verified the fact that common esters are not reduced by sodium borohydride.[1] The reduction of *N*-methyl-*N*-nitrosobenzamide at 5 °C in water with 1 equiv of sodium borohydride for 1 h gave a yield of 76% benzyl alcohol and 7% methyl benzoate. The reaction in water is much faster than in glyme, but the use of a nonprotic solvent appears to decrease considerably the possibility of ester formation.

At this point the reduction mechanism remains unclear. The metal borohydride may add directly to the carbonyl function of the nitrosoamide, or epimerization of the nitrosoamide to the diazotate (Scheme I) may take place first followed by the reduction of this intermediate before it can decompose to the ester. Since the diazotate is a short-lived intermediate,[6] it seems likely that this reaction follows a mechanism similar to the reduction of acid chlorides, that is, direct addition of borohydride to the carbonyl function.[2]

Warning. Many nitrosoamides are mutagenic without liver activation. These compounds should be considered contact carcinogens and must be handled with great caution.

Experimental Section

Proton magnetic resonance spectra were taken on a Varian XL-100 Spectrometer using $CDCl_3$ as the solvent, with 0.5% tetramethylsilane as the internal standard. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Melting points were determined in an Electrothermal capillary melting point apparatus. Purity determinations by gas–liquid chromatography (GLC) were carried out in a Shimadzu Model 4BM chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. An 8 ft 8% H1-EFF-1BP coated on a Gas-Chromosorb Q column was used (Applied Science Laboratories Inc., State College, Pa.). The acid chlorides used to prepare the amides were obtained from Aldrich Chemical Co., Milwaukee, Wis.

Preparation of Methylamides. *N*-Methylbenzamide, mp 78–80 °C (lit.[12] mp 80 °C); *N*-methyl-2-phenylacetamide, mp 56–7 °C (lit.[13] mp 58 °C); *N*-methylbutyramide, bp 110–11 °C (15 mmHg) (lit.[14] bp 156 °C (90 mmHg)); *N*-methylmyristoylamide, mp 76–8 °C (lit.[14] mp 78.4 °C); *N*-methyldodecanoyl amide, mp 68 °C (lit.[14] mp 67–9 °C); and *N*-methyldecanoylamide, mp 57–8 °C (lit.[14] mp 57.3 °C) were prepared by dissolving methylamine hydrochloride in 5% aqueous sodium hydroxide solution followed by addition of the acid chloride.

Preparation of Nitrosoamides. These compounds were prepared from the corresponding amides by published methods, see Table II.

Reduction of *N*-Methylnitrosoamides with $NaBH_4$. A typical reduction procedure was as follows: A 0.5 M solution of nitrosoamide in glyme was cooled to 0 °C in a salt–ice water bath and sodium borohydride was added in small lots over a period of 5 to 10 min. Once the addition was complete, the cooling bath was removed and the mixture stirred at room temperature for 2–8 h. The reaction mixture was cooled to 5 °C and ice chips were added. Excess sodium borohydride was decomposed with 10% hydrochloric acid. The solution was extracted with dichloromethane, washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered through a pad of magnesium sulfate and the solvent was removed on a rotary evaporator. The crude product was distilled and/or analyzed by GLC; 1-tetradecanol was recrystallized from aqueous ethanol. All products were compared and found to be identical with authentic samples of the primary alcohols. Reaction times and product yields are given in Table I.

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Registry No.—*N*-Methylbenzamide, 613-93-4; *N*-methyl-2-phenylacetamide, 6830-82-6; *N*-methylbutyramide, 17794-44-4; *N*-methylmyristoylamide, 7438-09-7; *N*-methyldodecanoylamide, 27563-67-3; *N*-methyldecanoylamide, 23220-25-9; methylamine hydrochloride, 593-51-1; benzoyl chloride, 98-88-4; benzeneacetyl chloride, 103-80-0; butanoyl chloride, 141-75-3; myristoyl chloride, 112-64-1; dodecanoyl chloride, 112-16-3; decanoyl chloride, 112-13-0; sodium borohydride, 16940-66-2.

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Dienic Reactivity of 3,5-Cycloheptadien-1-one

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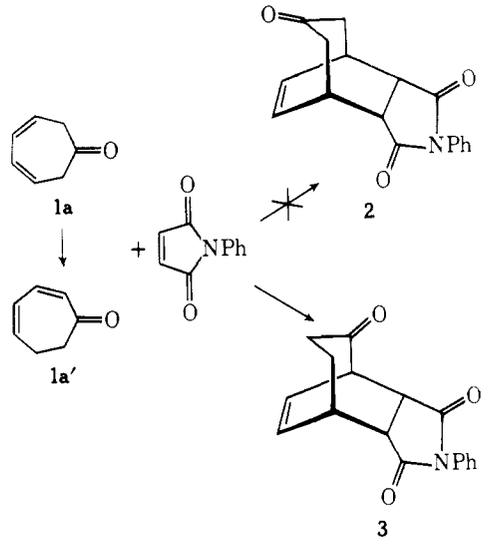
The reaction of 3,5-cycloheptadienone (**1a**) with *N*-phenylmaleimide was shown[2,3] to afford the Diels–Alder adduct **3** rather than the expected adduct **2** (eq 1). Presumably the



(1)

dienic reactivity of cycloheptadienone **1** is low and under the reaction conditions the 3,5-isomer **1a** is transformed via enolization into the 2,4-isomer **1a**, leading subsequently to the adduct **3**.[4] This lack of dienic reactivity of the 3,5-isomer **1a** and the anomalously short wavelength absorption (λ_{max} 217 nm) have been attributed to a nonplanar diene moiety as its most stable conformation. Indeed, molecular models indicate considerable strain for the planar conformation of the diene.

Consequently, it came to us as some surprise when the singlet oxygenation of **1a** gave the apparently unfavorable 3,5-type Diels–Alder adduct instead of the expected ene-type reaction.[5] In view of this unusual result, we decided to examine the dienic reactivity of 3,5-cycloheptadienones **1a–d** with potent dienophiles such as 4-phenyl-1,2,4-triazolin-3,5-dione. In all cases the Diels–Alder adduct **4** of the 3,5-isomers **1** was formed in high yield. The results are summarized in Table I and exhibited in Scheme I. Structure proof of the adducts **4**

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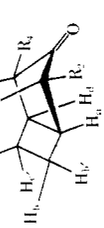
Table I. Yields, Physical Constants, and Spectral Data on Diels–Alder Adducts and Derivatives

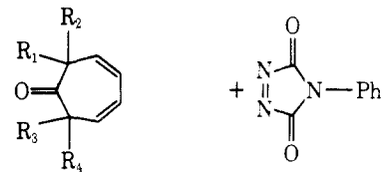
	registry no.	R_1	R_2	R_3	R_4	yield, %	phys[a] const mp, °C	^{1}H NMR type	H no.	δ	(J, Hz)	IR, cm^{-1}
4a	68782-14-9	H	H	H	H	78	199–200 (ethanol)	H_a, H_d	2	5.10	m	(KBr) 3030, 1775,
								H_b, H_c	2	6.50	m	1700, 1595,
								R_1, R_2	2	2.86	AB[b]	1400, 875
								R_3, R_4	2	3.13		
								C_6H_5	5	7.35	br s	
4b[c]	6878-15-0	Me	Me	Me	Me	84	231–232 (ethanol)	H_a, H_d	2	4.45	m	(KBr) 3030, 2975,
								H_b, H_c	2	6.35	m	1770,
								R_1, R_3	6	1.15	s	1695,1400,1280-
								R_2, R_4	6	1.30	s	,1120
								C_6H_5	5	7.25	m	
4c[c]	68782-16-1	*i*-Pr	Me	Me	Me	93	170–171 (ethanol)	H_d	1	4.60	m	(KBr) 3030, 2970,
								H_a	1	4.75	m	1770, 1690,
								H_b, H_c	2	6.45	m	1405, 1280
								R_1 CH_3	6	0.95	d (7.0)	
								R_1 CH	1	2.15	sept (7.0)	
								R_2, R_3, R_4	9	1.25	s	
										1.33	s	
										1.45	s	
								C_6H_5	5	7.34	m	
4d[c]	68782-17-2	*t*-Bu	Me	Me	Me	87	176–177 (ethanol)	H_d	1	4.65	m	(KBr) 3025, 2965,
								H_a	1	4.95	m	1770, 1700,
								H_b, H_c	2	6.60	m	1395, 1300
								R_1	9	1.28	s	
								R_3	3	1.35	s	
								R_2, R_4	6	1.55	s	
								C_6H_5	5	7.45	m	
6c	68782-18-3	*i*-Pr	Me	Me	Me	92	69–70 (ethanol)	H_d	1	4.25	m	($CHCl_3$) 3030,
								H_a	1	4.40	m	2970, 1770,
								H_b, H_b', H_c, H_c'	4	2.15	m	1700, 1400, 890
								R_1 CH_3	6	0.98	dd (7.0)	
								R_1 CH	1	1.80	sept (7.0)	
								R_2, R_3, R_4	9	1.20	s	
										1.28	s	
										1.34	s	
								C_6H_5	5	7.36	m	

7c[d]	68782-19-4	*i*-Pr	Me	Me	Me	54	wax		(CHCl$_3$) 3040, 2980, 1685, 1515, 890
								H_d	1	5.07	m	
								H_a	1	5.20	m	
								H_b, H_b'	4	1.84	m	
								H_c, H_c'	6	1.05	dd (7.0)	
								R_1 CH$_3$	1	2.15	sept (7.0)	
								R_1 CH		1.27	s	
										1.33	s	
										1.40	s	
								R_2, R_3, R_4	9			
8c	68782-20-7	*i*-Pr	Me	Me	Me	72	liquid[e]					(CCl$_4$) 2985, 1730, 1470, 1383
								H_a, H_d	2	2.48	m	
								H_b, H_b'	4	1.70	m	
								H_c, H_c'				
								R_1 CH$_3$	6	0.78	dd (7.0)	
								R_1 CH	1	1.38–1.98	m	
										0.81	s	
								R_2, R_4, R_3	9	1.05	s	

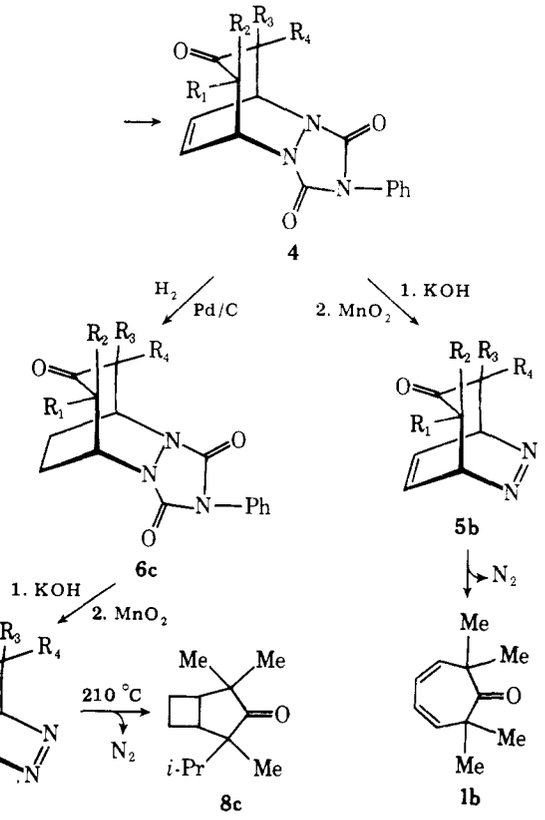
[a] Satisfactory elemental analysis. [b] $J_{H_a(H_d)} - J_{R_1(R_2)} = 3.44$ Hz, $J_{R_1} - J_{R_2} = -17.23$ Hz. [c] Refer to structure **4a** for the assignments of the distinct protons. [d] Refer to structure **6c** for the assignments of the distinct protons. [e] Collected by VPC on a 3-ft column packed with 10% SE 30 on Chromosorb P, column temperature 120 °C, gas flow 35 mL/min.



Scheme I



1a, R_1, R_2, R_3, R_4 = H
b, R_1, R_2, R_3, R_4 = Me
c, R_1 = *i*-Pr; R_2, R_3, R_4 = Me
d, R_1 = *t*-Bu; R_2, R_3, R_4 = Me



rests on satisfactory elemental analyses and H-NMR and IR spectral data.

In addition, the following chemical transformations were performed on the 3,5-adduct. KOH-catalyzed hydrolysis of adduct **4b** (R_1 = R_2 = R_3 = R_4 = Me) followed by MnO_2 oxidation led to the initial 3,5-cycloheptadien-1-one **1b** in 66% yield. The intermediary bicyclic azoderivative **5b** was too unstable for isolation and lost nitrogen in situ to afford **1b**. On the other hand, catalytic hydrogenation of the 3,5-adduct **4c** over Pd/C led to the saturated adduct **6c** in 92% yield (cf. Table I). KOH-catalyzed hydrolysis and MnO_2 oxidation gave the bicyclic azo derivative **7c** in 54% yield (cf. Table I) as waxy solid. On heating at 210 °C, **7c** smoothly lost nitrogen affording the bicyclic ketone **8c** in 72% yield (cf. Table I).

These results clearly establish the dienic reactivity of the 3,5-cycloheptadien-1-ones **1**; however, potent dienophiles are essential. For example, the substituted derivative **1c** did not react with *N*-phenylmaleimide, while **1a** was reported[2,3] to lead to the isomerized 2,4-adduct **2**.

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Registry No.—**1a**, 1121-65-9; **1b**, 20023-66-9; **1c**, 68782-21-8; **1d**, 68782-22-9; 4-phenyl-1,2,4-triazolin-3,5-dione, 4233-33-4.

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An Improved Synthesis of Diammonium Acetyl Phosphate[1]

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We have described a scheme for using ATP-requiring enzymes as catalysts in large-scale organic synthesis, based on the regeneration of ATP from ADP by phosphorylation with acetyl phosphate (AcP) (eq 1 and 2).[3] We have prepared the

$$\mathrm{AMP} + \mathrm{ATP} \rightleftharpoons 2\mathrm{ADP} \quad (1)$$

$$\mathrm{ADP} + \mathrm{AcP} \rightleftharpoons \mathrm{ATP} + \mathrm{Ac} \quad (2)$$

acetyl phosphate required in this scheme by a synthesis based on acylation of anhydrous phosphoric acid with ketene, followed by reaction with anhydrous ammonia.[4] This procedure had the advantage, compared with previous syntheses, that the acetyl phosphate precipitated from a methanol/ethyl acetate solution at the conclusion of the synthesis as its diammonium salt. This material was easily filtered (unlike the phosphate slimes obtained on precipitation of many acetyl phosphate salts from water) and dried. The procedure had two disadvantages. First, it required a ketene generator. Ketene generation using an apparatus of the type normally found in research laboratories is a relatively slow process, and this equipment is, in any event, not universally available. Second, reaction of the initially produced mixture of acylated phosphoric acids with ammonia was carried out by passing ammonia gas over the rapidly stirred reaction mixture. In practice, close attention to detail was required to achieve good yields with this procedure, presumably because the reaction was both rapid and heterogeneous and because acetyl phosphate itself reacts with excess ammonia. Here we describe a modified procedure for the preparation of diammonium acetyl phosphate which differs in two respects from that described earlier: first, acetic anhydride is used as acylating agent rather than ketene; second, reaction of the mixture of acetylphosphoric acids is accomplished by adding this mixture to a saturated *solution* of ammonia in methanol (eq 3). This procedure is much more easily carried out than that based on ketene and is more reproducible when applied to large preparations. It differs from previous preparations employing acetic anhydride as acylating agent in using anhydrous phosphoric acid rather than triethylammonium phosphate as the starting

$$1.8\mathrm{CH_3COCCH_3} + \mathrm{H_3PO_4} \xrightarrow[3.7\ \mathrm{h},\ 0\ ^\circ\mathrm{C}]{\mathrm{EtOAc}} \xrightarrow[-30\ \mathrm{to}\ -10\ ^\circ\mathrm{C}]{\mathrm{NH_3/CH_3OH}} \underset{86\%}{\mathrm{CH_3COP(O^-NH_4^+)_2}} \quad (3)$$

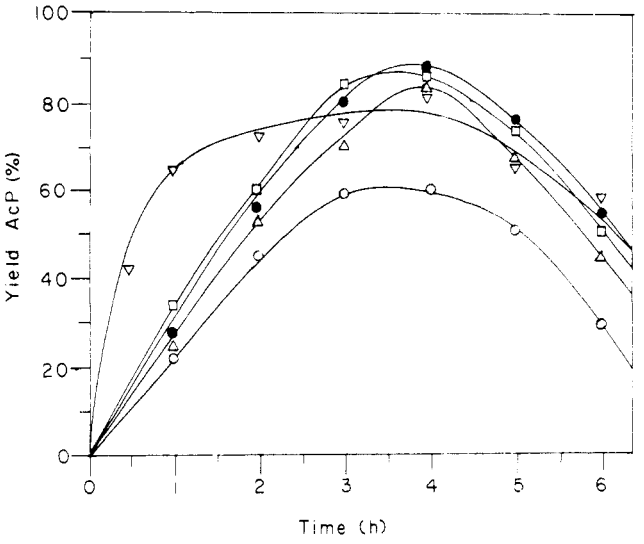

Figure 1. Yields of diammonium acetyl phosphate obtained by acylation of phosphoric acid with acetic anhydride. Reactions were carried out at 0 °C in ethyl acetate, and aliquots of the reaction mixtures were removed and added to methanol saturated with anhydrous ammonia at −10 °C. The molar ratios of acetic anhydride/phosphoric acid used were (○) 1.0, (△) 1.5, (●) 1.8, (□) 2.0, and (▽) 3.0.

material and in the convenience of the workup procedure.[5]

Several experimental variables are important for the success of this new procedure. First, the temperature of the acylation reaction is critical. The best yields were obtained by carrying out the acylation at 0 °C and the reaction with methanolic ammonia at −30 to −10 °C. When the acylation was conducted at −15 °C, yields of acetyl phosphate were low (5%, instead of the 86% observed under optimal conditions); at temperatures higher than 0 °C, the yields also dropped, although less sharply. Second, both the ratio of acetic anhydride/phosphoric acid and the duration of the acylation reaction were important. Figure 1 summarizes data obtained in several variations of these parameters. These plots indicate the fraction of the solid isolated at the end of the reaction, which was diammonium acetyl phosphate, and correspond approximately to the yield of acetyl phosphate; the remainder appeared to be predominantly ammonium phosphates. The best reaction conditions (0 °C, $Ac_2O/H_3PO_4 = 1.8$, $t = 3.7$ h) gave a yield of diammonium acetyl phosphate of 86% based on H_3PO_4; the purity of this material was also 86%.

This acetyl phosphate has been used successfully in our laboratory for enzymatic reactions without further purification. Its storage stability appears to be indistinguishable from that of material obtained using the earlier preparation.[4] In general, ammonium ion is innocuous as a component in enzymatic reactions, although instances are known in which ammonium ion acts as an enzymatic inhibitor.[6] If the ammonium ion should prove undesirable in a particular reaction, it can be exchanged for sodium by ion exchange.[4]

This procedure is the most convenient one available for the preparation of acetyl phosphate, particularly on laboratory scale. For larger scale preparations, however, ketene might still be the preferred acylating reagent for economic reasons. We have examined the applicability of the ammonia treatment described here to the mixture of acylated phosphoric acids prepared from ketene as described previously[4] and found that reaction of this mixture with a solution of ammonia in methanol rather than with ammonia vapor gives yields of acetyl phosphate indistinguishable from that obtained in this work. Since this workup procedure is both more convenient and more reproducible than that described previously,[4] it should be used even when ketene is used as acylating agent.

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