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Enamines With Isobenzofuroxan: A Novel Synthesis Of Quinoxaline-di-N-oxides

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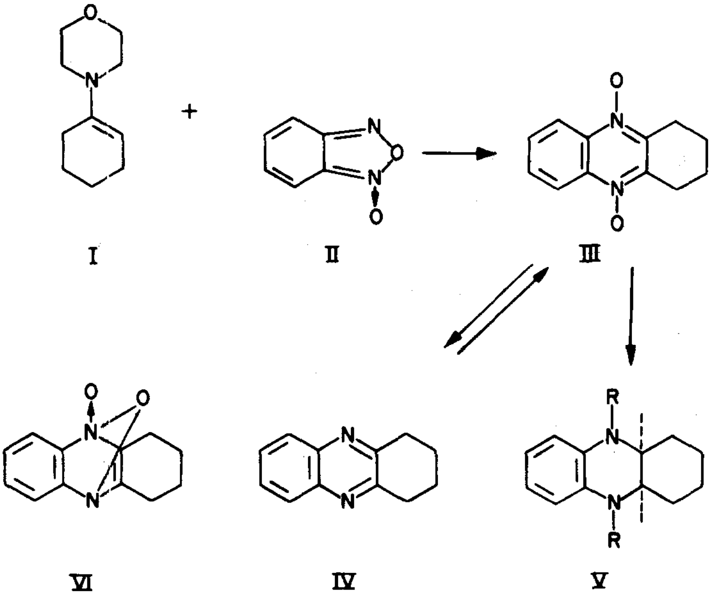
We should like to report a new route to quinoxaline-di-N-oxides from the reaction of enamines with isobenzofuroxan. In a typical run, addition of 1-morpholino-1-cyclohexene (I) to a warm methanolic solution of isobenzofuroxan (II) produced a deep red coloration and a rise in temperature of the reaction mixture. The pale red solid obtained in 48% yield by concentration of the solution melted at 183 - 185° dec. (1). Recrystallization from methanol gave yellow prisms melting at 185° dec. Structure III was assigned to this product on the basis of the following evidence: (i) the n.m.r. spectrum, suggestive of a highly symmetrical structure, exhibited two identical multiplets centered at τ 1.68 and 2.34 (two aromatic protons each), and peaks at τ 6.96 (four allylic protons) and 8.04 (four aliphatic protons). (ii) the infrared spectrum showed strong bands at 1320 and 1300 cm^{-1} attributable to the N-oxide structure (2).

Reduction of III with sodium dithionite gave 1,2,3,4-tetrahydrophenazine (IV) in 85% yield (mixture m.p. with an authentic sample; infrared spectrum). Oxidation of IV with 40% peracetic acid gave III in good yield. This step coupled with the n.m.r. evidence, favored structure III over the comparatively strained structure VI.



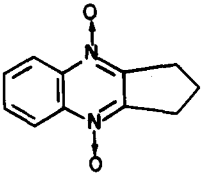
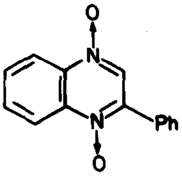
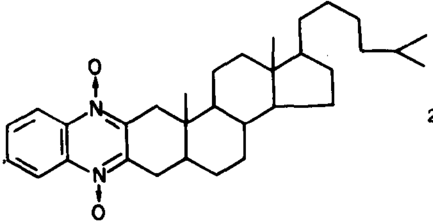
a, $R = H$

b, $R = \overset{O}{\overset{\|}{C}}-CH_3$

Addition of excess sodium borohydride to a solution of III in methanol gave Va in 85% yield. This product melted at 145° (methanol), formed readily a diacetyl derivative (Vb, m.p. 147° from benzene-petroleum ether), was dehydrogenated over palladium to phenazine, and was shown to be identical with an authentic sample of cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (mixture m.p., n.m.r., U.V., infrared) (3).

Table I shows a variety of enamines that reacted with II to give the corresponding quinoxaline-di-N-oxides (4).

TABLE I

Parent Ketone	Product	M.P.
Cyclohexanone (morpholino)	III	185^0 dec.
Cyclohexanone (pyrrolidino)	III	185^0 dec.
Cyclopentanone (morpholino)		182^0 dec.
Acetophenone (morpholino)		210^0
3-Cholestanone (morpholino)		208^0

The ease by which the above transformations may be accomplished recommends this new approach to the synthesis of quinoxalines and their derivatives via enamines. The applicability of this method for the preparation of heterocyclic steroids is now under investigation. We will report on the scope and generality of the reaction in due course.

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