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A SIMPLE SYNTHESIS OF RUTAECARPINE

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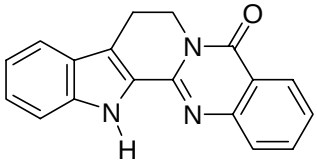
Abstract - Indoloquinazoline alkaloid rutaecarpine was efficiently synthesized by employing 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazoline-4,9-dione as a key intermediate, whose 9-carbonyl group was introduced by benzylidene formation, followed by ozonolysis.

Rutaecarpine (**1**) is one of the indoloquinazoline alkaloids of the Rutaceous plants such as *Evodia rutaecarpa* which has long been utilized for the treatment of inflammation-related disorders in the traditional oriental medicinal practice.[1] Recent research revealed that such an antiinflammatory activity stemmed from the attribution of rutaecarpine by a quite potent and selective inhibitory activity onto COX-2.[2] Addition to antiinflammatory activity, the vasorelaxing,[3] antiplatelet,[4] and antianoxic activities[5] were reported for rutaecarpine. The derivative, dehydroevodiamine (**2**) was found to show a potent and promising activity on the Alzheimer disease.[6] A general and efficient synthetic method is required to provide the sufficient quantity of rutaecarpine and related compounds for pursuing further biological properties on experimental animals.



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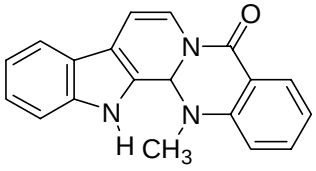

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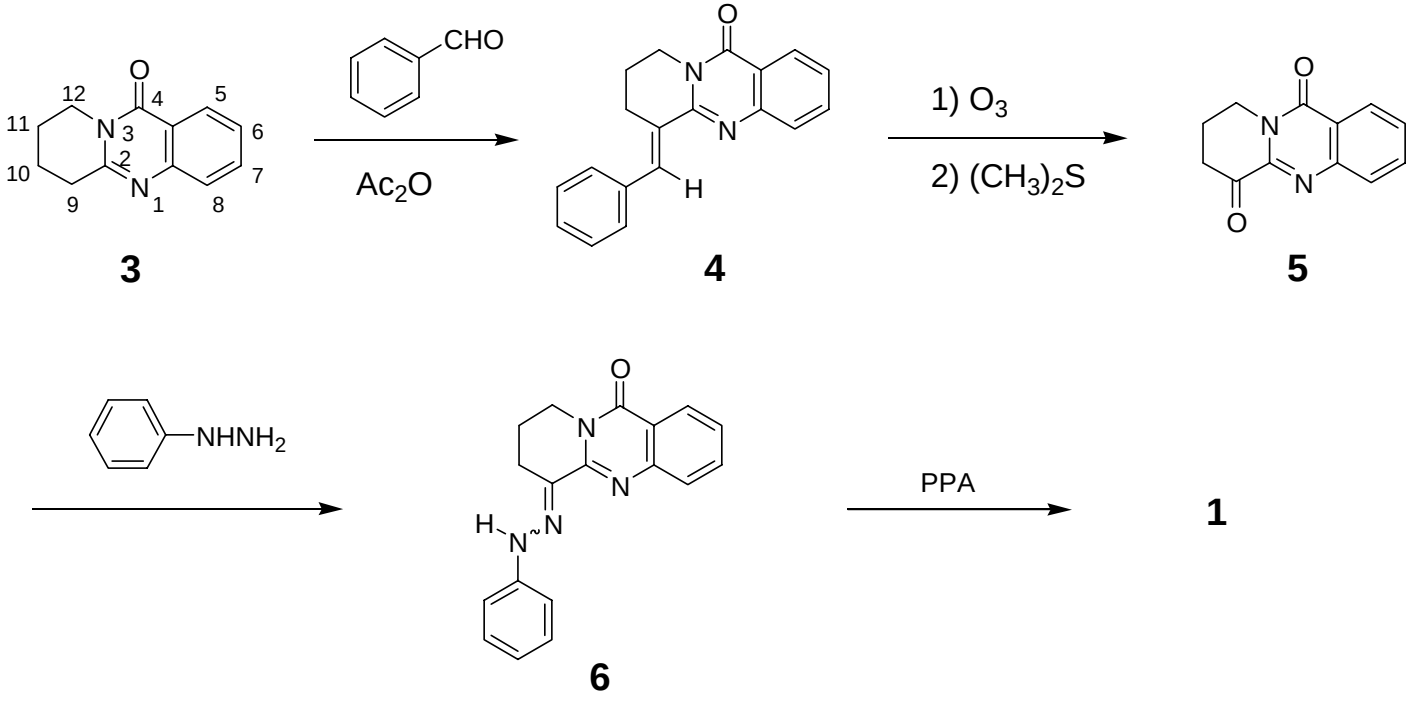
Since Schöpf and Steuer first synthesized rutaecarpine under the so-called physiological condition by condensing anthranilic acid with 5,6-dihydro-4-carboline,[7] several synthetic methods have been

reported. Most of them, regardless of either biosynthesis[8] or chemical synthesis[9] employ 5,6-dihydro-4-carboline or its precursor *N*-formyltryptamine as a key intermediate which was condensed with anthranilic acid by a iminoketene cycloaddition reaction. This method has, however, somewhat limited general applicability due to the scope of available staring carboline and/or its precursor. The Fischer indole synthesis has also been applied for 9-phenylhyrazono-9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]-quinazolin-4-one, which was prepared by either a condensation of corresponding 9,9-dibromo compound with phenylhydrazine or a condensation of **3** with phenyldiazonium chloride.[10] This approach also suffered from low yield (35%) of hydrazone formation reactions that could be a bottle-neck for the synthesis of the derivatives and/or related compounds of rutaecarpine in large quantity.

As a part of our search for a simple synthetic method for **1**, that might be applicable to the synthesis of its derivatives as well as related compounds, we herein report a synthesis of rutaecarpine from 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazoline-4,9-dione (**5**) as a key intermediate which may improve the yield of hydrazone formation.

RESULTS AND DISCUSSION

The prerequisite 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazolin-4-one (**3**) was prepared by employing previously reported method from anthranilic acid and 2-piperidone.[9] Since the reactivity at



the 9 position of **3** has been established,[11] Thummel's two step introduction of a carbonyl group at 9 position was pursued.[12] The condensation of **3** with benzaldehyde in the presence of acetic anhydride afforded corresponding benzylidene derivative (**4**), which was subjected to ozonolysis to give **5** in 83% yield after reductive work up. The ketone (**5**) was converted to corresponding phenylhydrazone, which was then treated with polyphosphoric acid to afford the desired rutaecarpine in 95% of two-step yield.

In conclusion, a simple synthetic sequence for the preparation of rutaecarpine was established employing 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazoline-4,9-dione as a key intermediate. The introduction of a carbonyl group at the 9 position of starting 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]-quinazolin-4-one was accomplished by benzylidene formation, followed by ozonolysis.

EXPERIMENTAL

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). The starting 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazolin-4-one (**3**) was prepared from anthranilic acid and 2-piperidone by employing previously reported method.[13] Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

9-Benzylidene-9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazolin-4-one (4). A mixture of 3.43 g (17.2 mmol) of **3** and 7.86 g (74.2 mmol) of benzaldehyde in 20 mL of acetic anhydride was refluxed for 48 h. Excess benzaldehyde and acetic anhydride was removed under reduced pressure. To the residue was added 100 mL of water. Resulting mixture was made basic with 50% aqueous NaOH and extracted with CH_2Cl_2 (50 mL x 3). The organic layers were combined, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 5.83 g of an oily material which was chromatographed on silica gel, eluting with CH_2Cl_2. The latter fractions gave 4.88 g (99%) of white needles after crystallization from the eluent: mp 139-140 ℃. IR (KBr) ν 1664, 1606, 1530, 1470, 1390, 1340, 1306, 773, 758, 689 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.4, 1.5 Hz, 1H), 8.26 (dd, J = 9.2, 1.2 Hz, 1H), 7.70-7.74 (m, 2H), 7.36-7.51 (m,

6H), 4.17 (dd, *J* = 7.2, 4.5 Hz, 2H), 2.96 (dd, *J* = 7.2, 4.5 Hz, 2H), 2.06 (quintet, *J* = 7.2 Hz, 2H). *Anal*. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.25; H, 5.66; N, 9.76.

9,10,11,12-Tetrahydro-4*H*-pyrido[2,1-*b*]quinazoline-4,9-dione (5). A solution of 0.90 g (3.12 mmol) of **4** in 50 mL of CH_2Cl_2 was cooled in acetone-dry ice bath, and ozone was bubbled through the solution until the solution turns blue. Excess ozone was purged by bubbling oxygen, and 10 mL of $(CH_3)_2S$ was added into the mixture. Evaporation of the solvent afforded 0.65 g of semi solid which was chromatographed on silica gel, eluting with CH_2Cl_2. The latter fractions gave 0.56 g (83%) of pale yellow needles after crystallization from the eluent: mp 180-181 ℃. IR (KBr) *v* 1720, 1670, 1607, 1580, 1470, 1338, 1310, 1240, 1196, 1154, 913, 778, 694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 8.1, 1.40 Hz, H5), 8.00 (d, *J* = 7.8 Hz, H8), 7.83 (td, *J* = 7.2, 1.5 Hz, H7), 7.64 (td, *J* = 7.2, 1.5 Hz, H6), 4.34 (t, *J* = 5.8 Hz, 2H), 2.95 (t, *J* = 6.5 Hz, 2H), 2.38 (quintet, *J* = 6.5 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 190.1, 161.0, 145.9, 144.2, 134.5, 129.4, 129.0, 126.5, 121.8, 42.1, 37.3, 20.4. *Anal*. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.36; H, 4.59; N, 13.15.

Rutaecarpine (1). To a solution 2.46 g (0.01 mol) of the ketone (**5**) in 20 mL of 95% EtOH was slowly added 1.40 g (0.013 mol) of feshly distilled phenylhydrazine. The resulting precipitate was collected and was mixed with 10 g of polyphosphoric acid in a heavy-walled beaker. The mixture was heated at 180 ℃ for 1.5 h. After cooling, the mixture was made basic with 10% NaOH and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a solid material which was recrystallized from EtOAc to provide the desired product as pale yellow needles (2.73 g, 95%): mp 259-260 ℃. (lit.,[13] mp 259 ℃). IR (KBr) *v* 3340 (N-H), 1655 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, NH), 8.27 (d, *J* = 8.2, 1H), 7.75-7.51 (m, 3H), 7.35 (t, *J* = 8.2, 1H), 7.31-7.21 (m, 2H), 7.10 (t, *J* = 8.2, 1H), 4.52(t, *J* = 6.9, 2H), 3.16(t, *J* = 6.9, 2H). ^{13}C NMR(75 MHz, $CDCl_3$) δ 161.5, 147.3, 145.0, 138.3, 134.3, 127.2, 127.0, 126.4, 126.2 (two carbons), 125.5, 121.0, 120.5, 120.0, 118.4, 112.0, 41.1, 19.6.

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REFERENCES

1. J. H. Chu, *Science Record (China)* 1951, **4**, 479 (*Chem. Abstr.*, 1952, **46**, 11589b).
2. T. C. Moon, M. Murakami, I. Kudo, K. H. Son, H. P. Kim, S. S. Kang, and H. W. Chang, *Inflamm. Res.*, 1999, **48**, 621.
3. W. F. Chiou, C. J. Chou, J. F. Liao, A. Y. Sham, and C. F. Chen, *Eur. J. Pharmacol*., 1994, **257**, 59; G. J. Wang, X. C. Wu, C. F. Chen, L. C. Lin, Y. T. Huang, J. Shan, and P. K. Pang, *J. Pharmacol. Exp. Ther.*, 1999, **289**, 1237.
4. W. S. Sheen, I. L. Tsai, C. M. Teng, F. N. Ko, and I. S. Chen, *Planta Med.*, 1996, **62**, 175.
5. J. Yamahara, T. Yamada, T. Kitani, Y. Naitoh, and H. Fujimura, *Chem. Pharm. Bull.*, 1989, **37**, 1820.
6. C. H. Park, Y. J. Lee, S. H. Lee, S. H. Choi, H. S. Kim, S. J. Jeong, S. S. Kim, and Y. H. Seo, *J. Neurochem.*, 2000, **74**, 244; C. H. Kim, S. H. Kim, W. Choi, Y. J. Lee, J. S. Kim, S. S. Kang, and Y. H. Seo, *Planta Med.*, 1996, **62**, 405.
7. C. Schöpf and H. Steuer, *Ann.*, 1947, **558**, 124; C. Schöpf, *Angew. Chem*., 1937, **50**, 779; C. Schöpf, *Angew. Chem*., 1937, **50**, 797.
8. M. Yamazaki and A. Ikuta, *Tetrahedron Lett.*, 1966, 3221; M. Yamazaki, A. Ikuta, T. Mori, and T. Kawana, *Tetrahedron Lett.*, 1967, 3317.
9. Y. Yasahina, R. H. F. Manske, and R. Robinson, *J. Chem. Soc*., 1927, 1708; T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles*, 1976, **4**, 23; T. Kametani, T. Higa, C. V. Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, **98**, 6186; H. Möhrle, C. Kamper, and R. Schmid, *Arch. Pharm.*, 1980, **313**, 990; T. J. Bergman and S. Bergman, *Heterocycles*, 1981, **16**, 347.
10. J. Kökösi, I. Hermecz, G. Szász, and Z. Mészáros, *Tetrahedron Lett.*, 1981, **22**, 4861.
11. E. Oripov, Kh. M. Shakhidoyatov, Ch. Sh. Kadyrov, and N. D. Abdullaev, *Khim. Geterosikl. Soedin*., 1979, **5**, 684.
12. R. P. Thummel, F. Lefoulon, D. Cantu, and R. Mahadeavan, *J. Org. Chem*., 1984, **49**, 2208.
13. T. Kametani, C. V. Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *J. Am. Chem. Soc*., 1977, **99**, 2306.