of the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline derivative (**2**) with glyoxylic acid (**3**). However, a limitation of the method was found, as described in this report.



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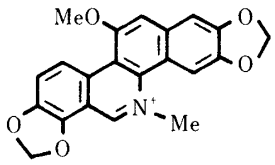
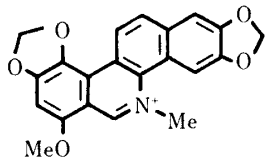
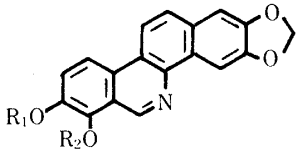


1a



1b



4 : R_1=Me, R_2=Et
5 : R_1=H, R_2=Me

Chart 1

Two synthetic sequences developed by Dyke *et al.*[5] (Chart 2; path A) and by Robinson *et al.*[6] and other groups[7] (Chart 2; path B) are well-known as preparative methods for benzo[*c*]phenanthridine alkaloids. About five years ago, since the former method was thought to be suitable for syntheses of benzo[*c*]phenanthridine alkaloids having oxygen functions at

the 7- and 8-positions, we[8] applied the method to the preparation of *O*-ethylisodecarine (**4**) and confirmed the structure of decarine[9] (**5**).

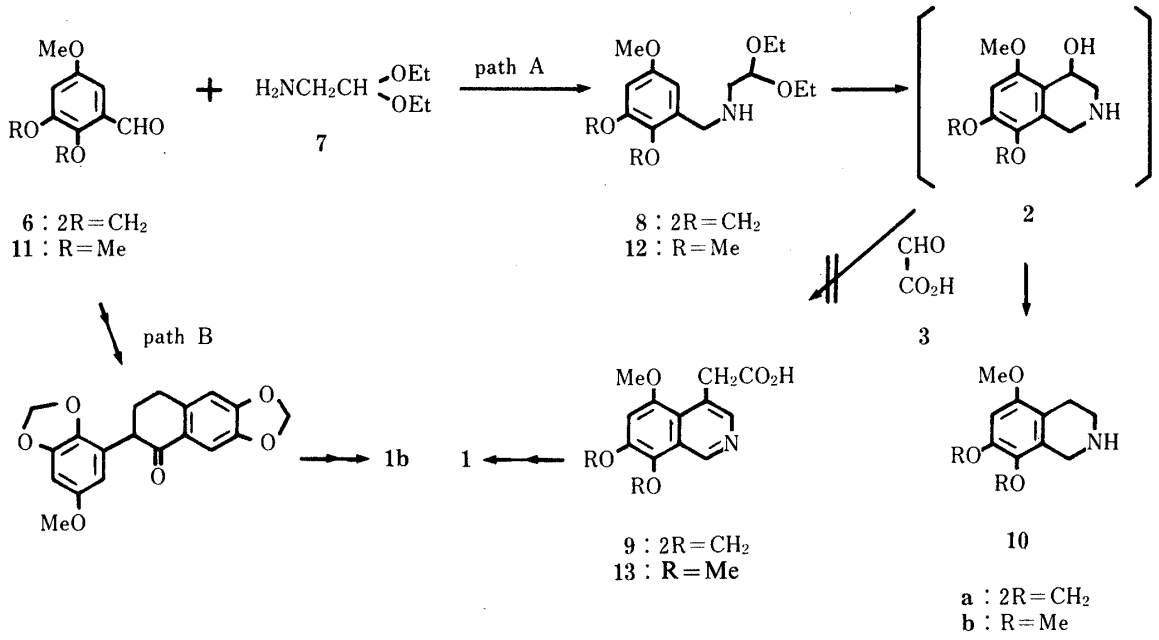


Chart 2

On the other hand, three structures (**1a**, **1b**, and **1**) had been proposed for chelirubine (**1**) by Slavík,[3b] by Onda,[3c] and by ourselves,[2a] respectively. As reported in the preceding paper,[10] our attempts to synthesize the compound having our structure (**1**) and the other compound having the structure (**1b**) proposed by Onda through the Robinson method failed. However, during these trials, we[11] were able to synthesize 5-methoxy-2,3-methylenedioxybenzaldehyde (**6**). Theoretically, when the Dyke method is applied to this benzaldehyde (**6**), the compound having our proposed structure (**1**) should be formed. Therefore, we attempted to synthesize our product (**1**) from this benzaldehyde through the Dyke method.

Catalytic reduction of a solution of the benzaldehyde (**6**) and aminoacetaldehyde diethyl acetal (**7**) in ethanol over platinum oxide gave the desired aminoacetal derivative (**8**) in 82% yield. Unfortunately, all attempts to prepare 5-methoxy-7,8-methylenedioxy-4-isoquinolineacetic acid (**9**) by treatment with 6 N hydrochloric acid followed by addition of glyoxylic acid (**3**) failed. However, the presence of the desired 4-hydroxy-1,2,3,4-tetrahydroisoquinoline product (**2**: $2R=CH_2$) in the reaction mixture was shown by the finding that 5-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**10a**) was produced by treatment of this aminoacetal derivative (**8**) under reductive conditions;[12] the cyclized 4-hydroxy-1,2,3,4-isoquinoline intermediates (**2**) underwent hydrogenolysis to give the 1,2,3,4-tetrahydroisoquinoline derivative (**10a**). Furthermore, 2,3,5-trimethoxybenzaldehyde[11,13] (**11**) gave the aminoacetal derivative (**12**) which also failed to provide the 5,7,8-trimethoxy-4-isoquinolineacetic acid (**13**) in the Dyke reaction, but gave 5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**10b**) under the reductive conditions. These chemical results were explicable only by assuming that an attack of glyoxylic acid (**3**) at the C_4-position of the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline product (**2**) was sterically hindered by the methoxy group situated at the *peri*-position of the cyclized product (**2**). In other words, the Dyke method has a limitation; it is not applicable to the preparation of benzo[*c*]phenanthridine alkaloids having an alkoxy group at the C_{10}-position.

Experimental

Instruments, *etc.*, were as described in the preceding paper.[1)]

5-Methoxy-2,3-methylenedioxybenzylaminoacetaldehyde Diethyl Acetal (8)——A solution of 2,3-methylenedioxy-5-methoxybenzaldehyde[11)] (**6**) (3.00 g) and aminoacetaldehyde diethyl acetal (**7**) (2.22 g) in abs. EtOH (70 ml) was hydrogenated over PtO_2 (0.024 g) at room temperature under atmospheric pressure. The catalyst was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Distillation of the residue at 187 °C (2 mmHg) gave a colorless oil (4.08 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1172, 1123, and 1053 (acetal). ^{1}H-NMR (CCl_4) δ: 1.18 (6H, t, J=7.0 Hz, $CH_2C\underline{H}_3\times2$), 1.52 (1H, s, NH), 2.60 (2H, d, J=5.0 Hz, $NC\underline{H}_2CH$), 3.26—3.60 (4H, m, $OC\underline{H}_2CH_3\times2$), 3.66 (2H, s, $ArCH_2N$), 3.71 (3H, s, OCH_3), 4.49 (1H, t, J=5.0 Hz, $CH_2C\underline{H}(O)_2$), 5.84 (2H, s, OCH_2O), 6.26 (2H, s, arom. H×2). MS *m/z*: 297 (M^+ 6.7%), 165 (100%).

Treatment of this material with glyoxylic acid according to the reported method[5,8)] failed to give the desired 5-methoxy-7,8-methylenedioxy-4-isoquinolineacetic acid (**9**).

5-Methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (10a) Hydrochloride——A solution of the aminoacetal (**8**) (0.21 g) in 6 N HCl (6.76 ml) was added to a suspension of 10% Pd–C (0.035 g) in EtOH (5 ml) saturated with hydrogen gas. The reaction mixture was hydrogenated at room temperature under atmospheric pressure for 48 h. After the absorption of hydrogen gas had ceased, the precipitate formed during the hydrogenation was dissolved by heating. The catalyst was removed by filtration under warming, and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH gave colorless needles (0.085 g), mp 279—284 °C. *Anal.* Calcd for $C_{11}H_{13}NO_3\cdot HCl$: C, 54.22; H, 5.79; N, 5.75. Found: C, 53.99; H, 5.68; N, 5.67. IR ν_{max} cm^{-1}: 2770—2470 (N^+H). ^{1}H-NMR (CF_3COOH) δ: 3.10 (2H, t, J=6.0 Hz, $ArC\underline{H}_2CH_2$), 3.55—3.85 (2H, m, $CH_2C\underline{H}_2N^+$), 3.92 (3H, s, OCH_3), 4.48 (2H, br t, J=*ca.* 5.0 Hz, $ArCH_2N^+$), 5.99 (2H, s, OCH_2O), 6.66 (1H, s, arom. H), 7.66 (2H, br s, N^+H_2).

2,3,5-Trimethoxybenzylaminoacetaldehyde Diethyl Acetal (12)——A solution of 2,3,5-trimethoxybenzaldehyde[11,13)] (**11**) (1.96 g) and aminoacetaldehyde diethyl acetal (**7**) (1.33 g) in abs. EtOH (60 ml) was hydrogenated over PtO_2 (0.015 g) at room temperature under atmospheric pressure. The catalyst was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Distillation of the residue at 175—178 °C (3 mmHg) gave a colorless oil (2.48 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1160—1060 (acetal). ^{1}H-NMR δ: 1.20 (6H, t, J=7.0 Hz, $CH_2C\underline{H}_3\times2$), 1.96 (1H, s, NH), 2.75 (2H, d, J=5.5 Hz, $NC\underline{H}_2CH$), 3.35—3.90 (4H, m, $OC\underline{H}_2CH_3\times2$), 3.79 (6H, s, $OCH_3\times2$), 3.82 (5H, s, OCH_3 and $ArCH_2N$), 4.61 (1H, t, J=5.5 Hz, $CH_2C\underline{H}(O)_2$), 6.41 (2H, s, arom. H×2).

Treatment of this material with glyoxylic acid according to the reported method[5,8)] failed to give the desired 5,7,8-trimethoxy-4-isoquinolineacetic acid (**13**).

5,7,8-Trimethoxy-1,2,3,4-tetrahydroisoquinoline (10b) Hydrochloride——A solution of the aminoacetal (**12**) (0.205 g) in 6 N HCl (6.75 ml) was added to a suspension of 10% Pd–C (0.035 g) in EtOH (5 ml) saturated with hydrogen gas. The reaction mixture was hydrogenated at room temperature under atmospheric pressure for 24 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from isoPrOH gave colorless needles (0.094 g), mp 230—233 °C. *Anal.* Calcd for $C_{12}H_{17}NO_3\cdot HCl$: C, 55.49; H, 6.99; N, 5.39. Found: C, 55.49; H, 6.95; N, 5.32. IR ν_{max} cm^{-1}: 2770—2470 (N^+H). ^{1}H-NMR (CF_3COOH) δ: 3.07 (2H, t, J=6.0 Hz, $ArC\underline{H}_2CH_2$), 3.50—3.80 (2H, m, $CH_2C\underline{H}_2N^+$), 3.93 (3H, s, OCH_3), 3.96 (6H, s, $OCH_3\times2$), 4.58 (2H, br t, J=*ca.* 4 Hz, $ArCH_2N^+$), 6.70 (1H, s, arom. H), 7.65 (2H, br s, N^+H_2).

References and Notes

1) Part LV: H. Ishii, T. Ishikawa, Y.-I. Ichikawa, M. Sakamoto, M. Ishikawa, and T. Takahashi, *Chem. Pharm. Bull.*, **32**, 2984 (1984).
2) *a*) H. Ishii, T. Deushi, and K.-I. Harada, the 16th Symposium on the Chemistry of Natural Products, Osaka, October 1972, Symposium Papers, p. 327; *b*) H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Lett.*, **1975**, 319; H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K.-I. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.*, **26**, 864 (1978).
3) *a*) J. Slavík and L. Slavíková, *Coll. Czech. Chem. Commun.*, **20**, 21 (1955); J. Slavík, *ibid.*, **20**, 198 (1955); J. Slavík and L. Slavíková, *ibid.*, **25**, 1667 (1960); J. Slavík and F. Šantavý, *ibid.*, **37**, 2804 (1972); C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962); M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nôgeikagaku Kaishi*, **39**, 168 (1965); *b*) J. Slavík, L. Dolejš, V. Hanuš, and A. D. Cross, *Coll. Czech. Chem. Commun.*, **33**, 1619 (1968); *c*) M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, *Chem. Pharm. Bull.*, **18**, 1435 (1970).
4) For a review of the chemistry of these alkaloids see, R. H. F. Manske, "The Alkaloids," ed. by R. H. F. Manske, Academic Press, New York, London, Vol. 4, 1954, p. 253; *idem*, *ibid.*, Vol. 7, 1960, p. 430; *idem*, *ibid.*, Vol. 10, 1968, p. 485; F. Šantavý, *ibid.*, Vol. 12, 1970, p. 417; V. Preininger, *ibid.*, Vol. 15, 1975, p. 241; F. Šantavý, *ibid.*, Vol. 17, 1979, p. 493; H. Ishii and T. Ishikawa, *Yakugaku Zasshi*, **101**, 663 (1981).
5) S. F. Dyke and M. Sainsbury, *Tetrahedron*, **23**, 3161 (1967); S. F. Dyke, B. J. Moon, and M. Sainsbury, *Tetrahedron Lett.*, **1968**, 3933; S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, **24**, 1467 (1968); M.

Sainsbury, S. F. Dyke, and B, J, Moon, *J. Chem. Soc.* (*C*), **1970**, 1797; J. M. Bobbitt, "Advances in Heterocyclic Chemistry," ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, London, Vol. 15, 1973, p. 99; W. J. Gensler, S. F. Lawless, A. L. Bluhm, and H. Dertouzos, *J. Org. Chem.*, **40**, 733 (1975).

6) T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.*, **1937**, 835; A. S. Bailey and R. Robinson, *ibid.*, **1950**, 1375; A. S. Bailey, R. Robinson, and R. S. Staunton, *ibid.*, **1950**, 2277; A. S. Bailey and C. R. Worthing, *ibid.*, **1956**, 4535.
7) K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *J. Chem. Soc.*, **1957**, 4760; H. R. Arthur and Y. L. Ng, *ibid.*, **1959**, 4010; K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *ibid.*, **1959**, 4012; K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961); T. Kametani, K. Kigasawa, M. Hiiragi, O. Kusama, E. Hayashi, and H. Ishimaru, *Chem. Pharm. Bull.*, **19**, 1150 (1971); T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocycl. Chem.*, **10**, 31 (1973); K.-Y. Zee-Cheng and C. C. Cheng, *ibid.*, **10**, 85, 867 (1973).
8) H. Ishii, T. Ishikawa, and Y.-I. Ichikawa, *Chem. Pharm. Bull.*, **26**, 514 (1978).
9) J. Vaquette, J.-L. Pousset, R.-R. Paris, and A. Cavé, *Phytochemistry*, **13**, 1257 (1974); H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Yakugaku Zasshi*, **96**, 1458 (1976); H. Ishii, T. Ishikawa, and J. Haginiwa, *ibid.*, **97**, 890 (1977).
10) H. Ishii, K.-I. Harada, T. Ishida, T. Deushi, T. Masuda, M. Sakamoto, Y.-I. Ichikawa, T. Takahashi, M. Ishikawa, and T. Ishikawa, *Chem. Pharm. Bull.*, **32**, 2971 (1984).
11) H. Ishii, T. Ishikawa, T. Deushi, K.-I. Harada, T. Watanabe, E. Ueda, T. Ishida, M. Sakamoto, E. Kawanabe, T. Takahashi, Y.-I. Ichikawa, K. Takizawa, T. Masuda, and I.-S. Chen, *Chem. Pharm. Bull.*, **31**, 3024 (1983).
12) W. J. Gensler, K. T. Shamasundar, and S. Marburg, *J. Org. Chem.*, **33**, 2861 (1968).
13) L. E. Smith and F. B. LaForge, *J. Am. Chem. Soc.*, **53**, 3072 (1931); J. R. Merchant, R. M. Naik, and A. J. Mountwalla, *J. Chem. Soc.*, **1957**, 4142; W. Baker, N. C. Brown, and J. A. Scott, *ibid.*, **1939**, 1922.