Tetrahedron Letters, Vol.31, No.16, pp 2353-2356, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

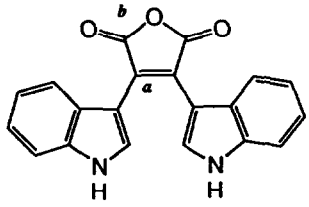
A CONVENIENT SYNTHESIS OF BISINDOLYL- AND INDOLYLARYL-MALEIC ANHYDRIDES

Peter D. Davis*, Rino A. Bit and Stephen A. Hurst

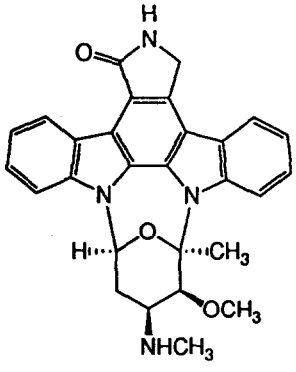
Roche Products Ltd., P.O.Box 8, Welwyn Garden City, Herts., AL7 3AY, U.K.

Summary: *The reaction of indolyl-3-glyoxylyl chlorides, easily prepared from the corresponding indoles, with arylacetic acids provides indolylaryl maleic anhydrides including bisindolyl maleic anhydrides .*

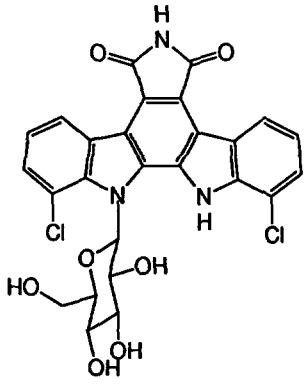
Bisindolyl maleic anhydrides such as **1** are potentially useful intermediates in the synthesis[1,2] of indolocarbazole alkaloids including staurosporine (**2**)[3] rebeccamycin (**3**)[4] and the arcyriaflavins (**4**)[5]. They are also precursors of a series of inhibitors of protein kinase C[6]. For the expeditious preparation of these inhibitors we required a synthesis of bisindolyl maleic



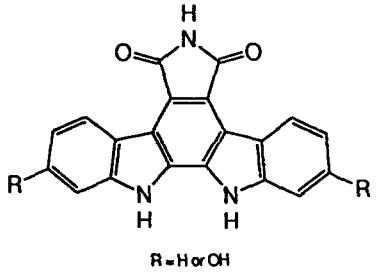
1



2



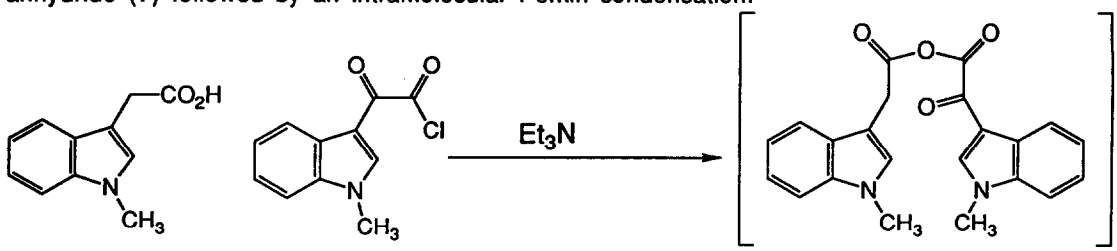
3



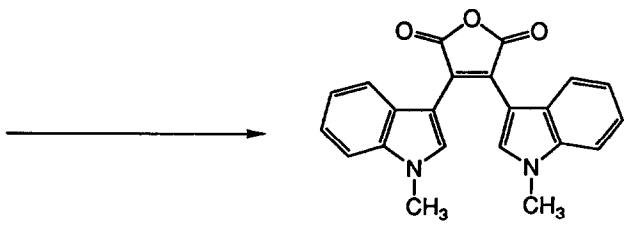
4

anhydrides which was both mild enough to tolerate a wide range of substituent functionalities and flexible enough to allow preparation of unsymmetrical bisindolyl and indolylaryl maleic anhydrides. The reported syntheses using, respectively, indolyl Grignard reagents[1] and indolylacetic acid dianions[2] were unsuitable for our purpose.

Our strategy was to form the carbon-carbon double bond ***a*** in an intramolecular process following formation of the (more easily formed) carbon-oxygen bond ***b*** by intermolecular reaction. Thus, 1-methyl-3-indolylacetic acid (**5**) was treated with 1-methylindole-3-glyoxylyl chloride (**6**) in the presence of triethylamine to give bis(1-methyl-3-indolyl)maleic anhydride (**8**) in 36% isolated yield. We have no evidence for the mechanism of this reaction, but it seems likely to proceed via initial formation of the mixed anhydride (**7**) followed by an intramolecular Perkin condensation.



5 **6** **7**



8

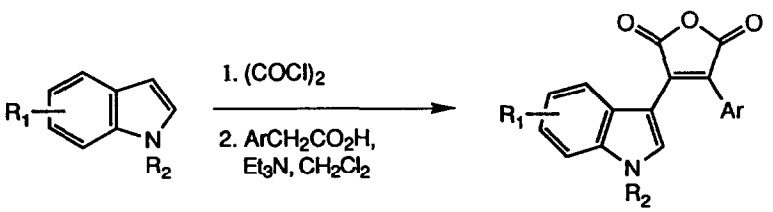
The reaction is equally successful with other substituted indolylglyoxylyl chlorides and also with phenyl-, naphthyl- and heteroaryl-acetic acids. The glyoxylyl chlorides were formed by treatment of the indoles with oxalyl chloride[7] and were used without purification. The yields of maleic anhydrides in the table are therefore isolated, overall yields based on the starting indole.

Although the reaction fails when free indole NH groups are present these groups can be protected in both the glyoxylyl chloride (with eg. a benzyl group) and the acetic acid (with eg. a benzyl or *p*-toluenesulphonyl group).

A related preparation[9] of bisphenyl- and phenylheteroaryl- maleic anhydrides is the modified Perkin reaction of glyoxylic acids with acetic acids in refluxing acetic anhydride. Although we have applied this procedure to the preparation of indolylaryl maleic anhydride **9** the

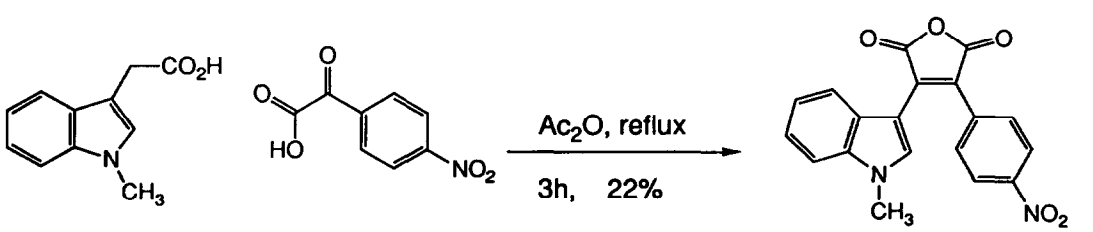
method cannot be applied to the preparation of bisindolyl compounds since it fails entirely with indolyl-3-glyoxylic acids, probably due to the decreased reactivity towards nucleophiles of a carbonyl group attached to an indole at the 3-position.[10]

Table. Preparation of indolylaryl maleic anhydrides



R_1	R_2	Ar	Overall Yield[a] %
H	methyl	1-methyl-3-indolyl	36
2-methyl	methyl	1-methyl-3-indolyl	33
5-(methoxycarbonyl)	methyl	1-methyl-3-indolyl	55
H	3-cyanophenyl[b]	1-methyl-3-indolyl	64
H	methyl	1-benzyl-3-indolyl	29
H	benzyl	1-methyl-3-indolyl	24
H	methyl	1-*p*-toluenesulphonyl-3-indolyl	35
H	methyl	phenyl	23
H	methyl	4-methoxyphenyl	43
H	methyl	1-naphthyl	24
H	methyl	3-thienyl	27

a. Based on starting indole b. Starting indole prepared as in reference 8.



9

The indolylglyoxylyl chloride cyclisation represents a convenient and flexible synthesis of indolylaryl maleic anhydrides under mild conditions.

Bis(1-methyl-3-indolyl)maleic anhydride:

Oxalyl chloride (0.63g, 5mmol) was added to a stirred solution of 1-methylindole (0.66g, 5mmol) in dichloromethane (50ml) at 0° C. After 15 min. solvent was evaporated *in vacuo* and the residue (1-methylindole-3-glyoxylyl chloride) redissolved in dichloromethane (50ml) and added dropwise to a stirred solution of 1-methyl-3-indolylacetic acid (0.95g, 5mmol) and triethylamine (1.0g, 10mmol) in dichloromethane (20ml). After 4h the mixture was concentrated *in vacuo* and chromatographed on silica gel with dichloromethane/methanol (98:2) as eluent. 2,3-Bis(1-methyl-3-indolyl)maleic anhydride (0.64g, 36%) was obtained as a red solid of melting point 275-277°C. NMR (300MHz, d_6-DMSO, δppm/TMS): 8.00, s, 2H (indoles 2 position), 7.55, d (J=7.5Hz), 2H, (aromatic), 7.15, t (J=7.5Hz), 2H, (aromatic), 6.90, d (J=7.5Hz), 2H (aromatic), 6.80, t (J=7.5Hz), 2H, (aromatic), 3.95, s, 6H, (N-Me).

Acknowledgement: We thank Ms. S. Turner for her contribution to this work.

References:

1. M. Brenner, H. Rexhausen, B. Steffan and W. Steglich *Tetrahedron* **44**, 2887 (1988).

2. J. Bergman and B. Pelcman *Tetrahedron Letters* **28**, 4441 (1987).

3. S. Omura, Y. Iwai, A. Hirano, A. Nagakawa, J. Awaya, H. Tsuchiya, Y. Takahashi and R. Masuma *J. Antibiot.* **30**, 275 (1977).

4. D. E. Nettleton, T. W. Doyle, B. Krishnan, G. K. Matsumoto and J. Clardy *Tetrahedron Letters* ***26***, 4011 (1985).

5. W. Steglich, B. Steffan, L. Kopanski and G.E. Eckhardt *Angew. Chem., Int. Ed. Eng.* **19**, 459 (1980).

6. P. D. Davis, C. H. Hill and G. Lawton, *British Patent Application* No. 8803048

7. M. E. Speeter and W. C. Anthony *J. Am. Chem. Soc.* **76**, 6208 (1954).

8. E. J. Glamkowski, J. M. Fortunato, T. C. Spaulding, J. C. Wilker and D. B. Ellis *J. Med. Chem* **28**, 66 (1985).

9. E. K. Fields, M. L. Winzenburg and S. J. Behrend *U.S. Patent* 4,596,867 (1986).

10. W. A. Remers in *Heterocyclic Compounds Vol. 25,Part III*, W. J. Houlihan (Ed.); Wiley, New York (1979), p. 372.

(Received in UK 2 March 1990)