NOVEL REARRANGEMENT OF 8*H*-ISOQUINO[2,1-*b*][2]BENZAZOCINES TO 3-PHENYLPYRROLO[2,1-*a*]ISOQUINOLINES AND RELATED COMPOUNDS

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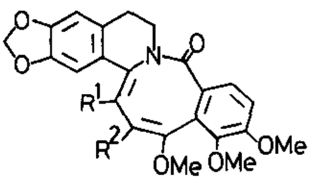
Abstract—— The 8*H*-isoquino[2,1-*b*][2]benzazocines (**1**) were efficiently transformed to the 3-phenylpyrrolo[2,1-*a*]isoquinolines (**3**) and related compounds by transannular reactions.

Pyrrolo[2,1-*a*]isoquinolines have so far been synthesized by a variety of methods1) including a representative cycloaddition of isoquinoline derivatives. Now we wish to describe here a novel synthesis of pyrrolo[2,1-*a*]isoquinolines by transannular reaction of 8*H*-isoquino[2,1-*b*][2]benzazocines (**1**)2) which have been obtained *via* the 1,3-dipolar cycloaddition of 8-methoxyberberinephenolbetaine (**2**)3) with acetylenic dipolarophiles in excellent yields.



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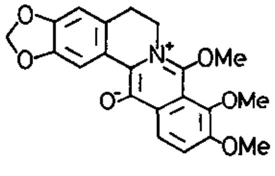

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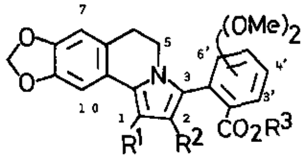


3a: 3',4'-(OMe)$_2$
3b: 5',6'-(OMe)$_2$

Heating of the azocine (**4**) in methanol containing 10% hydrochloric acid for 2 hr afforded the pyrrolo[2,1-*a*]isoquinoline (**5a**)4) [mp 190.5-191°, *m/e* 523 (M^+), ν5) 1721, 1700, λ5) 294 (4.24), 325 (4.29), δ5) 7.19 (1H, s), 6.93 (2H, s), 6.56 (1H, s)] in 75% yield. A similar treatment of **4** in ethanol gave the corresponding ethyl ester (**6a**) [mp 187-188°, *m/e* 537 (M^+)] in 87% yield. On the other hand, refluxing of **4** in methanol containing dry hydrogen chloride for 1 hr afforded **5a** and its regioisomer (**5b**)4) [mp 191.5-192°, *m/e* 523 (M^+), ν 1717, 1694, λ 292 (4.22), 326.5 (4.26), δ 7.63 (1H, d, *J*=9), 7.25 (1H,s), 6.88 (1H, d, *J*=9), 6.52 (1H, s)] in 42 and 45% yield, respectively. Treatment of the tri-esters (**5a**, **5b** and **6a**) with 10% hydrochloric acid in acetic acid gave the mono-esters (7a) [46%, mp 140-141°, *m/e* 407 (M^+), ν 1729, λ 332 (4.25), δ 6.26 (1H, d, *J*=4), 6.06 (1H, d, *J*=4)], (7b) [26%, mp 178-179°, *m/e* 407 (M^+), ν 1720, 1694, λ 245.5sh (4.31), 292 (4.23), 334 (4.28), δ 6.30 (1H, d, *J*=4), 5.91 (1H, d, *J*=4)] and (8a) [35%, mp 121-122°, *m/e* 421 (M^+), ν 1715], respectively. Direct hydrolysis of 4 with 10% hydrochloric acid in acetic acid yielded two regioisomeric carboxylic acids, (9a) [14%, mp 214-215.5°, *m/e* 393 (M^+), ν 1703, λ 332.5 (4.32), δ 7.03 (2H, s)], and (9b) [33%, mp 239-241°, *m/e* 393 (M^+), ν 1684, λ 246sh (4.12), 293 (4.14), 332.5 (4.22), δ 7.68 (1H, d, *J*=9), 6.88 (1H, d, *J*=9)], esterification of which with diazomethane afforded 7a and 7b in 90 and 88% yield, respectively. Reaction of 4 with trifluoroacetic acid for 2 hr at room temperature yielded the dibenzo[*b*,*h*]-1*H*-pent[*b*]indolizidine (10) [mp 204-205.5°, ν 1730, 1715, 1670, δ 7.82 (1H, s), 7.61 (1H, d, *J*=8.5), 7.04 (1H, d, *J*=8.5), 6.53 (1H, s)] in 84% yield and pyrolysis of 4 at 250°C for 10 min afforded the methyl ether (11) [mp 249.5-251°, *m/e* 523 (M^+), ν 1748, 1706, 1665, δ 7.72 (1H, s), 7.60 (1H, d, *J*=8.5), 6.98 (1H, d, *J*=8.5), 6.51

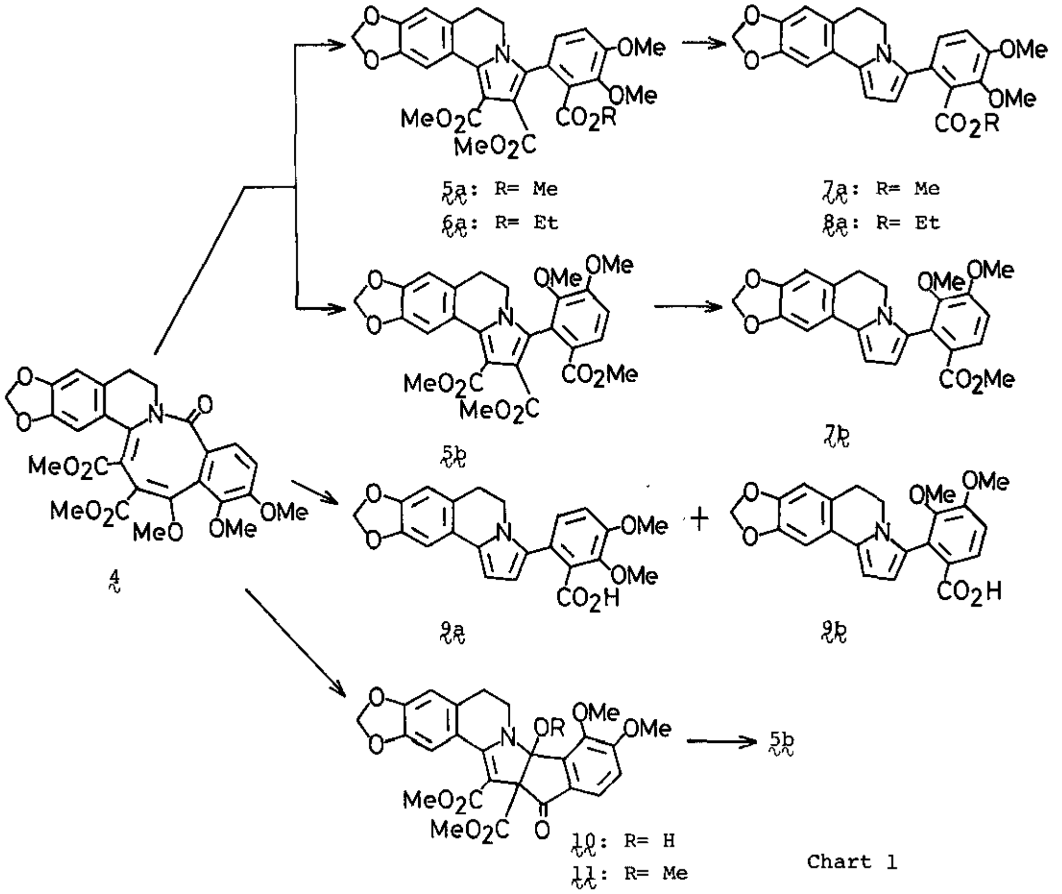


Chart 1

(1H, s)] in 40% yield. On treatment with 10% hydrochloric acid in methanol, **10** and **11** gave the tri-ester (**5b**) as a sole product in 87 and 95% yield, respectively. Similar ring contractions were effected to convert the another azocine (**12**) to the pyrroloisoquinolines by acidic treatment or pyrolysis and the results were summarized in Chart 2. Whereas the regioisomers (**3a**)[4] were usually the major products in the reaction of **4**, the regioisomers (**3b**)[4] were predominantly obtained in that of **12**. Namely, the aqueous acidic alcoholysis of **12** afforded **13a** and **13b** in a 2:3 ratio, while anhydrous acidic methanolysis and direct hydrolysis gave exclusively **13b** and **9b**, respectively. The pyrolysis of **12** was accompanied by elimination of methanol to yield **14**

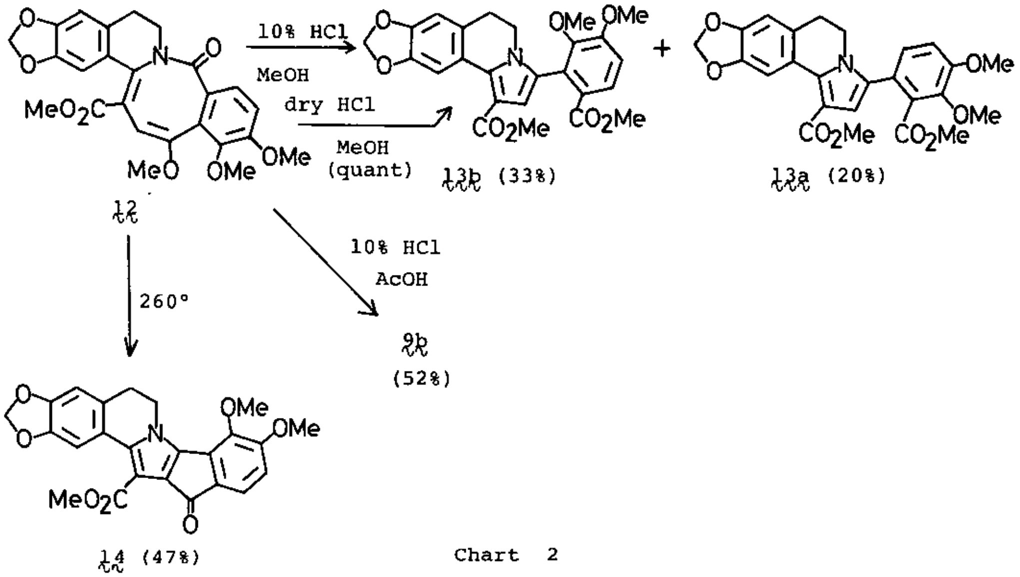
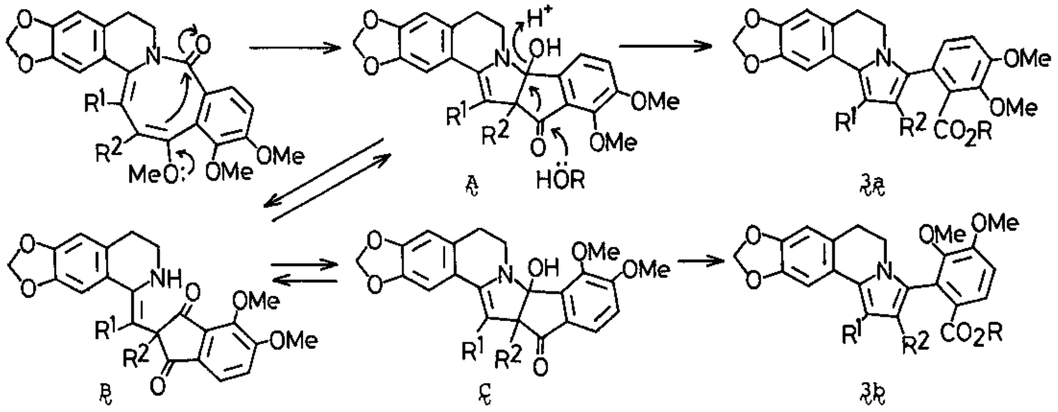


Chart 2

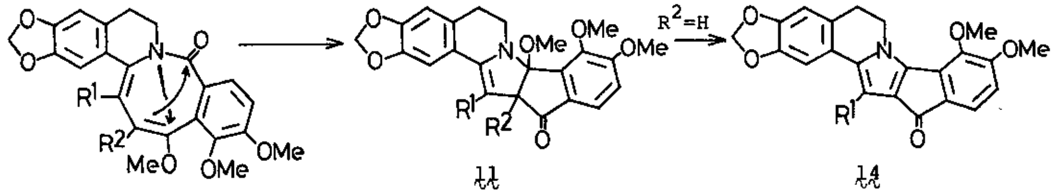
Possible reaction pathway for the above ring isomerization could be shown as follows. In an acidic alcoholysis the pentacyclic intermediate (**A**) would initially be formed by transannular cyclization and it slowly isomerize to the regioisomer (**C**) *via* the diketone (**B**). The subsequent ring opening by alcohol (**A** → **3a** and **C** → **3b**) would irreversibly take place (Pathway I). Therefore the product-ratios of two regioisomers (**3a**/**3b**) would be varied by the reaction conditions and the substrates due to the differences of the relative rates between isomerization and ring opening steps. On the other hand, the pyrolysis would proceed through the Pathway II[6] to give the product (**11** and **14**) regiospecifically.

Thus, a novel transformation of isoquinobenzazocines into 3-phenylpyrroloisoquinolines has been developed.

Pathway I



Pathway II



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REFERENCES AND FOOTNOTES

1. T. Uchida and K. Matsumoto, *Synthesis*, 1976, 209; Y. Tominaga, S. Hidaki, Y. Matsuda, G. Kobayashi, and K. Sakemi, *Yakugaku Zasshi*, 1979, 99, 540; K. Matsumoto, T. Uchida, and L.A. Paquette, *Synthesis*, 1979, 746; T. Kato, T. Chiba, and T. Sasaki, *Yakugaku Zasshi*, 1979, 99, 1051; T. Eicher and D. Krause, *Tetrahedron Lett.*, 1979, 1213; B.E. Maryanoff and D.F. McComsey, *ibid.*, 1979, 3797; M. Iwao and T. Kuraishi, *Bull. Chem. Soc. Japan*, 1980, 53, 297; A. Ohsawa, Y. Abe, and H. Igeta, *ibid.*, 1980, 53, 3273.
2. M. Hanaoka, A. Wada, S. Yasuda, C. Mukai, and T. Imanishi, *Heterocycles*, 1979, 12, 511.
3. J.L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, 1976, 98, 6714; M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, 1977, 6, 895.
4. The regioisomers having 3′,4′- and 5′,6′-dimethoxyl groups are designated as **a** and **b**, respectively. Conjugation of 2′-alkoxycarbonyl or 2′-carboxyl group with the benzene ring is prevented in regioisomer **a** due to the presence of two ortho-substituents. Therefore, the 2′-carbonyl band of **a** in IR spectrum appeared at higher wave number than that of **b**, and **a** lacked UV absorption at *ca.* 290 nm due to benzoic acid derivative (see spectral data of **7a**,**b** and **9a**,**b**).
5. IR, UV, and NMR spectra were measured in KBr disk, MeOH, and $CDCl_3$, respectively.
6. *cf.* N. Dennis, A.R. Katritzky, and M. Ramaiah, *J. Chem. Soc. Perkin I*, 1976,2281.

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