Heteropentalenes. The Oxidation of Pyrazolo[1,2-a]benzotriazoles

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The dye-sensitized photo-oxidation of 1,3-dimethylpyrazolo[1,2-a]benzotriazole (3) affords 4-benzo-triazol-1-yl-3,4-epoxypentan-2-one (5) and 4-benzotriazol-1-ylpent-3-en-2-one (6), as well as the corresponding benzotriazol-2-yl derivatives (7) and (8), in inert solvents, while in methanol the methoxy-hydroperoxides (9) and (10) are obtained. The mechanism of the reaction as well as the effects of steric hindrance (substituting a t-butyl for a methyl group in the starting material), of the temperature, and of trapping agents, have been investigated. A comparison with other oxidative methods shows that under the conditions in which singlet oxygen is liberated from diphenylfuran endoperoxide, the ketones (6) and (8) are formed together with the nitroso-derivative (16), while peracid oxidation affords exclusively product (16).

A number of reactions between singlet oxygen and 1,3-dipolar systems have been described; the latter comprise both open-chain compounds such as diazo-derivatives,[1-5] nitrones,[6] sulphur and pyridinium ylides,[7] and azomethinimines,[8] and heterocyclic betaines, such as sydnones and related compounds.[9-13] The formation of a labile adduct is generally postulated, but in every case the products actually isolated result from extensive fragmentation, so that only an indirect understanding of the primary addition is possible.

Our attention was drawn to a particular class of hetero-cyclic betaines, namely the heteropentalene mesoionic betaines, a class of compound which has been only little investigated up to now.[14] We found that two new compounds in this series, the deeply coloured 5H-pyrazolo[1',2':1,2][1,2,3]triazolo-[5,4-a]phenazin-4-ium inner salts (1) and (2), undergo self-sensitized photo-oxidation without fragmentation.[15]

We therefore considered the model system pyrazolo[1,2-a]-benzotriazole (3) and (4) both under photosensitized oxygen-ation and in other oxidative conditions, hoping to gain a better understanding of the reaction mechanism.[16]

Results

The Rose Bengal sensitized photo-oxidation of 1,3-dimethyl-pyrazolo[1,2-a]benzotriazole (3) in methyl cyanide gave four products (Scheme 1), which were separated by column chromatography and obtained in 87% total yield (see Table 1). Traces of the nitro-derivative (15) were also observed. The structures (5)—(8) were assigned to these products on the basis of their elemental analyses and spectroscopic data (see Table 2). In particular, the 1-substituted benzotriazole derivatives (5) and (6) and the 2-substituted benzotriazole derivatives (7) and (8) were distinguished on the basis of their u.v. spectra (cf. ref. 17) and the symmetry of the aromatic [1]H n.m.r. signal. In both series the epoxy-ketones (5) and (7) were characterized, inter alia, by the signal of the oxiran proton, and the α,β-unsaturated ketones (6) and (8) by the olefinic proton signal.

Thus, the photosensitized oxidation of compound (3) differs from that of the conjugated systems (1) and (2)[15] in two respects: (i) both epoxy-ketones and unsaturated ketones are formed from (3), whereas only the former are obtained from (1) and only the α,β-unsaturated aldehydes are obtained from the demethylated derivative (2); and (ii) the addition takes place in two directions, compound (3), giving both 1- and 2-substituted benzotriazole derivatives, while 1-substituted derivatives are exclusively obtained from compounds (1) and (2).

Changing the conditions of the photo-oxidation, e.g.

(1) R = Me
(2) R = H
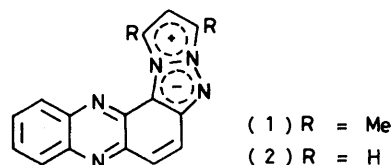
sensitizer and solvent, caused a limited variation of the ratio of the epoxy-ketones vs. the unsaturated ketones and had no significant effect on the ratio of 1-substituted vs. 2-substituted benzotriazole (see Table 1). However, the reaction takes a different course in methanol, the previously mentioned ketones (5)—(8) being obtained in less than 30% total yield, while the main products are the two methoxy-hydroperoxides (9) and (10) (Scheme 2). These compounds are sufficiently stable to allow chromatographic separation, although with some decomposition to benzotriazole. Their spectroscopic properties (see Table 2) agree with the assigned structure, which was further confirmed by treatment with triphenyl-phosphine yielding the α,β-unsaturated ketones (6) and (8), respectively, as observed in reactions with other methoxy-hydroperoxides.[18]

It is apparent that the direction of the initial attack to give 1- or 2-benzotriazole derivatives is not influenced by the polarity of the solvent; however, methanol intercepts some intermediates. Another trapping experiment was attempted with trimethylsilyl phenyl ketone (TSPK), which has been shown by Ando[5] to intercept some oxidizing species (carbonyl oxides) in the case of the photo-oxidation of diazo-compounds. In our case this additive had some influence on the product distribution, in general diminishing the yield of the unsaturated ketones (6) and (8), without affecting the yield of the epoxy-ketones (5) and (7) (see Table 1). However silyl benzoate, the product expected from the trapping experi-ment,[5] was not obtained. The effect of steric hindrance on the direction of the addition was then investigated. Thus, the t-butyl derivative (4) was synthesized and photo-oxidized under the same conditions as for the parent compound (3). As shown in Table 1, this compound behaves similarly to (3), giving four products with structures (11)—(14). Again, the ratio of 1-substituted vs. 2-substituted benzotriazoles is only slightly affected.

Finally, the results of the dye-sensitized photo-oxidation of compound (3) were compared with those obtained under different oxidative conditions and its reaction with thermally generated singlet oxygen was attempted. Owing to the limited stability of the photo-oxides, a singlet oxygen precursor which would be effective at low temperature was needed. Thus,
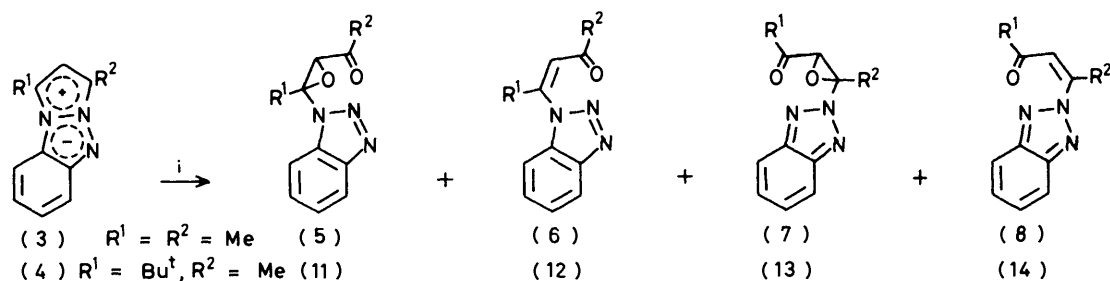
(3) $R^1 = R^2 = Me$ (5)   (6)   (7)   (8)
(4) $R^1 = Bu^t, R^2 = Me$ (11)   (12)   (13)   (14)

Scheme 1. *Reagents:* i, *hv*, sensitizer, O_2

Table 1. Percent yield of the products of photo-oxidation

| Substrate | Solvent | Conditions [a] | T /°C | Product yield (%) | | | | | | | |
				(5)	(6)	(7)	(8)	(9)	(10)	(15) [b]	(16)
(3)	MeCN	RB, *hv*	+17	20	17	38	12				
	MeCN	RB, TSPK, *hv*	+17	25	1	40	1				
	CH_2Cl_2	TPP, *hv*	+17	29	8	42	12				
	CH_2Cl_2	TPP, TSPK, *hv*	+17	28	2	27	10				
	CH_2Cl_2	TPP, *hv*	−60	2	20	13	27				
	CH_2Cl_2	DPFE	−60 to −20		9		11			2	14
	MeOH [c]	RB, *hv*	+17	7	11	4	6	29	17		
	$CHCl_3$	CPA	+5								85
				(11)	(12)	(13)	(14)				
(4)	MeCN	RB, *hv*	+17	9	22	33	14				

[a] RB, Rose Bengal 0.1 mg/ml; TPP, tetraphenylporphine, 0.1 mg/ml; TSPK, trimethylsilyl phenyl ketone, 10 mg/ml; DPFE, diphenylfuran endoperoxide, prepared *in situ* (see Experimental section); *hv*, irradiated at λ >500 nm; CPA, *m*-chloroperbenzoic acid in equimolar amounts. [b] Observed in traces (t.l.c.) also in sensitized photo-oxidations. [c] Some benzotriazole, arising from decomposition of products (9) and (10) during chromatographic separation, was obtained.

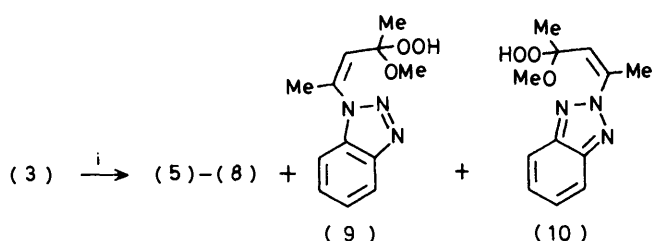**Table 2.** Relevant spectroscopic properties of the new compounds

| Compound | N.m.r. (δ, in $CDCl_3$) | | | | I.r. (cm⁻¹, in Nujol) | U.v. (log ε) (nm in EtOH) | |
	Me	CH	MeO	OOH			
(5)	1.8, 2.05	3.95			1 720	293 (4.62)	257 (4.9)
(6)	1.9, 2.55	6.4			1 695		
(7)	2.0, 2.2	3.8			1 720, 1 560	284 (4.56)	255 (4.79)
(8)	2.15, 2.6	6.1			1 685, 1 560		
(9)	1.25, 2.2	6.2	3.05	10.3	3 200		
(10)	1.35, 2.35	6.0	3.2	10.1	3 200, 1 560		
(16) [a]	2.15, 2.25	6.2			1 500, 1 270		
	Bu^t	Me					
(11)	1.25	2.2	4.2		1 715		
(12)	1.25	1.6	6.65		1 695, 1 620		
(13)	1.1	1.55	4.0		1 715, 1 560		
(14)	1.3	1.65	6.75				

[a] ¹H N.m.r. spectrum: one aromatic proton at δ 6.35; ¹³C n.m.r. spectrum; C–NO at δ 142.3 p.p.m.
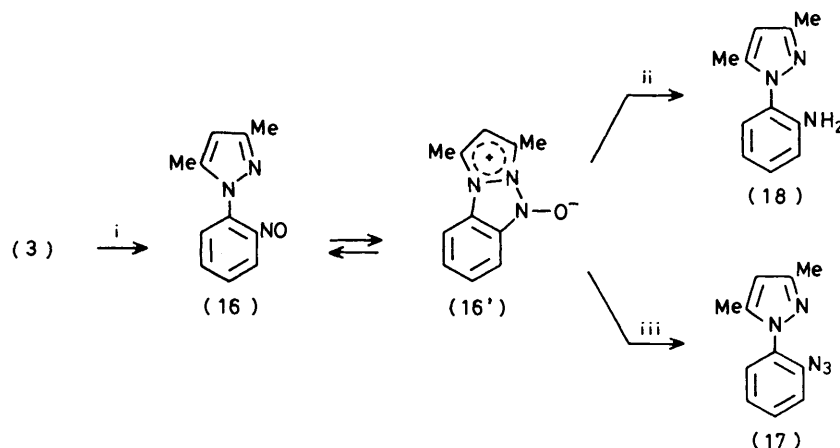
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compound (3) was added to a solution of 2,5-diphenylfuran endoperoxide (DPFP) at −70 °C and the mixture was allowed to warm up to generate singlet oxygen.[19] A reaction occurred which was complete by the time the temperature reached −20 °C. Chromatographic work-up of the mixture afforded two of the products obtained by photo-oxidation, *i.e.* the unsaturated ketones (6) and (8), together with a small amount of the nitro-derivative (15) and a further product, a colourless crystalline material in 14% yield; although the spectral properties of this material appeared at first sight to be puzzling (*e.g.* one high-field aromatic proton in the ¹H n.m.r. spectrum

and the corresponding high-field signal in the ¹³C n.m.r. spectrum), its structure, 3,5-dimethyl-1-(2-nitrosophenyl)-pyrazole, was firmly established by catalytic reduction to the amine (18) and by conversion with hydrazoic acid into the azide (17), a characteristic reaction of the nitroso-group.[20] Thus the unusual spectral properties of this compound can be attributed to the fact that it exists as the dipolar valence tautomer (16'). This structure is further supported by the significant loss of 71 a.m.u. ($C_2H_3N_2O$) from the molecular ion in the mass spectrum.

Compound (3) was then treated with *m*-chloroperbenzoic

Scheme 2. *Reagents:* i, *h*ν, sensitizer, O_2, MeOH

the carbonyl oxide in aprotic media involves intramolecular rearrangement to the epoxy ketones (5) and (7) or loss of oxygen to give the unsaturated ketones (6) and (8). When discussing the oxidation of (1) and (2),[15] we had hypothesized that steric hindrance influences the conformation, and thus the reactivity, of the carbonyl oxides, and this is further supported in the present case. If R = H these conjugated carbonyl oxides are certainly stabilized in a planar *trans*-form (21) (Scheme 5). However, if R ≠ H, as in the present case, the substituent will exercise some hindrance and the more crowded form (22), or a 1,2-dioxole (23), will also be

Scheme 3. *Reagents:* i, *m*-Cl·$C_6H_4CO_3H$; ii, H_2, Pd–C; iii, HN_3

acid at room temperature (Scheme 3). In this case the only product obtained was the above mentioned compound (16), this time in 85% yield.

Discussion

The dye-sensitized photo-oxidation of the pyrazolo-benzo-triazoles (3) and (4) may be confidently considered as involving singlet oxygen, since it does not proceed in the absence of the dye. Moreover it proceeds similarly in different solvents and with different known singlet-oxygen sensitizers and it is efficiently quenched by DABCO, a known physical quencher of singlet oxygen. The triplet energy of compound (3) is unknown, since it does not phosphoresce; however it is unlikely to be so low that it is sensitized by the dye. Therefore, the alternative hypothesis of energy transfer from the dye to compound (3), followed by reaction of triplet (3) with ground state oxygen, is discarded.

This type of mesoionic betaine, which is a heterocyclic analogue of the pentalenic dianion, presents a non-bonding molecular orbital (NBMO) with a significant coefficient at the four centres adjacent to the pentalene junction.[14] Thus, reaction with singlet oxygen could, in principle, take place in different ways. The experiments show that in the case of compounds (3) and (4), reaction takes place concurrently in two directions, while in the case of the conjugated analogues (1) and (2) only one mode of attack was observed. For the mechanism of the addition, it was thought that the reaction proceeds *via* carbonyl oxides (19) and (20), which were invoked also in the case of the oxidation of some diazo-derivatives [1-5] and azomethinimines.[8] In the present case this hypothesis is substantiated by the formation of the methoxy hydroperoxides (9) and (10) when the oxidation is carried out in methanol (Scheme 4). The further reactions of

likely.* The stabilized carbonyl oxides (21) will finally lose an oxygen atom to yield the unsaturated ketone.

In accordance with this hypothesis, the yield of the α,β-unsaturated ketones is more influenced by the nature of the media (polarity of the solvent, presence of TSPK) than the yield of the epoxy-ketones.

In the other case, however, the non planar carbonyl oxides will directly evolve to the 1,2-dioxoles and to the keto-epoxides and no intermolecular reactions such as oxygen transfer or trapping by trimethylsilyl ketone will take place.

Another indication of the existence of two conformers of different energy comes from the experiments at low temperature. Here the greater stability of the carbonyl oxide in conformation (21) is dominant and results in a redress in the balance in favour of the unsaturated ketones.

Whether or not the singlet oxygen addition is interpreted as involving cycloaddition to the azomethinimine and the azomethinylide portions of the molecule to give (19′) and (20′), followed by cycloreversion to give the carbonyl oxides, as has been proposed in an analogous case,[8] is speculative. The formation of traces of the nitro-derivative (15) in the photo-oxidation can be taken as indication that the adduct (19′) can undergo cycloreversion also in the opposite direction (Scheme 4). Furthermore, the minimal influence of the solvent polarity on the direction of the attack can be taken as an indication of the concertedness of the reaction or, at least, of the absence of intermediates significantly more polar than the starting materials along the reaction pathway.

The reaction of compound (3) with peracids takes a different course, resulting in attack only at the nitrogen atom in position

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* Indeed, preliminary study showed that the demethylated compound (3; $R^1 = R^2 = H$) yields only unsaturated aldehydes and no epoxy-derivatives.
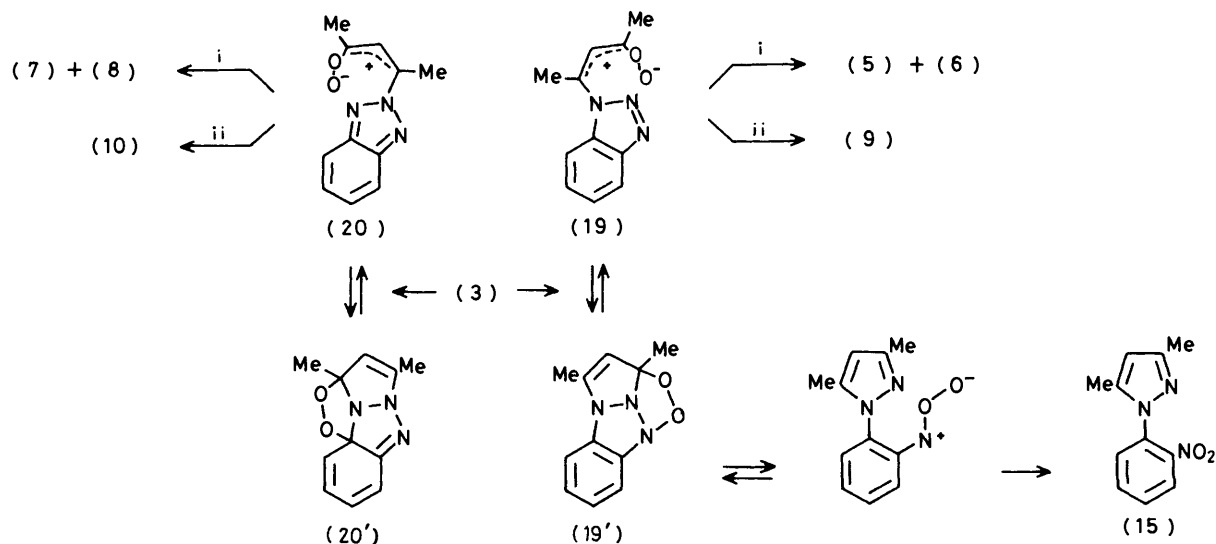
Scheme 4. *Reagents:* i, inert medium; ii, MeOH
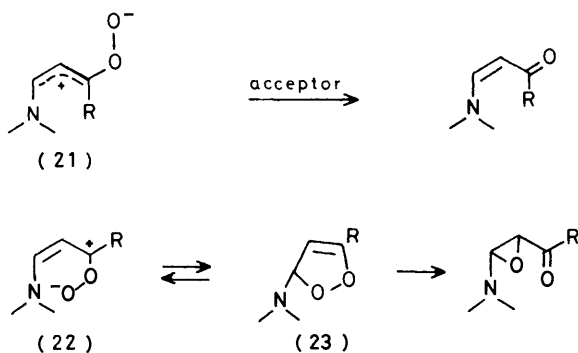
Scheme 5.

4. By comparison, it can be noted that compound (1) undergoes attack by peracids exclusively at the carbon atom in position 13a.[21] Thus again the difference between singlet oxygen and peracid oxidation, which is certainly related to the different geometric and electronic requirements of the two reagents, is observed in these mesomeric betaines, although the mode of the reaction changes with the structure. The reaction with furan endoperoxides takes an intermediate course yielding both the ketones (6) and (8), and product (16); it apparently acts in two ways, *viz.* as a source of singlet oxygen, which yields compounds (6) and (8) and as a source of another oxidizing species, such as a carbonyl oxide[22] or a hydroperoxide, which reacts analogously to a peracid.

Experimental

The u.v. visible spectra were recorded on a Perkin-Elmer 200 spectrophotometer, the n.m.r. spectra (^{1}H and ^{13}C) on a Perkin-Elmer R-12 instrument or a Brucker WP 80 instrument, using Me$_4$Si as internal standard, and the i.r. spectra on a Perkin-Elmer 257 spectrophotometer. M.p.s are uncorrected. 1,3-Dimethylpyrazolo[1,2-*a*]benzotriazole (3) was prepared and purified as described elsewhere.[23] Commercial (Merck and Carlo Erba) spectroscopic grade solvents were used after distillation (after treatment with Na$_2$CO$_3$ in the case of CH$_2$Cl$_2$). Column chromatography was performed with silica gel 60 HR (Merck). Benzanthrone, 2,5-diphenylfuran, trimethylsilyl

phenyl ketone and trimethylsilyl benzoate were prepared and purified according to the standard procedures. Rose Bengal (Fluka) and *meso*-tetraphenylporphine (Fluka) were used as obtained.

3-Methyl-1-t-butylpyrazolo[1,2-a]*benzotriazole* (4).—This compound was prepared analogously to compound (3). Thus *o*-nitrophenylhydrazine (3.9 g, 0.023 mol) and pivaloylacetone (3.4 g, 0.03 mol) were refluxed in ethanol (90 ml) for 90 min. After decolouration with charcoal, the solvent was evaporated and the raw material recrystallized from cyclohexane, to give 3-methyl-1-(*o*-nitrophenyl)-5-t-butylpyrazole (3.2 g, 56%), m.p. 96 °C (Found: C, 64.8; H, 6.7; N, 16.2. Calc. for C$_{14}$H$_{17}$N$_3$O$_2$: C, 64.8; H, 6.6; N, 16.3%).*

A sample of this compound (3.0 g) and triethyl phosphite (5 ml) were then added and the mixture was heated for a further 20 h. The solvent was evaporated and the residue chromatographed on a silica-gel column, eluting with benzene–ethyl acetate (9 : 1). The fraction containing product (4), recrystallized from light petroleum (b.p. 40—70 °C). yielded the product (1.4 g, 53%), m.p. 77—78 °C (Found: C, 74.1; H, 7.5; N, 18.4. Calc. for C$_{14}$H$_{17}$N$_3$: C, 73.9; H, 7.5; N, 18.5%); 1.54 (s, Bu^t), 2.56 (s, Me), and 6.35 (s, 7 H).

General Procedure for the Dye-sensitized Photo-oxygenations.—Solutions containing 2 mg per ml of either (3) or (4), saturated with oxygen in an immersion-well apparatus, were irradiated with a medium-pressure mercury arc (Philips HPK 125 W) through a yellow filter ($\lambda_{tr} > 500$ nm) under the conditions shown in Table 1. The irradiation was obtained until the starting material had completely disappeared (t.l.c., *ca.* 10—20 min). The solvent was evaporated and the residue chromatographed on a silica-gel column, eluting with benzene–ethyl acetate (9 : 1). The fractions containing the photo-oxides were purified by recrystallization from cyclohexane.

Oxidation with 2,5-*Diphenylfuran Endoperoxide.*—A solution of 2,5-diphenylfuran (1.96 g) and benzanthrone (0.035 g) in CH$_2$Cl$_2$ (300 ml) was cooled at -70 °C in an immersion-well apparatus and irradiated with a medium-pressure mercury

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* This structure was assigned rather than the isomeric 5-methyl-1-(*o*-nitrophenyl)-3-t-butylpyrazole on the basis of the *X*-r analysis (B. Bovio, personal communication).

Table 3. Analytical data of the new compounds

		Analysis						
		Found				Calculated		
Compound	M.p. (°C)	C	H	N	Formula	C	H	N
(5)	69—70	60.8	5.2	19.3	$C_{11}H_{11}N_3O_2$	60.8	5.1	19.4
(7)	96—97	61.0	5.0	19.4	$C_{11}H_{11}N_3O_2$	60.8	5.1	19.4
(6)	Oil	65.6	5.5	20.6	$C_{11}H_{11}N_3O$	65.7	5.5	20.9
(8)	69—70	65.6	5.6	20.6	$C_{11}H_{11}N_3O$	65.7	5.5	20.9
(16)	101—103	65.6	5.5	20.7	$C_{11}H_{11}N_3O$	65.7	5.5	20.9
(11)	87—88	65.0	6.6	16.2	$C_{14}H_{17}N_3O_2$	64.8	6.6	16.2
(13)	51—52	64.7	6.5	16.0	$C_{14}H_{17}N_3O_2$	64.8	6.6	16.2
(12)	73—74	69.3	7.0	17.4	$C_{14}H_{17}N_3O$	69.1	7.0	17.3

arc through a Pyrex filter until the starting material had completely disappeared (t.l.c., ca. 15 min). The light was turned off, product (3) (0.4 g) was added and the mixture was allowed to warm up slowly. At −20 °C the reaction was virtually complete. The solvent was evaporated and the residue chromatographed on a silica-gel column, eluting with cyclohexane–ethyl acetate (8 : 2).

Reaction of the Substituted 4-Methoxypent-2-en-4-yl Hydroperoxides (9) and (10) with Triphenylphosphine.—To a solution of either product (9) or (10) (0.249 g, 0.001 mol) in benzene (5 ml) was added a solution of triphenylphosphine (0.262 g, 0.001 mol) in benzene (2 ml) and a slightly exothermic reaction was set up. After 8 h, the solvent was evaporated off and the residue chromatographed on a silica-gel column, eluting with benzene–ethyl acetate (9 : 1). The unsaturated ketones (6) and (8) were isolated in 50 and 70% yields, respectively, along with some benzotriazole and a quantitative yield of triphenylphosphine oxide.

Peracid Oxidation of Compound (3).—To a solution of compound (3) (0.406 g, 0.002 mol) in $CHCl_3$ (20 ml) was added an equimolar amount of m-chloroperbenzoic acid in $CHCl_3$ (30 ml) during 30 min, keeping the temperature at ca. 5 °C. The solution was allowed to reach room temperature and after 10 min was washed with saturated aqueous $NaHCO_3$, dried and evaporated. Chromatography on a silica-gel column, with benzene–ethyl acetate (9:1) as eluant, yielded crude (16) (0.344 g, 85%) which was recrystallized from cyclohexane.

Reactions of 3,5-Dimethyl-1-(o-nitrophenyl)pyrazole (16).—(a) A solution of compound (16) (20 mg) in EtOH (5 ml) was hydrogenated at room temperature in the presence of 10% Pd on charcoal. After filtration, evaporation of the solvent yielded quantitatively 1-(o-aminophenyl)-3,5-dimethylpyrazole (18), identified by comparison with an authentic sample.

(b) To a solution of compound (16) (40 mg) in AcOH (1.5 ml), NaN_3 (30 mg) was added. After 14 h the solution was evaporated and the residue was treated with aqueous $NaHCO_3$ with cooling and then extracted with benzene. Evaporation of the organic layer afforded the pure azide (17) (30 mg, 73%), which was identified by comparison with an authentic sample.[23]

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