

aqueous solution of the corresponding aldehyde (obtained from the Aldrich Chemical Co.) and $\text{NH}_2\text{OH}\cdot\text{HCl}$, m.p. 112.5–113.0° and 130.0–130.5°, respectively.

Quaternizations. In synthesizing the mono 2- and 4-formyl alkyl pyridinium halide oximes a 2:1 molar ratio of halide to tertiary oxime was used. In the "bis" series a 1:3 molar ratio was employed.

Procedure A. A mixture of the pyridine oxime and halide was dissolved in sufficient ethanol and refluxed for the period of time specified in Tables I and II.

Procedure B. A mixture of oxime and halide was dissolved in about 100 ml. of ethanol and heated at 60° in a 200-ml. capped pressure bottle for specified periods of time. The reaction mixtures were cooled to room temperature and the products of reaction removed by filtration. In several cases, it was necessary to add absolute ether to effect complete precipitation. The products were recrystallized from absolute ethanol.

pK_a Values. The pK_a values were determined at room temperature (25–27°), from potentiometric titration data, assuming pK_a to be the pH of half neutralization. In each case approximately 100 mg. of oxime dissolved in 5 ml. of water was titrated with 0.1*N* sodium hydroxide.

Analysis. Elemental analyses were performed by standard procedures. For determination of nitrogen (Dumas) the

weighed samples were layered over with V_2O_5 prior to ignition. Since the oxime ether hydrohalides are isomeric with the desired quaternized oximes it was necessary to establish purity by independent determination. This was achieved readily by potentiometric titration since the oxime ether hydrohalides have pK_a values of less than 5, whereas the pK_a values of the quaternized oximes are 7.8–8.5.

Where mixtures of oxime ether hydrohalide and quaternary oximes were obtained, separation was accomplished by fractional crystallization from ethanol or by separation from neutral aqueous solution. At pH 6–7 the oxime ether (and also any unreacted pyridine aldoxime) could be extracted from aqueous solution with CHCl_3 leaving the quaternary compound in the aqueous layer.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Polycyclic Compounds Containing Nitrogen. I. The Diels-Alder Reaction of 1-Nitro-1-alkenes

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As a preliminary to investigations involving substituted nitrocyclohexenes and their analogs as intermediates for the preparation of polycyclic compounds containing ring nitrogen, the reaction of various 1-nitro-1-alkenes with 2,3-dimethyl-1,3-butadiene was reexamined. The nitroalkenes studied have the general formula, $\text{RCH}=\text{CHNO}_2$, where R is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl, and 2-ethoxyethyl. The majority of the adducts were characterized by conversion to the corresponding dibromides which were readily purified by crystallization. Two of the dibromides were not crystalline; in these instances the corresponding cyclohexenones were prepared by the Nef reaction. Reduction of the nitrocyclohexenes to the corresponding cyclohexylamines is described.

Investigations concerned with the synthesis of polycyclic compounds containing ring nitrogen by routes involving the Diels-Alder reaction demanded a reinvestigation of the use of 1-nitro-1-alkenes as dienophiles. The present paper records this work.

It has previously been shown that 1-nitro-1-alkenes participate as dienophiles in the Diels-Alder reaction.³ In general, however, the yield of

adduct has been low whenever the preparation has involved an open-chain diene; the number of such cases previously studied is very small.

2,3-Dimethylbutadiene was chosen for our work because of its ready availability and its reactivity. 2-Methoxybutadiene was also employed in a few cases.⁴

Experimental conditions employed for such reactions by previous investigators have varied from heating an ether solution of the reactants under reflux to heating the reactants in a sealed tube at 150°. We have found that no adduct was isolable from 1-nitro-1-pentene and 2,3-dimethyl-1,2-butadiene when a mixture of the two was allowed to

(1) From a thesis submitted by A. B. Ross in partial fulfillment of the requirements for the Ph.D. degree, University of Maryland, June 1957.

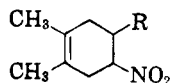
(2) Monsanto Chemical Company Fellow, 1956–57.

(3) H. L. Holmes, *Org. Reactions*, IV, 60 (1948); K. Klager, *J. Org. Chem.*, 20, 650 (1955); W. E. Noland, H. I. Freeman, and M. S. Baker, *J. Am. Chem. Soc.*, 78, 188 (1956); J. D. Roberts, C. C. Lee, and W. H. Saunders, *J. Am. Chem. Soc.*, 76, 4501 (1954); W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, 17, 1641 (1952); W. C. Wildman and D. R. Saunders, *J. Org. Chem.*, 19, 381 (1954); A. Etienne, A. Spire, and E. Toromanoff, *Bull. soc. chim. France*, 750 (1952); E. E. Van Tamalen, and R. J. Thiede, *J. Am. Chem. Soc.*, 74, 2615 (1952); D. V. Nightin-

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(4) See paper, II, *J. Org. Chem.*, in press.

TABLE I
4-ALKYL-1,2-DIMETHYL-5-NITROCYCLOHEXENES



R	Time of reaction, hrs.	Yield, %	B.P., °C.	Pressure, mm.	n_D^{25}
Methyl ^a	8, 12	68.5 ^f , 72	71	0.6	1.4796
Ethyl ^b	16	77.5 ^f	105	4	—
Propyl ^c	24	69.5	113–114	5	1.4790
Isopropyl ^d	16	31.5, 35 ^f	105	3	1.4819
Butyl	33	73	124–126	3	1.4784
Isobutyl	32	65, 68.5 ^f	115–116	3	1.4752
Amyl	32	65 ^f	129–130	3	1.4756
Hexyl ^e	24	77–78	116	0.3	1.4763
2-Ethoxyethyl	34, 40	69 ^f , 80.5 ^f	112–114	1	1.4785

^a M.p. 34.5–35.0°; *Anal.* Calcd. for C₁₃H₁₅NO₂: C, 63.88; H, 8.93. Found: C, 63.25, 63.22; H, 8.76, 8.84. ^b M.p. 32.5–32.8°; *Anal.* Calcd. for C₁₀H₁₇NO₂: C, 65.49; H, 9.35; N, 7.65. Found: C, 65.23, 65.19; H, 9.16, 9.09; N, 7.68, 7.84. ^c Lit.¹¹ b.p. 146–147° (12 mm.); d_4^{20} 1.0035. M_D^{20} Calcd.: 56.19. Found: 56.32. *Anal.* Calcd. for C₁₁H₁₉NO₂: C, 66.97; H, 9.71. Found: C, 67.53, 67.32; H, 9.41, 9.49. ^d *Anal.* Calcd. for C₁₁H₁₉NO₂: C, 66.97; H, 9.71. Found: C, 67.29, 67.53; H, 9.55, 9.68. ^e *Anal.* Calcd. for C₁₄H₂₅NO₂: C, 70.25; H, 10.53; N, 5.85. Found: C, 69.97, 70.15; H, 10.55, 10.58; N, 6.25, 6.29. ^f Acetonitrile was used as a solvent; in the other reactions no solvent was employed.

stand at room temperature for a week: 79% of the alkene was recovered. Likewise, heating 1-nitro-1-butene or 1-nitro-1-pentene with the same diene under reflux resulted in very low yields of adduct.

Satisfactory yields of adduct were, however, obtained by heating the reactants at 100° in a glass liner contained in a steel vessel of the type used for high pressure hydrogenations. The yield of adduct was little influenced by the presence of a large excess of diene; standard practice was to use a ratio of nitroalkene to diene of 1 : 1.5, but ratios up to 1 : 6.8 were studied. Likewise, use of acetonitrile or nitroethane as solvents gave no improvement of yield; on the other hand, acetic acid, benzene, or benzene containing trichloroacetic acid proved unsatisfactory⁵ as solvents for the reaction.

The nitroalkenes and diene were stable under the conditions chosen; 1-nitro-1-pentene, 1-nitro-1-octene and 2,3-dimethylbutadiene were heated individually at 100° in the apparatus for 12, 31, and 12 hours respectively. Recoveries of the respective substances were 91, 78, and 92%. Much smaller recoveries of 1-nitro-1-octene were obtained when it was heated under similar conditions in acetonitrile or nitroethane. Apparently the solvent promotes polymerization of the olefin. However, acetonitrile and nitroethane were found to be quite satisfactory solvents for the reaction. It appears, therefore, that the Diels-Alder process can compete favorably with other processes in these solvents. Some of the early reactions were carried out in acetonitrile in the hope that the highly polar solvent might promote an advantageous polarization of the reactants. However, experience proved that the higher yields obtained in these early experiments could also be obtained

when excess diene alone was used as solvent. In the later experiments, therefore, no foreign solvent was used.

The times necessary for optimum yields are profoundly influenced by the character of the R-group in the 1-nitro olefin, RCH=CHNO₂; Table I (see experimental part) shows this influence. Longer reaction times were required as the alkyl group increased in length, and α -substitution appears to have a considerable influence on the yield.⁶ These effects are not surprising inasmuch as the yield of adduct is determined by the balance of a number of competing reactions; polymerization of each reactant undoubtedly competes with the normal Diels-Alder addition, and copolymerization is certainly not excluded.

A number of experiments involving 3-methyl-1-nitro-1-butene and 2,3-dimethyl-1,3-butadiene showed that little improvement in yield resulted from increasing reaction time from 16 to 24 hours. On the other hand 1-nitro-1-pentene reacted with the same diene under the same conditions to produce more than twice as much adduct. 4-Methyl-1-nitro-1-pentene behaved similarly. Whether this behavior is a reflection of steric or polar effects, or both, is debatable; we are inclined toward the belief that the low yields of adduct obtainable from 3-methyl-1-nitro-1-butene are attributable to the steric effect of the branch in the chain in a position adjacent to the reaction site.⁷

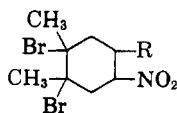
The nitrocyclohexenes were characterized by conversion to dibromides which were low-melting solids. Two of the dibromides failed to crystallize,

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TABLE II
4-ALKYL-1,2-DIBROMO-1,2-DIMETHYL-5-NITROCYCLOHEXANES



R	M.P., °C.	% Carbon		% Hydrogen		% Bromine		% Nitrogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Methyl	52.0-52.3	32.84	33.04	4.59	4.72	48.57	48.59	4.26	4.00
Ethyl	53.0	35.01	33.09	4.99	4.74	46.59	48.70	4.08	3.92
			34.95		5.08		46.56		4.08
Propyl	34.5	37.00	35.12	5.36	4.99	44.76	46.26	3.92	4.15
			36.85		5.35		44.72		3.92
Isopropyl	53.7-54.2	37.00	37.07	5.36	5.25	44.76	44.48	3.92	4.25
			36.89		5.46		44.54		3.92
Isobutyl	40.3-41.3	38.83	36.83	5.70	5.42	43.07	44.63	3.78	4.64
			39.07		5.69		42.91		3.78
Amyl	33.0-33.5	40.54	39.12	6.02	5.68	41.50	42.95	3.64	3.75
			40.44		5.93		41.68		3.64
Hexyl	43.6-44.0	42.11	40.48	6.31	6.04	40.03	41.68	3.51	3.46
			42.16		6.33		40.37		3.51
			42.06		6.11		40.26		3.75

and the parent substances were therefore converted into the corresponding 6-alkyl-3,4-dimethyl-2-cyclohexen-1-ones by the Nef reaction.⁸ Evidence for a shift during or subsequent to the Nef reaction in the location of the double bond of the adduct into conjugation with the carbonyl is provided in the ultraviolet spectra of the two ketones. The principal absorption of 3,4-dimethyl-6-*n*-butyl-2-cyclohexene-1-one was found at 226 $m\mu$ ($\epsilon = 11,800$); that of 3,4-dimethyl-6-(2-ethoxyethyl)-2-cyclohexen-1-one was found at the same wave-length, ($\epsilon = 10,800$).

The absorption spectra of a series of 3-alkyl-2-cyclohexene-1-ones have been studied.⁹ Maxima appear in the range between 223.5 and 226.5 $m\mu$ with values of ϵ of 15,000 to 16,600. These absorption maxima are at a longer wave length and have much larger ϵ -values than would substances in which the double bond was not conjugated with the carbonyl.¹⁰

Hydrogenation of 1,2,4-trimethyl-5-nitrocyclohexene, I, and 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene, II, to the corresponding cyclohexylamines was noteworthy in that the rate of absorption of hydrogen in the presence of an Adams' platinum catalyst was rapid until one molecular equivalent of hydrogen was absorbed and then very slow until four molecular equivalents had been absorbed. When, however, a 10% palladium-carbon catalyst was employed in the reduction of 4-ethyl-1,2-dimethyl-5-nitrocyclohexene, III, and of II, no abrupt change in rate of absorption occurred, and four equivalents of hydrogen

were absorbed rather rapidly. When hydrogenation of III was stopped after three molecular equivalents of hydrogen had been absorbed, only the saturated amine could be isolated. This behavior is but another example of the tendency of nitrocyclohexenes, at least those with isolated double linkages, to be converted by hydrogenation over a platinum catalyst to the corresponding cyclohexane prior to reduction of the nitro group.¹¹

Dibromides of the nitrocyclohexenes were prepared as reference compounds. The dibromides from the *n*-butyl- and the 2-ethoxyethyl-substituted cyclohexenes melted below room temperature. For further characterization these substances were converted by means of the Nef reaction to the corresponding cyclohexenones which were further characterized by preparation of their 2,4-dinitrophenylhydrazones.

EXPERIMENTAL

Melting points are corrected and were determined in a Hershberg apparatus. Boiling points are uncorrected. We are indebted to Miss Kathryn Gerdeman, Dr. Mary Aldridge, and Miss Jane Swan for the microanalyses. Ultraviolet spectra were determined by use of a Beckman spectrophotometer, Model DU.

Nitroalcohols. The required nitro alcohols were prepared according to the method of Sprang and Degering.¹² Of the alcohols prepared only 4-ethoxy-1-nitro-2-butanol is a new substance. It boils at 107-109° (1 mm.); n_D^{25} 1.4436. Standard procedure was to add 100 ml. of 10*N* sodium hydroxide

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(10) F. A. Miller, in *Organic Chemistry*, H. Gilman, ed., John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. 3, p. 165.

slowly over a period of 40 min. to a cold mixture of 1 mole of freshly distilled aldehyde and 1 mole of nitromethane, well stirred mechanically, in a one-liter, three-necked folded flask. The mixture was held at the same temperature, 5–10°, for an hour after all of the alkali had been added, then neutralized with 500 ml. of cold 2*N* acetic acid, and finally saturated with salt. The product was taken up in ether, and the solution further extracted. Ether, unreacted aldehyde, and nitromethane were removed from the dried ether solution in a nitrogen atmosphere under the pressure of a water pump, and the residue was distilled under reduced pressure in a nitrogen atmosphere through a 10-inch Vigreux column. It was found to be important to avoid heating the alcohol for long periods of time. Concentration of the ether solution under diminished pressure and reasonably rapid distillation of the residual alcohol aid in obtaining satisfactory yields of product.

Nitroalkyl Acetates. Acetates were prepared from the alcohols by treatment at 60° with acetic anhydride in the presence of a bit of concentrated sulfuric acid. About half of the necessary anhydride was added rapidly to the stirred alcohol followed by the balance at such a rate that the temperature remained around 60°. After an additional 2 hr., acetic acid and excess acetic anhydride were removed by distillation in a nitrogen atmosphere under about 25 mm. pressure. The residue was distilled through a 10-in. Vigreux column under a few millimeter's pressure of nitrogen.

Neither boiling point nor refractive index of the following acetates used in this work appear in the literature: 2-methyl-1-(nitromethyl)propyl, b.p. 82–85° (2.5 mm.), n_D^{25} 1.4345; 1-(nitromethyl)amyl, b.p. 105° (3 mm.), n_D^{25} 1.4337; 3-methyl-1-(nitromethyl)butyl, b.p. 86–88° (1 mm.), n_D^{25} 1.4381; 1-(nitromethyl)hexyl, 100–103° (1.5 mm.), n_D^{25} 1.4385; 1-(nitromethyl)heptyl, b.p. 114–116° (1 mm.), n_D^{25} 1.4374; 3-ethoxy-1-(nitromethyl)propyl, b.p. 106–107° (1.5 mm.), n_D^{25} 1.4347.

Nitroalkenes. The nitroalkyl acetates were converted to the corresponding alkenes by heating a vigorously stirred solution of the acetate in benzene in the presence of anhydrous sodium carbonate under reflux in an apparatus provided with a Dean-Stark water trap.¹³ The mixture was heated and stirred until no more water was collected. The procedure adopted required 0.5 mole of acetate, 800 ml. of benzene, and 0.5 mole of anhydrous sodium carbonate. After removal of sodium acetate and sodium carbonate by filtration, the benzene solution was concentrated under about 25 mm. pressure in a nitrogen atmosphere, and the residue distilled through a 10-in. Vigreux column under nitrogen (1 to 35 mm.). Either one or both of the following physical constants do not appear in the literature for the following substances: 3-methyl-1-nitro-1-butene, b.p. 67° (14 mm.), n_D^{25} 1.4522; 1-nitro-1-hexene, b.p. 54–55° (1.5 mm.), n_D^{25} 1.4531; 4-methyl-1-nitro-1-pentene, b.p. 50–51° (0.8 mm.), n_D^{25} 1.4500; 4-ethoxy-1-nitro-1-butene, b.p. 75° (2 mm.), n_D^{25} 1.4547.

2,3-Dimethyl-1,3-butadiene. This diene was prepared in the usual way.¹⁴

4-Alkyl-1,2-dimethyl-5-nitrocyclohexenes. Apparatus for

(13) H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

(14) L. W. Newton and E. R. Coburn, *Org. Syntheses, Coll. Vol. 3*, 313 (1955).

the Diels-Alder additions consisted of a well stirred electrically-heated oil bath which was provided with a thermostat and in which was supported at 270-ml. steel bomb of the type used in high-pressure hydrogenations. The bomb was provided with a glass liner, and was approximately two-thirds immersed in the oil.

In the glass liner were mixed 0.05 moles of nitroalkene, 0.25 moles of diene, and sometimes 20 ml. of solvent. A few mg. of hydroquinone was added, and nitrogen was bubbled through the mixture for 5 min. The liner was then stoppered, placed in the bomb, and after closure of the latter, heated in the oil bath at 100° for the desired time. After completion of the reaction, solvent and/or excess diene were removed under reduced pressure; distillation of the residue yielded in succession unreacted nitroalkene and then adduct as an almost colorless oil. Table I summarizes a number of such experiments. The yields reported are for once-distilled products; in some cases the products were redistilled or recrystallized from methanol or ethanol for analysis.

The 3,5-dinitrobenzoyl derivative, m.p. 181–182°, was obtained as a cream colored powder from chloroform-hexane (1:1).

Anal. Calcd. for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.29, 58.18; H, 6.56, 6.28; N, 11.85.

The picrate, yellow needles from 50% ethanol, melted at 222–223°.

2-(2-Ethoxyethyl)-4,5-dimethylcyclohexylamine. A solution of 5.93 g. of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene in 40 ml. of acetic acid and 0.5 g. of Adams' catalyst were shaken with hydrogen at one atmosphere and 23°. One molar equivalent of hydrogen was taken up in 40 min. After 2 more hr. only 4% of the remaining calculated amount of hydrogen had been taken up. The catalyst was removed by filtration and hydrogenation was continued in the presence of 2 g. of 10% palladium on charcoal. The remaining three molar equivalents of hydrogen were taken up in 3560 min. The solution was filtered, evaporated under reduced pressure, and treated with conc. sodium hydroxide. The amine was taken up in ether and benzene, and the solvents were evaporated leaving 4.83 g. (93%) of a light yellow oil, n_D^{25} 1.4626.

The picrate formed shiny yellow blades from 50% methanol and melted at 150–151°.

Anal. Calcd. for $C_{18}H_{25}N_3O_8$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.77, 50.83; H, 6.46, 6.28; N, 13.21, 13.25.

The benzoyl derivative separated in clusters of colorless microneedles from 50% ethanol and melted at 132–132.5°.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 75.20; H, 9.63; —OC₂H₅, 14.85. Found: C, 75.38, 75.08; H, 9.83, 9.80; —OC₂H₅, 15.04.

The α -naphthylurea derivative was prepared and recrystallized from methanol; m.p. 204–205°.

A solution of 6.48 g. of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene in 50 ml. of acetic acid and 3.0 g. of 10% palladium on charcoal were shaken with hydrogen at one atmosphere and 23°. Three molar equivalents of hydrogen were taken up in 45 min., and an additional 240 min. was required for absorption of the fourth molar equivalent of hydrogen. The amine was isolated as described above, to yield 4.49 g. (79.5%) of an almost colorless oil, n_D^{25} 1.4632.

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