Mechanism of the Kohler Synthesis of 2-Isoxazoline 2-Oxides from 1,3-Dinitroalkanes[1]

ARNOLD T. NIELSEN AND T. G. ARCHIBALD[2]

Organic Chemistry Branch, Chemistry Division, Code 6056, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

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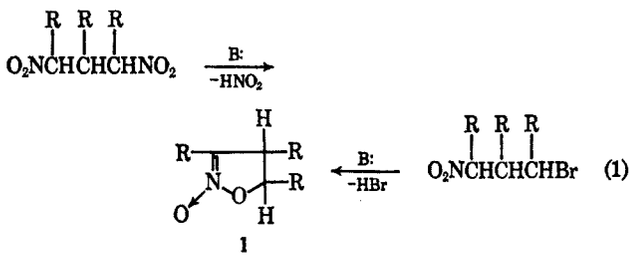
Formation of 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**) from 1,3-dinitro-1,2,3-triphenylpropane (**2**) has been shown to involve an intramolecular nitrite ion displacement in the intermediate **2** mononitronate anion. Contrary to the generally accepted mechanism for this reaction, it has been shown that a nitro olefin intermediate is not involved. 1-Nitro-1,2,3-triphenylpropene (**13**) has been synthesized from 1,2-dinitro-1,2,3-triphenylpropane by heating with ethanolic potassium acetate. In basic solution **13** forms a nitronate anion which undergoes rapid C-1 protonation to 3-nitro-1,2,3-triphenylpropene (**16**); no isoxazoline 2-oxide is formed from **13** or **16**. A product described by other workers as nitro olefin **13** has been shown to be a stable molecular complex composed of two *cis*-α-nitrostilbene molecules and one *trans*-stilbene molecule. Additional evidence against a nitro olefin intermediate was obtained by reaction of **2** with sodium methoxide in methanol-O-*d* to form 3,4,5-triphenyl-2-isoxazoline 2-oxide-5-*d*, and reaction of *cis*-α-nitrostilbene-α'-*d* with phnylnitromethane in methanolic sodium methoxide to form 3,4,5-triphenyl-2-isoxazoline 2-oxide-4-*d*. The stereochemistry of **3** has been shown to be *trans* by reduction of it to known *trans*-3,4,5-triphenyl-2-isoxazoline. Mechanisms of isoxazole formation from **3** and alkane-1,3-bisnitronic acids are also discussed briefly.

The Kohler synthesis of 2-isoxazoline 2-oxides (**1**) involves base-catalyzed cyclization of 1,3-dinitroalkanes[3-7] or 3-halo-1-nitroalkanes (eq 1).[4,8-11] These



heterocyclic compounds represent the best known examples of cyclic nitronic esters; most are stable crystalline compounds in contrast to the very unstable acyclic nitronic esters.[12] 2-Isoxazoline 2-oxide syntheses were discovered and developed by Kohler and coworkers (1924–1930)[3,8] and extended by Dornow[4] and others.[5,6,8-11] The reaction employing 3-halo-1-nitroalkanes may lead to nitrocyclopropanes.[8a,e,g,13]

1,3-Dinitroalkanes required in the synthesis of known 2-isoxazoline 2-oxides are conveniently prepared *in situ* in one of two ways, employing amines or sodium ethoxide catalysts in alcohol solvent: (1) by condensation of aldehydes or Schiff bases with α-nitro esters or phenylnitromethanes,[3,4] and (2) by Michael addition of phenylnitromethanes to α-nitrostilbenes.[5] (Attempted addition of diethyl nitromalonate or ω-nitroacetophenone to α-nitrostilbene gave recovered reactants in the present work.) Certain 1,3-dinitroalkanes have been isolated by Dornow and are rapidly converted into 2-isoxazoline 2-oxides by treatment with ethyl amine in ligroin.[4] 3-Bromo-1-nitroalkanes are prepared by bromination of the required carboxylic esters or ketones.[4,8] Yields of **1** are *ca.* 30–90%.

The complete scope of the synthesis has not been established. With 1,3-dinitroalkanes, known successful syntheses appear limited to compounds having aryl or carbonyl groups on the carbon atoms bearing the nitro groups. Acyclic secondary alkane-1,3-bisnitronate anions having no aryl or acyl substituents on the nitronate carbon are reasonably stable in basic medium and do not form nitro olefins or 2-isoxazoline 2-oxides.[14] We found that reaction of 1,3-dinitro-1,2-diphenylpropane[4c] with ethanolic sodium ethoxide gave black tars and no crystalline product under conditions whereby 3,4,5-triphenyl-2-isoxazoline 2-oxide is readily formed from 1,3-dinitro-1,2,3-triphenylpropane. With 3-bromo-1-nitroalkanes no additional activation of the bromine or special structural features appear to be required.[10,11]

The mechanism of formation of 2-isoxazoline 2-oxides (**1**) has been shown in the present work *not* to involve a nitro olefin intermediate. The mechanism departing from 1,3-dinitroalkanes has been found to require a nitrite ion displacement from a 3-nitro-1-nitronate anion intermediate. This appears to be the first example of nitrite ion displacement from a nitroalkane by nitronate anion. The first examples of displacement of a nitro group as nitrite ion from a saturated carbon atom (from α,*p*-dinitrocumene by thiophenoxide and malonate ions) have been reported recently.[15] The

(1) A preliminary account of a portion of this work has appeared: A. T. Nielsen and T. G. Archibald, *Tetrahedron Lett.*, 3375 (1968).

(2) National Research Council Postdoctoral Research Associate, 1967–1968.

(3) (a) E. P. Kohler and G. R. Barrett, *J. Amer. Chem. Soc.*, **46**, 2105 (1924); (b) E. P. Kohler and N. K. Richtmyer, *ibid.*, **50**, 3092 (1928); (c) E. P. Kohler and N. K. Richtmyer, *ibid.*, **52**, 2038 (1930).

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(5) (a) D. E. Worrall, *J. Amer. Chem. Soc.*, **57**, 2299 (1935); (b) D. E. Worrall, *ibid.*, **62**, 3253 (1940).

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(8) (a) E. P. Kohler, *J. Amer. Chem. Soc.*, **46**, 503 (1924); (b) E. P. Kohler, *ibid.*, **46**, 1733 (1924); (c) E. P. Kohler, *ibid.*, **47**, 3030 (1925); (d) E. P. Kohler and G. R. Barrett, *ibid.*, **48**, 1770 (1926); (e) E. P. Kohler and J. B. Shohan, *ibid.*, **48**, 2425 (1926); (f) E. P. Kohler, *ibid.*, **50**, 221 (1928); (g) E. P. Kohler and S. F. Darling, *ibid.*, **52**, 1174 (1930); (h) E. P. Kohler and A. R. Davis, *ibid.*, **52**, 4520 (1930).

(9) H. Shechter and F. Conrad, *ibid.*, **76**, 2716 (1954).

(10) V. A. Tartakovski, B. G. Gribov, I. A. Savost'yanova, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1644 (1965); *Chem. Abstr.*, **64**, 2080 (1966).

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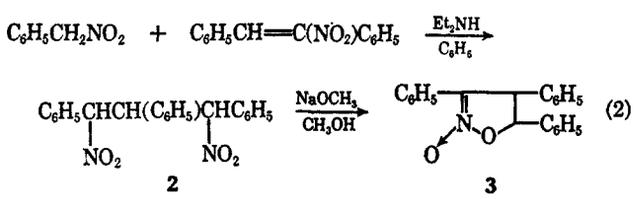
(13) E. P. Kohler, *ibid.*, **38**, 889 (1916).

(14) H. Feuer and S. Markofsky, *J. Org. Chem.*, **29**, 935 (1964).

(15) N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 5714 (1967).

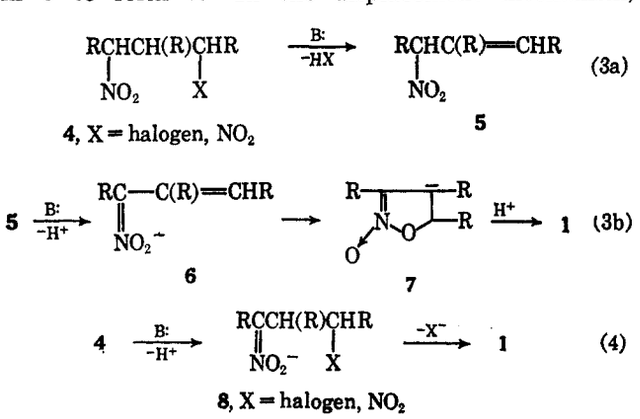
mechanism of 2-isoxazoline 2-oxide formation from 3-halo-1-nitroalkanes involves intramolecular displacement of bromide ion by nitronate oxygen attack in a 3-bromo-1-nitronate intermediate, $^{-}O_2N{=}C(R)CH(R)CH(R)Br$.

We have examined in detail the conversion of 1,3-dinitro-1,2,3-triphenylpropane (**2**) into 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**). Compound **2** has been synthesized previously by Heim[16] in unstated yield by condensation of benzaldehyde with phenylnitromethane, employing ethanolic methylamine–sodium carbonate catalysts.[17] A better procedure was found which involves Michael addition of phenylnitromethane to *cis*-α-nitrostilbene in benzene solvent with diethylamine catalyst (eq 2).



1,3-Dinitro-1,2,3-triphenylpropane (**2**) on heating for a few minutes in methanolic sodium methoxide gave a 79% yield of isoxazoline **3** and an 88% yield of nitrite ion (polarographic analysis). Based on ultraviolet (uv) spectral data the conversion **2** → **3** has been shown to be quantitative. It is not necessary to isolate the dinitroalkane intermediate. 3,4,5-Triphenyl-2-isoxazoline 2-oxide has been prepared in 62% yield by condensation of phenylnitromethane with α-nitrostilbene in hot methanolic sodium methoxide.[3a] It has also been prepared in 45–65% yield by reaction of α-nitrostilbene with ethanolic piperidine[4a] or ammonia[5a] at room temperature. These alternate syntheses are believed to proceed through **2** mononitronate anion.

Two mechanisms [an addition mechanism (3) and a displacement mechanism (4)] may be considered for the Kohler 2-isoxazoline 2-oxide synthesis from 1,3-dinitro- and 3-halo-1-nitroalkanes. In the reaction of 1,3-dinitroalkanes the generally accepted mechanism involves a nitro olefin intermediate (**5**, or its α,β isomer)[3a,4c,5a,b,14,18–21] and intramolecular nucleophilic addition of nitronate oxygen to the olefinic double bond in **6** to form **7**. In the displacement mechanism,



(16) F. Heim, *Chem. Ber.*, **44**, 2016 (1911).
(17) Procedure of E. Knoevenagel and L. Walter, *ibid.*, **37**, 4502 (1904).
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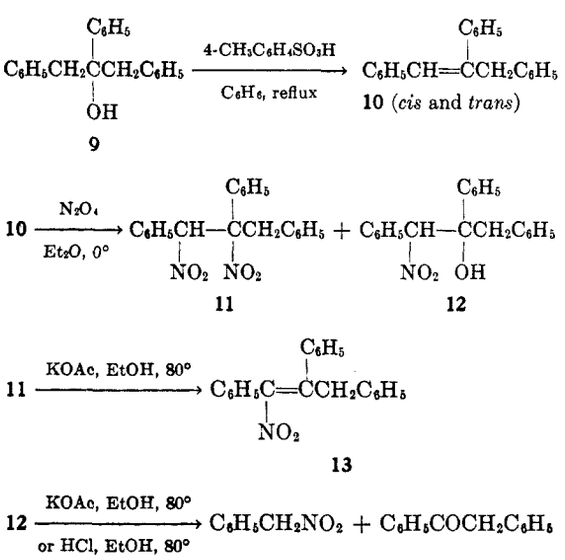
(19) P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **22**, 405 (1939).
(20) K. Rorig, *J. Org. Chem.*, **15**, 391 (1950).
(21) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, Interscience, New York, N. Y., 1962, pp 24, 112.

favored by all workers for 3-halo-1-nitroalkanes, the first step involves base attack to form mononitronate anion **8**. An intramolecular displacement of halide or nitrite ion by nitronate oxygen would lead to **1**. Until recently displacement of nitrite ion from a saturated carbon atom had been considered a most unlikely event.[1,15] Halide displacement by nitronate oxygen finds precedence in acylic nitronic ester syntheses from alkyl halides and alkali nitronates.[12,22,23]

Evidence favoring the nitro olefin mechanism for formation of 2-isoxazoline 2-oxides from 1,3-dinitroalkanes rests largely on the work of Heim.[16] From the base-catalyzed condensation of benzaldehyde with phenylnitromethane he isolated, in addition to α-nitrostilbene (50% yield) and a small amount of dinitroalkane **2**, a very low yield of what he considered to be 1-nitro-1,2,3-triphenylpropene (**13**). However, it has never been established that **13** produces isoxazoline **3** on treatment with base. Also, Heim gave no evidence that his compound was 1-nitro-1,2,3-triphenylpropene (**13**). We have now prepared an authentic sample of **13** and its β,γ isomer by unambiguous routes and shown these nitro olefins not to be converted into 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**) under any conditions, including those of the Kohler synthesis whereby 1,3-dinitroalkane **2** forms **3**.

1-Nitro-1,2,3-tripnenylpropene (**13**) was obtained in a synthesis departing from 1,2,3-triphenylpropanol (**9**) (Scheme I).

SCHEME I



Nitro alcohol **12** failed to dehydrate to nitro olefin **13** in the presence of acidic or basic catalysts. Instead, it underwent retroaldol cleavage to phenylnitromethane and desoxybenzoin. Hindered ketols and nitro alcohols are known to undergo relatively facile retroaldol

(22) A. Young, O. Levand, W. K. H. Luke, and H. O. Larson, *Chem. Commun.*, 230 (1966).
(23) This synthesis usually leads to the products of decomposition of acyclic nitronic esters—aldehydes or ketones and oximes. The reaction is the basis of a synthetic method: H. B. Hass and M. L. Bender, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 932.

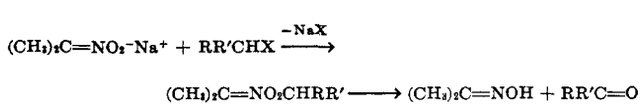


TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF NITROSTYRENE AND NITROSTILBENE DERIVATIVES (95% ethanol)

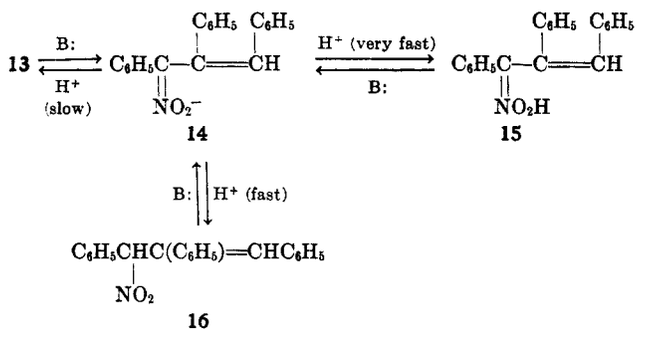
Compound	λ_{max}, mμ (ϵ_{max})	Ref
3	285 (17,700)	*a*
13	223 (10,500 sh), 243 (13,800)	*a*
14[b]	236 (22,500), 306 (19,600)	*a*
15[c]	233 (22,900), 285 (21,900)	*a*
16	233 (6500), 262 (12,000)	*a*
20	275 (16,200)	*a*
$C_6H_5CH{=}CH_2$	245.3 (15,000)	27
$C_6H_5CH{=}CHNO_2$	228 (7800), 311 (16,600)	29
cis-$C_6H_5CH{=}CHC_6H_5$	224 (24,400), 280 (10,450)	28
trans-$C_6H_5CH{=}CHC_6H_5$	228.5 (16,400), 295.5 (29,000), 307.5 (28,300)	28
cis-$C_6H_5CH{=}C(NO_2)C_6H_5$	228 (12,200), 316 (12,100)	30
trans-$C_6H_5CH{=}C(NO_2)C_6H_5$	281 (21,500)	30
cis-$C_6H_5CH{=}C(C_6H_5)CHOHC_6H_5$	260 (15,800)	31, 32
trans-$C_6H_5CH{=}C(C_6H_5)CHOHC_6H_5$	262 (16,000)	31, 32
$C_6H_5CH{=}NO_2^-Na^+$[d]	305 (20,000)	*e*
$C_6H_5CH{=}NO_2H$[c]	280 (20,000)	*e*

[a] Present investigation: $c \cong 1 \times 10^{-4}$ *M*. [b] 10^{-2} *M* sodium hydroxide solution. [c] Prepared by acidification of the sodium salt with 10% aqueous hydrochloric acid. [d] 10^{-4} *M* sodium hydroxide solution. [e] Present investigation: $c \cong 5 \times 10^{-5}$ *M*.

cleavage.[24] In another attempted synthesis of **13**, epimeric 1-bromo-1-nitro-1,2,3-triphenylpropanes were recovered after heating with ethanolic sodium ethoxide or sodium hydride in benzene.

Reactions of 1-nitro-1,2,3-triphenylpropene (**13**) were followed in dilute ethanol solutions by examination of uv spectra (Table I). In ethanolic sodium hydroxide **13** rapidly formed nitronate anion **14**.[25] Acidification of **14** led instantly to the corresponding nitronic acid (**15**) (Scheme II). Tautomerization of **15** *via* anion **14**

SCHEME II



resulted in rapid C-1 protonation to produce the isomeric β,γ-nitro olefin, 3-nitro-1,2,3-triphenylpropene (**16**). On standing, an ethanolic solution of **16** equilibrated to a mixture of **13** and **16**, λ_{max} 257 mμ, making this solution basic regenerated nitronate anion **14**. The observed C-1 protonation of **14** to form the β,γ-nitro olefin **16**, rather than terminal C-3 protonation to form the α,β isomer **13**, indicates noncoplanarity of the double bonds in this 1,3-diene system. In planar conjugated alkene or diene-1-nitronates terminal C protonation is observed with formation of a conjugated nitro olefin.[26] Noncoplanarity in anion **14** is supported by its uv spectrum which does not show the expected absorption maximum near 350–370 mμ.[26] Also, noncoplanarity of phenyl and nitro groups attached to the olefinic double bond in nitro olefins **13** and **16** is indicated by the uv spectra. These spectra are more like that of styrene[27] than those of *cis*- or *trans*-stilbene[28] and their nitro derivatives.[29,30] They resemble the spectra of the 1,2,3-triphenyl-1-propen-3-ols.[31,32] The stereochemistry of compounds **13–16** is not apparent from the uv spectral data collected in Table I. 3,4,5-Triphenyl-2-isoxazoline 2-oxide (**3**) clearly is not formed from nitro olefins **13** or **16** under conditions whereby it is formed rapidly from 1,3-dinitro-1,2,3-triphenylpropane (**2**).[25]

3,4,5-Triphenylisoxazole (**18**), a dehydration product of **3** formed in basic media, is also not produced from nitro olefins **13** or **16**. It is formed rather easily from isoxazoline 2-oxide **3** in aqueous ethanolic sodium hydroxide solution at reflux temperature within a few minutes, or at 25° in a few hours.[3a,5a] We have confirmed this result, but find no reaction to occur with **3** in ethanol with butylamine catalyst (30°, 1 week). It was shown by Worrall[5a] that dibenzoylphenylmethane monoxime is formed in this reaction (alcoholic ammonia catalyst) and is readily converted into isoazole **18** with hot hydrochloric acid or sodium hydroxide solution. These data are in agreement with a mechanism involving base attack at C-5 of **3** leading to **17** (eq 5) in an oximino ketone producing reaction characteristic of nitronic esters.[12,23,33] The formation of isoxazoles from 3-oximino ketones in acidic or basic medium is a well-established reaction.[34]

(24) (a) Ketol $C_6H_5CHOHCH(CH_3)COCH_3$ is known to undergo retrogression to benzaldehyde and 2-butanone in ethanolic sodium ethoxide faster than dehydration to the unsaturated ketone, $C_6H_5CH{=}C(CH_3)COCH_3$: M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959); (b) Y. N. Blokon and V. M. Belikov, *Izv. Akad. Nauk SSSR*, 528 (1967).

(25) 1,3-Diphenyl-1,3-dinitropropene is reported to form a nitronate anion, $C_6H_5C(NO_2){=}CHC(C_6H_5){=}NO_2^-$, in basic media and no isoxazoline 2-oxide or isoxazole derivative: T. Severin and H. J. Böhme, *Chem. Ber.*, **101**, 2925 (1968).

(26) A. T. Nielsen, *J. Org. Chem.*, **27**, 2001 (1962).

(27) A. Burawoy and J. P. Critchley, *Tetrahedron*, **5**, 340 (1959).

(28) R. N. Beal and E. M. F. Roe, *J. Chem. Soc.*, 2755 (1953).

(29) R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

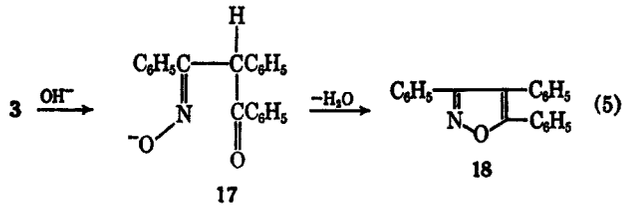
(30) J. P. Freeman and T. E. Stevens, *ibid.*, **23**, 136 (1958).

(31) R. E. Lutz and E. H. Rinker, Jr., *J. Amer. Chem. Soc.*, **77**, 366 (1955).

(32) H. O. House and D. J. Reif, *ibid.*, **77**, 6525 (1955).

(33) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 226 (1968).

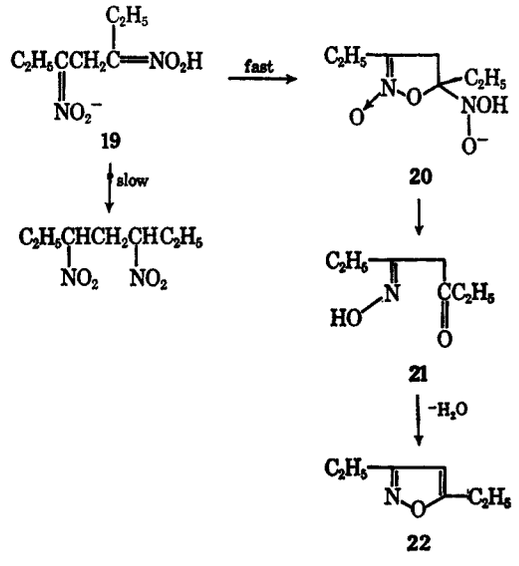
(34) Ref 21, p 6 ff.



17 18 (5)

There is another isoxazole synthesis departing from certain 1,3-dinitroalkanes which is pertinent and of comparative interest in this discussion. It is the formation of 3,5-dialkylisoxazoles fron nonfunctionally substituted secondary 1,3-dinitroalkanes [$RCH(NO_2)CH(R')CH(NO_2)R$ (R = alkyl, not H; R' = alkyl or H)], which we have reexamined briefly. Isoxazoline 2-oxides have not been isolated as intermediates.[14] The reaction does not occur in basic medium. Unsubstituted secondary alkane-1,3-bisnitronate anions are stable in basic solution.[14,35] Isoxazoles are produced only upon acidification of these bisnitronate anions. The reaction appears to involve intramolecular nitronate oxygen addition to the C=N bond of a nitric acid, as suggested by Feuer.[14] It does not involve a direct displacement of nitrite ion by nitronate anion, nor a nitro olefin intermediate. Also, the reaction does not involve a Nef hydrolysis of one nitronic acid to carbonyl, followed by reduction of the second nitronic acid to oxime by nitroxyl,[36] since we have found 3,5-diethylisoxazole formation to occur between pH 1 and 7 without formation of 3,5-dinitroheptane or 3,5-heptanedione. Alkane-1,3-bisnitronic acids exist in solution with a high concentration of mononitronate anion (pK^{I}_{aci} 2–4; pK^{II}_{aci} 8–9).[37] Anions such as **19** are stabilized by intramolecular hydrogen bonding and are quite resistant to Nef hydrolysis.[37] Also, certain secondary nitronate anions undergo C protonation relatively slowly.[37] Intramolecular attack by nitronate oxygen in **19**, with possible formation of an intermediate such as **20** and loss of nitrous acid to form oxime **21**, would lead to 3,5-diethylisoxazole (**22**) (Scheme III).

SCHEME III



A most interesting and surprising finding in the present investigation is that the compound, mp 102–103°, which Heim[16] reported to be 1-nitro-1,2,3-triphenylpropene is not the latter (**13**, yellow needles, mp 82–83°). Also, it is not the β,γ isomer, 3-nitro-1,2,3-triphenylpropene (**16**, white plates, mp. 80–82°). From the reaction of benzaldehyde with phenylnitromethane (methylamine–sodium carbonate catalyst; exposure to air for an extended period) Heim isolated a small amount of yellow crystals, mp 102–103°, in unstated yield which gave elemental analyses corresponding to the molecular formula $C_{21}H_{17}NO_2$, and which he described as 1-nitro-1,2,3-triphenylpropene (**13**). Pagano[38] also prepared what he described as nitro olefin **13** by persulfate oxidation of sodium phenylmethanenitronate in aqueous medium (mp 102–103°, 2% yield). No molecular weight data were reported by these workers. The principal product from both of these reactions is *cis*-α-nitrostilbene (50–58% yield). It was not possible to repeat Heim's preparation of his compound, which was evidently formed in minute yield. Pagano's procedure[38] in our hands gave a 6.7% yield of a substance, mp 101–102°. Our evidence now shows this material to be a stable molecular complex of *cis*-α-nitrostilbene and *trans*-stilbene.

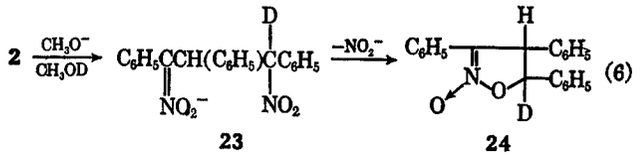
A substance, believed to be identical with Heim's compound, was easily prepared by dissolving 2 mol-equiv of *cis*-α-nitrostilbene and 1 mol-equiv of *trans*-stilbene in methanol; it precipitated from solution almost immediately in 84% yield, mp 101–102°. The complex can be sublimed unchanged or separated into its components by differential sublimation. Its mass spectrum at low potential revealed only parent peaks of 225 and 180, corresponding to its components. The observed molecular weight determined by vapor osmometry was 217 (approximately one-third of that calculated for $C_{42}H_{34}N_2O_4$, 630.7). The ir and uv spectra of the complex resemble closely the sum of the spectra of its components. In the nmr spectrum of the complex the vinyl proton singlet appears at 505 Hz compared with 495 Hz (relative to tetramethylsilane) in *cis*-α-nitrostilbene alone in the same solvent. This effect may be an example of molecular complexing which is a normal van der Waals aggregate involving a *cis*-α-nitrostilbene acceptor and a *trans*-stilbene donor, rather than a true charge-transfer complex.[39]

Heim[16] observed that treatment of his compound with methanolic sodium methoxide gave a small amount of a white solid which he considered to be a methanol addition product, although he gave no melting point and no evidence for this structure. We have repeated this experiment and shown the white product to be stilbene; in dilute solution the α-nitrostilbene is destroyed by the base treatment forming benzaldehyde and sodium phenylmethanenitronate. Small amounts of *trans*-stilbene must form in the reaction mixtures leading to α-nitrostilbene in the experiments of Heim[16] and Pagano.[38] *trans*-Stilbene has, in fact, been isolated as a product of reaction of phenylnitromethane with 10% aqueous sodium hydroxide; at reflux temperature (100°) it is formed in *ca.* 1% yield; after several hours at 160° the yield is 85–95%.[40]

3,4,5-Triphenyl-2-isoxazoline 2-oxide formation from

(35) F. T. Williams, Jr., P. W. K. Flanagan, W. J. Taylor, and H. Shechter, *J. Org. Chem.*, **30**, 2674 (1965).
(36) J. Armand, *Bull. Soc. Chim. Fr.*, 3246 (1965).
(37) A. T. Nielsen and H. F. Cordes, *Tetrahedron Suppl. 1*, **20**, 235 (1964).
(38) A. H. Pagano, Ph.D. Dissertation, The Ohio State University, 1960; *Dissertation Abstr.*, **21**, 59 (1960).
(39) M. D. Bentley and M. J. S. Dewar, *Tetrahedron Lett.*, 5043 (1967).
(40) W. Wislicenus and A. Endres, *Chem. Ber.*, **36**, 1194 (1903).

1,3-dinitroalkane **2** was examined in methanol-O-*d*. No deuterium incorporation at C-4 occurred as shown by the nmr spectrum of the product. Some deuterium incorporation into the 3 position of the intermediate nitronate anion occurs, leading to deuterio anion **23** (eq 6). Intramolecular displacement of nitrite ion in

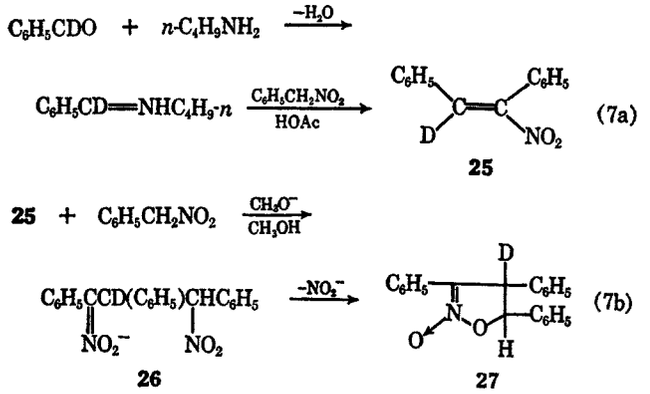


(6)

23 **24**

23 leads to the 2-isoxazoline 2-oxide-5-*d*, **24**. A nitro olefin mechanism would require deuterium incorporation at C-4 of **24**.

3-Nitro-1,2,3-triphenylpropane-1-nitronate-2-*d* anion (**26**) was synthesized *in situ* by condensation of phenylnitromethane with *cis*-α-nitrostilbene-α'-*d* (**25**, prepared from benzaldehyde-*d*) in methanolic sodium methoxide (eq 7). It cyclized to the 2-isoxazoline-4-*d* 2-oxide **27** (88% deuterium incorporation at C-4), a result impossible with a nitro olefin intermediate.[41]



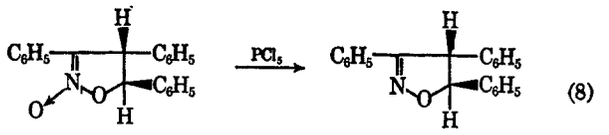
(7a)

25

(7b)

26 **27**

The stereochemistry of phenyl substituents in isoxazoline **3** at C-4, C-5 was established as *trans* by reduction of **3** with phosphorous pentachloride to known *trans*-3,4,5-triphenyl-2-isoxazoline (**28**) (eq 8).[3a,42] The nmr

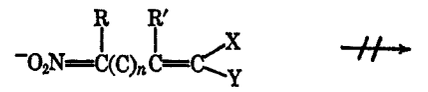


(8)

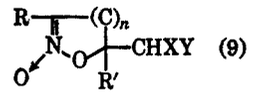
trans **3** J_{HH} = 4.4 Hz *trans* **28** J_{HH} = 5.6 Hz

spectra of **3** and trans **28** agree with the stereochemical assignment. The spectra of these compounds show similar C-4,C-5 proton coupling constants which are much lower than the value found for *cis* **28** (J_{HH} = 10.5 Hz). Reported values of coupling constants for other 3-phenyl-4,5-substituted 2-isoxazolines (measurement in deuteriochloroform) range from 3.75 to 6.62 Hz for the *trans* isomers (5.83 for *trans* **28**) and 9.43 to 11.37 Hz for the *cis* isomers (9.50 for *cis* **28**).[42] *cis* **3** has not been prepared.

Nucleophilic addition of nitronate oxygen to electrophilic olefinic double bonds has not been observed (eq 9). No examples have been found in the present study or elsewhere in the literature. We have examined certain new reactions which might be expected to be highly favorable for such intramolecular nucleophilic addition leading to cyclic nitronic esters (**30**) from acyclic nitronate anions having an activated double bond (**29**).



29, X, Y = H, alkyl, aryl, CN, CO_2Et, COR", NO_2; n = 0, 1, 2



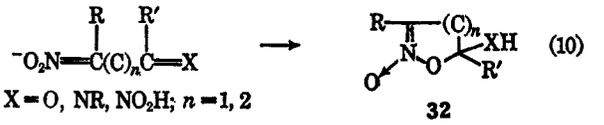
(9)

30

Condensations were run which, *in situ*, would lead to **29**. Systems examined include Michael additions of nitroethane and phenylnitromethane to ethyl 1-octynoate and 1-phenyl-1-butyn-3-one, aldol condensation of benzaldehyde with 1,3-diphenyl-4-nitro-1-butanone, and reaction of compounds 1,1-dicyano-2-phenyl-4-methyl-5-nitro-1-pentene and 4-nitro-1-phenyl-1-buten-3-one with base. Starting materials or retrogression products resulted from these attempted reactions. No evidence of formation of cyclic nitronic esters (**30**) was found.

The ambident nucleophile, carbonitronate ($>\bar{C}-NO_2 \leftrightarrow >C=NO_2^-$), prefers to undergo nucleophilic addition to electrophilic double bonds on carbon (Michael[43] and Henry[44] reactions). Displacement reactions of this anion, on the other hand, are most frequently observed to occur on oxygen.[12,22,23,33,45] Certain displacements by nitronate carbon which have been observed have been shown to occur by a radical anion mechanism.[45-47]

Nucleophilic additions of nitronate oxygen to carbon–heteroatom double bonds (C=O, C=N) (**31**) have been observed (eq 10). Cyclic nitronic esters (**32**) may result from these additions.[48-50] 3,5-Dialkylisoxazole formation from alkane-1,3-bisnitronic acid mononitronate anions (**19** → **22**) is believed to involve such an addition in the initial step.[14] New examples of this reaction have been found and are now under investigation in this laboratory.



(10)

31, X = O, NR, NO_2H; n = 1, 2 **32**

(41) Certain 2,2-disubstituted 1,3-dinitroalkanes (incapable of nitro olefin formation) should form 2-isoxazoline 2-oxides. The reported preparation of one such compound, α,α'-dinitro-β-phenyl-β-methylglutarate, bp 150° (1 mm),[4c] was repeated (base-catalyzed condensation of ethyl nitroacetate with acetophenone). However, the product, bp 105–106° (0.1 mm), unidentified, has no phenyl peaks in its nmr spectrum and the acetophenone is recovered (90%). The same product, derived exclusively from the ester, is evidently formed in the reported base-catalyzed condensation of cyclohexanone with ethyl nitroacetate: bp 120° (0.8 mm).[4c]

(42) M. C. Aversa, G. Cum, and M. Crisafulli, *Gazz. Chim. Ital.*, **98**, 42 (1968).

(43) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(44) G. Jones, *ibid.*, **15**, 204 (1967).

(45) V. I. Erashko, S. A. Shevelev, and A. A. Fainzelberg, *Usp. Khim.*, **35**, 1740 (1966).

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Experimental Section[51]

1,3-Dinitro-1,2,3-triphenylpropane (2).—Phenylnitromethane (27.4 g, 0.2 mol) and benzaldehyde (10.6 g, 0.1 mol) were mixed with 10 drops of ethanol, methylamine hydrochloride (0.1 g) and potassium carbonate (0.05 g) were added, and the mixture was allowed to stand for 1 week at 25°. The ethanol was then evaporated, benzene (20 ml) and diethylamine (1 g) were added, and the mixture was allowed to stand at 25° for 4 days. The solution was concentrated to a small volume and the residue was filtered; the collected solid was washed with water and recrystallized from ethanol to yield *cis*-α-nitrostilbene [5.0 g, mp 73° (lit.[16,17] mp 75°)]. The filtrate was evaporated at 60° (1 mm) for 3 hr and allowed to cool. Trituration of the remaining semisolid with ethanol gave 4.5 g (12%) of 1,3-dinitro-1,2,3-triphenylpropane, mp 174–176°, after recrystallization from ethanol: lit.[16] mp 177–178.5°; ν_{KBr} 1520, 1330 cm^{-1} (NO_2); essentially no electronic absorption above 220 mμ. The nmr spectrum showed a complex phenyl proton signal centered at τ 2.6 (15 protons), benzyl proton (C-1, C-3) signals at 4.05 (2, d, J = 9.0 Hz), and C-2 proton signal at 5.5 (1, t, J = 9.0 Hz). In some reactions using the above procedure a large amount of 3,4,5-triphenyl-2-isoxazoline-2-oxide (**3**) was also isolated, mp 163° (lit.[3a] mp 162°). Heating neat compound **2** at 250° for 10 min caused no change.

Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73; mol wt, 362.37. Found: C, 69.70; H, 4.93; N, 7.61; mol wt 355 (benzene).

***trans*-3,4,5-Triphenyl-2-isoxazoline 2-Oxide (3) from 1,3-dinitro-1,2,3-triphenylpropane** (2).—A solution of 1,3-dinitro-1,2,3-triphenylpropane (**2**, 0.1002 g) in 5 ml of methanol containing sodium methoxide (0.2 g) was heated under reflux for 3 min, quickly cooled, and filtered. The solid was washed with water and recrystallized from methanol to yield 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**): 0.065 g, 79%; mp 163° [when mixed with an authentic sample,[3a] mp 162–163°, the melting point was not depressed (lit.[3a] mp 162°)]; nmr phenyl signal centered at τ 2.4 (15 protons), C-4 proton at 5.11 (d), C-5 proton at 4.55 (d, J_{HH} = 4.4 Hz). Extending the period of heating resulted in formation of large amounts of triphenylisoxazole, mp 210–212°. The filtrate from the above reaction was analyzed for nitrite ion polarographically:[52] yield, 88%.

A solution of 1,3-dinitro-1,2,3-triphenylpropane (**2**) in 95% ethanol (5×10^{-5} M) containing sodium ethoxide (1.0×10^{-4} M) on standing at 25° showed the appearance of the absorption band for 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**) (285 mμ) and no other absorption bands. After 53 min only compound **3** was present as indicated by the extinction coefficient which was equal to that of pure **3** (ϵ_{max} 17,700). Increasing the base concentration to 0.35 M in an attempt to establish a pseudo-first-order rate constant for the reaction led to conversion of the isoxazoline 2-oxide into 3,4,5-triphenylisoxazole (**20**): λ_{max} 275 mμ; 60% yield in 50 min at 25° (pure **20** has ϵ_{max} 16,200).

Reduction of **3** with phosphorous pentachloride (procedure of Kohler and Barrett[3a]) gave *trans*-3,4,5-triphenyl-2-isoxazoline (*trans* **28**), mp 135–137°,[3a] 140°.[21] *cis*-3,4,5-Triphenyl-2-isoxazoline (*cis* **28**) was prepared for comparison purposes by reaction of hydroxylamine with 3-chloro-1,2,3-triphenylpropan-1-one,[53,54] mp 166–168° (lit.[21] mp 167°). The nmr spectra of these compounds are discussed in the text.

3,4,5-Triphenyl-2-isoxazoline-5-*d* 2-Oxide (24).—A solution of 0.2 g of 1,3-dinitro-1,2,3-triphenylpropane (**2**) in 2 ml of methanol-O-*d* containing 0.05 g of sodium methoxide was heated under reflux for 5 min. Working up as in the preparation of **3** led to the 5-deuterio compound, **24**, mp 162–163°; its nmr spectrum showed 90% deuterium incorporation into C-5; the phenyl peaks centered at τ 2.4 (15 protons) remained, the C-5 proton signal was essentially absent, and the C-4 proton signal collapsed to a singlet at 5.11.

cis*-α-Nitrostilbene-α'-*d (25).—Reaction of benzaldehyde-*d*[55] with phenylnitromethane by the method of Robertson[56] gave *cis*-α-nitrostilbene-α'-*d* (**25**): mp 73–74°; vinyl singlet at τ 1.75 reduced in intensity indicating 75% deuterium labeling.

3,4,5-Triphenyl-2-isoxazoline-4-*d* 2-Oxide (27).—A solution of *cis*-α-nitrostilbene-α'-*d* (**25**, 0.5 g, 0.0022 mol) and phenylnitromethane (0.4 g, 0.0029 mol) in 10 ml of methanol containing sodium methoxide (0.2 g) was heated under reflux for 5 min, quickly cooled, and filtered. Recrystallization from ethanol gave the 4-deuterio compound (**27**), 0.4 g, mp 163°; the nmr spectrum showed the phenyl peaks centered at τ 2.4 (15 protons), the C-4 proton signal was much reduced in intensity, and the C-5 proton doublet collapsed to a singlet at 4.55.[57] Relative area ratios determined by integration indicated an over-all deuterium retention at C-4 of 88% (corrected for the deuterium assay of **25**).

3,4,5-Triphenylisoxazole (18).—A solution of 3,4,5-triphenyl-2-isoxazoline 2-oxide (**3**, 0.2 g) in 10 ml of ethanol containing 0.2 g of sodium ethoxide was heated under reflux for 5 min and allowed to cool. The 3,4,5-triphenylisoxazole was filtered and washed with ethanol: 0.16 g (85%); mp 210–212° (lit.[18] mp 212–213°). In a parallel run employing butylamine catalyst (1.0 g) and a reaction time of 1 week at 30° there was recovered 0.2 g (100%) of unchanged **3**.

1,2,3-Triphenylpropene (10).—1,2,3-Triphenyl-2-propanol (**9**) was prepared by reaction of benzylmagnesium chloride with ethyl benzoate in ether.[58,59] The crude dried product, mp 50–60° (lit. mp 85–86,[59b] 86–87°[58]), was used without purification for dehydration to the olefin. To 20 g of this material and 18 g of *p*-toluenesulfonic acid was added 50 ml of benzene; the solution was heated under reflux overnight (*ca.* 16 hr); and 1 mol-equiv of water was collected in the Dean–Stark trap. The solution was concentrated to remove solvent and the residue was washed with water and distilled to yield 15.4 g of an oily mixture of *cis–trans* isomers of 1,2,3-triphenylpropene (**10**): bp 140–150° (0.6 mm) [lit.[59b] bp 215–219° (11 mm)]; 70% yield based on benzyl chloride [lit. mp 62–63,[59a] 62,[59b] and 63°[59b] for *cis* or *trans* isomers (stereochemistry unknown)]. The nmr spectrum of the product indicated high purity and showed phenyl and vinyl absorption centered at τ 2.7, a vinyl singlet at 3.54 (0.33 proton), and benzyl singlets at 5.9 (0.67 proton) and 6.25 (0.33 proton) indicating a 3:2 mixture of stereoisomers.

1-Nitro-1,2,3-triphenylpropan-2-ol (12).—Dinitrogen tetroxide gas was passed into a cold solution of 1,2,3-triphenylpropene (4.0 g, 0.015 mol; mixture of *cis* and *trans* isomers described above), contained in 30 ml of ether, and cooled to 0° in an ice bath until saturated (approximately 0.5 hr). The solution was kept at 0° for 0.5 hr and allowed to warm to 25° during 1 hr. After evaporation of *ca.* one-half of the solution contained in an open beaker in the hood, a solid separated which was removed by filtration and recrystallized from ethanol to yield 0.45 g of alcohol **12**: mp 106–107° (7.5% yield); ν_{KBr} 3550 (OH), 1550, 1360 (NO_2) cm^{-1}; phenyl peaks centered at τ 2.8 (15 protons), C-3 benzyl protons (2, pair of doublets, J = 14 Hz) centered at 6.43 and 6.78, C-1 benzyl singlet at 4.0 (one proton), and a broad OH signal centered at 6.3.

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.41; H, 5.63; N, 4.11.

A 0.1-g sample of alcohol **12** and 0.05 g of potassium acetate in 10 ml of ethanol was heated under reflux for 5 min. The solution was cooled and filtered to yield desoxybenzoin, 24 mg (47%), mp 52–52.5°, after recrystallization from methanol; its infrared and nmr spectra were identical with the spectra of an authentic sample.

In a parallel run with **12** employing 1 drop of concentrated hydrochloric acid, rather than potassium acetate, and a reflux time of 10 min there was obtained 20 mg (40%) of desoxybenzoin, mp 52–52.5°, after recrystallization from methanol. The filtrate was made basic with 5% aqueous potassium hydroxide and diluted to 100 ml with 95% ethanol. The uv spectrum of this solution showed a strong band at 300 mμ characteristic of

(51) Melting points were determined on a Kofler block and are corrected. The uv spectra were determined on a Cary Model 11 spectrophotometer (95% ethanol), ir spectra on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer (10–20% solutions in deuteriochloroform). Mass spectra were determined on a Hitachi Model RMU-6E (80 eV). Magnesium sulfate was employed as a drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

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(53) H. Rupe and F. Schneider, *Chem. Ber.*, **28**, 957 (1895).

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(57) This value was inadvertently reported as τ 5.10 in our preliminary communication.[1]

(58) A. Klages and S. Heilmann, *Chem. Ber.*, **37**, 1447 (1904).

(59) (a) A. Orechoff, *ibid.*, **47**, 89 (1914); (b) M. S. Eventova and N. I. Shapchenko, *Vestn. Mosk. Univ., Ser. II, Khim.*, **16**, No. 1, 71 (1961); *Chem. Abstr.*, **57**, 7143 (1962). These workers report a 60–65% yield of **9** using Klages' procedure.[58]

phenylmethanenitronate anion (*cf.* Table I). Acidification of this solution with 10% aqueous hydrochloric acid led to a band at 281 mμ characteristic of phenylmethanenitronic acid (*cf.* Table I); on standing this absorption maximum decayed rapidly.

1,2-Dinitro-1,2,3-triphenylpropane (11).—The ether solution remaining after removing the 1-nitro-1,2,3-triphenylpropan-2-ol (**12**) by filtration (above) was diluted with 50 ml of ether and extracted three times with 50 ml of water and five times with 50-ml portions of 10% aqueous potassium hydroxide solution. The ether solution was evaporated to dryness in air and the residual oil was extracted twice with 50 ml of hot hexane. The remaining insoluble oil was triturated with cold ethanol to yield slightly impure 1,2-dinitro-1,2,3-triphenylpropane (**11**), mp 125–128°. Recrystallization from methanol gave pure **11**: mp 127–129°; 0.65 g (12%); ν_{KBr} 1550, 1360 cm^{-1} (NO_2); phenyl proton complex centered at τ 2.7, C-1 benzyl singlet at 3.64, and two C-3 benzyl protons (pair of doublets) at 6.29, 6.58 (J = 15 Hz).

Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73; mol wt, 362.37. Found: C, 69.69; H, 5.11; N, 7.69; mol wt, 360 (chloroform).

1-Nitro-1,2,3-triphenylpropene (13).—A 0.65-g sample of 1,2-dinitro-1,2,3-triphenylpropane (**11**) and 0.35 g of potassium acetate in 30 ml of ethanol was heated under reflux for 5 min. After chilling at −15° for 4 hr, the product was filtered and recrystallized from methanol to yield 0.45 g (79%) of 1-nitro-1,2,3-triphenylpropene as yellow needles: mp 82–83°; ν_{KBr} 1520, 1360 cm^{-1} (NO_2); phenyl proton complex centered at τ 2.75 (15 protons) and C-3 benzyl proton singlet (two protons) at 6.25; uv maxima in Table I. In a parallel run employing 0.1 g of **11** the yield of **13** was 84%.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44; mol wt, 315.35. Found: C, 79.89; H, 5.48; N, 4.37; mol wt, 309 (chloroform).

3-Nitro-1,2,3-triphenylpropene (16).—To 0.11 g of 1-nitro-1,2,3-triphenylpropene (**13**) in 10 ml of ethanol was slowly added 10 ml of 10% aqueous potassium hydroxide solution. After standing for 2 hr at 25°, 10 ml of water was added; acetic acid was then added until the solution became cloudy. After standing overnight, 3-nitro-1,2,3-triphenylpropene was removed by filtration: white plates; 55 mg (50%); mp 80–82° (attempted recrystallization from ethanol gave an oil). On admixture with isomeric 1-nitro-1,2,3-triphenyl propene (**13**), mp 82–83°, the melting point was depressed to 60–80°. The ir spectrum of **16** (KBr) showed bands at 1650 and 1355 cm^{-1} (NO_2); the nmr spectrum showed a complex phenyl signal and a vinyl singlet centered at τ 2.6 and a C-3 benzyl proton doublet at 3.4 (J = 1 Hz); uv absorption bands for **16** are listed in Table I. The ethanolic solution of **16** was unstable; an additional peak at 240 mμ slowly appeared, which after 24 hr merged with the two original peaks to a broad band appearing at 257 mμ (ε 11,500); prolonged standing resulted in a decrease in intensity of this 257-mμ band.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.18; H, 5.61; N, 4.37.

Solutions of either nitro olefin **13** or **16** (1.0×10^{-4} M) in 1.0×10^{-2} M ethanolic sodium ethoxide gave 1,2,3-triphenylpropene-1-nitronate anion (**14**): λ_{max} 306 mμ (ε 19,600), 236 (22,500). Acidification of this solution with a 10% aqueous hydrochloric acid gave 1,2,3-triphenylpropene-1-nitronic acid (**15**): λ_{max} 285 mμ (ε 21,900), 233 (22,900). On standing 24 hr there appeared a band at 257 mμ (ε 14,100); making the solution basic with 10% aqueous potassium hydroxide regenerated nitronate anion **14**: λ_{max} 306 mμ.

***cis*-α-Nitrostilbene–*trans*-Stilbene Molecular Complex.**—*trans*-Stilbene (0.3 g, 0.0016 mol) and *cis*-α-nitrostilbene (0.71 g, 0.0032 mol) were dissolved in 20 ml of warm methanol. Cooling gave a precipitate of yellow needles which was recrystallized from ethanol to yield 0.84 g (84%) of the molecular complex: mp 101–102° (lit.[16,38] mp 102–103°); ν_{KBr} 1510, 1320 cm^{-1} (NO_2); λ_{max} 322 mμ (ε 38,000), 308 (48,000), 287 (47,500); phenyl and vinyl proton signals at τ 2.3–3.0 and vinyl singlet at 1.60. The mass spectrum of this complex at 12.5 eV showed two parent peaks, m/e 225 and 180.

The preparation of the complex was also carried out by ammonium persulfate oxidation of sodium phenylmethanenitronate according to the procedure of Pagano,[38] except that a reaction temperature of 25° was employed for 12 hr; 6.7% yield of yellow needles, mp 101–102°, was obtained. Pagano reports a 2% yield, mp 102–103°.[38] Attempts to repeat the preparation of the complex by Heim's original procedure,[16] or modifications of it, were unsuccessful.

Anal. Calcd for $C_{41}H_{24}N_2O_4$: C, 79.78; H, 5.43; N, 4.44; mol wt, 630.7. Found: C, 79.84; H, 5.50; N, 4.55; mol wt, 217 (benzene).

The complex could be sublimed and collected on a cold finger: mp 101–102°. In a differential sublimator (graded temperature in the collection tube) the complex was separated into its components: more volatile, white *trans*-stilbene, mp 124°; unseparated yellow complex in the middle zone; and least volatile, yellow *cis*-α-nitrostilbene, mp 73°. The components were identified by comparison with authentic samples (spectra and mixture melting points). *cis*-α-Nitrostilbene showed the following characteristics: ν_{KBr} 1520, 1330 cm^{-1} (NO_2); phenyl proton signals at τ 2.3–3.0, vinyl singlet at 1.75. *trans*-Stilbene showed phenyl proton signals at τ 2.3–2.8, vinyl singlet at 2.90. Uv maxima are listed in Table I.

To a solution of 0.1 g of the complex in 5 ml of methanol was added 10 ml of methanolic sodium methoxide (prepared from 0.1 g of sodium). The color of the solution changed immediately from yellow to colorless; *trans*-stilbene precipitated from the solution on chilling, mp 110–115°, and was identified by comparison of its nmr and ir spectra with those of an authentic sample.

1-Nitro-1,2-3-triphenylpropane.—To benzylmagnesium chloride [prepared from 1.5 g (0.012 mol) of benzyl chloride and 0.5 g (0.021 mol) of magnesium] was added a solution of 2.2 g (0.01 mol) of *cis*-α-nitrostilbene in 50 ml of ether. Hexane (50 ml) was then added and the resulting precipitate was quickly filtered and added to 50 ml of ether. A 10% solution of bromine in ether was slowly added to this mixture until no more decolorization of the added bromine was observed. A red oil separated, and the supernatant ether solution was decanted. The oil was washed by stirring with dilute aqueous hydrochloric acid, then triturated first with ether and then with hexane. Trituration of the remaining semisolid with ethanol gave 0.2 g (6.4%) of 1-nitro-1,2,3-triphenylpropane, mp 155–156°. It was purified by sublimation: mp 157–158°; ν_{KBr} 1540, 1330 cm^{-1} (NO_2); complex phenyl proton signal centered at τ 2.5, C-1 benzyl proton at 4.05 (d, J = 12 Hz), C-2 benzyl proton at 5.9 (multiplet), and C-3 benzyl protons (two) as pair of doublets at 7.25 (J = 6 Hz) and 7.26 (J = 8 Hz); no electronic absorption bands above 220 mμ.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41; mol wt 317. Found: C, 79.86; H, 6.18; N, 4.40; mol wt, 318 (benzene).

1-Bromo-1-nitro-1,2,3-triphenylpropane Epimers.—The above ethanol solution remaining after separation of 1-nitro-1,2,3-triphenylpropane was concentrated to remove solvents and the residue was crystallized from acetone to yield 1-bromo-1-nitro-1,2,3-triphenylpropane (epimer A). Recrystallization from ethanol gave colorless plates: mp 108–109°; 0.2 g, 5%; ν_{KBr} 1540, 1340 cm^{-1} (NO_2); phenyl proton signal centered at τ 2.6, C-2 benzyl proton at 5.32 (dd, J = 6, 8 Hz), C-3 benzyl protons (2) as pair of doublets at 6.78 (J = 6 Hz) and 6.79 (J = 8 Hz).

Anal. Calcd for $C_{21}H_{18}BrNO_2$: C, 63.63; H, 4.54; N, 3.53; Br, 20.20. Found: C, 62.84; H, 4.62; N, 3.25; Br, 20.10.

The acetone solution remaining after crystallization of epimer A was concentrated to remove solvent and the residue was crystallized from ethanol to yield 0.2 g (5%) of 1-bromo-1-nitro-1,2,3-triphenylpropane (epimer B): colorless needles; mp 116–117°; ν_{KBr} 1540, 1340 cm^{-1} (NO_2); phenyl proton signal (much simpler than that for epimer A) centered at τ 2.6, C-2 benzyl proton at 5.57 (dd, J = 6, 8 Hz), and C-3 benzyl protons (two) as a pair of doublets at 6.60 (J = 6 Hz) and 6.61 (J = 8 Hz).

Anal. Calcd for $C_{21}H_{18}BrNO_2$: C, 63.63; H, 4.54; N, 3.53; Br, 20.20. Found: C, 63.51; H, 4.55; N, 3.46; Br, 20.36.

3,5-Diethylisoxazole.—Disodium heptane-3,5-bisnitronate (0.1 mol) was prepared from 2-nitrobutyl acetate and sodium propane-1-nitronate in aqueous solution according to the procedure of Feuer and Markovsky.[14] An aliquot of this solution was acidified with cold 20% hydrochloric acid (pH 1). The mixture was extracted with ether and the ether was removed by evaporation. A portion of the residue (containing 3,5-diethylisoxazole) was treated with saturated aqueous cupric acetate solution and diluted with methanol to produce a homogeneous solution. No pre-

cipitate of copper enolate salt was observed. 3,5-Diethylisoxazole gave no precipitate with cupric acetate solution in methanol, but 3,5-heptanedione formed an insoluble copper salt, mp 209–212°.[60] A second aliquot of the heptane-3,5-bisnitronate solution was treated with solid potassium dihydrogen phosphate to change the pH to *ca.* 7. The solution then became cloudy and, after standing overnight, was extracted with ether. The ether was evaporated and the residue steam distilled to yield 3,5-diethylisoxazole and nitropropane as the only products (identified by comparison of nmr spectra with those of authentic samples). Acidification of a third aliquot of this solution with acetic acid gave 3,5-diethylisoxazole which was separated from the reaction mixture by extraction with ether followed by distillation: bp 78° (28 mm) [lit.[14] bp 65° (11 mm)]. The compound was identified by comparison of its nmr spectrum with that of an authentic sample.

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Registry No.—**3**, 19018-61-2; **11**, 19018-97-4; **12**, 19018-98-5; **13**, 19018-99-6; **14**, 12321-52-7; **15**, 19019-00-2; **16**, 19019-01-3; **20**, 19018-62-3; **24**, 19019-16-0; **27**, 19019-17-1; 1-nitro-1,2,3-triphenylpropane, 19019-18-2; 1-bromo-1-nitro-1,2,3-triphenylpropane, 19019-19-3; $C_6H_5CH{=}NO_2^-Na^+$, 12321-46-9; $C_6H_5CH{=}NO_2H$, 19019-20-6.

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The Alkyl Nitrate Nitration of Active Methylene Compounds. VI. The Nitration of Esters in Liquid Ammonia

HENRY FEUER AND ROBERT P. MONTER

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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The nitration of aliphatic and phenyl acetate esters with alkyl nitrates in the presence of potassium amide in liquid ammonia gives not only α-nitro esters **1** but also nitroalkanes **2** and dialkyl carbonates **3**. In addition to these compounds, another α-nitro ester **4** forms when the alkoxy portion of the ester and alkyl nitrate are not the same. Compounds **2** and **3** arise from a fragmentation reaction and compound **4** from a transesterification reaction, both of which occur during the nitration step, and not during subsequent acidification. These reactions are not caused by direct base attack on the resulting α-nitro ester, however, except when the latter is tertiary.

In continuation of our studies of the alkyl nitrate nitration,[1] we are now reporting on its application to the preparation of α-nitro esters.

General methods which have been employed for the preparation of α-nitro esters are the Victor Meyer reaction as modified by Kornblum and coworkers,[2] and the carboxylation of nitroalkanes in the presence of magnesium alkoxide.[3-5] The latter method does not seem to be applicable to the preparation of tertiary α-nitro esters.

Attempts by Wislicenus and coworkers[6,7] to prepare ethyl α-nitrophenylacetate by treating ethyl phenylacetate with ethyl nitrate in the presence of potassium ethoxide led only to phenylnitromethane and diethyl carbonate. Emmons and Freeman, using acetone cyanohydrin nitrate in the presence of a 100% excess of sodium hydride to nitrate monosubstituted malonic or acetoacetic esters, developed a general synthesis of α-nitro esters.[8]

In the present study, the alkyl nitrate nitration of esters was investigated in such systems as potassium *t*-butoxide–THF,[2a] potassium *t*-butoxide–DMF,[2d] and potassium amide–liquid ammonia.[2e] Of these only the latter was found to be useful in regard to work-up and yield. The reaction afforded not only α-nitro esters **1** but also cleavage products, namely nitroalkanes **2** and dialkyl carbonates **3**. Moreover, in cases where the carboxylic and nitrate esters differed in their alkoxy portions, another α-nitro ester **4** was obtained, resulting apparently from a transesterification reaction (eq 1).

$$\mathrm{RCH_2CO_2R'} \xrightarrow[2.\ \mathrm{H^+}]{1.\ \mathrm{KNH_2\text{-}liquid\ NH_3/R''ONO_2}} \underset{\mathbf{1}}{\mathrm{RCH(NO_2)CO_2R'}} + \mathrm{RCH_2NO_2} + \underset{\mathbf{3}}{\mathrm{R'OCOR''}} + \underset{\mathbf{4}}{\mathrm{RCH(NO_2)CO_2R''}} \quad (1)$$

(**2**)

In order to determine optimum reaction conditions, various reaction parameters were studied with ethyl and *t*-butyl caproates. The latter was chosen because amide formation was found to be negligible.[9] Because of amide formation, only a 10% excess of potassium amide could be employed in the conversion of ethyl esters into their anions. In the case of *t*-butyl esters, a 100% excess of potassium amide could be used; this

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