When acetone was used as the acidification solvent, a 66% yield was obtained. When water was used, the yield was 60%.

**Dimethyl (−)-*trans*-Epoxysuccinate (III) from Barium (−)-*trans*-Epoxysuccinate.**—A 2000-g. sample of 85% pure barium epoxysuccinate (6.36 moles) was suspended in 6 l. (149 moles) of dry methanol. The mixture was cooled to 10–15° and 452 ml. (832 g. of 8.49 moles) of concentrated sulfuric acid added slowly with stirring during 4 hr. After standing overnight 240 g. (2 moles) of anhydrous magnesium sulfate was added and the mixture refluxed with stirring for 5 hr. Upon addition of 187 g. (1.87 moles) of powdered calcium carbonate the temperature was raised to 60°, the methanol solution filtered through a heated funnel, and the solvent removed at reduced pressure.

In this way 820 g. (5.12 moles) of ester was obtained as a first crop and 92 g. by sublimation or recrystallization of the residue for a 96% yield of nearly pure white dimethyl epoxysuccinate, m.p. 72–75°. Sublimation at 50–80° (2 mm.) yielded large colorless needles, m.p. 74–75°. $[\alpha]^{25}_D$ −125° (*c*, 1.0 in ethanol).

*Anal.* Calcd. for $C_6H_8O_5$: C, 45.00; H, 5.04. Found: C, 45.03; H, 5.14.

Methyl (−)-*trans*-epoxysuccinate also was prepared in 70–75% yields by Fischer esterification of the free acid.

**Preparation of (−)-*trans*-Epoxysuccinamide (IV) from Dimethyl (−)-*trans*-Epoxysuccinate.**—A 70.0-g. sample (0.437 mole) of dimethyl epoxysuccinate was stirred with 200 ml. of cold ammonium hydroxide (29% ammonia), using a strong stirrer in an open beaker for 10–15 min. The ester dissolved as the amide separated, and the product was removed by filtration and washed with a little cold water. The crude dry epoxysuccinamide weighed 60 g., m.p. 203–206°. Recrystallization from water gave 52 g. (97% yield) of pure material, m.p. 205–208° dec. $[\alpha]^{25}_D$ −68° (*c*, 1.0 in water).

*Anal.* Calcd. for $C_4H_6N_2O_3$: C, 36.92; H, 4.65; N, 21.54. Found: C, 36.67; H, 4.40; N, 21.59.

**(−)-*trans*-Epoxysuccinonitrile (V) from (−)-*trans*-Epoxysuccinamide.**—A stirred mixture of 5.4 g. (0.0415 mole) of dry epoxysuccinamide and 30 ml. of phosphorus oxychloride was heated rapidly under dry nitrogen. During 35 min. the amide dissolved as the temperature of the oil bath was raised from 80–100°, and 5 min. later heating was discontinued. After cooling to room temperature, excess phosphorus oxychloride was removed by distillation at 10-mm. pressure (water aspirator), and epoxysuccinonitrile separated as the concentration progressed. The crude product was removed by filtration, sucked very dry, washed twice with ice–water, and purified by sublimation at 85° (0.1 mm.). The purified substance, 1.9 g. (49% yield) formed thick white prisms, m.p. 130–130.5°. $[\alpha]^{25}_D$ −71° (*c*, 1.0, ethanol).

*Anal.* Calcd. for $C_4H_2N_2O$: C, 51.06; H, 2.14; N, 29.78. Found: C, 51.10; H, 1.92; N, 29.29.

Many other techniques of nitrile formation failed when applied to (−)-*trans*-epoxysuccinamide.

**Determination of the Half-lives of 1,2-Disubstituted Ethylene Oxides in Acetic Acid Solution with Pyridine Hydrobromide at 30°.**—Pyridine hydrobromide was used as a nonvolatile source of hydrobromic acid. The pyridine released during reaction of the hydrobromic acid with the epoxide was measured by potentiometric titration of aliquots at intervals with perchloric acid. The acetic acid solutions were maintained at 30° ± 0.1° in a thermostat-controlled water bath.

In the determinations in Table III, *a* is the millimolar concentration of the epoxide, *b* is the millimolar concentration of pyridine hydrobromide, and *x* is the millimolar quantity of epoxide consumed at *t* minutes.

TABLE III

TITRATIONS AND CALCULATIONS FOR DETERMINATION OF THE HALF-LIFE OF EPOXYSUCCINIC ACID IN PYRIDINIUM BROMIDE–ACETIC ACID AT 30°

| *t*, min. | $V_{cor}$, ml. | $x$ | $a - x$ | $b - x$ | $\frac{a\,b - x}{b\,a - x}$ |
|---|---|---|---|---|---|
| 0 | 0.000 | 0.0000 | 0.0906 | 0.5000 | 1.00 |
| 242 | .060 | .0098 | .0808 | .4902 | 1.10 |
| 1376 | .277 | .0455 | .0451 | .4549 | 1.83 |
| 1809 | .324 | .0532 | .0374 | .4468 | 2.16 |

Log $[a\,(b - x)/b\,(a - x)]$ was plotted against time to give second-order curves, and the slopes of these curves were substituted into the second-order rate equation to determine half-times. For example, a 59.8-mg. sample of epoxysuccinic acid (mol. wt. 132) was dissolved in 25 ml. of acetic acid. This was mixed with 25 ml. of 0.1 *M* pyridine hydrobromide in acetic acid. The solution was immersed in a water bath at 30°, and 10-ml. aliquots were withdrawn at intervals *t* and titrated potentiometrically with 0.1635 *N* perchloric acid. Blanks were treated similarly.

**Acknowledgment.**—The authors are grateful to Dr. D. B. Seeley for the fermentative preparation of the epoxysuccinic acid, to Glenn Hess for the half-life titrations, and to Charles Scott for technical assistance.

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# Derivatives of Primary Nitroalkanes. Preparation of Isoxazolines

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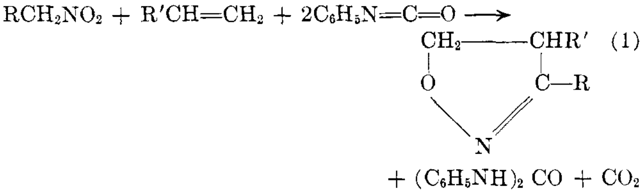
Although various methods[1–5] have been used for derivative formation and identification of primary nitroalkanes, none of these possesses the advantages of producing crystalline solids with sharp melting points in a single stage reaction. In seeking such a method our attention was directed to the recent work of Mukaiyama and Hoshino[6] in which they treated primary nitroalkanes with phenyl isocyanate in the presence of various olefins, using a tertiary amine as a catalyst, and obtained the corresponding substituted isoxazolines.



$$RCH_2NO_2 + R'CH{=}CH_2 + 2C_6H_5N{=}C{=}O \longrightarrow \text{(isoxazoline)} + (C_6H_5NH)_2CO + CO_2 \quad (1)$$

Nitrile oxides are the probable intermediates. Most of the compounds prepared were liquids or low melting solids unstable to heat; nevertheless, the method possesses merit because it is simple and direct and seems capable of development into a satisfactory method for routine derivative formations.

Not all olefins give isoxazolines by this procedure, and many which do react give very low yields of isoxazolines. The unsuitability of many olefins for this type of reaction was demonstrated by the unsatisfactory results obtained with hexachlorocyclopentadiene, cyclohexene, and cholesteryl acetate using phenyl isocyanate, 1-nitrobutane, and triethylamine. Dipropylfuroxane (from dimerization of butanenitrile oxide) was the only reaction product which could be isolated from all three reactions. Unconjugated double bonds in six-membered rings were

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[1] O. C. Dermer and J. W. Hutcheson, *Proc. Okla. Acad. Sci.*, **23**, 60 (1943).

[2] N. Kharasch and J. L. Cameron, *J. Am. Chem. Soc.*, **73**, 3864 (1951).

[3] N. Kharasch, *J. Chem. Educ.*, **33**, 585 (1956).

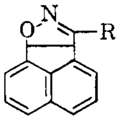
[4] R. B. Langford and D. D. Lawson, *ibid.*, **34**, 510 (1957).

[5] M. B. Winstead, R. G. Strachan, and H. W. Heine, *J. Org. Chem.*, **26**, 4116 (1961).

[6] T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).

TABLE I

DERIVATIVES OF PRIMARY NITROALKANES. 3-ALKYLACENAPHTHO[1,2,*d*]-2-ISOXAZOLINES

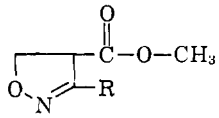


| Nitroalkane | Yield, %[a] | M.p., °C. | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|
| $C_2H_5NO_2$ | 50.24 | 130 | 80.36 | 5.30 | 6.70 | 80.64 | 5.50 | 6.67 |
| $CH_3(CH_2)_2NO_2$ | 56.38 | 104 | 80.68 | 5.87 | 6.27 | 80.58 | 5.79 | 6.27 |
| $CH_3(CH_2)_3NO_2$ | 48.88 | 112 | 80.97 | 6.37 | 5.90 | 80.73 | 6.19 | 6.07 |
| $CH_3(CH_2)_6NO_2$ | 36.09 | 60 | 81.68 | 7.58 | 5.01 | 81.60 | 7.56 | 5.13 |
| $CH_3(CH_2)_7NO_2$ | 41.65 | 62 | 81.87 | 7.90 | 4.77 | 81.85 | 7.93 | 4.60 |
| $O_2N(CH_2)_4NO_2$ | 2.66 | 199 | 80.74 | 4.84 | 6.73 | 80.25 | 4.93 | 6.59 |

[a] Based on nitroalkane. Equimolar amounts of nitroalkanes and acenaphthylene were used.

TABLE II

ISOXAZOLINES FROM PRIMARY NITROALKANES AND METHYL ACRYLATE. METHYL 3-ALKYL-2 ISOXAZOLINE-4-CARBOXYLATES



| Nitroalkane | Yield,[a] % | B.p., °C. (mm.) | $n^{24}D$ | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5NO_2$ | 46.62 | 78 (0.8) | 1.4583 | 50.34 | 6.34 | 9.79 | 50.16 | 6.42 | 9.93 |
| $CH_3(CH_2)_2NO_2$ | 45.04 | 85 (0.8) | 1.4578 | 53.49 | 7.06 | 8.91 | 53.62 | 6.94 | 9.09 |
| $CH_3(CH_2)_3NO_2$ | 47.31 | 96 (1.0) | 1.4570 | 56.12 | 7.66 | 8.18 | 55.90 | 7.82 | 8.19 |

[a] Based on nitroalkane. Equimolar amounts of nitroalkane and methyl acrylate were used.

found by Quilico[7] not to add to nitrile oxides. This would explain the absence of isoxazoline products from the cyclohexene and the cholesteryl acetate. The hexachlorocyclopentadiene may be too sterically hindered to add to nitrile oxides. Dimethyl itaconate and $\beta$-nitrostyrene appeared to give adducts which were viscous oils and were not further investigated. Benzoquinone, 1,4-naphthoquinone, and 2,3-dichloro-1,4-naphthoquinone gave intractable tars from which only *sym*-diphenylurea could be isolated in pure form. Quinones are reported to react directly with isocyanates to give quinone imides.[8] The diene, cyclopentadiene dimer, gave only a mono-isoxazoline, presumably involving the double bond in the bridged (and hence strained) ring. Benzonitrile oxide and phenyl azide also give monoadducts with cyclopentadiene dimer.[9,10]

From numerous preliminary experiments it was concluded that olefins with substituents capable of electron donation to the double bond are most satisfactory, and that acenaphthylene is ideally suited for the purpose. Table I shows the results obtained with several primary nitroalkanes, including one diprimary dinitroalkane (1,4-dinitrobutane), which gave an alkane bis-(isoxazoline). It will be noted that nitromethane is not included among the primary nitroalkanes derivatized. Steinkopf[11] has shown that it reacts differently with phenyl isocyanate to form nitroacetanilide and nitromalonanilide.

Mukaiyama and Hoshino[6] propose that the phenyl isocyanate serves to remove water from the nitroalkane, converting it to a nitrile oxide which then adds to the olefin double bond to form an isoxazoline. In accord with this postulation are the observations of various authors on addition reactions of nitrile oxides prepared by other methods, especially by the dehydrohalogenation of hydroxamic acid chlorides with bases.[12,13]

It would seem that other dehydrating agents should be able to replace phenyl isocyanate satisfactorily and that certain of them might offer advantages in isolation of the product. *sym*-Diphenylurea is partially soluble in most organic solvents and is separated from the desired isoxazoline product with some difficulty. Water soluble by-products would be more conveniently removed than is diphenylurea. Accordingly attempts were made to substitute acetic anhydride or phosphorous oxychloride for the phenyl isocyanate.

Acetic anhydride, nitroethane, methyl acrylate, and pyridine gave methyl 3-methyl-2-isoxazoline-4-carboxylate as a viscous yellow liquid in 9% conversion. The same reaction with phenyl isocyanate instead of acetic anhydride gave the same product in over 46% conversion. Other nitroalkanes gave similar results (Table II). Phosphorus oxychloride, nitroethane, acenaphthylene, and triethylamine gave 3-methylacenaphtho-[1,2,*d*]-2-isoxazoline in 41% conversion, and because of the solubility of the by-products (phosphoric and hydrochloric acids), the isoxazoline was isolated much more easily. The same reaction with phenyl isocyanate instead of phosphorus oxychloride gave the same product in 50% conversion, but required several recrystallizations from methanol to obtain an analytically pure material.

It is concluded that primary nitroparaffins can be readily converted to isoxazolines using either phenyl

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[7] A. Quilico, N. Barbulescu, P. Grunanger, and M. R. Langellar, *Tetrahedron Letters*, 89 (1961).

[8] H. Staudinger and R. Endle, *Ber.*, **50**, 1044 (1917).

[9] A. Quilico, P. Grunanger, and R. Mazzini, *Gazz. chim. ital.*, **82**, 349 (1952) [*Chem. Abstr.*, **48**, 2039e (1954)].

[10] K. Alder, G. Stein, and H. Finzenhagen, *Ann.*, **485**, 211 (1931).

[11] W. Steinkopf and H. M. Daege, *Ber.*, **44**, 497 (1911).

[12] A. Quilico and G. S. D'Alcontres, *Nature*, **166**, 227 (1950).

[13] G. LoVecchio and F. Monforte, *Gazz. chim. ital.*, **83**, 416 (1953) [*Chem. Abstr.*, **49**, 2961 (1955)].

isocyanate or phosphorus oxychloride as dehydrating agents, the former providing some small advantages in yields, the latter some advantages in isolation of product.

## Experimental

**3a,4,4a,7a,8,8a-Hexahydro-3-propyl-4,8-methano-5H-indeno-[5,6,*d*]isoxazole.**—Seventy-five milliliters of dry benzene was placed in a round-bottomed flask equipped with a mechanical stirrer and a reflux condenser fitted with a calcium chloride drying tube. To this were added 47.6 g. (0.4 mole) of phenyl isocyanate, 20.6 g. (0.2 mole) of 1-nitrobutane, 13.2 g. (0.1 mole) of cyclopentadiene dimer, and 10 drops of triethylamine. The reaction mixture was stirred 1 hr. at room temperature, followed by a 1-hr. reflux period. The solution was cooled and filtered. The *sym*-diphenylurea obtained was recrystallized from ethanol to yield 36.90 g. (86.9% conversion), m.p. 235–236°. The solvent was removed with a water aspirator and the residue triply distilled under vacuum, yielding 7.38 g. (26.23% conversion) of the isoxazoline, b.p. 122° (0.7 mm.); $n^{24}\mathrm{D}$ 1.5209.

*Anal.* Calcd. for $C_{14}H_{19}NO$; C, 77.37; H, 8.81; N, 6.45. Found: C, 77.42; H, 8.79; N, 6.48.

**Attempted Preparation of an Isoxazoline from Hexachlorocyclopentadiene and 1-Nitrobutane.**—To 40 ml. of benzene was added 16.7 g. (0.14 mole) of phenyl isocyanate, 7.2 g. (0.07 mole) of 1-nitrobutane, 19.1 g. (0.07 mole) of hexachlorocyclopentadiene, and 5 drops of triethylamine. The reaction mixture was stirred 3 days at room temperature and the reflux period omitted. It was then cooled and the *sym*-diphenylurea filtered and recrystallized from ethanol, m.p. 232–235°. The filtrate was distilled and yielded 18.42 g. of hexachlorocyclopentadiene, b.p. 59–60° (0.8 mm.), and a few grams of dipropylfuroxane, b.p. 82–85° (0.8 mm.); $n^{24}\mathrm{D}$ 1.4785. Identification was made by infrared analysis.

Similar results were obtained with cholesteryl acetate, cyclohexene, dimethyl itaconate, β-nitrostyrene, benzoquinone, 1,4-naphthoquinone, and 2,3-dichloro-1,4-naphthoquinone.

**3-Alkyl Acenaphtho[1,2,*d*]-2-isoxazolines.**—The following general procedure was followed: to 15 ml. of benzene were added 4.53 g. (0.038 mole) of phenyl isocyanate, 0.019 mole of 1-nitroalkane, 2.89 g. (0.019 mole) of acenaphthylene, and 2 drops of triethylamine. The reaction mixture was stirred for 1 hr. and refluxed for 1 hr. The solution was then cooled, filtered, and evaporated.

**Methyl 3-Alkyl-2-isoxazoline-4-carboxylates.**—The following general procedure was followed: to 75 ml. of benzene was added 35.7 g. (0.30 mole) of phenyl isocyanate, 0.15 mole of nitroalkane, 12.9 g. (0.15 mole) of methyl acrylate, and 3 drops of triethylamine. The reaction mixture was stirred for 1 hr., refluxed for 1 hr., cooled, and filtered. The solvent was removed and the residue was vacuum distilled to obtain the pure but oily product.

**Methyl 3-Methyl-2-isoxazoline-4-carboxylate (Acetic Anhydride as the Dehydrating Agent).**—To 22.0 g. (0.216 mole) of acetic anhydride was added 16.2 g. (0.216 mole) of nitroethane, 18.6 g. (0.216 mole) of methyl acrylate, and 39.3 g. (0.49 mole) of pyridine. The reaction mixture was stirred for 1 hr. followed by 2 hr. of refluxing on a steam bath. The low boiling constituents were removed with a water aspirator. This material had a green color which turned orange on standing. The remainder of the reaction mixture was triply distilled under vacuum. A small amount, 2.79 g. (9.02% conversion), of the product, b.p. 78–79° (1 mm); $n^{26}\mathrm{D}$, 1.4561, was obtained.

*Anal.* Calcd. for $C_6H_9NO_3$: C, 50.53; H, 6.34; N, 9.79. Found: C, 50.29; H, 6.54; N, 10.40.

**3-Methylacenaphtho[1,2,*d*]-2-isoxazoline (Phosphorus Oxychloride as the Dehydrating Agent).**—To 100 ml. of chloroform in a three-necked round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a calcium chloride drying tube, and a dropping funnel was added 3.04 g. (0.02 mole) of acenaphthylene, 1.50 g. (0.02 mole) of nitroethane, and 9.07 g. (0.896 mole) of triethylamine. The solution was cooled to 0° in an ice bath and then 3.06 g. (0.02 mole) of phosphorus oxychloride was added dropwise over a 15-min. period. After the addition of phosphorus oxychloride was completed, the reaction mixture was stirred 30 min. at ice-bath temperatures. The ice bath was removed and the reaction mixture refluxed 30 min. The chloroform was evaporated leaving a solid which was washed with petroleum ether (30–60°) and then with water. The product was recrystallized from methanol, m.p. 129–131°, and 1.55 g. (37.07% conversion) was obtained.

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# Formation of 2,2,4,4,6,6-Hexamethyl-1,3,5-cyclohexanetrione from Dimethylketene and from Its Polymers

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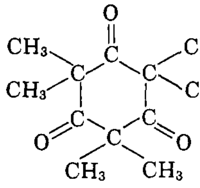
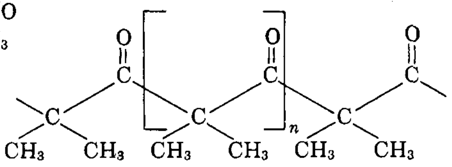
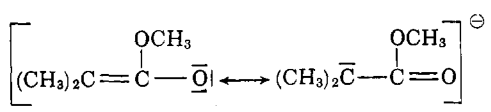
The dimerization reaction of dimethylketene forming tetramethyl-1,3-cyclobutanedione has been known for a long time, but recently[1,2] a cyclic trimer was obtained from dimethylketene. The structure of 2,2,-4,4,6,6-hexamethyl-1,3,5-cyclohexanetrione (I) was assigned to it.


I


II

The reaction described by us[1] occurs readily in the presence of aluminum halides and, depending on the experimental conditions, the polymerization can stop after the addition of three monomeric units or can continue to the formation of linear macromolecules having structure II. Erickson and Kitchens[2] subsequently have obtained compound I in high yield by heating dimethylketene or tetramethyl-1,3-cyclobutanedione at 110° in the presence of sodium methoxide.

The mechanism of the reaction proposed by these authors involves the successive addition of two molecules of dimethylketene to carbanion III



$$\left[(\mathrm{CH_3})_2\mathrm{C}{=}\overset{\mathrm{OCH_3}}{\mathrm{C}}{-}\overline{\underline{\mathrm{O}}}| \longleftrightarrow (\mathrm{CH_3})_2\overline{\mathrm{C}}{-}\overset{\mathrm{OCH_3}}{\mathrm{C}}{=}\mathrm{O}\right]^{\ominus}$$

III

such that the polymerization stops with removal of the methoxyl anion. A mechanism of this type is similar to that indicated by Shashoua and co-workers for the polymerization of isocyanic compounds.[3]

The interpretation of the formation of hexamethyl-1,3,5-cyclohexanetrione, according to Erickson, does not agree with what we observed for the low-temperature polymerization of dimethylketene in the presence of basic substances. In fact, with organometallic compounds of the first three groups of the periodic table as catalysts, dimethylketene reacts rapidly,[4] yielding,

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(1) G. F. Pregaglia, G. Mazzanti, and M. Binaghi, *Makromol. Chem.*, **48**, 234 (1961).

(2) J. L. E. Erickson and C. Kitchens, *J. Org. Chem.*, **27**, 460 (1962).

(3) V. E. Shashoua, W. Sweeny, and R. F. Tietz, *J. Am. Chem. Soc.*, **82**, 867 (1960).

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