Photochemistry of 4,6-Disubstituted Pyrimidine *N*-Oxides [1]

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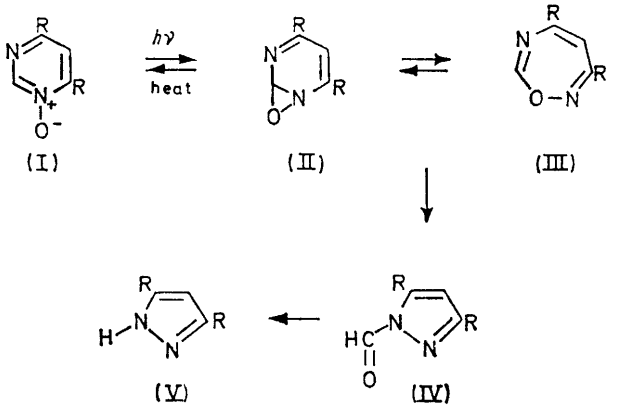
Photolysis of 4,6-di-R-pyrimidine 1-oxides (R = Ph or Bu^t) in methanol with a high-pressure mercury arc and a Rayonet RPR 2537 Å lamp, respectively, leads to 3,5-di-R-pyrazoles. In the case R = Ph, in addition to the pyrazole, 2-methoxy-4,6-diphenylpyrimidine is obtained. This compound is considered to be formed *via* an oxaziridine intermediate, the existence of which was indicated by the liberation of iodine from potassium iodide.

DI- AND TRI-SUBSTITUTED pyrimidine *N*-oxides have been shown to rearrange photochemically by a process probably involving an initial attack of the oxygen atom at C(6),[1a] resulting in a 1a*H*-oxaziridino[2,3-*a*]pyrimidine intermediate. No indication of attack of the oxygen at C(2) of the pyrimidine ring was observed. This regiospecificity is in good agreement with the results of PPP–SCF calculations,[2] but contradicts those based on LCAO–MO theory, predicting a preferential addition to C(2).[3] Although the products obtained on irradiation of monosubstituted pyrimidine *N*-oxides [3] seem to confirm the latter theory, a recent report reveals that in these compounds also there is a tendency for the oxygen atom to attack at C(6).[4]

Since in the reactions of the pyrimidine 1-oxides described so far the substituents at positions 2, 4, and 6 have been relatively small, we became interested in the behaviour of 4,6-disubstituted pyrimidine *N*-oxides in which the 4- and 6-substituents are bulky, hoping that steric interference at these positions would direct the cyclisation to the unsubstituted position 2. We therefore studied the photochemical behaviour of the 4,6-di-R-pyrimidine 1-oxides (I; R = Ph or Bu^t).

The photolysis of 4,6-diphenylpyrimidine 1-oxide in acetone is reported to yield a complex mixture from which no product was isolated.[5] In our hands photolysis of a methanolic 5×10^{-3}M-solution of 4,6-diphenylpyrimidine 1-oxide (I; R = Ph) with a high-pressure mercury arc (Hanau TQ 150) yielded a mixture from which, by t.l.c., two main products, *i.e.* 3,5-diphenylpyrazole (V; R = Ph) (11%) and 2-methoxy-4,6-diphenylpyrimidine (X) (6%) could be isolated. No indication of the formation of 4,6-diphenylpyrimidine was obtained. Both products were identified by comparison (^{1}H n.m.r., i.r., and mass spectra) with authentic compounds.

To our knowledge, this is the first example of a photochemically induced ring contraction of a pyrimidine *N*-oxide to a pyrazole. In this reaction the initia attack of the oxygen must take place at C(2). Apparently attack at C(6) is strongly disfavoured owing to steric hindrance by the phenyl group.† Although the mechanism of this ring contraction is not completely elucidated, we suggest the following pathway: (*a*) cyclisation at C(2); (*b*) ring expansion to a 1,2,6-oxadiazepine (III); (*c*) ring contraction to a 3,5-disubstituted *N*-formylpyrazole (IV), which undergoes deformylation to (V).



SCHEME 1

An equilibrium between the oxaziridinopyrimidine (II) and the 1,2,6-oxadiazepine (III) has been proposed but never established; however, it shows a great similarity to the equilibrium between a 1,3-oxazepine and its oxanorcaradiene isomer, which was recently established [6] in the thermal rearrangement of 2-phenyl-1,3-oxazepine to *N*-formyl-2-phenylpyrrole. In order to investigate the feasibility of the photodeformylation (IV) ⟶ (V) (as recently observed during the photolysis of 6-methyl- and 6,9-dimethyl-purine 1-oxides [7]) attempts were made to prepare (IV) by a procedure analogous to that for the preparation of *N*-formylindole.[8] These attempts failed, however (see Experimental section). The possibility that (V) is formed from an intermediate 4,6-diphenyl-

† Ground-state addition of an amide ion to a pyrimidine ring usually takes place at position 4(6); in the case of 4,6-diphenylpyrimidine the addition of an amide ion has been found to occur at C(2) (J. P. Geerts and H. C. van der Plas, unpublished data).

[1] This paper is regarded as Part LII of the series 'Pyrimidines' and Part VI of 'Photoreactions of Diazines.' For Part LI(V) see (*a*) F. Roeterdink and H. C. van der Plas, Contributed Paper of the Euchem Research Conference: Useful Preparative Aspects of Photochemistry, Gent, 1975; for Part L see (*b*) J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Org. Magnetic Resonance*, 1975, **7**, 85.

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[5] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 231.

[6] T. Tezuka, O. Seshimoto, and T. Mukai, *Tetrahedron Letters*, 1975, 1067.

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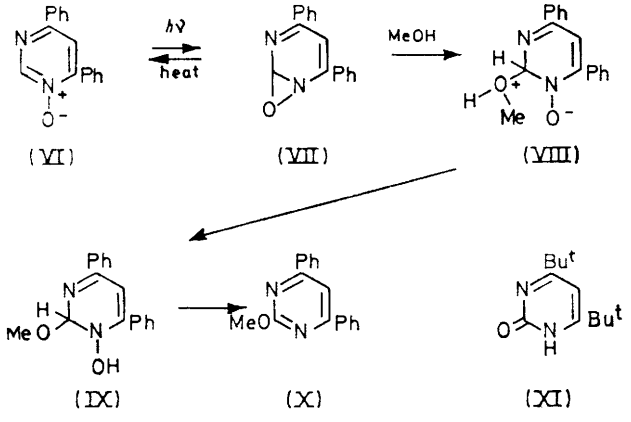
[8] L. Alessandri and M. Passerini, *Gazzetta*, 1921, **51**[I], 262.

pyrimidin-2-one was ruled out by irradiation of this compound under the same conditions; only starting material was recovered.

The intermediate formation of an oxaziridine in the photoreactions of heteroaromatic *N*-oxides is generally accepted,[5] but despite many efforts these species have never been isolated; even recent nanosecond flash photolysis experiments gave no indication of its intermediary existence.[9,10] The only chemical 'proof' hitherto available is the 'trapping' of the oxaziridine by primary or secondary amines during the photolysis of 2-cyanoquinoline 1-oxides.[11,*] We believe that the formation of 2-methoxy-4,6-diphenylpyrimidine (X) in the present reaction can also be considered as a good indication of the intermediary existence of an oxaziridine. Furthermore, irradiation of 4,6-diphenylpyrimidine 1-oxide in the presence of a seven-fold molar amount of



SCHEME 2

potassium iodide in water produced iodine. Since 4,6-diphenylpyrimidine 1-oxide shows no oxidising properties towards iodide ion in the dark, and oxaziridines are known to be strong oxidising agents which are capable of liberating iodine from potassium iodide,[13] this experiment strongly supports the presence of an oxaziridine as intermediate. Since no deoxygenation was observed, the oxaziridine intermediate is the oxidising species and not atomic oxygen. Identical experiments were performed with 2,4,6-trimethylpyrimidine 1-oxide and 4-chloro-2,6-dimethylpyrimidine 1-oxide. In both experiments a twelve-fold molar amount of potassium iodide was needed to liberate iodine. This can be considered as an indication that in the case of the 4-R-2,6-dimethylpyrimidine 1-oxides (R = Me or Cl) the oxaziridine has a shorter lifetime. It has been reported that during the irradiation of 3,6-diphenylpyridazine *N*-oxide no oxaziridine intermediate is formed.[10] Photolysis of this *N*-oxide, in our hands, in the presence of a fifty-fold molar amount of potassium iodide in water did not produce iodine. From these results we conclude that the photochemical behaviour of heteroaromatic *N*-oxides is not uniform. In some cases the first step is oxaziridine formation; in others the products are formed directly from the excited state of the *N*-oxide.

The possibility that the methoxy-derivative (X) is formed from 4,6-diphenylpyrimidine arising by deoxygenation of the *N*-oxide was ruled out by irradiation of 4,6-diphenylpyrimidine in methanol: no 2-methoxy-4,6-diphenylpyrimidine 1-oxide was formed. Irradiation of 4,6-diphenylpyrimidine 1-oxide in benzene gave as main product only 3,5-diphenylpyrazole (V; R = Ph) (9%).

In agreement with the foregoing results, pyrazole formation was also observed during the light-induced conversion of 4,6-di-t-butylpyrimidine 1-oxide (I; R = Bu^t) in methanol with light of wavelength 254 nm. Besides the pyrazole (V; R = Bu^t) (23%) 4,6-di-t-butylpyrimidin-2-one (XI) (10%) was also isolated. No indication of the formation of 2-methoxy-4,6-di-t-butylpyrimidine was obtained. The formation of both products (V; R = Bu^t) and (XI) indicates that in this case also the attack of the oxygen atom takes place at C(2).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a JEOL JNM-C60 spectrometer (Me_4Si as internal standard). Mass spectra were recorded with an A.E.I. MS902 instrument.

General Photolysis Procedure.—A solution of 4,6-diphenylpyrimidine 1-oxide (I; R = Ph) (0.4 g) in methanol (500 ml) or benzene (500 ml) was irradiated under nitrogen with a Hanau TQ 150 high-pressure mercury arc through a quartz filter. 4,6-Di-t-butylpyrimidine 1-oxide (I; R = Bu^t) was irradiated under the same conditions as reported earlier.[1a]

The intermediacy of the oxaziridine during photolysis was indicated as follows. A solution of 4,6-diphenylpyrimidine 1-oxide (3.5 mg) and potassium iodide (15.8 mg) in water (4 ml) was irradiated for 5 min with the mercury arc. The formation of iodine was proved by addition of this solution, directly after irradiation, to an aqueous starch solution, which immediately gave the typical blue colour. The same solution did not produce iodine when kept in the dark. Also, irradiation of an aqueous solution of potassium iodide did not give iodine.

Starting Materials.—(1) 4,6-Diphenylpyrimidine [14] and 3,6-diphenylpyridazine *N*-oxide [10] were prepared as described in the literature.

(2) 4,6-*Diphenylpyrimidine* 1-*oxide* (I; R = Ph). 30% Hydrogen peroxide (12.5 g) was slowly stirred into a solution of maleic anhydride (84 g) in chloroform (280 ml) cooled in ice. After stirring for 2 h 4,6-diphenylpyrimidine (8.2 g) was added. The mixture was kept in a refrigerator for 5 days. The precipitated maleic acid was filtered off, and the filtrate was washed with aqueous potassium carbonate.

* It was reported recently [12] that 4-alkoxyisoquinolines are formed in the photolysis of isoquinoline 2-oxide derivatives.

[9] C. Lohse, *J.C.S. Perkin II*, 1972, 229.
[10] K. B. Tomer, N. Harrit, J. Rosenthal, O. Buchardt, P. L. Kumler, and I. Creed, *J. Amer. Chem. Soc.*, 1973, **95**, 7402.
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[13] J. S. Splitter and M. Calvin, *J. Org. Chem.*, 1965, **30**, 3427.
[14] H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, 1957, **90**, 942.

The chloroform layer was dried (K_2CO_3), filtered, and evaporated *in vacuo*. Recrystallisation of the residue from light petroleum (b.p. 60—80 °C) gave the 1-*oxide* (I; R = Ph) (3.2 g, 37%); m.p. 107—108 °C; δ ($CDCl_3$) 7.4—7.5 (m), 7.75 [H(5), s], 7.9—8.1 (m), and 9.00 [H(2), s] (Found: C, 77.15; H, 5.1. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.85%).

(3) 2-*Methoxy*-4,6-*diphenylpyrimidine* (X). A solution of 2-chloro-4,6-diphenylpyrimidine (484 mg) in methanol containing sodium methoxide (204 mg) was refluxed for ½ h. After neutralisation with CO_2 the solution was evaporated and the residue recrystallised from light petroleum (b.p. 60—80 °C) to give the *methoxy-derivative* (381 mg, 80%), m.p. 81—82 °C; δ ($CDCl_3$) 4.20 (OCH_3, s), 7.5—7.65 (m), 7.82 [H(5), s], and 8.1—8.3 (m); *m/e* 262 (M^+) and 232 ($M^+ - CH_2O$) (Found: C, 77.9; H, 5.4. $C_{17}H_{14}N_2O$ requires C, 77.85; H, 5.4%).

(4) 3,5-*Diphenylpyrazole* (V; R = Ph). This compound was prepared according to a modified procedure.[15] Hydrazine sulphate (9.75 g) was dissolved in 2.5N-sodium hydroxide (60 ml). Dibenzoylmethane (17 g) and ethanol (50 ml) were added. The mixture was stirred at 50—60 °C for 4 h, and the temperature was then slowly raised till the solvent evaporated off. 3,5-Diphenylpyrazole crystallised out and was recrystallised from light petroleum (b.p. 100—140 °C); yield 6 g (36%), m.p. 199 °C (lit.,[16] 199 °C).

(5) 4,6-*Di-t-butylpyrimidine* (with A. Koudijs). To a solution of pyrimidine (3.20 g), pivalic acid (20.6 g), and silver nitrate (0.6 g) in sulphuric acid (10%; 40 ml) at 70 °C, ammonium peroxodisulphate (27.4 g) was added during 1 h.[17] The mixture was then stirred for another ½ h. After neutralisation with 25% sodium hydroxide the solution was extracted with ether. Evaporation of the extract left a residue which was purified on a silica gel column (eluant $CHCl_3$). Distillation *in vacuo* yielded 4,6-di-t-butylpyrimidine (4.7 g, 61%), b.p. 101—102 °C at 13 mm Hg; δ ($CDCl_3$) 1.40 (CMe, s), 7.33 [H(5), s], and 9.11 [H(2), s]; *m/e* 192 (M^+), 177 ($M^+ - CH_3$), and 150 ($M^+ - C_3H_6$) * (Found: C, 75.25; H, 10.5. $C_{12}H_{20}N_2$ requires C, 74.95; H, 10.5%).

(6) 4,6-*Di-t-butylpyrimidine* 1-*oxide* (I; R = Bu^t) (with A. Koudijs). This compound was prepared by the procedure given for 4,6-diphenylpyrimidine 1-oxide [see section (2)]. 4,6-Di-t-butylpyrimidine (4.0 g) gave the N-*oxide* (1.8 g, 42%), m.p. 115—116 °C; δ ($CDCl_3$) 1.40 (CMe_3, s), 1.58 CMe_3, s), 7.30 [H(5), s], and 8.88 [H(2), s]; *m/e* 208 (M^+) and 193 ($M^+ - CH_3$) (Found: C, 68.85; H, 9.7. $C_{12}H_{20}N_2O$ requires C, 69.2; H, 9.7%).

(7) 4,6-*Di-t-butylpyrimidin*-2-*one* (with A. Koudijs). According to the procedure given in section (5), t-butylation of 2-ethoxypyrimidine (2.0 g) gave 2-ethoxy-4,6-di-t-butylpyrimidine (2.6 g, 68%). The product (300 mg) was refluxed with concentrated hydrochloric acid (25 ml) during 1 h. Evaporation followed by neutralisation with ammonia and extraction with chloroform gave 4,6-*di-t-butylpyrimidin*-2-*one* (100 mg, 38%), m.p. 223—224 °C, δ ($CDCl_3$) 1.34 (CMe_3, s), 4.9br (NH), and 6.45 [H(5), s]; *m/e* 208 (M^+), 193 ($M^+ - CH_3$), and 166 ($M^+ - C_3H_6$) (Found: C, 69.0, H, 9.54. $C_{12}H_{20}N_2O$ requires C, 69.2; H, 9.7%).

Attempt to prepare 1-*Formyl*-3,5-*diphenylpyrazole*.[8]—3,5-Diphenylpyrazole (6.00 g) in absolute ether was treated, with cooling, with the Grignard reagent obtained from magnesium (0.65 g) and methyl iodide (4.04 g) in ether. After completion of the reaction by heating, isopentyl formate (3.54 g) was added dropwise and with cooling. Immediately after the initial addition of the formate the mixture changed from a yellow-brown suspension to a dark red solution. After 80 min, crushed ice was added. A precipitate was obtained and the supernatant ethereal layer was separated. This layer was combined with ethereal extracts of the aqueous layer. On evaporation the starting material was nearly quantitatively recovered.

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* It is generally observed that compounds containing a t-butyl group in a position adjacent to nitrogen undergo a fragmentation with loss of C_3H_6.

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[16] O. Widman, *Ber.*, 1916, **49**, 477.
[17] J. M. Anderson and J. K. Kochi, *J. Amer. Chem. Soc.*, 1970, **92**, 1651.