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CONVERSION OF INDOLE INTO QUINAZOLINE: A NEW QUINAZOLINE SYNTHESIS

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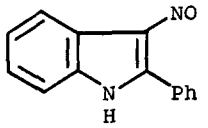
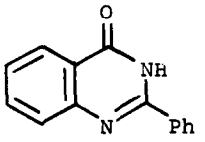
The reaction of 2-phenylisatogen with tetracyanoethylene or trichloroacetonitrile leads to the formation of 2-phenylquinazoline-4(3H)-one (I) by a ring expansion, which occurs via intermediates formed by 1,3-dipolar cycloaddition[1,2]. This is the only precedent for conversion of indole into quinazoline. We now describe a new convenient synthesis of quinazolines by means of the intramolecular rearrangement of an indole derivative.

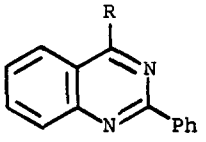
Heating 3-nitroso-2-phenylindole (II) with more than 3 moles of $POCl_3$ or TsCl in sulfolane at 200° for 1 hr, followed by dilution with water, caused 2-phenylquinazoline-4(3H)-one (I) to separate in 90 or 68% yield respectively. Refluxing II with excess $POCl_3$ in DMF for 5 hr gave also I in 40% yield. This ring expansion proceeds without doubt via the second-order Beckmann rearrangement of the imino oxime tautomeric form of II, because the initial reaction solution



(II)



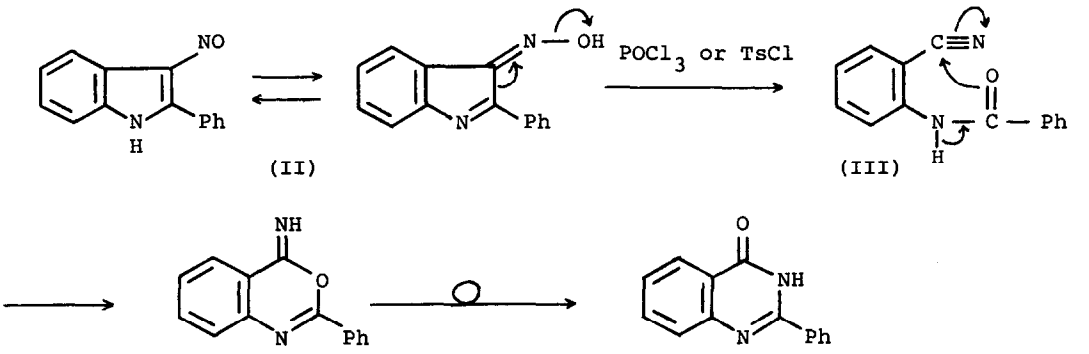
(I)



(IV) R = NHPh (V) R = $NHCH_2Ph$

includes only the intermediate 2-benzoylaminobenzonitrile (III)[3]. For example, refluxing a mixture of II and $POCl_3$ or TsCl in DMF for 30 min, or maintaining the mixture under stirring at room temperature for 3 hr, evaporation of the solvent under reduced pressure and dilution with water yielded III as the major product. Further treatment of the isolated III with the same reagents under the same conditions gave I[4]. These facts suggest that the mechanism depicted in Scheme is the most reasonable. The first stage of this reaction mechanism is reminiscent

of the Bedford-Partridge reaction, in which an isatin 3-oxime is pyrolyzed into 3-aminobenzonitrile[5].



The reaction of II with excess $POCl_3$ in sulfolane in the presence of amines has been tried to obtain the corresponding 4-aminoquinazolines in a single step. Heating a mixture of II, 3 moles of $POCl_3$ and 5 moles of aniline in sulfolane at 200° for 3 hr gave 4-anilino-2-phenylquinazoline (IV)[6], mp 249°, in 50% yield. Similarly, 4-benzylamino-2-phenylquinazoline (V), mp 118°, was obtained in 65% yield. This procedure offers a convenient synthetic method for preparation of 4-aminoquinazoline derivatives. When TsCl instead of $POCl_3$ was used in this reaction, the desired 4-aminoquinazolines could not be obtained. Therefore, a probable key intermediate is 4-chloro-2-phenylquinazoline drived from I by action of existent $POCl_3$.

REFERENCES

1) W. E. Noland and D. A. Jones, J. Org. Chem., 27, 341 (1962).
2) W. E. Noland and R. F. Modler, J. Am. Chem. Soc., 86, 2086 (1964).
3) M. Körner, J. prakt. Chem., [2], 36, 155 (1887).
4) Treatment of III with dry hydrogen chloride gas in absolute ethanol gave also I in quantitative yield. Such an acid-catalyzed cyclization of o-acylaminonitriles to quinazoline-4(3H)-ones is known and well documented in the literature: E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles", Interscience Publishers, 1970.
5) G. R. Bedford and M. W. Partridge, J. Chem. Soc., 1633 (1959).
6) Satisfactory analytical and spectral data were obtained for all the products.