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THE OXIDATION OF HETEROCYCLIC SYSTEMS BY MOLECULAR OXYGEN—IV[1]

THE PHOTOSENSITIZED AUTOXIDATION OF OXAZOLES

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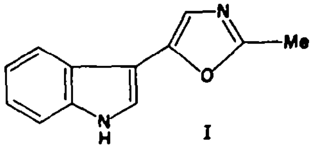
Abstract—Oxazoles are sensitive to photooxidation and undergo reaction under mild conditions. The oxidation appears to produce isoimides (not isolated) which readily rearrange to tertiary amides. Thus, both 2-methyl-4,5-diphenyloxazole and 4-methyl-2,5-diphenyloxazole are transformed to N-acetyldibenzamide by air oxidation in the presence of visible light in methanol containing methylene blue. Other oxidations of oxazole-containing systems, including the natural product pimprinine, are described.

DURING studies on the reaction of indole derivatives with molecular oxygen[1c] we had occasion to study the photosensitized autoxidation of the mold metabolite pimprinine (I).[3]


I

While pimprinine appeared to suffer extensive decomposition when oxygenated in the presence of azobisisobutyronitrile, photooxidation led to cleaner results. On illumination with a 150-watt floodlamp with methylene blue as a sensitizer, methanol as solvent, and air as the oxidizing agent, nearly complete conversion to indole-3-carboxylic acid took place.[4] This result indicated a marked sensitivity of the oxazole ring toward air-oxidation under these conditions and prompted us to carry out the investigations on oxazole photooxidation described below.

Because of its structural similarity to pimprinine, 2-methyl-5-phenyloxazole (II) was chosen as the initial system for further study. In the presence of air, light and sensitizer, a methanol solution of II was converted, over a period of two days, to benzoic acid (83%) and a neutral nonvolatile product, $C_{11}H_{13}NO_3$ (10%). The latter shows singlets in the NMR at τ 7·82 ($COMe_3$) and 6·43 (OMe_3), as well as a doublet at 3·50 and peaks characteristic of the phenyl protons. The IR spectrum shows intense absorption at 3420 and a broad band at 1680 cm^{-1}. The above spectral

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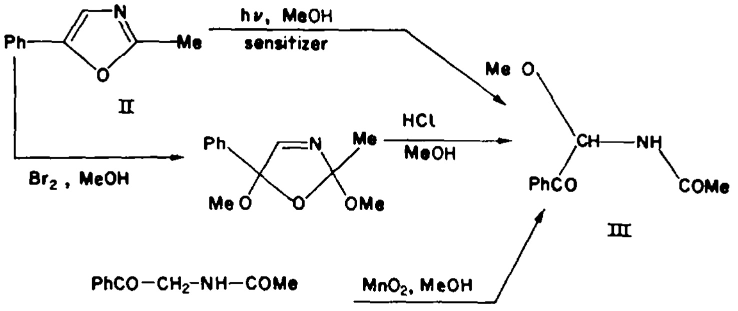
[1] For previous papers in this series see:
[a] H. H. Wasserman and A. Liberles, *J. Amer. Chem. Soc.* **82**, 2086 (1960);
[b] H. H. Wasserman and A. Doumaux, *Ibid.* **84**, 4611 (1962);
[c] H. H. Wasserman and M. B. Floyd, *Tetrahedron Letters* No. 29, 2009 (1963).

[2] N.S.F. Predoctoral Fellow; 61–65; N.I.H. Predoctoral Fellow, 1965. Taken from the doctoral dissertation of M. B. Floyd, Yale University, 1966.

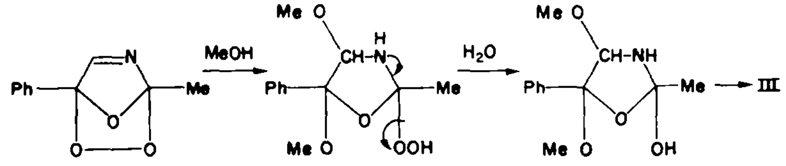
[3] B. S. Joshi, W. I. Taylor, B. S. Bhate and S. S. Karmarkar, *Tetrahedron* **19**, 1437 (1963).

[4] The stability of the indole ring to photooxidation is shown by the very slow change of 2,3-diphenylindole under these conditions.

evidence is compatible with structure III for the oxidation product, and this assignment was confirmed by the following independent preparations of α-acetamido-α-methoxyacetophenone. Reaction of 2-methyl-5-phenyloxazole with bromine and methanol gave an oil which, on treatment with methanolic HCl yielded III. Alternatively, the same product could be prepared directly by the oxidation of α-acetamidoacetophenone with manganese dioxide in methanol.[5]

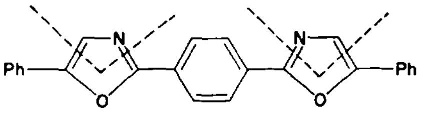


Formation of III thus appears to follow a reaction path commonly observed in furan photoxidation.[6] The initially formed ozonide-like peroxide IV is converted in methanol to a methoxy hydroperoxide V (or isomer with OMe at C-2 and OOH at C-5). Solvolysis of the hydroperoxide by water would lead to the hemiketal system VI, convertible to III by loss of methanol.



IV V VI

In the related dye-photosensitized autoxidation of 1,4-bis-(5-phenyloxazol-2-yl)-benzene (VIII) nearly quantitative yields of benzoic and terephthalic acids were obtained, again illustrating the ready destruction of the oxazole ring under these relatively mild conditions.



VIII

While the isolation of III indicates one mode of oxazole reaction in photosensitized autoxidation, this result does not shed light on the main course of the oxidation leading to indole-3-carboxylic acid from I, and benzoic acid from II and VII. Insight into this type of oxidative breakdown was provided by studies on trisubstituted

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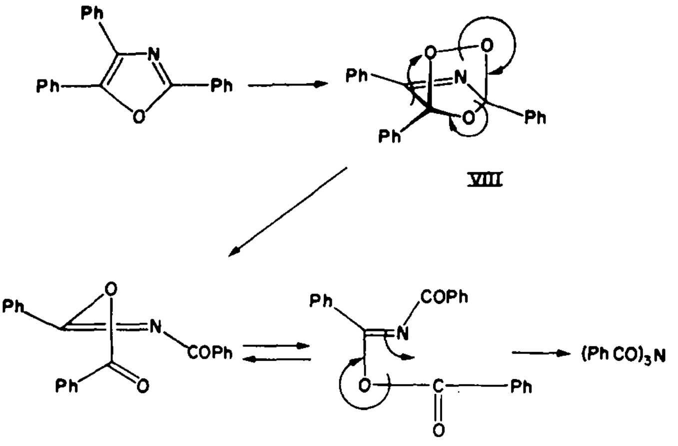
[5] For early studies on MnO_2 oxidation of amines see R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.* 77, 4399 (1955).

[6] [a] C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.* **86**, 3879 (1964); [b] G. O. Schenck, *Angew. Chem.* **69**, 579 (1957) and Refs therein.

systems which yielded other products resulting from cleavage of the C_4–C_5 bond.

When 2,4,5-triphenyloxazole was exposed to air and light in the usual manner, tribenzamide m.p. 209–210° was formed as the main product (55%). Small amounts of benzoic acid and benzamide were also produced. Tribenzamide, identical with the known product prepared by the method of Titherly,[7] shows strong, broad absorption in the IR centered at about 1695 cm^{-1}. The IR spectrum thus clearly distinguishes the triamide structure from the isomeric N-aroylisoimide which should show enol-ester absorption at about 1750 cm^{-1}.[8]

Chart I



VIII

IX

Two mechanisms may be considered to account for the formation of the triamide from the trisubstituted oxazole. As shown in Chart I, the transannular peroxide (VIII) formed in the first step could undergo rearrangement to form the N-benzoylisoimide (IX). The isoimide would then be expected to undergo further intramolecular rearrangement to the triamide.[9,10] The decomposition of the intermediate

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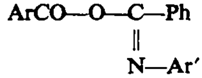
[7] A. W. Titherly, *J. Chem. Soc.* **85**, 1688 (1904).

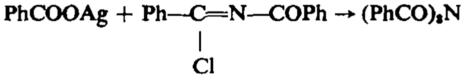
[8] D. Y. Curtin and L. L. Miller, *Tetrahedron Letters* No. 23, 1869 (1965) report IR absorption at 1750 cm^{-1} (KBr), (ester C=O), and at 1680 cm^{-1} (C=N) for the isoimide:



$$\begin{array}{l} \text{ArCO—O—C—Ph} \\ \qquad\qquad\quad \| \\ \qquad\qquad\quad \text{N—Ar}' \end{array}$$

Ar = Ph; Ar′ = 2,4-dinitrophenyl

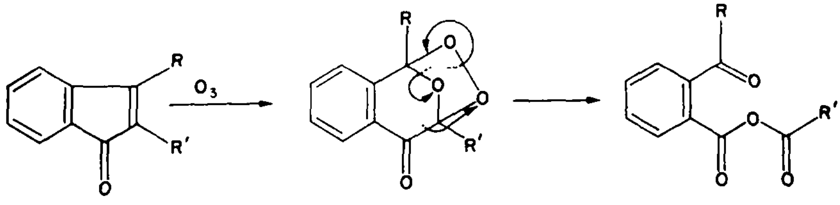
[9] Curtin and Miller[8] have pointed out that only in very special cases have isoimides been isolated. Reactions which should have yielded this functional group have nearly always led, instead, to the corresponding imide. In the present work, attempts to prepare the isoimide, IX, by reaction of silver benzoate with N-benzoylbenzimidoyl chloride, according to the procedure used for the preparation of N-arylisoimides,[8] gave only tribenzamide and dibenzamide.



$$\begin{array}{l} \text{PhCOOAg + Ph—C=N—COPh} \rightarrow \text{(PhCO)}_3\text{N} \\ \qquad\qquad\qquad\qquad\; | \\ \qquad\qquad\qquad\qquad\; \text{Cl} \end{array}$$

[10] Although the *anti*-isomer of the isoimide would form initially, and rearrangement through the four-membered transition state would probably take place preferentially through the *syn* form as shown, one would expect rapid interconversion between *syn* and *anti* forms in a polar solvent such as methanol.[8]

VIII to the isoimide IX has many analogies in the rearrangement of related peroxidic systems. For example, the dye-sensitized photooxidation of tetraphenylfuran in acetone yields the enol-benzoate of dibenzoylphenylmethane as one of the major products.[1a] Likewise, 2,3-disubstituted indenones are converted by ozone to mixed anhydrides of type XIV, most probably by a similar process (XIII, arrows).[11,12]

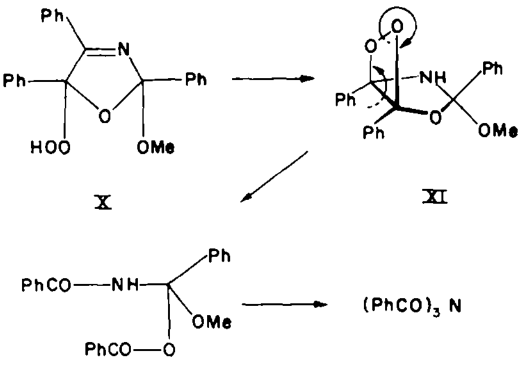


XIII XIV

In Chart II, an alternate mode of formation of the isoimide intermediate (IX) is shown. Reaction of the transannular peroxide VIII with methanol to form the methoxy hydroperoxide (X) followed by cyclization to XI and ring cleavage as shown would form XII, convertible to IX by loss of methanol.

While the evidence does not distinguish between the above two modes of formation of the isoimide, the sequence in Chart I seems to be in better accord with the fact that

Chart II



X XI

XII

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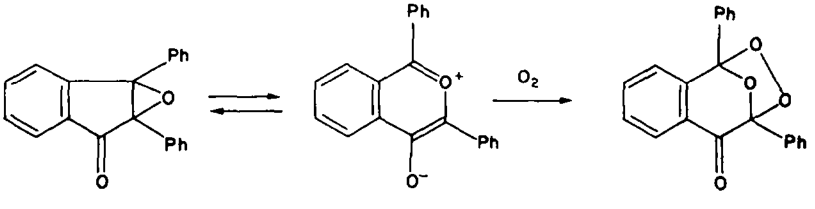
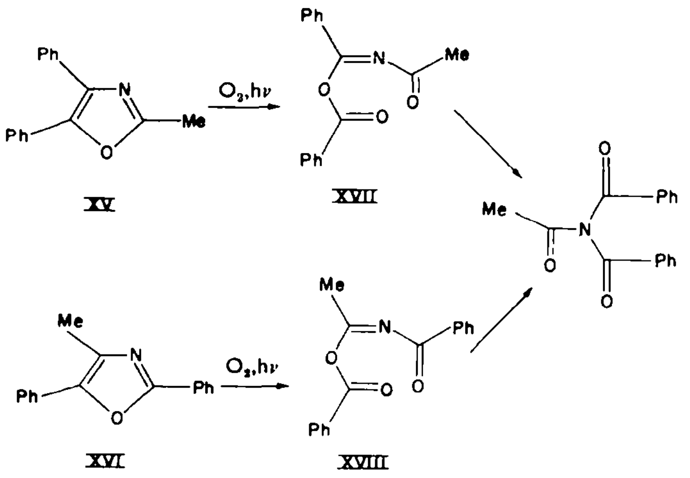
[11] R. Criegee, P. DeBruyn and G. Lohaus, *Liebigs Ann.* 583, 19 (1953).

[12] Another example of this mode of breakdown of peroxidic systems is found in the sensitized oxygenation of the epoxide of 2,3-diphenylindenone: E. F. Ullman, *J. Amer. Chem. Soc.* 86, 5357 (1964). Presumably the intermediate here is also the ozonide-like system, XIII.



tribenzamide was obtained when the solvent was changed from methanol to chloroform. In the latter medium, formation of an intermediate corresponding to X would be unlikely.

The generality of triamide formation in the photooxidation of oxazoles was further shown in studies on 2-methyl-4,5-diphenyloxazole (XV) and 4-methyl-2,5-diphenyloxazole (XVI). From each of these systems N-acetyldibenzamide was formed in high yield. This result is in accord with the formation of isoimide intermediates XVII and XVIII which would then rearrange to the same tertiary amide.



Formation of isoimides would thus account for the isolation of indole-3-carboxylic acid from pimprinine, and of benzoic acid from the 5-phenyloxazole derivatives. The anhydride-like intermediates would be sensitive toward hydrolytic cleavage, and this reaction course would certainly compete with the rearrangement to triamides. Furthermore, one would expect the triamides to be reactive acylative agents capable of undergoing hydrolysis or methanolysis. In cases where the 4-position of the oxazole ring is unsubstituted, photooxidation could lead to triamides containing the N-formyl group, and this result has recently been observed in the photooxidation of 2,5-diphenyloxazole.[13]

EXPERIMENTAL[14]

Photosensitized autoxidations

The standard photosensitized autoxidations described were carried out according to the following general procedure: The reaction vessel was a 3-necked round-bottomed flask of approximately twice the volume of solvent used. Air, from the laboratory line, was passed through two Drierite towers in

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[13] H. A. MacKay, private communication.

[14] M.ps and b.ps are uncorrected. IR spectra were determined on a Perkin-Elmer 421 Spectrometer. NMR spectra were obtained with the Varian Model A-60 Spectrometer. UV spectra were taken with a Cary 11-S Spectrophotometer. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tennessee, and by Dr. A. Bernhardt and his associates, Mulheim, (Ruhr) Germany. The MeOH used in photooxidation reactions was Fisher anhydrous grade and used without further purification.

a slow stream and then under the surface of the reaction solution. The light source was a 150-watt floodlamp placed 1 ft from the nearest surface of the flask which was covered on 3 sides with an Al foil reflector. Reactions were carried out at ambient temp. If decolorization of the sensitizer was observed, additional sensitizer was added. The nature of the sensitizer, amount used and length of reaction are noted explicity in the detailed experimental description below.

Photooxidation of pimprinine

Pimprinine (0·38 g, 9 mMole) was dissolved in 400 ml MeOH containing 5 mg methylene blue. The standard photooxidation reaction was carried out for 120 hr. The MeOH was removed *in vacuo*, and the residue dissolved in 100 ml ether. This solution was extracted with 30 ml 5% NaOH aq. The aqueous portion was acidified with conc. HCl and extracted with three 100 ml portions ether. The combined ethereal solutions were washed once with water and then dried. Evaporation of the ether gave 0·29 g (95%) of indole-3-carboxylic acid, m.p. 219° (dec), (lit.,[15] 218–220°); $\lambda_{max}^{95\%EtOH}$ 281 mμ (log 4·06).[16]

Photooxidation of 2-methyl-5-phenyloxazole

A solution of 2-methyl-5-phenyloxazole[17] (1·59 g, 10 mMole) in 1600 ml MeOH containing 5 mg methylene blue was photooxidized in the standard manner for 48 hr. Following removal of the solvent *in vacuo*, the resulting residue was dissolved in 30 ml ether. The solution was extracted quickly with 40 ml ice-cold 10% Na_2CO_3aq. The aqueous layer was acidified with excess conc.HCl and extracted twice with 50 ml portions ether. The combined extracts were dried and evaporated to give 1·02 g (83%) benzoic acid. The neutral ether layer from the original extraction was washed with water and dried (Na_2SO_4). Evaporation of the ether gave on oily residue which deposited crystals from benzene–pet. ether, 0·20 g (10%), m.p. 110–112°. The analytical sample was recrystallized from hexane–AcOEt, m.p. 115–116°, $\lambda_{max}^{95\%EtOH}$ 253 mμ (log ϵ 4·32), 274 mμ (logϵ 4·09). The compound was identified as ω-acetamido-ω-methoxyacetophenone. (Found: C, 63·98; H, 6·41; N, 6·96. Calc. for $C_{11}H_{13}NO_3$: C, 63·75; H, 6·32; N, 6·76%.) When the photooxidation was carried out in MeOH–pyridine solution, PhCOOMe (35%) was isolated as the only neutral product along with PhCOOH (50%).

ω-Acetamido-ω-methoxyacetophenone

(a) *By oxidation of ω-acetamidoacetophenone with manganese dioxide in methanol.* Manganese dioxide (8·69 g, 0·10 mole), was added to a solution of ω-acetamidoacetophenone (0·89 g, 5 mMole) in 100 ml MeOH, and the suspension stirred at room temp for 48 hr. The mixture was filtered through a short alumina column, which was washed with 50 ml MeOH, and the combined MeOH solutions evaporated yielding a semicrystalline residue. This was dissolved in 5 ml benzene and then developed on 20 g Grace silica gel deactivated with 5% water (0·5 cm column). Elution was performed with benzene progressively enriched in $CHCl_3$ (about 800 ml total) and then with pure $CHCl_3$. Pure ω-acetamido-ω-methoxyacetophenone was found in the $CHCl_3$ eluant. The yield was 0·19 g (18%), m.p. 113–114·5°. The IR and NMR spectra of this material are identical with the spectra of the product obtained from the photooxidation reaction.

(b) *By oxidation of 2-methyl-5-phenyloxazole with bromine in methanol.* A solution of 3·18 g (0·02 Mole) of the oxazole and 3·92 g (0·04 Mole) of anhydrous AcOK in 50 ml MeOH was cooled to −5° in an ice-salt mixture. While cooling was maintained, 3·20 g (0·02 Mole) Br_2 in 20 ml MeOH was added dropwise over a period of 2 hr during stirring. The mixture was then allowed to stand at room temp for 4 hr and the salt which separated removed by filtration. The MeOH was evaporated, 85 ml ether added, the solution filtered, and the ether removed yielding 5·19 g of a pale yellow oil, b.p. 87–90°/300 μ, $\lambda_{max}^{CHCl_3}$ 1664 cm^{-1}. The oil (300 mg) was dissolved in 15 ml MeOH, and treated with 2 ml conc HCl. The solution was allowed to stand at room temp for 30 min and then the bulk of the MeOH was removed *in vacuo*. Water (10 ml) was added to the residue, and the mixture extracted with two 20 ml portions ether. The combined ethereal extracts were washed with sat

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[15] R. Majima, *Ber. Dtsch. Chem. Ges.* **55**, 3867 (1922).

[16] D. Jerchel and R. Staab-Muller, *Z. Naturforsch.* **9b**, 411 (1954).

[17] S. Gabriel, *Ber. Dtsch. Chem. Ges.* **43**, 1284 (1910).

NaCl aq and dried ($CaSO_4$). Removal of the ether gave 240 mg crystalline ω-acetamido-ω-methoxyacetophenone, m.p. 112–113·5° (ca. 75%) after recrystallization from pet. ether–AcOEt. The identity of this material with that obtained from the above MnO_2 oxidation was established by NMR spectral comparison.

Photooxidation of 1,4-*bis-(5-phenyloxazol-2-yl)benzene*

The bisphenyloxazolylbenzene (0·73 g) (Aldrich Chemical Co.) in 1 l. dry pyridine and 200 ml EtOH was photooxidized for 46 hr in the presence of 5 mg methylene blue. The solvent was removed *in vacuo* and the residue treated with 50 ml ether and 50 ml 5% NaOH aq. The ether layer was washed with two 30 ml portions of water, dried and evaporated, leaving 0·11 g amorphous solid which could not be crystallized or characterized. Upon acidification of the basic solution, 0·31 g (94%) terephthallic acid precipitated. The IR spectrum (KBr) was identical to that of an authentic sample. The solution was extracted with ether and the ether layer dried and evaporated to give 0·44 g (90%) PhCOOH.

Photooxidation of 2,4,5-*triphenyloxazole*

The triphenyloxazole, m.p. 113–115°, (2·97 g, 0·01 Mole) prepared according to the procedure of Japp and Murray[18] was photooxidized for 52 hr in 2·1 MeOH with about 10 mg methylene blue. The solvent was removed and the crystalline product triturated with 100 ml ether and then filtered. The unsoluble residue was tribenzamide (1·8 g, 55%) m.p. 209–210° after recrystallization from EtOH. The mixture m.p. with a sample of tribenzamide prepared by the method of Titherley was undepressed.[19] $\lambda_{max}^{95\%EtOH}$ 249 mμ (log ε 4·47); broad IR carbonyl absorption at 1695 cm^{-1}. (Found: C, 76·46; H, 4·66; N, 4·10. Calc. for $C_{21}H_{15}NO_3$: C, 76·58; H, 4·59; N, 4·25%.) The ether filtrate was separated into neutral and acidic portions. The neutral fraction contained 0·20 g benzamide; the acid fraction yielded 0·49 g PhCOOH. Photooxidation of 2,4,5-triphenyloxazole was also carried out in $CHCl_3$. Air was bubbled into a solution of 0·74 g of the oxazole containing 5 mg methylene blue in 475 ml $CHCl_3$ at 4° for 2 hr. Triphenylphosphine (1·32 g) was added and the solution stirred for 2 hr. The solvent was removed and the residue dissolved in 40 ml hot CCl_4. The cooled solution deposited 0·42 g (51%) tribenzamide, m.p. 208–120°.

Oxidation of 2,4,5-*triphenyloxazole with hydrogen peroxide and sodium hypochlorite*

A solution of 1·78 g (6 mMole) of the oxazole in 50 ml ether and 50 ml MeOH was cooled in an ice-bath, and 2·40 ml (22 mMole) 30% H_2O_2 was added. During magnetic stirring, 24 ml (18 mMole) of 0·76M NaOCl solution was added dropwise over a period of 1 hr. The bulk of the organic solvent was removed *in vacuo*, water (75 ml) was added, and the solution extracted with two 50 ml portions ether. The extracts were dried with $CaSO_4$ and evaporated to give 1·68 g yellow solid. Recrystallization from benzene yielded 0·36 g (20%) tribenzamide, m.p. 190–200° (on recrystallization from abs. EtOH, m.p. 210–212°). The benzene filtrate was diluted with hexane (1:1) and cooled, to yield 0·42 g (31%) dibenzamide, m.p. 144–147° after recrystallization from EtOH.

Photooxidation of 2-*methyl-4,5-diphenyloxazole*

The oxazole, prepared by the procedure of Japp and Murray,[18] (2·35 g, 0·01 Mole) was dissolved in 1800 ml MeOH containing 5 mg methylene blue. The standard photooxidation reaction was carried out for 6 hr. Evaporation of the MeOH gave 2·30 g of a clear viscous oil which crystallized (86%) on prolonged standing. The analytical sample was recrystallized from benzene–hexane, m.p. 84–86°. $\lambda_{max}^{95\%EtOH}$ 247·5 mμ (log ε 4·38). (Found: C, 71·83; H, 4·85; N, 5·24. Calc. for $C_{16}H_{13}NO_3$: C, 71·90; H, 4·90; N, 5·24%.) The IR spectrum shows a broad carbonyl absorption at ca. 1700 cm^{-1}. The reported[20] m.p. for N-acetyldibenzamide is 84·5–85·5°.

Photooxidation of 4-*methyl-2,5-diphenyloxazole*

The oxazole, (2·35 g, 0·01 Mole) prepared according to the procedure of Cleland and Niemann,[21] was dissolved in 1800 ml MeOH containing 5 mg methylene blue. The standard photooxidation

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[18] F. R. Japp and T. S. Murray, *J. Chem. Soc.* **63**, 474 (1893).

[19] A. W. Titherley, *J. Chem. Soc.* **85**, 1688 (1904).

[20] Q. E. Thompson, *J. Amer. Chem. Soc.* **73**, 5841 (1951).

[21] G. H. Cleland and C. Niemann, *J. Amer. Chem. Soc.* **71**, 841 (1949).

reaction was carried out for 7 hr. Removal of the solvent gave 2·65 g (99%) oil which crystallized on trituration with hexane. Recrystallization from benzene–hexane gave the triamide, m.p. 85–87° undepressed on admixture with N-acetyldibenzamide from photooxidation of 2-methyl-4,5-diphenyloxazole.

Reaction of N-*benzoylbenzimidoyl chloride with silver benzoate*

N-benzoylbenzimidoyl chloride (1·22 g, 5 mMole), prepared by the method of Titherley and Worall,[22] was added to 50 ml dry ether containing 1·14 g (5 mMole) PhCOOAg, and the suspension was stirred magnetically for 94 hr. An IR spectral examination of the ether phase at this time revealed the presence of substantial amounts of starting material. The ether was evaporated, and the residue was treated with 150 ml acetone. After stirring for 20 min the suspension was freed of insoluble material by filtration, the acetone was removed and the residue treated with pentane (50 ml). The insoluble residue (0·23 g) was shown by IR spectral examination to be tribenzamide. The pentane-soluble material consisted of a mixture of compounds, including N-benzoylbenzimidoyl chloride and benzonitrile.

[22] A. W. Titherley and E. Worrall, *J. Chem. Soc.*, **97**, 839 (1910).