Tetrahedron Letters No. 33, pp 2899 - 2902, 1976. Pergamon Press. Printed in Great Britain.

# A NEW SYNTHESIS OF FLAVINS

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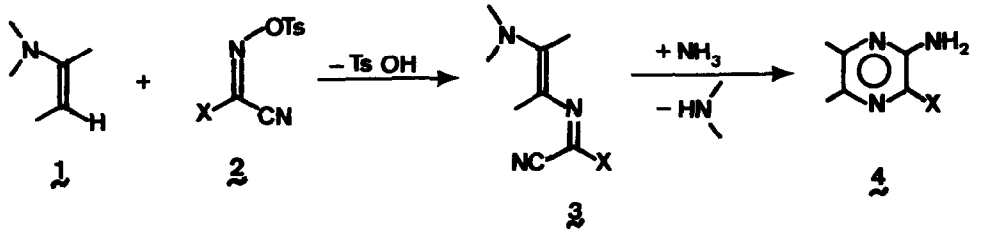
(Received in U.K. **18 June 1976** ; accepted for publication **28 June 1976**)

Flavins have been extensively studied because of their implications in biological redox reactions and several synthetic routes to riboflavin or model flavin compounds have been described in the literature. [1,2,3]

We now wish to report a new synthetic approach to isoalloxazines using methyl 1-alkyl-2-amino-1,5,6,7-tetrahydro-3-quinoxaline carboxylates as key intermediates. These compounds have been obtained according to the method recently described by us for the synthesis of 2-aminopyrazines 4 from 2-azadienes 3 and ammonia. [4,5]



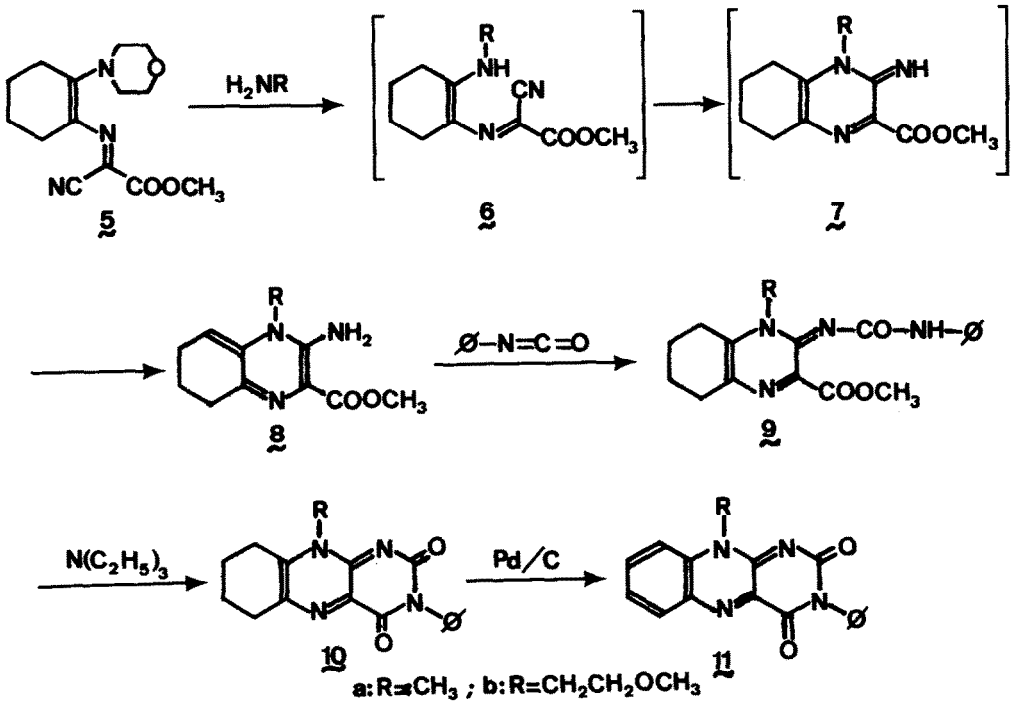

1 2 3 4

X = CN, $COOCH_3$

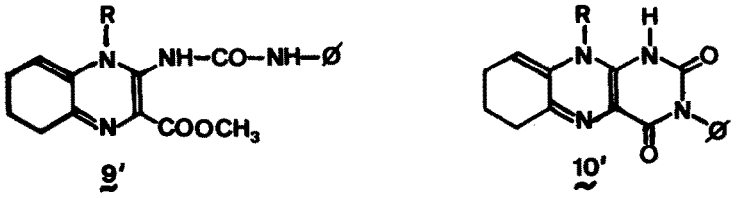
Ts = $O_2S-C_6H_4-CH_3$-p

Thus, when 2-azadiene 5 prepared from the reaction of 1-morpholinocyclohexene with oxime 2 (X = $COOCH_3$) was treated with methylamine and 2-methoxyethylamine at room temperature, 1-alkyl-2-amino-3-carboxymethylpyrazines 8a and 8b respectively were obtained. The structures of the aminopyrazines 8a and 8b were deduced from the

elemental analysis and spectroscopic data. [6] As already shown for ammonia, [5] the reaction proceeds through a nucleophilic attack of the primary amine at 4 position of the azadiene 5. The transamination reaction product 6 thus formed readily cyclizes to the iminopyrazine 7 which rearranges to the more stable amino compound 8.




The reaction of aminopyrazines 8 with phenylisocyanate at room temperature led to the N-acylated pyrazines 9 which upon treatment with triethylamine cyclized to 3-phenyl-6,7,8,9-tetrahydroisoalloxazines 10. The structures of compounds 9 and 10 were deduced from elemental analysis and spectroscopic data.[6] Absence of a vinylic proton in the $^{1}H$ NMR spectra of both compounds excluded the tautomeric structures 9' [7] and 10'.



Dehydrogenation of tetrahydroisoalloxazines 10a and b was achieved using Pd/C in boiling decalin and the structures of the resulting isoalloxazines 11a and b were in agreement with the elemental analysis and the spectroscopic data, especially the UV spectra which exhibited the characteristic absorption bands near 435, 335 and 266 nm. [6] The physical properties of compounds 8 to 11 and the yields of each step of the synthesis have been compiled in the Table together with the UV data.

Table : Physical properties and UV absorptions of compounds 8 to 11

| | | mp (°C) | Yields (%) | Recristallisation | UV in EtOH 96° ; λ max (nm), $10^{-3}$ ε |
|---|---|---|---|---|---|
| 8 | a | 212-213 | 84 | $CH_3OH$ | 360 (4.8) ; 319 (33.2) ; 225 (11.0) |
| | b | 161-162 | 90 | $C_2H_5OH$ | 371 (4.3) ; 320 (31.6) ; 312 (31.4) ; 230 (8.8) |
| 9 | a | 176-177 | 65 | $CH_3OH$ | 400 (10.0) ; 299 (18.8) ; 236 (10.6) |
| | b | 168-169 | 64 | $CH_3OH$ | 402 (9.4) ; 298 (17.4) ; 233 (10.2) |
| 10 | a | 256-257 | 80 | $C_2H_5OH$ | 416 (12.5) ; 318 (2.0) ; 266 (17.4) |
| | b | 213-214 | 82 | $CH_3OH$ | 420 (12.6) ; 320 (1.4) ; 267 (17.4) |
| 11 | a | 299-300 | 85 | $C_2H_5OH$ | 435 (9.5) ; 335 (7.8) ; 266 (34.9) ; 216 (31.2) |
| | b | 224-225 | 80 | $CH_3OH$ | 434 (8.7) ; 337 (7.6) ; 267 (30.0) |

a : R = $CH_3$ ; b : R = $CH_2$-$CH_2$-$OCH_3$

Reactions of isocyanates other than phenylisocyanate with 1-alkyl-2-aminopyrazines 8 and synthesis of various flavins including lumiflavins by this new method are under investigation.

## REFERENCES AND NOTES

† Laboratoire associé au C.N.R.S. n° 135

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6. Satisfactory elemental analysis were obtained for all compounds 8 to 11 reported herein. The $^1$H-NMR spectra of 8a, b in $CDCl_3$ exhibited a triplet near 4.7 ppm corresponding to the vinylic proton. Infrared NH and carbonyl absorptions appeared near 3300-3200 and 1650 for 8, 3350-1720 and 1650 for 9, 3350-1700 and 1650 for 10 and 1720 and 1680 $cm^{-1}$ for 11. For comparative UV data of flavins 11a, b, see ref 3.

7. In contrast, treatment of 8a with ethylchoroformate resulted in the formation of a mixture of amino (-NH-COOEt) and imino (=N-COOEt) compounds in an approximate ratio of 1/1 in chloroform ; unpublished results.