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AN INVESTIGATION OF THE REACTION OF PRIMARY NITROALKANES WITH ACETIC ANHYDRIDE/SODIUM ACETATE

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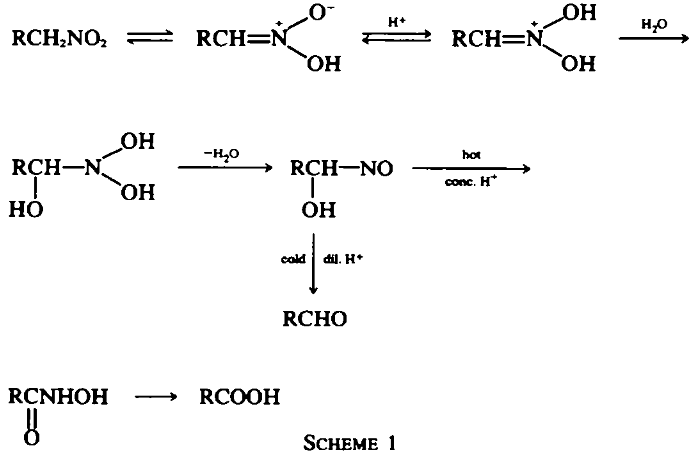
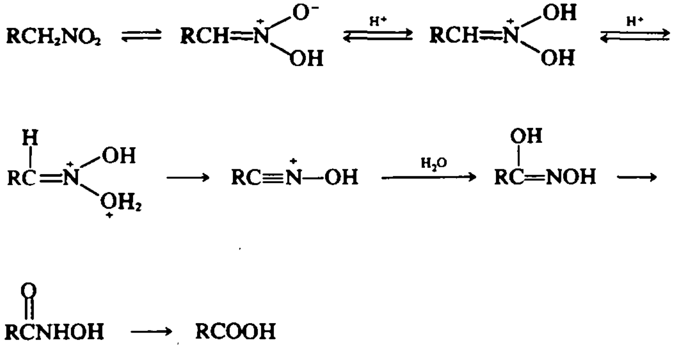
Abstract—Oxidation of primary nitroalkanes by acetic anhydride/sodium acetate has been found to be more complex than previously suspected. Phenylnitromethane, with acetic anhydride/sodium acetate at 60–80°, for example, gives a mixture of benzoic anhydride, triacethylhydroxylamine and acetanilide, through the mixed anhydride $C_6H_5CH{=}\overset{O^-}{\overset{|}{N^+}}{-}OCOCH_3$ as a key intermediate. Evidence in support of this latter species has been obtained by carrying out the oxidation in the presence of dimethyl acetylenedicarboxylate as a 1,3-dipolarophile, when 3-phenyl-4,5-dicarbomethoxyisoxazole is formed in 82% yield. A number of other 3-alkyl- and 3-aryl-4,5-dicarbomethoxyisoxazoles have been prepared in a similar manner.

Aldol-type condensation of primary and secondary nitroalkanes with aldehydes and ketones is seldom a straightforward process, and a variety of different types of products can be obtained depending on the reaction conditions employed.[1] During an investigation into new methods for the synthesis of 1,2,3-triazinium betaines[2] we required as starting materials a number of nitro-olefins of the general structure $C_6H_5\overset{NO_2}{\overset{|}{C}}{=}CRR'$ (R, R' ≠ H) and we attempted to prepare these by condensation of phenylnitromethane with ketones. All attempts to effect condensation with basic catalysts were unsuccessful, however, and the starting materials were recovered unchanged. No condensation occurred either, when acetic anhydride/sodium acetate was employed, but under these conditions the phenylnitromethane was smoothly oxidised in high yield to benzoic acid. This type of oxidation has been known for a hundred years, and various interpretations have been advanced of the nature of the reactions and intermediates involved. None of these appeared to us to be satisfactory, however, and hence we undertook a detailed investigation of the oxidation of phenylnitromethane by acetic anhydride/sodium acetate.

Oxidation of primary nitroalkanes to carboxylic acids was first discovered by Meyer[3] in 1873, who showed that treatment of the aci-salts of nitroalkanes with hot dilute mineral acids resulted in formation of a carboxylic acid and hydroxylamine. The products obtained from this type of reaction are, however, significantly dependent on the strength and nature of the acid employed, and formation of carboxylic acids generally proceeds most efficiently when hot, concentrated (4–31 N) sulphuric acid is used.[1] It has been suggested[4–6] that under these conditions oxidation occurs via a mechanism similar to that involved in the Nef reaction (Scheme 1), although Dewar[7] has proposed an alternative mechanism (Scheme 2) in which a protonated nitrile oxide is formed. There is, however, no



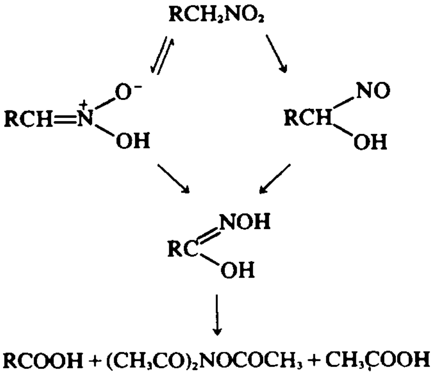
Scheme 1



Scheme 2

evidence to support this latter mechanism, while a considerable amount of data, both chemical and kinetic has been amassed in support of the mechanism shown in Scheme 1.[4–6]

Primary nitroalkanes are inert to acetic anhydride alone, but in the presence of bases such as sodium acetate in acetic anhydride, oxidation to carboxylic acids has been observed. Urbanski[8] has formulated the overall process as shown in Scheme 3, and interpreted the observation of transient, intense blue colours during reaction as being indicative of formation of α-hydroxy nitroso species (transient blue and green colours are frequently observed in the Nef reaction). He did not, however, offer any explanation as to why a Nef type reaction should occur so readily in the presence of base, whereas most reactions of this type occur only in acidic media.

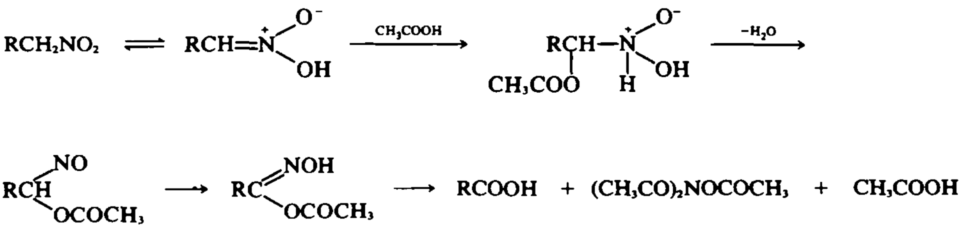


Scheme 3

Nenitzescu[9] has suggested an alternative explanation for these reactions in acetic anhydride (Scheme 4). The aci-form of phenylnitromethane is known to react with hydrogen chloride under anhydrous conditions to give phenylhydroximoyl chloride,[10] and Nenitzescu forwarded his explanation on the basis that addition of acetic acid was equally feasible. This "mechanism", however, is even less attractive than that suggested by Urbanski; in particular, it is difficult to see how this sequence of reactions could be operative in the absence of acetic acid, as the oxidation does not require this latter compound.

It is evident from the above discussion that the reactions of primary nitroalkanes with acetic anhydride have been poorly understood, especially with respect to the detailed mechanism(s) and nature of the reactive intermediates involved in the overall oxidation to carboxylic acids. We have therefore investigated the oxidation of phenylnitromethane under these conditions in some detail, the present, as a result, a new mechanistic interpretation.

Oxidation of phenylnitromethane with acetic anhydride/sodium acetate at reflux temperature proceeded violently and gave, after a standard hydrolytic work-up procedure, a 78% yield of benzoic acid. At lower temperature (60–80°) the reaction proceeded much more smoothly; benzoic acid



Scheme 4

(85%) was isolated from the reaction mixture upon hydrolytic work-up together with a small amount (12%) of a second, neutral compound which was readily identified as acetanilide. The reaction was then carried out under strictly anhydrous conditions, viz anhydrous sodium acetate and acetic anhydride which had been distilled from phosphorus pentoxide. Using a non-aqueous work-up procedure, the products were found to be benzoic anhydride (73%) and triacetylhydroxylamine (53%).

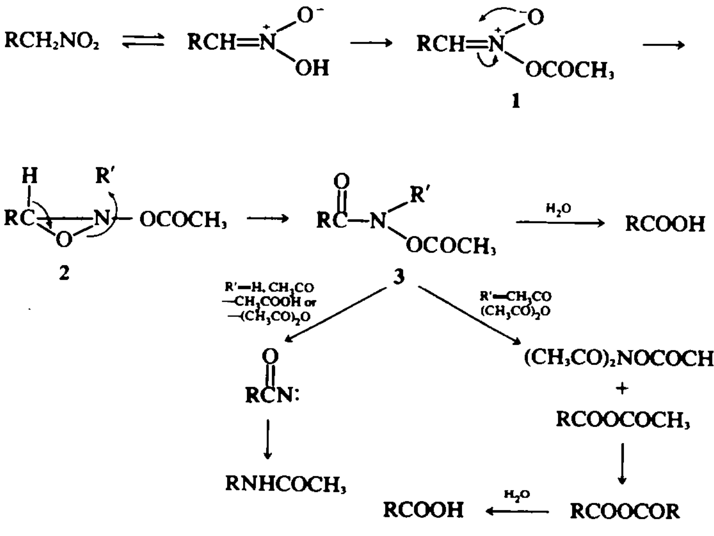
All of the above results can be accommodated by the reactions shown in Scheme 5, i.e. initial acetylation of the nitronate anion to give the mixed anhydride **1**, which isomerises to the oxazirane **2**; rapid decomposition of this latter unstable intermediate then gives either or both of the hydroxamic derivatives **3** (R′ = H or $OCOCH_3$), from which the various reaction products are derived.

Formation of **1** seems reasonable, although very little is known of the chemistry of mixed anhydrides of primary nitronic acids. It has been claimed[9] that treatment of phenylnitromethane with ketene gives **1** as a stable, crystalline solid, but this claim is specious. In a much more recent investigation, Hawks[11] found that acetylation of the thallium(I) salts of a variety of primary nitroalkanes, including phenylnitromethane, at −78° under carefully controlled conditions gave products whose properties were fully consistent with those expected for nitronic-acetic anhydrides. In the present study, acetylation of the thallium(I) salt of phenylnitromethane at 0° gave acetyl phenylhydroximate **3** ($R = C_6H_5$, R′ = H).[12-14] Subsequent treatment of this compound with acetic anhydride/sodium acetate under the standard reaction conditions used for phenylnitromethane gave either benzoic acid, when the reaction mixture was neutralised with aqueous sodium hydroxide solution, or benzoic anhydride when a nonhydrolytic isolation procedure was used. The intermediacy of the oxazirane **2** in the conversion of **1** into **3** is also reasonable. Oxaziranes have been prepared by other methods[15,16] and are known to undergo rapid acid-catalysed isomerism[17] similar to that shown for **2**→**3**.

The remaining reactions shown in Scheme 5 are then quite straightforward. Reaction of **3** (R′ = $OCOCH_3$) with acetate ion gives triacetylhydroxylamine and acetic–benzoic anhydride; mixed anhydrides are known, however, to be thermally unstable and to rearrange readily to give a 1 : 1 mixture of the two symmetrical anhydrides.[18] Formation of the small amount of acetanilide by a Curtius-type reaction presumably involves α-elimination of either acetic acid or acetic anhydride from **3** (R′ = H or $OCOCH_3$ respectively) and production of a nitrene or nitrene-like intermediate.

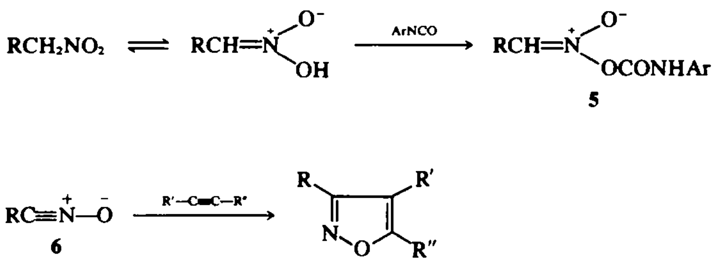
One obvious method by which the intermediacy of **1** can be indicated is by its utilisation as a 1,3-dipole. Reaction of phenylnitromethane with acetic anhydride–sodium acetate was therefore carried out under the standard reaction conditions, but in the presence of one molar equivalent of dimethyl acetylenedicarboxylate. 3 - Phenyl - 4,5 - dicarbomethoxyisoxazole was isolated in 82% yield. Similar reactions were carried out with a number of other primary nitroalkanes, and details of the conversions are listed in Table 1.

The success of these 1,3-dipolar cycloaddition reactions does not, of course, establish that **1** is the actual 1,3-dipole involved. In a closely related series of reactions it has been shown[19] that treatment of primary nitroalkanes with isocyanates and



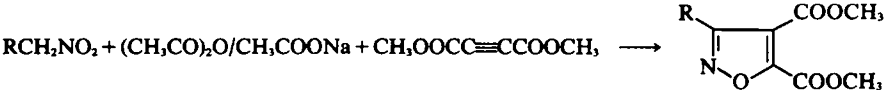
R = C_6H_5; R′ = H^+ or CH_3CO

Scheme 5



Scheme 6

Table 1. Preparation of 4,5-Dicarbomethoxyisoxazoles



R	Yield, %[a,b]	m.p., °C	Anal Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
CH_3	40	b.p. 74–6/0·05 mm	48·25	4·55	7·03	48·66	4·78	7·13
C_2H_5	30	b.p. 92–4/0·2 mm	50·71	5·20	6·57	50·87	5·16	6·58
C_6H_5	82	62–3[c]						
4-$CH_3C_6H_4$	49	67·5–9	61·09	4·76	5·09	61·00	4·97	4·91
4-$O_2NC_6H_4$	39	104–5	50·99	3·29	9·15	50·80	3·50	9·15
4-BrC_6H_4	62	93–5	45·90	2·96	4·12	45·25	3·25	4·19

[a] Refers to pure redistilled or recrystallised material.
[b] No attempt was made to optimise yields.
[c] Lit. m.p. 62–3°: L. Erichomovitch and F. L. Chubb, *Can. J. Chem.* **44**, 2095 (1964).

a catalytic amount of triethylamine in the presence of acetylenes also gives isoxazoles (Scheme 6); the reactive 1,3-dipole under these conditions, however, is believed to be the nitrile oxide **6**. The intermediates **1** and **5** are effectively similar, and it could be argued with reference to Scheme 6 that **5** rather than the nitrile oxide **6** is the active 1,3-dipole involved in cycloaddition. Alternatively, and with reference to Scheme 5, it could be argued that the mixed anhydride **1** undergoes rapid loss of acetic acid to generate a nitrile oxide, i.e. **6**, and that this then functions both as the 1,3-dipole in the cycloaddition reactions and as the precursor to the various products formed in the oxidation reaction.

Two simple reactions can be used to indicate that **6** is the effective dipolar species involved in the reaction outlined in Scheme 6, whereas **1** (Scheme 5) is the effective 1,3-dipole in the cycloaddition reactions listed in Table 1. Firstly, with reference to Scheme 6, generation of the reactive intermediate in the absence of an added dipolarophile resulted in dimerisation of the nitrile oxide **6** and formation of the corresponding furoxan.[19] In the case of the reaction shown in Scheme 5 ($R = C_6H_5$), absence of the dipolarophile resulted only in formation of benzoic acid. No diphenylfuroxan could be detected in the reaction mixture, while a standard control experiment showed that this compound was perfectly stable under the reaction conditions. Secondly, while nitrile oxides are moderately stable compounds,[20] they are excellent 1,3-dipoles for use in cycloaddition reactions, and readily react with a wide variety of unsaturated substrates such as olefins,[21-24] acetylenes[25,26] and nitriles.[27,28] The dipolar species **1** generated in the present study was, however, found to be highly selective with respect to dipolarophile and to be apparently very much less reactive than the corresponding nitrile oxide **6**; thus, while **1** underwent reasonably efficient cycloaddition with dimethyl acetylenedicarboxylate, substitution of either maleic anhydride or diphenylacetylene as dipolarophile failed to give any products of cycloaddition. Consequently, it can be tentatively concluded that a nitrile oxide is not involved in the reaction of primary nitroalkanes with acetic anhydride/sodium acetate in the presence of a dipolarophile.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage microscope apparatus, and are uncorrected. Microanalyses were performed by Mr A. R. Saunders of the University of East Anglia. Infrared spectra were recorded on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer using standard liquid film and Nujol mull techniques. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer R12, 60 MHz, spectrometer, using tetramethylsilane as internal standard. TLC refers to use of Merck pre-prepared silica plates and chloroform as eluent, unless otherwise specified.

Starting materials. Phenylnitromethane[29] and the *p*-bromo-,[30] *p*-methyl-,[31] and *p*-nitro-[31] derivatives were prepared by standard literature procedures. Dimethyl acetylenedicarboxylate was redistilled prior to use, and acetic anhydride was purified by distillation from phosphorus pentoxide. Anhydrous sodium acetate was used as supplied. Diphenylfuroxan was a gift from Dr A. J. Boulton.

Reaction of phenylnitromethane with sodium acetate and acetic anhydride: isolation of acetanilide, benzoic acid and benzoic anhydride. A mixture of phenylnitromethane (10 g, 0·073 mole), anhydrous sodium acetate (6 g, 0·073 mole) and acetic anhydride (22 ml) was heated to 60–70° for 4·5 h. The mixture was allowed to cool, carefully basified in the cold with 10% aqueous sodium hydroxide solution, and extracted with chloroform (3 × 50 ml). The combined extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure to give a tan-coloured solid. This was crystallised from a chloroform–petroleum ether (b.p. 60–80°) mixture to give 1·2 g (12%) of colourless plate shaped crystals, m.p. 114–5°, which were easily identified (NMR, IR, MS and m.p.) as acetanilide.

The aqueous layer obtained above was acidified with concentrated hydrochloric acid, extracted with chloroform (3 × 50 ml) and the combined extracts washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure to give a colourless solid. This was recrystallised from a benzene–petroleum ether (b.p. 60–80°) mixture to give 7·4 g (85%) of benzoic acid.

For a non-hydrolytic work-up, the following procedure was employed: after completion of the reaction, the mixture was cooled, diluted with chloroform (200 ml), the precipitated sodium acetate removed by vacuum filtration through Keiselguhr, and the solvent removed from the filtrate by evaporation under reduced pressure. The residual pale yellow oil was distilled to give 3·53 g (53%) of triacetylhydroxylamine as a colourless oil, b.p. 96–98°/12 mm (Lit.[8] b.p. 96–98°/12 mm), and 6 g (73%) of a further colourless oil, b.p. 195–200°/12 mm (Lit.[32] b.p. 210–20°/20 mm), which was identified (TLC, IR and NMR) as benzoic anhydride by comparison with a genuine sample.

Acetylation of the thallium(I) salt of phenylnitromethane: isolation of acetyl phenylhydroximate. A solution of thallium(I) ethoxide[33] (9·2 g, 0·037 mole) in anhydrous diethyl ether (100 ml) was added dropwise during 15 min to an ice-cold, well stirred solution of phenylnitromethane (5 g, 0·037 mole) in anhydrous diethyl ether (400 ml). The thallium(I) salt of phenylnitromethane precipitated immediately from the reaction mixture as a thick creamy paste. NO ATTEMPT SHOULD BE MADE TO ISOLATE OR DRY THIS COMPOUND, AS IT CAN BE TREACHEROUSLY EXPLOSIVE. The reaction mixture was stirred for a further 15 min, and then acetyl chloride (4 g, 0·05 mole) was added dropwise over 5 min. The colour of the suspended salt changed from cream to colourless as the reaction proceeded, and the temperature of the mixture was slowly allowed to rise to ambient over 2 h. Thallous chloride was removed by vacuum filtration, the filtrate was washed until acid free with saturated sodium bicarbonate solution, then with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure. The colourless solid thus obtained was recrystallised from a chloroform–petroleum ether (b.p. 60–80°) mixture to give 2·3 g (35%) of pure product as colourless micro-needle shaped crystals, m.p. 124–6° (Lit.[34] m.p. 125°). This product was identified (IR, NMR, MS and m.p.) as acetyl phenylhydroximate by comparison with a genuine sample.

Reaction of acetyl phenylhydroximate with sodium acetate and acetic anhydride: isolation of benzoic acid. A mixture of acetyl phenylhydroximate (3 g, 0·017 mole), anhydrous sodium acetate (1·38 g, 0·017 mole), acetic acid (1·08 g, 0·017 mole) and acetic anhydride (12 ml) was heated to 60–70° for 4·5 h. The mixture was allowed to cool, when TLC analysis showed that there was no starting material left, that there was no acetanilide present, and that the sole product of reaction was benzoic anhydride. The mixture was carefully basified with 10% aqueous sodium hydroxide solution and extracted with chloroform (3 × 40 ml); the combined extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure. This gave no product. The aqueous layer was then acidified with concentrated hydrochloric acid, when a colourless solid precipitated. This was extracted into chloroform (3 × 50 ml), the combined extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure. The residual solid was recrystallised from a chloroform–petroleum ether (b.p. 60–80°) mixture to give 1·98 g (97·5%) of benzoic acid. Repetition of this reaction under anhydrous conditions and using a non-hydrolytic work-up procedure gave benzoic anhydride in 90% yield.

Preparation of 3-phenyl-4,5-dicarbomethoxyisoxazole. A mixture of phenylnitromethane (5 g, 0·037 mole), anhydrous sodium acetate (3 g, 0·037 mole), dimethyl acetylenedicarboxylate (5·2 g, 0·037 mole) and acetic anhydride (12 ml) was heated to 60–70° for 4·5 h. The mixture was allowed to cool, diluted with chloroform (100 ml), the precipitated sodium acetate removed by filtration through Keiselguhr, the solvent removed by evaporation under reduced pressure, and the residue distilled. This gave 8·0 g (82%) of a colourless high boiling oil, b.p. 139–40°/0·05 mm, which upon dilution with a small quantity of carbon tetrachloride, cooling to − 15° and trituration with petroleum ether (b.p. 40–60°) crystallised as colourless needle shaped crystals, m.p. 62–3° (Lit.[25] m.p. 62–3°).

The NMR spectrum ($CDCl_3$) showed an aromatic multiplet (5H) at 2·05 to 2·60 ppm, and two singlets (each 3H) at 5·99 and 6·10 ppm. The IR spectrum showed an intense, broad band at 1728 cm^{-1}.

Preparation of 3-p-nitrophenyl-4,5-dicarbomethoxyisoxazole. A mixture of *p*-nitrophenylnitromethane (4 g, 0·022 mole), anhydrous sodium acetate (1·8 g, 0·022 mole), dimethyl acetylenedicarboxylate (3·12 g, 0·022 mole) and acetic anhydride (48 ml) was heated to 60–70° for 8 h. The mixture was allowed to cool, diluted with chloroform (100 ml), the precipitated sodium acetate removed by filtration through Keiselguhr, and the solvents removed by evaporation under reduced pressure. The residual pale yellow oil was triturated with petroleum ether (b.p. 40–60°) and cooled to − 80° when crystallisation occurred.

The product was removed by vacuum filtration and recrystallised from an ethyl acetate–petroleum ether (b.p. 40–60°) mixture to give 2·75 g (39%) of pure product as pale yellow microleaflets, m.p. 104–5°.

The NMR spectrum ($CDCl_3$) showed an aromatic AB quartet (4H, $J = 9{\cdot}6$ Hz) centered at 1·80 ppm, and two singlets (each 3H), at 5·94 and 6·08 ppm. The IR spectrum showed a broad carbonyl band at 1735 cm^{-1}.

Preparation of 3-p-bromophenyl-4,5-dicarbomethoxyisoxazole. A mixture of *p*-bromophenylnitromethane (4 g, 0·0185 mole), anhydrous sodium acetate (1·52 g, 0·0185 mole), dimethyl acetylenedicarboxylate (2·64 g, 0·0185 mole) and acetic anhydride (48 ml) was heated to 60–70° for 8 h. The resulting dark brown mixture was allowed to cool and the solvent removed by evaporation under reduced pressure. The dark brown residue was successively extracted with portions of hot petroleum ether (b.p. 60–80°, 3 × 250 ml), from which, on cooling, a crystalline solid separated. The crystalline precipitates were collected by filtration, combined, and recrystallised from petroleum ether (b.p. 60–80°) to give 3·98 g (62%) of pure product as colourless, prism shaped crystals, m.p. 93–5°.

The NMR spectrum ($CDCl_3$) showed a singlet (4H) at 2·39 ppm for the aromatic protons, and two singlets (each 3H) at 5·98 and 6·10 ppm. The IR spectrum showed a broad carbonyl band at 1735 cm^{-1}.

Preparation of 3-p-methylphenyl-4,5-dicarbomethoxyisoxazole. A mixture of *p*-methylphenylnitromethhane (5 g, 0·032 mole), anhydrous sodium acetate (2·75 g, 0·032 mole), dimethyl acetylenedicarboxylate (4.7 g, 0·032 mole) and acetic anhydride (48 ml) was heated to 60–70° for 6 h. The mixture was allowed to cool, the solvents removed by evaporation under reduced pressure, and the residue, a dark brown solid, successively extracted with portions of hot petroleum ether (b.p. 60–80°, 3 × 250 ml). Cooling of the extracts resulted in ready crystallisation of a solid which was collected by vacuum filtration and recrystallised from petroleum ether (b.p. 60–80°) to give 4·5 g (49%) of pure product as colourless crystals, m.p. 67·5–9°.

The NMR spectrum showed an AB quartet (4H, $J = 7{\cdot}8$ Hz) centered at 2·60 ppm and three singlets (each 3H) at 6·05, 6·16 and 7·60 ppm. The IR spectrum showed a broad carbonyl band at 1738 cm^{-1}.

Preparation of 3-methyl-4,5-dicarbomethoxyisoxazole. A mixture of 1-nitroethane (7·5 g, 0·1 mole), anhydrous sodium acetate (8·2 g, 0·1 mole), dimethyl acetylenedicarboxylate (9·5 g, 0·067 mole) and acetic anhydride (48 ml) was heated to 60–70° for 8 h. The dark brown mixture was allowed to cool, excess acetic anhydride removed by distillation under reduced pressure, the residue diluted with chloroform (200 ml), and the resulting precipitate of sodium acetate removed by vacuum filtration through Kieselguhr. The filtrate was concentrated to a small bulk under reduced pressure and the resultant brown oil distilled at 0·1 mm, no attempt being made at fractionation. NMR analysis of the colourless oil thus obtained showed it to be a mixture of the desired isoxazole and triacetylhydroxylamine. The oil was therefore diluted with chloroform (100 ml) and the solution shaken with dilute sodium hydroxide (10%) to remove triacetylhydroxylamine; the organic layer was separated, washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure. Distillation of the residue gave 4·7 g (40%) of 3-methyl-4,5-dicarbomethoxyisoxazole as a colourless oil, b.p. 74–6°/0·05 mm.

The NMR spectrum consisted of three singlets (each 3H) at 6·06, 6·18 and 7·59 ppm. The IR spectrum showed a broad carbonyl band at 1730 cm^{-1}.

Preparation of 3-ethyl-4,5-dicarbomethoxyisoxazole. Preparation and isolation of this product were carried out as described for the 3-methyl analogue. 3-Ethyl-4,5-dicarbomethoxyisoxazole was obtained in 30% yield as a colourless oil, b.p. 92–4°/0·2 mm.

The NMR spectrum showed two singlets (each 3H) at 6·04 and 6·17 ppm, a quartet (2H) centered at 7·64 ppm and a triplet (3H) centred at 8·70 ppm. The IR spectrum showed a broad carbonyl band at 1730 cm^{-1}.

Control reaction of diphenylfuroxan with sodium acetate and acetic anhydride. A mixture of diphenylfuroxan (2 g, 0·008 mole), anhydrous sodium acetate (1·38 g, 0·017 mole), acetic acid (1·08 g, 0·017 mole) and acetic anhydride (12 ml) was heated to 60–70° for 4·5 h. At the end of this time no change was apparent (TLC). The mixture was allowed to cool, diluted with water (30 ml), carefully basified with dilute sodium hydroxide solution, and extracted with chloroform (3 × 40 ml). The combined extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and the solvent removed by evaporation under reduced pressure. The residue was recrystallised from a chloroform–petroleum ether (b.p. 60–80°) mixture to give 2 g (100% recovery) of colourless needle shaped crystals identified (IR, NMR and m.p.) as diphenylfuroxan.

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