Tetrahedron Letters, Vol. 33, No. 21, pp. 2995-2998, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

An Alternative Total Synthesis of Rutaecarpine and Vasicolinone Alkaloids[1]

József Kökösi[a], György Szász[a] and István Hermecz[b]*

[a] Institute for Pharmaceutical Chemistry, Semmelweis University of Medicine
[b] Chinoin Pharmaceutical and Chemical Works Ltd. P.O.Box 110. H-1325 Budapest, Hungary

Abstract: Rutaecarpine (**6**) and vasicolinone (**9**) alkaloids were alternatively prepared by Fischer indolization of 3-(phenylhydrazonomethyl)pyrroloquinazolinone (**4**) under thermal and acidic conditions, respectively.

Recently we reported[2] a facile total synthesis of rutaecarpine[3] (**6**) alkaloid of *Evodia Rutaecarpa*, by the Fischer indolization of 6-phenylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one prepared from 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one alkaloid[4]. Earlier rutaecarpine syntheses[5] built up the connection between C and E or B and D rings of the pentacyclic skeleton.

Vasicolinone (**9**) was isolated[6] from *Adhatoda vasica*, and Kaneko *et al.* prepared[5c] it by the acid catalyzed cyclization of 2-chloro-3-[(3-indol)-ethyl]quinazolin-4-one and the subsequent dimethylation of 3-(2-aminophenyl)--1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**8**). In the cyclization step besides (**8**) or its *N*-formylated derivative (**7**) rutaecarpine (**6**) was also obtained in 9-44 % yields[5c].

Both types of alkaloids are of special interest in connection with their pharmacological activities[5a,7,8], and rutaecarpine is one of the constituent parts of the traditional ancient Chinese herbal medicines: Whu-Chu-Yu[9], and Shih-Hu[10].

Now we give account of a facile alternative total synthesis of rutaecarpine (**6**) and vasicolinone (**9**) by the Fischer indolization of 3-(phenylhydrazonomethyl)pyrroloquinazolinone (**4**) starting from anthranilic acid and 2-pyrrolidone.

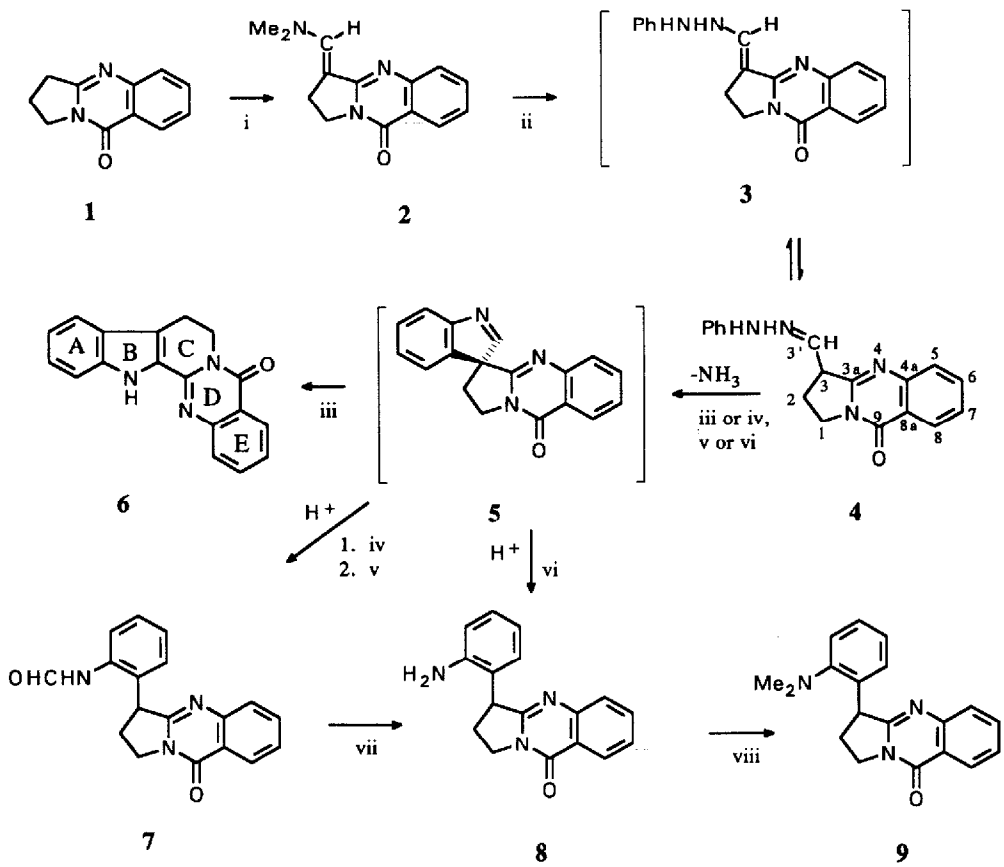
Reaction of anthranilic acid and 2-pyrrolidone, according to Kametani's method[11], in the presence of thionyl chloride[12] afforded deoxyvasicinone alkaloid (**1**) in 93 % yield[13]. The treatment of the active methylene group[8d] of deoxyvasicinone (**1**) by Vilsmeier-Haack reagent, phosphoryl chloride-dimethyl-

formamide, afforded 3-(dimethylamino)methylene derivative (**2**) (m.p.:179-180^{0}C) in 94 % yield[14].

The heating of an ethanolic suspension of dimethylaminomethylene derivative (**2**) with excess of phenylhydrazine for 3h gave phenylhydrazono compound (**4**) (m.p.: 162-164^{0}C) in 87 % yield. Besides the UV and ^{1}H NMR spectra, the signal of C(3) at 46.7 ppm and that of side-chain =CH- moiety at 136.9 ppm indicated the presence of hydrazono tautomer (**4**), instead of the hydrazine form (**3**)[15].

When a solution of the hydrazone (**4**) in Dowtherm A was heated above 160^{0}C, preferably between 180 and 190^{0}C for 30 min, the formed rutaecarpine (**6**) gradually precipitated, and after recrystallization from DMF rutaecarpine (**6**; m.p.: 258-260^{0}C) was obtained in 49 % yield in pure form.

In the first step the Fischer indolization of hydrazone (**4**) gave a



Scheme: i, $POCl_3$, DMF, rt, 1h, 60 °C, 3h; ii, $PhNH_2$, EtOH, Δ, 3h; iii, Dowtherm A, 160→190 °C, 0.5 h; iv, EtOH saturated with HCl gas, DMF, 0 °C; v, 4·HCl, $HOCH_2CH_2OH$, 160→180 °C, 20 min.; vi, 10% aq. HCl, BuOH, 100 °C, 4h; vii, HCl-MeOH, rt; viii, 37% aq.HCHO, $NaBH_3CN$, MeCN, rt, 2.5 h.

spiro[3*H*]indoleninpyrroloquinazolinone (**5**)[5c] besides ammonia, then in the next step **5** was rearranged into the more stable pentacyclic compound (**6**)[16].

This rearrangement is very similar to that of the 3,3-disubstituted indolenines into 2,3-condensed indolo derivatives[17]. The mechanism of this type of ring-expansion reaction was studied by Rodriquez *et al.*[18], and they pointed out that it is a proton catalyzed one. When the Fischer indolization of hydrazone (**4**), was carried out under acidic conditions 3-(2-aminophenyl)tetrahydropyrroloquinazolinones (**7** or **8**) were the main products, and the formation of rutaecarpine (**6**) could be detected only by TLC. So 3-(2--formamidophenyl)pyrroloquinazolinone (**7**) (m.p.: 218-220°C) was obtained in 42 % yield from hydrazone hydrochloride[19] (**4**.HCl) by heating in ethylene glycol at 160°C → 180°C for 20 min.

If hydrazone (**4**) was heated in 1:5 mixture of 10 % aqueous HCl and 1--butanol at 100°C for 4h 3-(2-aminophenyl)tetrahydropyrroloquinazolinone (**8**) (m.p.:81-83°C) was isolated in 42 % yield.

Under acidic conditions the spiroindoleninpyrroloquinazolinone (**5**), after the protonation on indolenine nitrogen, suffered a retrograde aldol reaction to give the ring-opened pyrroloquinazolinone (**7**).

The acid catalyzed rearrangement of hydrazone (**4**) is sensitive to the nature of the acid catalyst. When conc. sulfuric acid or PPA was used only tar formation occured.

From **7**, after hydrolysis of formamido group, or from (**8**) vasicolinone (**9**) was obtained quantitatively by dimethylation of the amino group with 37% aqueous HCHO in the presence of $NaBH_3CN$ in acetonitrile at ambient temperature, according to Kaneko et al.[5c]

References and Notes

1. Nitrogen Bridgehead Compounds. Part 84. Part 83: Hermecz I.; Horváth Á. *J. Heterocycl. Chem.* in press.

2. Kökösi J.; Hermecz I.; Szász Gy.; Mészáros Z. *Tetrahedron Lett.* **1981**, *22*, 4861-4862.

3. Asahina Y. *Acta Phytochim.* **1922**, *1*, 67.

4. Fitzgerald J. S.; Johns S. R.; Lamberton J. A.; Redcliffe A. H. *Aust. J. Chem.* **1966**, *19*, 151-159.

5a. Bergman J. *Alkaloids* **1983**, 21, 29-54 and references cited therein.
b. Bergman J.; Bergman S. *J. Org. Chem.* **1985**, *50*, 1246-1255.
c. Kaneko C.; Chiba T.; Kasai K.; Miwa C. *Heterocycles* **1985**, *23*, 1385-1390.

6. Johne S.; Gröger D.; Hesse M. *Helv. Chim. Acta* **1971**, *54*, 826-834.

7a. Raymond-Hamet. *Compt. Rend.* **1945**, *220*, 792-793.
b. Ruyun J. Drugs of the Future **1985**, *10*, 556.

c. Shoji N.; Umeyama A.; Takemoto T.; Kajiwara A.; Ohizumi Y. *J. Pharm. Sci.* **1986,** *75,* 612-613.
d. Yamahara J.; Yamada T.; Kitani T.; Naitoh Y.; Fujimura H. *Chem. Pharm. Bull.* **1989,** *37,* 1820-1822.
e. Yamahara J.; Yamada T.; Kitani T.; Naitoh Y.; Fujimura H. *J. Ethnopharmacol.* **1989,** *27,* 185-192.
f. Gillner M.; Bergman J.; Cambillan C.; Gustafsson J. A. *Carcinogenesis* **1989,** *10,* 651-654.
g. Kano Y.; Zong Q.; Komatsu K. *Chem. Pharm. Bull.* **1991,** *39,* 690-692.

8a. Amin A. H.; Mehta D. R.; Samarth S. S. *Prog. Drug. Res.* **1970,** *14,* 218-268 and references cited therein.
b. Arya V. P. *Drugs of the Future* **1981,** *6,* 373-374.
c. Johne S. *Alkaloids* **1986,** *29,* 99-140 and references cited therein.
d. Hermecz I.; Vasvári-Debreczy L. *Adv. Het. Chem.* **1986,** *39,* 281-385 and references cited therein.

9. Chu J. H. *Science Record (China)* **1951,** *4,* 279-284 [*CA* **1952,** *46,* 11589].

10. Ning-Taoli, Ho-I Houg, *Yao Hsueh Hsueh Pao* **1966,** *13,* 265-272 [*CA* **1966,** *65,* 3922].

11. Kametani T.; Higa T.; Loc C. V.; Ihara M.; Koizumi M.; Fukumoto K. *J. Am. Chem. Soc.* **1976,** *98,* 6186-6188.

12. Garin J.; Merino P.; Orduna J.; Tejero T.; Uriel S. *Tetrahedron Lett.* **1991,** *32,* 3263-3264.

13. Kametani T.; Loc C. V.; Higa T.; Koizumi M.; Ihara M.; Fukumoto K. *J. Am. Chem. Soc.* **1977,** *99,* 2306-2309.

14. Shakhidyatov Kh. M.; Oripov E.; Isisbaev A.; Kadyrov Ch. Sh. *Khim. Prir. Soedin.* **1976,** 825-826.

15. UV (EtOH): λ_{max} 368 (logΣ 4.65); 315 (3.92); 284 (4.02); 276 (4.07); 224nm (4.30). IR (KBr): ν_{max} 3400; 3300-2600; 1660 cm^{-1} (C=O); ^{1}H-NMR (80MHz $CDCl_3$,TMS, ppm) δ 2.44 (*m,* 2H, 2-CH_2), 3.8-4.4 (*m,* 2H, 1-CH_2), 4.05 (*m,* 1H, 3-H), 7.64 (*d,* $J_{3,3'}$=6.8 Hz, 1H, 3'-CH), 6.5-7.9 (*m,* 8H, Ph+5-,6- and 7-H), 8.25 (*d,* *J*=8 Hz, 1H, 8-H), 10.05 (*s,* 1H, NH). ^{13}C-NMR (20.1MHz, $CDCl_3$, TMS, ppm), δ 45.0 (*t,* C-1), 24.4 (*t,* C-2); 46.7 (*d,* C-3), 149.8 (*s,* C-3a), 149.2 (*s,* C-4a), 125.9 (*d,* C-5), 134.3 (*d,* C-6 and C-7), 127.3 (*d,* C-8), 120.6 (*s,* C-8a), 160.1 (*s,* C-9), 136.9 (*d,* C-3'), 119.9, 129.2, 118.2, and 145.8 (carbons of Ph).

16. Semiempirical quantum chemical calculation by AM1 method indicated that the heat of formation of rutaecarpine (**6**) (322.58 KJ/mol) is about 70KJ/mol less then that of the most stable conformation of spiro compound (**5**) (391.18 KJ/mol).

17a. Wenkert E.; Dave K. G.; Gnewuch C. T.; Sprague P. W. *J. Am. Chem. Soc.* **1968,** *90,* 5251-5256.
b. Jackson A. H.; Naidoo B.; Smith P. *Tetrahedron* **1968,** *24,* 6119-6129.

18. Rodriquez J. G.; Benito Y.; Temprano F. *J. Heterocycl. Chem.* **1985,** *22,* 1207-1210.

19. To solution of hydrazone (**4**) in DMF saturated ethanolic hydrogen chloride was added at 0^{0}C. The precipitated hydrochloride salt of hydrazone (**4**) was filtered off. Yield 78 %, m.p.:> 217^{0}C (decomp).

(Received in UK 11 February 1992)