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DIELS–ALDER REACTIONS WITH 3,4-METHYLENEDIOXY-β-NITROSTYRENE

NMR STUDIES OF THE STRUCTURE AND STEREOCHEMISTRY OF ADDUCTS[1]

V. A. Landeryou and E. J. J. Grabowski,
Department of Chemistry, University of Rochester, Rochester, New York 14627
and
R. L. Autrey*
Oregon Graduate Center, Portland, Oregon 97225

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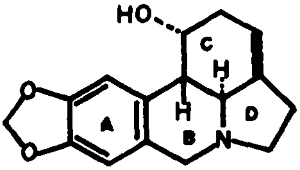
Abstract—Reaction between 3,4-methylenedioxy-β-nitrostyrene and 1-methoxybutadiene or methyl sorbate gave Diels–Alder adducts. Reaction between the dienophile and ethyl 5-chloro- or 5-benzoyloxypentadienoate gave either no reaction or aromatic products, (methylenedioxybiphenyl derivatives) derived from adducts. The structures of new compounds were obtained by NMR or by NMDR experiments.

In the course of studies directed toward the synthesis of *Amaryllidaceae* alkaloids of the lycorine skeleton (e.g., caranine, 1), we have obtained adducts from a number of dienes and 3,4-methylenedioxy-β-nitrostyrene (5). These studies are most closely related to research of Hill, *et al.*, which culminated in the syntheses of α- and β-lycorane[2] (2 and 3) and of ismine[3] (4).



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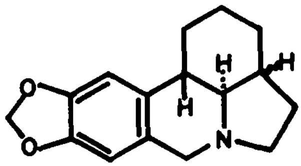
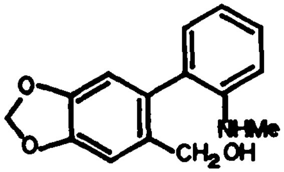


2, C:D cis
3, C:D trans



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For members of this family of alkaloids with the degree of complexity shown by the C ring of caranine, one wishes to find an adduct between the nitrostyrene 5 and α-pyrone (6) having the structure shown in 7 because that adduct has the correct relative stereochemistry at all three asymmetric centers in caranine and the chemistry required to modify it along the necessary lines is readily conceived. That the adduct may be expected to have the correct relationship between the oxygen at carbon 6 and the piperonyl group follows from the observation[4] that nitrostyrene adds to

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* To whom correspondence should be directed.

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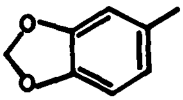

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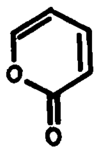

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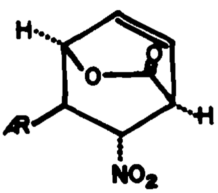

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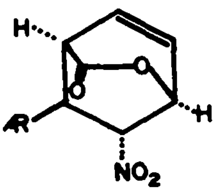

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cyclopentadiene to place the nitro group *endo*. That the end-for-end orientation will be as desired, in **7**, and not reversed, as in **8**, is less likely.[5] Other problems may be anticipated to arise from the facts that nitrostyrenes are sluggish dienophiles and heterocyclic compounds (furan and α-pyrone derivatives) that would lead to the correct steric relationship between the oxygen and the piperonyl moieties are poor dienes, often unstable under the forcing conditions used for sluggish reactions.

In an attempt to learn some answers to questions arising from the considerations set forth above, we sought the addition of 3,4-methylenedioxynitrostyrene to a number of cyclic and open-chain dienes. The dienes and a summary of the results are presented in Table 1.

TABLE 1. REACTIONS OF **5** WITH DIENES[a]

Diene	Product(s), yield[b]	Remarks
α-Pyrone	—	[c]
Furfuryl acetate	—	[d]
Furfural diacetate	—	[d]
1-Methoxybutadiene	**9**, 45%; **10**, 17%.	
1-Acetoxybutadiene	**11**, 15%.	[e]
Sorbic acid	—	
Sorbyl chloride	—	
Methyl sorbate	**12**, 19%	
5-Acetoxypentadienal	—	[f]
5-Benzoyloxypentadienal	—	[f]
Ethyl 5-benzoyloxypentadienoate	**14**, 12%; **15**, 8%; **16**, 12% and ethyl benzoate, 13%.	[f]
Ethyl 5-chloropentadienoate	**14**, 6%, **15**, 2%.	[f]

[a] See the Experimental for reaction conditions and controls.

[b] Based on dienophile; diene present in excess.

[c] Catalysis tried: $AlCl_3$, $SnCl_4$; see P. Yates and P. Eaton, *J. Am. Chem. Soc.* **82**, 4436 (1960). We also tried filtered and unfiltered UV light.

[d] Lewis acid catalysts caused polymerization of the diene.

[e] The product is not a new compound; see citation 2.

[f] For the preparation and characterization of this diene, see citation 7.

Proof of structure of the products. The application of NMR spectroscopy was crucial to the structure proofs. Because of the complexity of the bands, NMDR (nuclear magnetic double resonance) was used whenever possible to simplify spin multiplets, The acetoxybutadiene adduct **11** was assigned the structure and stereochemistry shown by Hill, *et al.*[2] They provided chemical proof of the structure and presented inferential arguments for the stereochemistry. The NMR spectra of **11** and the two stereoisomers **9** and **10** provide detailed evidence in support of the structures and stereochemistry; see Table 2.

TABLE 2. NMR SPECTRA[a]

Compound	**9**		**10**		**11**		**12**		**13**	
Hydrogen	δ	*J*'s	δ	*J*'s	δ	*J*'s	δ	*J*'s	δ	*J*'s
H-1	3·4		3·62		3·62		3·5		3·51	
$J_{1,2}$				12·0		12·5				12·0
$J_{1,6a}$	[b]			10·5		11·0		[b]		12·0
$J_{1,6e}$				6·0		6·5				4·0
H-2	4·79		4·95		5·02		5·39		4·65	
$J_{1,2}$		12·0		12·0		12·5		11·5		12·0
$J_{2,3}$		8·5		4·0		3·5		9·5		3·0
H-3	4·54		4·31		5·9		2·92		4·14	
$J_{2,3}$		8·5		4·0				9·5		
		3·0[c]		2·0[d]		[f]		3·0[e]		[g]
								J_3, Me 9·0		
H-6	2·39		6e: 2·61		6e: 2·63		3·5		[j]	
			6a: 2·01		6a: 2·06					
		[h]		J_{gem} 21·0		J_{gem} 17·0		[b]		
$J_{1,6a}$				11·5		[i]				
$J_{1,6e}$				6·5		6·0				
$J_{5,6e}$				3·0		3·5				
$J_{5,6a}$				0		0				
H-4, 5	5·81		6·02		6·00		5·70		[j]	
OCH_2O	5·90		5·92		5·90		5·89		5·88	
AR-H	6·68		6·72		6·72		6·65		6·68	
	3·38		3·39		2·03		3·49		3·31	
	$\mathrm{O\underline{Me}}$		$\mathrm{O\underline{Me}}$		$\mathrm{O\underline{Ac}}$		$\mathrm{O\underline{Me}}$		$\mathrm{O\underline{Me}}$	
						δMe	1·26			
								J_3, Me 9·0		

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[a] Compound in $CDCl_3$ soln, dissolved TMS as standard. Chemical shift in ppm downfield from TMS signal; coupling constants in Hz, rounded to nearest 0·5 Hz. Measurements on compounds **9**, **10** and **11** were made by Dr. L. D. Colebrook on a Varian HR-60 spectrometer; those (including all NMDR) on compounds **9**, **12** and **13** were made by Mr. W. R. Anderson, Jr. on a Varian HA-100 spectrometer.

[b] Hidden by OMe, *J*'s not observable.

[c] Possibly $^3J_{3,6}$; both dihedral angles ⩾80°; see N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field* pp. 110–1. Holden-Day, San Francisco (1964).

[d] Possibly $J_{3,4}$.

[e] Probably $^4J_{3,5}$; dihedral angle is ~80°; *ibid.*, p. 108.

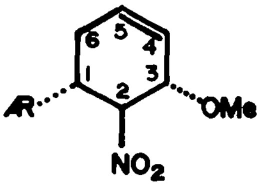
[f] H-3 is hidden by $\mathrm{OC\underline{H}_2O}$, *J*'s are not observable.

[g] Narrow multiplet, further narrowed by NMDR; individual *J*'s not determinable, all ⩽3 Hz.

[h] Too many peaks overlap for simple first-order treatment.

[i] The two central peaks of the doublet of doublets are so distorted by the $\mathrm{\underline{Me}CO}$ resonance that this *J* cannot be accurately measured from H-6; it is clear from H-1.

[j] The three ring methylene groups appear as a broad group from 1·24 to 2·34 ppm.



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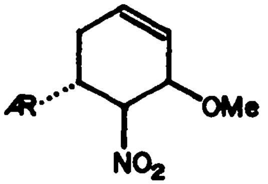

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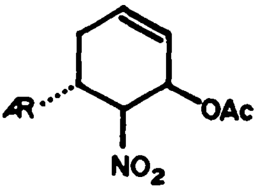

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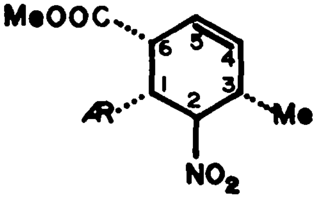

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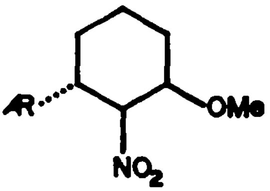

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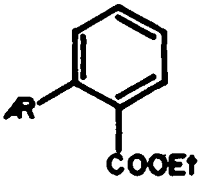

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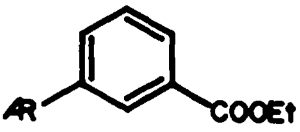

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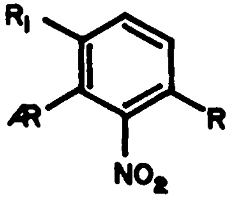

16

R_1 or R_2 = COOMe,
other = H

To consider only the most salient points, consider the hydrogens on carbons* 2 and 3. Previous knowledge[6] establishes that H-1 and H-2 will be *trans* and diaxial. In all five compounds the hydrogen on the carbon bearing the nitro group is strongly deshielded, appearing at lower field than any other aliphatic or allylic hydrogen except the one on the carbon bearing acetoxyl in **11** (and the methylenedioxy pair). It appears uncluttered, as a simple doublet of doublets in all the spectra. In all five compounds one coupling constant of the doublets is 12 ± 0·5 Hz, appropriate in magnitude for assignment to the *trans* diaxial $J_{1,2}$. That this assignment is correct is confirmed by double resonance experiments. The remaining J for H-2 is to be attributed to its coupling to H-3. In compounds **10** and **11**, which have strikingly similar spectra, this coupling constant is 4 ± 0·5 Hz, appropriate for the *cis* relationship required by Hill's suggested stereostructure for **11**. Substance **13**, prepared from **10** by hydrogenation, provides useful confirmation of the stereochemistry of **10** in that the coupling constants for H-2 are again appropriate for the axial–axial and axial–equatorial relationships between H-2 and hydrogens 1 and 3 in a ring not distorted from cyclohexane geometry by the presence of a double bond.

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* For convenience of discussion, the arbitrary numbering (i.e. not necessarily that corresponding to IUPAC nomenclature) is chosen, as in **9** or **12**, so that the piperonyl and nitro groups are attached to carbons 1 and 2.

Compound **9** is shown by its mode of synthesis and combustion analysis to be an isomer of **10**—it could prove to be a stereoisomer, or a structural isomer resulting from an alternate end-for-end sense in the addition. The latter possibility would be reflected in an increased complexity in the appearance of the band for H-2 arising from the fact that H-2 would then be adjacent to C-3 bearing two hydrogens. No such complexity obtains; but the coupling constant ($J_{2,3}$ = 8·5 Hz) is appreciably larger than that for the axial-ψequatorial array of the hydrogens 2 and 3 of compounds **10** and **11**, and is taken to prove that the array in **9** is axial-ψaxial.

For the structure of adduct **12**, four racemates[6] are possible: two have C-3 bear a Me group, *cis* or *trans* to nitro at C-2; the other two racemates have methoxycarbonyl at C-3. From the NMR spectrum one makes a choice between these two sets of pairs quite simply. The signal at highest field in the spectrum, other than the doublet at 1·26 ppm for the C-Me, is a multiplet due to the ring hydrogen on the carbon bearing Me. In two possible racemates (including **12**) that hydrogen is coupled to H-2. Irradiation of that hydrogen collapses the signal for H-2 to a doublet and proves that the carbons bearing the Me and nitro groups are adjacent. The remaining possibilities are that the Me and nitro groups are *cis*, or are *trans* as in **12**. The coupling constant $J_{2,3}$ is 9·5 Hz, large as is that for the *trans* groups in **9**, not small as are those for the *cis* groups in **10** and **11**.

The adducts from the addition of the nitrostyrene **5** to ethyl 5-benzoyloxypentadienoate and 5-chloropentadienoate did not survive the high temperature required to bring about reaction. The predominant products **14** and **15** arose from the initial adducts by loss of the elements of nitrous acid and either benzoic acid or hydrogen chloride to give the ethyl esters of 2- or 3-piperonylbenzoic acid. The structures of these products were deduced initially from noting that the IR spectra of crude products lacked, usually completely, the characteristic strong bands of the nitro group and showed the carbonyl group to be conjugated. When, after laborious isolation, pure substances were obtained, the UV and NMR spectra confirmed the speculation that the newly formed ring had become aromatic. The structures of **14** and **15** were then proven by rational syntheses.[7]

Compound **16** was not isolated in sufficient quantity for complete structure determination; however, several qualitative aspects of its NMR spectrum can be taken to point more strongly to the isomer represented by **16**, R_1 = H, R_2 = COOMe.

DISCUSSION

In seeking reaction between **5** and pyrone or furan derivatives, we made extensive use of UV spectroscopy in determining thermal stability of the dienes and in following consumption of both diene and dienophile; we studied reaction mixtures varying in composition from ones in which the two were little consumed to those in which they were almost totally destroyed and polymer formation was substantial. We tried catalysis by Lewis acids. We ran the reactions in boiling aromatic solvents, or in sealed, degassed tubes with and without solvent. We did not employ more than a 100% excess of diene. In those reactions where we obtained no product, we are reasonably confident of this conclusion down to the level of 2–3%. Because our interest was in the preparative value of the outcome we did not pursue the possible existence of product at lower levels.

In the instances of reaction wherein product was found, the structures of these products serve to confirm the observations that the Alder–Stein rules[8] and other predictive tools for the Diels–Alder reaction are, of course, not laws but simply conveniences. It is now firmly established[9] that in some cases where there is no appreciable polar contribution to orientation in the transition state, all four possible adducts are formed under conditions of kinetic control and one may ascertain the relevant thermodynamic parameters; their values are quite close together even though one product predominates. Thus, although the adduct from **5** and cyclopentadiene or acetoxybutadiene follows the Alder–Stein rule, with "maximum accumulation of double bonds" (= overlap, henceforth) occurring between the diene and the nitro group of the dienophile, the situation with methoxybutadiene (surely a very small structural change from acetoxybutadiene) is different. The same end-for-end orientation arising from polar considerations obtains, but both stereoisomers are found and that one predominates in which overlap involves the piperonyl group, not the nitro group. The same result is true in the methyl sorbate adduct—the single product is apparently structurally determined by polar considerations and apparently sterically determined by overlap with the piperonyl group.

Compare these results with those from the reaction between the same dienophile and ethyl 5-benzoyloxypentadienoate. It is clear that there is no striking control over the end-for-end sense of addition, even though the *relative* yields of products (Table 1) are not significant, though accurately determined. The reasons for this lack of significance are (1) that the structure of **16** is not known with certainty; (2) that the initial products lose benzoic acid which then reacts by ester exchange to destroy some unknown proportion of the two (or more) initial adducts by converting them or derivatives of them to free carboxylic acids lost in subsequent column chromatography. The product mixture, like that from styrene and methyl sorbate,[6] is very complex under our conditions. Boiling it in benzene divides it into soluble material and a black, presumably polymeric fraction of 13% (by weight). Column chromatography provides a large (29% by wt), oily fraction eluted by benzene; a total of 18% more material is eluted by solvents increasing in polarity through methanol; 40% remains on the column and is probably carboxylic acids. In one experiment, benzoic acid was obtained by direct sublimation from the crude reaction mixture. The large oily fraction was shown by VPC to contain at least 10 components, six of which, eluted between ethyl benzoate and ethyl 2-piperonylbenzoate, accounted for 13 mol% of the fraction and were not identified. The remaining 87% consisted of the four esters in Table 1. That these aromatic esters were indeed the products and were not the result of pyrolytic reactions during VPC was checked by IR spectroscopy on the material before gas chromatography: the spectrum showed only conjugated carbonyl absorption and was very similar to a composite of the spectra of the four principal products.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were measured on Perkin–Elmer Model 21 and 421 spectrophotometers; UV spectra were measured on a Cary Model 11 MS spectrophotometer. The piperonyl bands seen in the IR spectra are those shown to be characteristic.[10] Microanalyses were performed by A. Revilla at the University of Rochester and by Micro-Tech Laboratories, Skokie, Illinois. Vapor phase chromatography was done on a Wilkens Aerograph instrument, model A-90-p2, over 20% Dow Corning Silicone Grease 11 on 30/60 Chromosorb P.

Starting materials. Furfuryl acetate and sorbic acid were obtained from Distillation Products Industries; 1-methoxybutadiene was obtained from K & K Laboratories, Inc. Methylenedioxy-β-nitrostyrene,[11] α-pyrone,[12] furfural diacetate,[13] 1-acetoxybutadiene,[14] sorbyl chloride,[15] methyl sorbate[15] 5-acetoxy- and 5-benzoyloxypentadienal,[7] and ethyl 5-benzoyloxy- and 5-chloropentadienoate[7] were obtained as described, or by straightforward adaptations.

3-trans-(**9**) *and* 3-cis-*Methoxy*-1-(*3,4-methylenedioxyphenyl*)-trans-2-*nitrocyclohex-4-ene* (**10**)

3,4-Methylenedioxynitrostyrene, (2·896 g), 1-methoxybutadiene (2·526 g) and toluene (10 ml) were sealed in a Pyrex tube and heated to 105–110° for 50 hr. The cooled reaction mixture was diluted to 100 ml with MeOH and filtered. On standing, the filtrate deposited crystals, 709 mg (17%), m.p. 164–165°. Concentration of the mother liquor afforded a second isomer, 1·887 g (45%), m.p. 120–122°.

The high-melting crop was recrystallized from MeOH to give **10**, m.p. 164–165°; IR spectrum (KBr): OMe, 9·23; NO_2, 6·50, 7·32 μm, and piperonyl bands. (Found: C, 60·64; H, 5·68; N, 4·91. Calc. for $C_{14}H_{15}NO_5$: C, 60·65; H, 5·45; N, 5·05%).

The low-melting crop was recrystallized from MeOH to give **9**, m.p. 134–136°; IR spectrum (KBr): OMe, 9·23; NO_2, 6·50, 7·32 μm, and piperonyl bands. (Found: C, 60·70; H, 5·58; N, 5·00. Calc. for $C_{14}H_{15}NO_5$: C, 60·65; H, 5·45; N, 5·05%).

1-(*3,4-Methylenedioxyphenyl*)-trans-2-*nitro*-cis-3-*acetoxycyclohex-4-ene* (**11**)

This substance was prepared as described.[2] From 3,4-methylenedioxynitrostyrene (20·0 g) there was obtained 981 mg (3·1% yield, 15% conversion) of adduct **11**, m.p. 145–147°, lit.[2] m.p. 146–148°.

Methyl cis-2-(*3,4-methylenedioxyphenyl*)-trans-3-*nitro*-trans-4-*methylcyclohex-5-enecarboxylate* (**12**)

Methyl sorbate (0·756 g), 3,4-methylenedioxynitrostyrene (0·581 g) and xylene (6 ml) with a few mg hydroquinone were sealed in Pyrex and heated to 163–168° for 24 hr. The cooled reaction soln was heated with $CHCl_3$ and shown to contain about 40% nitrostyrene and 65–70% methyl sorbate by UV. The $CHCl_3$ soln was concentrated *in vacuo* to a thick slurry, then diluted with 40 ml pet. ether (b.p. 30–60°). The resulting mixture was heated to a boil, filtered hot, and the filtrate was cooled; it deposited crystals, 91 mg (9·5%), m.p. 180–182°. Concentration of the mother liquor provided a second crop, 90 mg (9·4%), m.p. 174–178°. Recrystallization from EtOAc gave colorless, stout needles of the tetrahydrobenzoate, m.p. 177–179°; IR spectrum (KBr): —COOMe, 5·81, 8·14; $—NO_2$, 6·50, 7·35 μm and piperonyl bands. (Found: C, 60·47; H, 5·27; N, 4·32. Calc. for $C_{16}H_{17}NO_6$: C, 60·18; H, 5·37; N, 4·39%).

1-(*3,4-Methylenedioxyphenyl*)-trans-2-*nitro*-cis-3-*methoxycyclohexane* (**13**)

In 5 ml EtOAc 0·554 g of **10** was hydrogenated over 56 mg 10% Pd/C in a Parr shaker at 22 psi for 75 min. The filtered soln was distilled *in vacuo* to yield 0·549 g, m.p. 128–129°, of colourless solid. Two recrystallizations from MeOH provided pure material, m.p. 130–132°. (Found: C, 60·10; H, 6·21; N, 5·06. Calc for $C_{14}H_{17}NO_5$: C, 60·21; H, 6·14; N, 5·02%).

Ethyl 2- and 3-piperonylbenzoate (**14** *and* **15**) *and the nitrobenzoate* **16**

A mixture of 3,4-methylenedioxy-β-nitrostyrene (3·863 g), ethyl 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneoate (4·922 g) and hydroquinone (0·083 g) was sealed in a pyrex tube at 10^{-5} mm and heated at 150–155° for 48 hr. The crude reaction mixture, which had become a heavy black oil, was boiled for 20 min with 100 ml benzene and filtered. The benzene-insoluble material (1·104 g; 12% by wt) a black solid insoluble in common organic solvents, was discarded. The benzene soln was concentrated to 15 ml and chromatographed over 130 g activity II neutral Woelm alumina. The first fraction, 300 ml benzene, contained 2·521 g orange oil which showed strong CO absorption between 5·78–5·83 μm. This fraction was examined by VPC and shown to contain a minimum of 10 components, 6 of which represented 13% of the mixture, as determined by relative peak area, and were not considered further. Three of the remaining components were identified as ethyl benzoate (13%), ethyl 2-piperonylbenzoate (12%) and ethyl 3-piperonylbenzoate (8·3%) by comparison IR and NMR spectra.[7] The final component was identified as ethyl 2-nitro-3-piperonylbenzoate or ethyl 3-nitro-2-piperonylbenzoate (12%). This identification was made on the basis of the analytical and spectral data obtained from a sample of this substance collected by VPC: yellow needles, m.p. 88–90°. (Found: N, 4·30. Calc. for $C_{16}H_{13}NO_6$: N, 4·44%).

Continuation of the chromatography on the crude reaction mixture with a gradual increase of solvent polarity through MeOH yielded only tars. Based on IR spectral examination we concluded that none of these fractions contained appreciable quantities of the desired adduct or its isomers.

Ethyl 2- *and* 3-*piperonylbenzoate* (**14** and **15**)

A pyrex tube containing ethyl 5-chloropenta-*trans*-2-*trans*-4-dienoate (2·492 g), 3,4-methylenedioxy-β-nitrostyrene (3·006 g) and hydroquinone (0·059 g) was sealed at 10^{-5} mm and heated for 42 hr at 147°. The heavy black oil, which partially solidified on cooling, was boiled with 100 ml benzene for 20 min and filtered. The benzene insoluble material (1·640 g, m.p. >360°) was discarded. The benzene soln was concentrated to 10 ml and chromatographed on 100 g activity II neutral Woelm alumina. A VPC analysis demonstrated that the fractions eluted with benzene contained principally starting materials and ethyl 2-piperonylbenzoate (6 %) and ethyl 3-piperonylbenzoate (2 %). Elution through MeOH yielded to materials displaying the IR characteristics expected of the desired adduct.

[1] This work is taken in part from the Ph.D. dissertations (Rochester) of V.A.L. (1964) and E.J.J.G. (1965).

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