SYNTHESIS OF RUTECARPINE AND RELATED INDOLE ALKALOIDS

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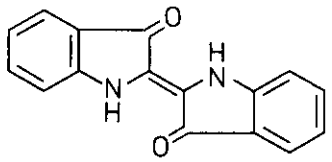
Abstract: A new route to quinazolinocarboline alkaloids, involving elimination of CF_3^- in the final step has been developed.

We have recently reported[1] that interaction of anhydrous hydrazine with indigo (1) results in formation of the quinazolinone (2b), whose structure has been corroborated[2] by an X-ray analysis as well as by an independent[1] synthesis. Treatment[1] of 2b with Raney nickel yields 2a.

The relation of 2a, that is now readily available in two steps from industrially produced starting materials, with certain alkaloids, such as rutecarpine (3) is obvious, and in principle it should be possible to convert 2a to 3 by direct alkylation. The aza-analogue of rutecarpine 4, can be prepared quantitatively[2] by treatment of 2b with formaldehyde in acetic acid.



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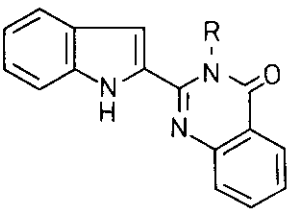
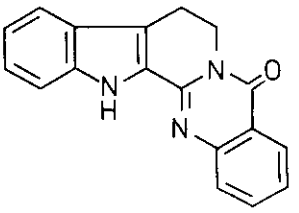


2 a R=H
b R=NH_2



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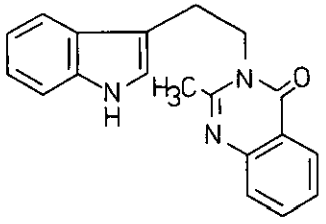

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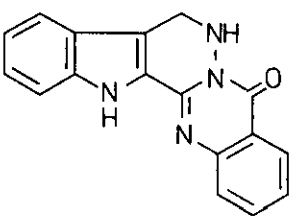

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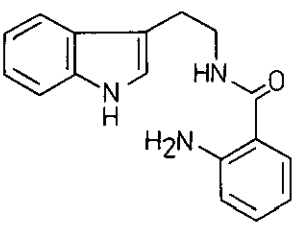
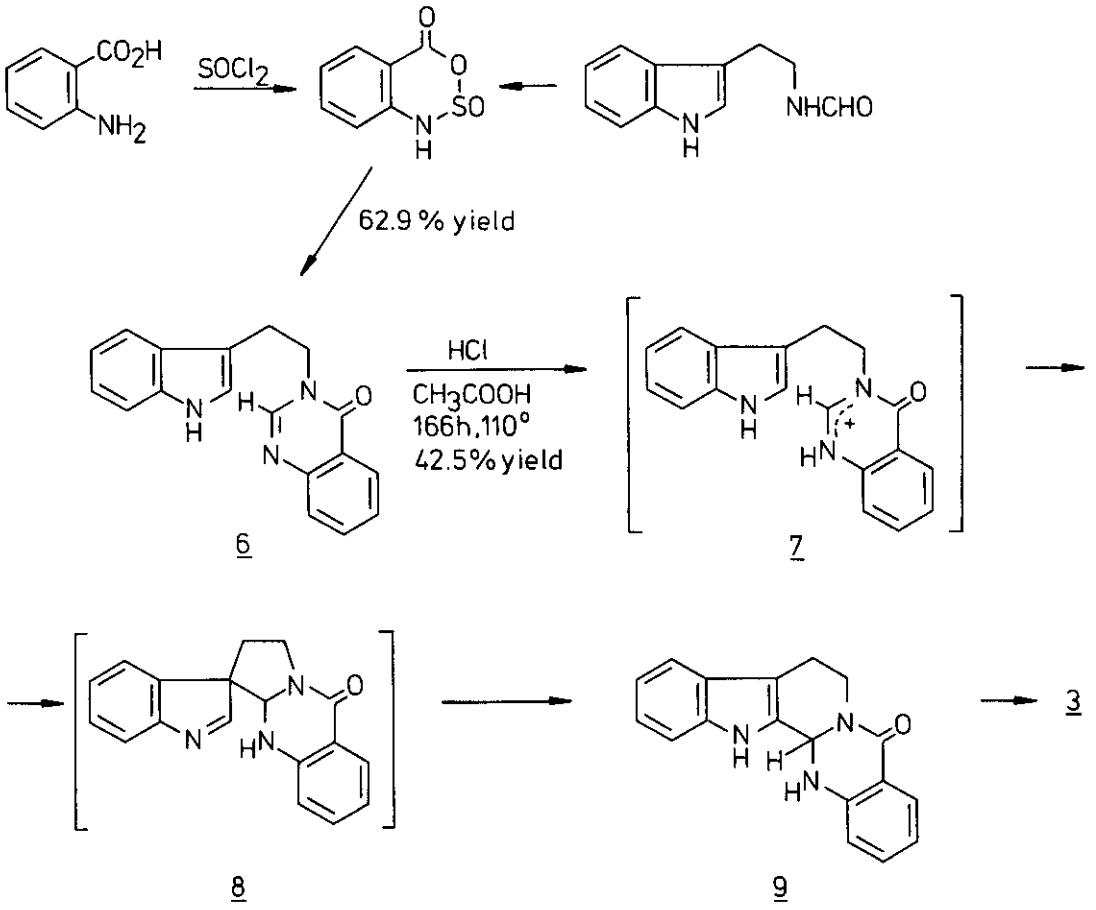


13

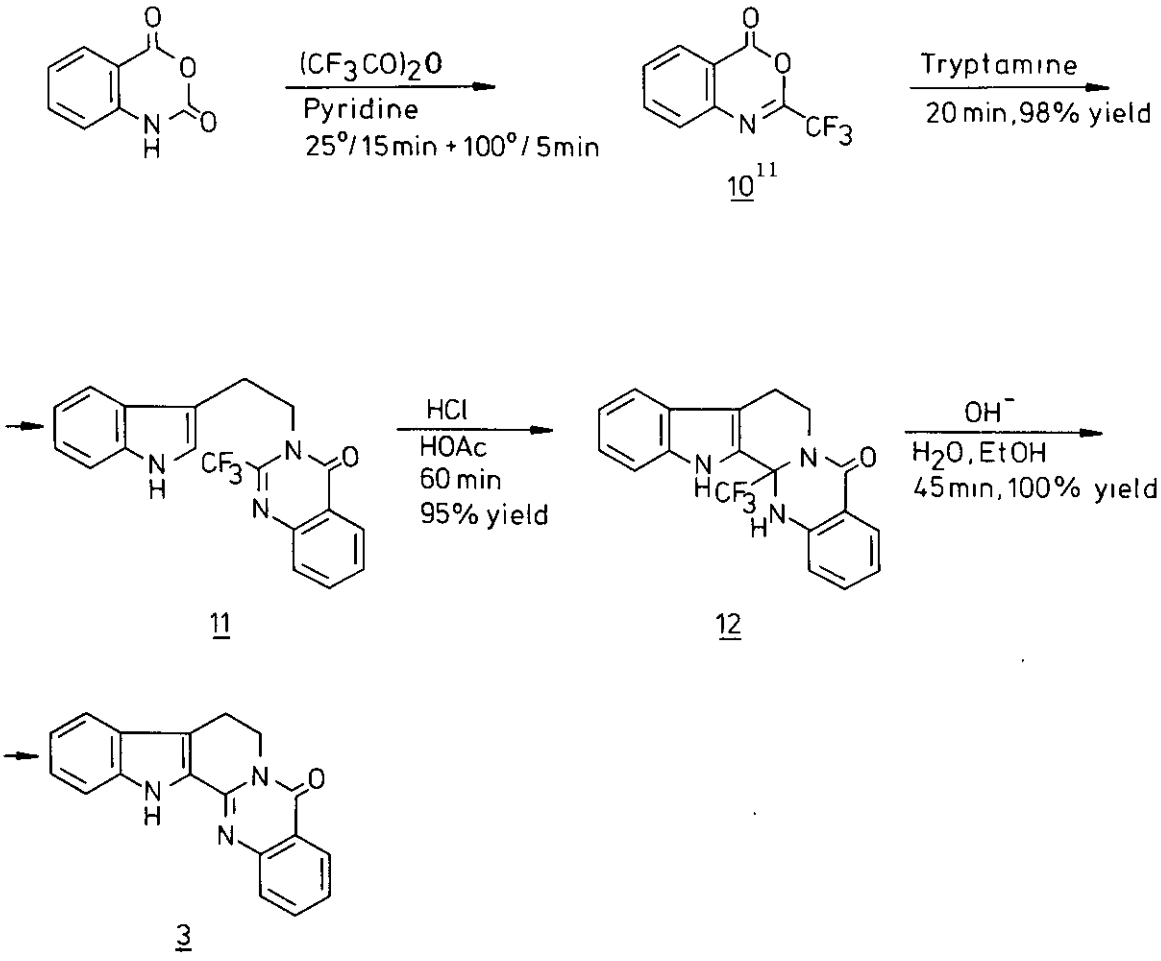
The project outlined above required reference samples of rutecarpine and we have now in this connection reinvestigated some literature procedures[3,4] and also developed some new efficient procedures for this alkaloid. The most recent and in several ways very interesting route to rutecarpine is due to Kametani.[3] Some of the problems involved in this synthesis are the low yield[5,6] of 6 coupled with the necessary chromatography of the multicomponent mixture and the long reaction time and relatively low yield in the final cyclization step. The cyclization step can be considered to involve the transformations, 6 → 7 → 8 → 9 → 3.



Scheme 1

This led us to develop the reactions indicated in Scheme 2, which were based on the following considerations. The azastabilized carbonium ion formed on protonation of 11 should be a much better electrophile than 7 due to the presence of the strongly electron withdrawing CF_3-group. In the final step generation of an anion under mild conditions followed by displacement of CF_3^- should be expected to yield (and indeed does) a much cleaner reaction mixture than the final dehydrogenation step required in Scheme 1.

The importance of the electron withdrawing CF_3-group for the initial step is evident from the fact that compound 5, readily prepared from tryptamine and 2-methyl-4*H*-3,1-benzoxazin-4-one, completely failed to cyclize under the given conditions. The fact that hortiacine[7] (*i.e.* 10-methoxyrutecarpine) could be similarly prepared indicates the generality of this synthesis of quinazolino-carboline alkaloids.



10[11]

11

12

3

Scheme 2

In connection with this work we have also found that a product obtained by Clauder[4] by heating 13 with triethyl orthoformate is not 3,14-dihydrorutecarpine (9) but is in fact identical with the noncyclized compound 6 (reported m.p. 178–179°C), as prepared by Kametani's route.[9] Recently 3,14-dihydrorutecarpine (9) (m.p. 214–216°C, optically active) has been identified as a natural product by Kamikado,[8] who also synthesized the compound (m.p. 227–230°C, synthetic racemate). The great difference in melting points between Kamikado's product and the purported 3,14-dihydrorutecarpine as reported by Clauder has thus now got an explanation. Some of the reactions included in Clauder's paper, also have to be corrected. Thus *e.g.* the purported $Hg(OAc)_2$ dehydrogenation (9 → 3) is in fact the oxidative cyclization (6 → 3). We have now found that such cyclizative couplings also can be induced by other reagents such as $FeCl_3$ or $Pd(OAc)_2$ in HOAc as well as MnO_2 (*cf.* ref. 10). But all those procedures are less efficient and much more time-consuming than the procedure according to Scheme 2.

Acknowledgements

We thank Drs. Danieli, Kametani and Kamikado for submission of samples and spectral data.

REFERENCES AND NOTES

1. J. Bergman and N. Eklund, *Tetrahedron Letters*, 3147 (1978).
2. J. Bergman and N. Eklund, to be published.
3. (a) T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara and K. Fukumoto, *J. Am. Chem. Soc.*, 99, 2306 (1977).
   (b) T. Kametani, T. Ohsawa, M. Ihara and K. Fukumoto, *Chem. Pharm. Bull.*, 26, 1922 (1978).
4. K. Horvath-Dora and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, 84, 3 (1975).
5. In our hands the yield of 6 never exceeded 10%. However, this compound can rapidly and efficiently be prepared by refluxing 13 in triethyl orthoformate.
6. (a) In this connection it should be noted that rutecarpine can also be prepared in good yield from 3,4-dihydro-β-carboline and the sulfinamide anhydride available from $SOCl_2$ and anthranilic acid.
   (b) T. Kametani, T. Higa, C. Van Loc, M. Ihara, M. Koizumi and K. Fukumoto, *J. Am. Chem. Soc.*, 98, 6186 (1976).
7. I.J. Pachter, R.F. Raffauf, G.E. Ullyot and O. Ribeiro, *J. Am. Chem. Soc.*, 82, 5187 (1960).
8. T. Kamikado, S. Murakoshi and S. Tamura, *Agric. Biol. Chem.*, 42, 1515 (1978).
9. The relatively low value of the melting point of compound 6 reported by Kametani[3] seems to indicate some of the difficulties involved in the purification of 6, using route 1.
10. B. Danieli and G. Palmisani, *Heterocycles*, 9, 803 (1978).
11. (a) This compound can also be prepared by cyclization of N-trifluoroacetylanthranilic acid.[11b]
   (b) L.A. Errede, H.T. Oien and D.R. Yarian, *J. Org. Chem.*, 42, 12 (1977).

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