The Alkyl Nitrate Nitration of Active Methylene Compounds. V. The Nitration of Ketones in Liquid Ammonia

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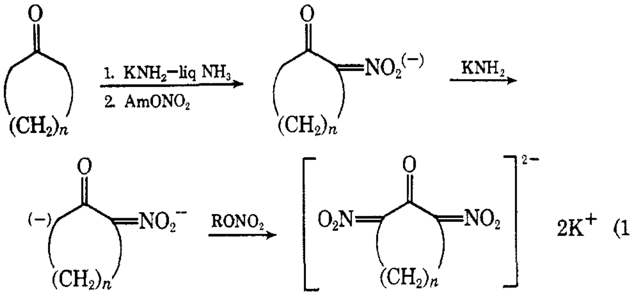
A novel and convenient method for the nitration of active methylene compounds with potassium amide and an alkyl nitrate in liquid ammonia is reported. Under dinitration conditions, cycloalkanones such as cyclopentanone, cyclohexanone, and cycloheptanone are converted into the corresponding dipotassium 2-keto-1,3-cycloalkanedinitronates in yields of 94, 94.5, and 85%, respectively. Under mononitration conditions the reaction with cycloalkanones leads to α-nitrocycloalkanones and to ω-nitrocarboxylic esters, which arise from a fragmentation reaction.

In continuation of our studies of the alkyl nitrate nitration of active methylene compounds, we are now reporting a substantial simplification and improvement over the previously employed method in which nitrations with alkyl nitrates were carried out in a potassium *t*-butoxide–tetrahydrofuran (THF) system (A) at about −50°.[1] The time-consuming preparation of sublimed potassium *t*-butoxide and of anhydrous peroxide-free THF has now been eliminated by performing nitrations in a potassium amide–liquid ammonia system (B) at about −33°.

Dinitration.—In system B, in which the reactions have been observed to be heterogeneous, the nitrations of the C_5–C_7 cycloalkanones gave the corresponding dipotassium 2-keto-1,3-cycloalkanedinitronates in yields which were comparable with or better than those obtained in system A, in which nitrations are usually homogeneous (eq 1).



(1)

3 4

$n = 2–5$

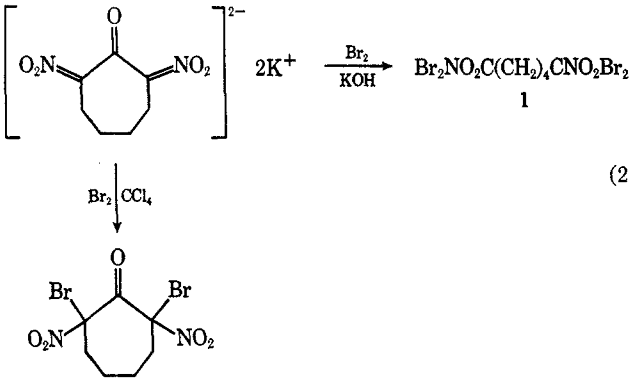
A comparison of the yields obtained in systems A and B are presented in Table I. In the case of cycloheptanone, the amount of dinitration in system A is based on the amount of 1,1,6,6-tetrabromo-1,6-dinitrohexane (**1**) obtained upon brominating the crude nitration product. Attempts to purify the crude salt formed in system A were unsuccessful. On the other hand, the salt obtained in system B could be purified by precipitation from its methanolic solutions with ether. The purity of dipotassium 2-keto-1,3-cycloheptanedinitronate was established by nonaqueous titration[2] and by its nmr spectrum. Aqueous bromination[3] gave compound **1** in 80.5% yield, while anhydrous bromination[4] afforded 2,6-dibromo-2,6-dinitrocycloheptanone in 16% yield (eq 2).

Table I

Alkyl Nitrate Dinitration of Cyclanones in Potassium *t*-Butoxide–THF and Potassium Amide–Liquid Ammonia[a]

	KO-*t*-Bu–THF		KNH_2–NH_3	
Ketone	Bromination product[b] yield, %	Disalt[c] yield, %	Bromination product[b] yield, %	Disalt[c] yield, %
Cyclopentanone	72[d]	98.5	88.8	94.2
Cyclohexanone	53[d]	74.6	51.8[e]	94.5[f]
Cycloheptanone	54[d]		80.5	85.2[g]

[a] Unless otherwise noted 2.0 equiv of base and approximately 2.2 equiv of amyl nitrate were employed. [b] Bromination product is α,α,ω,ω-tetrabromo-α,ω-dinitrohexane. [c] Disalt is dipotassium 2-keto-1,3-cycloalkanedinitronate. [d] See ref 1a and b. [e] This was obtained from the bromination of crude nitration product. The yield is based on starting cyclohexanone. [f] Potassium amide (3.0 equiv) and 3.0 equiv of amyl nitrate were employed. [g] Potassium amide (3.5 equiv) and 3.5 equiv of amyl nitrate were employed.



(2)

To find optimum conditions for dinitration, the influence of reaction temperature, time of anion formation, and concentration of base and alkyl nitrate were studied. The results are summarized in Table II. In the case of cyclopentanone and cyclohexanone, it was found that higher yields were obtained when nitrations were carried out at −33° rather than at −50°. Since the reactions are heterogeneous, these results reflect the faster rate at which anion formation occurs with increasing temperature. Anion formation of these two ketones at −33° was essentially complete in 30 min with 2 equiv of potassium amide. With the less acidic cycloheptanone, 3.5 equiv of base was required. With only 2 equiv of potassium amide and

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[1] For previous publications, see (a) H. Feuer, J. W. Shepherd, and C. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956); (b) H. Feuer and C. Savides, *ibid.*, **81**, 5826 (1959); (c) H. Feuer and B. F. Vincent, Jr., *J. Org. Chem.*, **29**, 939 (1964); (d) H. Feuer and P. M. Pivawer, *ibid.*, **31**, 3152 (1966).

[2] H. Feuer and B. F. Vincent, Jr., *Anal. Chem.*, **35**, 598 (1963).

[3] K. Klager, *J. Org. Chem.*, **20**, 646 (1955).

[4] H. Feuer, J. W. Shepherd, and C. Savides, *J. Amer. Chem. Soc.*, **79**, 5768 (1957).

Table II

Effect of Time of Anion Formation and Base Concentration on the Alkyl Nitrate Nitration of Cyclanones[a]

Ketone	Contact time,[b] hr	Base equiv	Disalt[c] yield, %
Cyclopentanone	0.5[d]	2.0	88.4
Cyclopentanone	0.5	2.0	94.2
Cyclohexanone	0.5[d]	2.0	53.4
Cyclohexanone	0.5	2.0	72.7
Cyclohexanone	2.0	2.0	76.1
Cyclohexanone	0.5	3.0	94.5
Cycloheptanone	0.5	2.0	61.7[e]
Cycloheptanone	2.0	2.0	73.3[e,f]
Cycloheptanone	2.0	2.0	19.3[e,g]
Cycloheptanone	0.5	3.0	72.9
Cycloheptanone	0.5	3.5	85.2

[a] In all cases the ratio of potassium amide to alkyl nitrate was approximately 1 unless noted otherwise. [b] The time at which the ketone and the basic solution were allowed to stir before the nitrate was added. The temperature was −33° unless noted otherwise. [c] Disalt is dipotassium 2-keto-1,3-cycloalkanedinitronate. [d] The reaction temperature was −50°. [e] Yield of dinitronate salt calculated from the amount of 1,6-dinitrohexane obtained from the aqueous acid cleavage of the crude nitration product. The cleavage reaction with pure salt proceeds in 91% yield. [f] A 25.3% yield of α-nitrocycloheptanone was obtained. [g] Amyl nitrate (3.0 equiv) was employed.

2.2 equiv of alkyl nitrate, cycloheptanone was converted into a mixture of dinitro and mononitro salts. To obtain optimum yields, equivalent amounts of base and alkyl nitrate had to be employed.[5]

In the nitration of cyclooctanone with 3.5 equiv of potassium amide and amyl nitrate, a 30% yield of the mononitrated product 2-nitrocyclooctanone (2) was isolated.[6]

The formation of mononitro compounds is a good indication that the dinitration proceeds stepwise. The yield of dinitrated product reflects the acidity of the corresponding α-ketocycloalkanenitronate which is converted by proton removal into a dianion 3 in a step similar to the anion formation of the starting cycloalkanone itself (eq 1).[7]

The result of further nitration of compound 2 in system B supports such conclusions since dinitration occurred to the extent of 28%. The amount of dinitration was established by converting the crude dinitronate salt 4 ($n = 5$) on aqueous bromination into 1,1,7,7-tetrabromo-1,7-dinitroheptane.

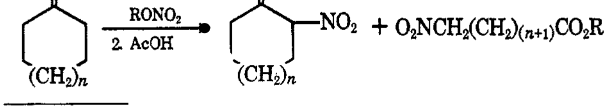
Table III

Comparison of the Results of Mononitration of Ketones in the Potassium Amide–Liquid Ammonia System *vs.* the Potassium *t*-Butoxide–Tetrahydrofuran System

	α-Nitro ketone		ω-Nitrocarboxylic ester	
Ketone	THF[a]	NH_3[b]	THF	NH_3
Cyclopentanone[c]	0	0	10	11
Cyclohexanone[d]	20	59.1	10	2
Cycloheptanone	65	79	4	1
Cyclooctanone	35	60	37	21
Cyclononanone	14	26[e]	60	45.5[e]
Cyclodecanone	14	17[e]	58	49.6[e]
Cyclododecanone	54	64	23	17
Propiophenone	16	29.6	...[f]	...[f]
α-Tetralone	59	71	...	...
4-Heptanone	39	54.5	...[g]	...[h]

[a] Potassium *t*-butoxide (1.65 equiv) and 1.1 equiv of alkyl nitrate in THF at −50° were employed. [b] Potassium amide (1.0 equiv) and 2 equiv of alkyl nitrate at −33° were employed. [c] Dipotassium 2-keto-1,3-cyclopentanedinitronate (19%) was obtained in THF while 29% was obtained in liquid NH_3. The self-condensation product, 2-(1-hydroxycyclopentyl)cyclopentanone, was also obtained but did not exceed 5%. [d] A duplicate run gave 51% α-nitrocyclohexanone and 5% amy 16-nitrohexanoate. [e] These data are taken from the unpublished work of Mr. M. Auerbach. [f] An 8% yield of ethyl benzoate and a 7% yield of benzoic acid were obtained. [g] Two cleavage products, amyl butyrate (25%) and 1-nitropropane (20%), were obtained. (The nitrating agent was amyl nitrate.) [h] Two cleavage products, ethyl butyrate (7.4%) and 1-nitropropane, were obtained. (The nitrating agent was ethyl nitrate.)

Mononitration.—Recently, it was reported[1d] that mononitration of cycloalkanones in system A led not only to α-nitrocycloalkanones but also to ω-nitrocarboxylic esters. In system B, the results have been found to be qualitatively similar (eq 3). However, as shown in Table III, in system B, the over-all amount of nitration was increased, and the amount of cleavage product was decreased. A limited study of reaction parameters indicated that a 2:1 ratio of nitrating agent to base was essential to obtain high yields for mononitration (see Table IV).



(3)

Table IV

Effect of Alkyl Nitrate to Base Ratio on the Mononitration of Cycloalkanones in System B

Ketone[a]	Base equiv	Alkyl nitrate equiv	α-Nitro ketone yield, %
Cycloheptanone	1	1.1	62
Cycloheptanone	2	1.1	3
Cycloheptanone	1	2.0	79
Cyclooctanone	1	1.1	54
Cyclooctanone	1	2.0	60

[a] In all experiments the ketone was stirred for 2 hr at −33° in the basic solution before the nitrate was added.

The application of this novel and convenient method to the nitration of other active methylene compounds is currently under investigation.[8]

Experimental Section

Equipment.—All infrared spectra were taken with a Perkin-Elmer recording spectrophotometer, Models 21 or 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrophotometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A-903 using a 4-ft SF-96 on Chromosorb W column and an Autoprep A-700 using a 10-ft SF-96 on Chromosorb column. Solvents were evaporated on a Rinco rotating evaporator.

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(5) In a control test, it was found that in system B at −33° alkyl nitrates were converted by potassium amide into the corresponding alkoxides. This

$$RONO_2 \xrightarrow{KNH_2} RO^- \xrightarrow{H^+} ROH$$

was not the case in system A even at temperatures as high as 0°.[1d]

(6) In system A, a 57% yield of compound 2 was obtained: unpublished results from the Ph.D. thesis of R. S. Anderson, Purdue University.

(7) For a more detailed discussion of the mechanism of the alkyl nitrate nitration, see ref 1b and d.

(8) In system B, adiponitrile and capronitrile are converted into dipotassium 1,4-dicyano-1,4-butanedinitronate and potassium 1-cyanopentanenitronate in yields of 80 and 67%, respectively (results obtained by M. Auerbach). In system A, the yields of these salts were, respectively, 93 and 55%.[1b]

Materials.—Ammonia was employed as received in pressure cylinders from the Matheson Co. Amyl nitrate, a generous gift from the Ethyl Corp., consisted of a mixture of *n*-amyl and isoamyl nitrate.

Dinitration of Ketones.—The following experiment is typical of the procedure employed. A solution of potassium amide (0.1 mol) was prepared by adding potassium (4.03 g, 0.10 g-atom) to 200 ml of liquid ammonia at −33°.[9] Dropwise addition of cyclopentanone (4.32 g, 0.05 mol) in 15 min and stirring for 30 min gave a white precipitate which became green when amyl nitrate (15.07 g, 0.11 mol) was added dropwise over 10 min.[10] Then the mixture was stirred for 30 min at −33°, 100 ml of anhydrous ether was added, and the ammonia was allowed to evaporate. Filtering and drying *in vacuo* gave 12.91 g of crude green dinitronate salt.

Dissolving 7.95 g of salt in a minimum amount of water followed by the dropwise addition of methanol gave, after filtering and drying *in vacuo*, 7.48 g (94.2% yield) of dipotassium 2-keto-1,3-cyclopentanedinitronate: explosion point 252° (lit.[1a] explosion point 259–261°); neut[2] equiv found 126, calcd 125; ir (Nujol), 1645 (C=O), 1661 (C=N), and 1220 and 1400 cm^{-1} ($C{=}NO_2^-$); nmr (D_2O), δ 2.73 (s, CH_2); uv max (90% C_2H_5OH), 216 mμ (log ϵ 3.67), 251 (3.57), 361 (3.97), and 4.13 (4.10); (H_2O), 223 mμ (log ϵ 3.60), 250 (3.56), and 401 (4.31).

Dipotassium 2-keto-1,3-cyclohexanedinitronate was obtained in 94% yield: explosion point 261°; neut[2] equiv found 131, calcd 132; ir (Nujol), 1653 (C=O), 1664 (C=N), and 1220 and 1160 cm^{-1} ($C{=}NO_2^-$); nmr (D_2O), δ 2.70 (t, β-CH_2) and 1.75 (m, γ-CH_2); uv max (90% C_2H_5OH), 214 mμ (log ϵ 3.52), 267 (3.60), and 424 (4.43); (H_2O), 231 mμ (log ϵ 3.87) and 386 (4.22). The salt was purified by dissolving the crude salt in an equal volume of water and methanol followed by precipitation with acetone.

Dipotassium 2-Keto-1,3-cycloheptanedinitronate.—The nitration procedure was similar to that described for cyclopentanone except that potassium (8.70 g, 0.22 g-atom), cycloheptanone (7.15 g, 0.06 mol), and amyl nitrate (30.0 g, 0.226 mol) were employed.

Dissolving the crude nitration product in 400 ml of methanol and precipitating with ether gave 15.1 g (85% yield) of dinitronate salt. An analytical sample of **dipotassium 2-keto-1,3-cycloheptanedinitronate** was obtained after five precipitations: mp 180–190° dec; ir (Nujol), 1600 (C=O) and 1225 and 1126 cm^{-1} ($C{=}NO_2^-$); nmr (D_2O), δ 2.66 (m, β-CH_2) and 1.67 (m, γ-CH_2); uv (90% EtOH), 212 mμ (log ϵ 3.75), 227 (3.50), and 343 (4.01); (H_2O), 220 mμ (log ϵ 3.72) and 343 (3.89).

Anal. Calcd for $C_7H_8N_2O_5K_2$: C, 30.22; H, 2.88; N, 10.08; K, 28.13; neut equiv, 139. Found: C, 29.45; H, 3.13; N, 10.13; K, 27.89; neut equiv, 139.

1,6-Dinitrohexane.—To a solution of 1.61 g (5.79 mmol) of dipotassium 2-keto-1,3-cycloheptanedinitronate (neut equiv 139) and 50 ml of water (pH 8.4—standardized Beckman Zeromatic pH meter) was added 1.57 g (12.8 mmol) of picolinic acid so that the pH of the solution was 5.8. After stirring an additional 12 hr at room temperature, the pH was 5.8. Extracting the solution with three 50-ml portions of ether, evaporating the combined extracts *in vacuo*, and recrystallizing from 95% ethanol gave 0.919 g (90.9% yield) of 1,6-dinitrohexane, mp 38–39° (lit.[11] mp 38–39°).

1,1,6,6-Tetrabromo-1,6-dinitrohexane (1).—A brominating solution was prepared by adding 4.28 g (26.6 mmol) of bromine to a solution of 6.41 g of 87% assay potassium hydroxide in 25 ml of water at −5°. To the solution was added dropwise dipotassium 2-keto-1,3-cycloheptanedinitronate (1.68 g, 6.05 mmol) dissolved in 20 ml of water at such a rate that the temperature did not exceed −5°. Then allowing the reaction mixture to stir 1 hr at 0° and 1 hr at ambient temperatures gave, after filtering and drying, 2.39 g (80.55%) of 1,1,6,6-tetrabromo-1,6-dinitrohexane, mp 85–86° (lit.[1a] mp 85–86°).

2,6-Dibromo-2,6-dinitrocycloheptanone.—To a stirred suspension of dipotassium 2-keto-1,3-cycloheptanedinitronate (6.09 g, 21.9 mmol) in 100 ml of carbon tetrachloride was added dropwise at ambient temperatures bromine (6.92 g, 43.2 mmol) in 25 ml of carbon tetrachloride. After the mixture was let stir for 1 hr, filtering, evaporating the solvent *in vacuo*, and recrystallizing the residue from isopropyl alcohol gave 1.28 g (16.5%) of **2,6-dibromo-2,6-dinitrocycloheptanone**: mp 109–110°; ir (KBr), 1740 (C=O) and 1575 and 1320 cm^{-1} (NO_2); nmr ($CDCl_3$), δ 2.6–3.2 (m, β-CH_2), and 2.0–2.5 (m, γ- and δ-CH_2).

Anal. Calcd for $C_7H_8N_2O_5Br_2$: C, 23.35; H, 2.24; N, 7.78; Br, 44.44. Found: C, 23.58; H, 2.46; N, 7.77; Br, 45.01.

Dipotassium 2-Keto-1,3-cyclooctanedinitronate. A. From Cyclooctanone.—The nitration procedure was similar to that described for cyclopentanone except that potassium (7.45 g, 0.190 g-atom), cyclooctanone (6.85 g, 0.05 mol), and amyl nitrate (20.0 g, 0.195 mol) were used.

Aqueous bromination of the crude nitration product as described in the preparation of compound 1 gave a 25% yield of 1,1,7,7-tetrabromo-1,7-dinitroheptane, mp 34–35° (lit.[1a] mp 35–36°).

Isolation of 2-Nitrocyclooctanone (2).—Stirring 14.83 g of dry crude nitration product in 100 ml of ether and 14.4 g of glacial acetic acid for 24 hr at ambient temperatures, filtering, and concentrating the ether layer *in vacuo* gave 1.85 g (30.2% yield) of 2-nitrocyclooctanone: bp 75–80° (0.03 mm); $n^{20}D$ 1.5032 (lit.[1d] $n^{20}D$ 1.5038).

B. From Compound 2.—The nitration procedure was similar to that described for cyclopentanone except that potassium (3.76 g, 0.096 g-atom), compound 2 (8.22 g, 0.048 mol), and amyl nitrate (14.07 g, 0.106 mol) were used.

Aqueous bromination of the crude nitration product as described in the preparation of compound 1 gave a 28.2% yield of 1,1,7,7-tetrabromo-1,7-dinitroheptane.

Acidification of the nitration product and work-up as described in part A led to a 55% recovery of compound 2.

Mononitration of Ketones.—The following experiment is typical of the procedure employed. Cycloheptanone (12.9 g, 0.115 mol) was added dropwise over 10 min to a solution of 0.115 mol of potassium amide (prepared from 4.5 g of potassium in the presence of ferric nitrate decahydrate) in 300 ml of liquid ammonia at −33°. After the mixture stirred for 2 hr, amyl nitrate (26.7 g, 0.21 mol) was added dropwise over 10 min at −45°. The mixture was stirred for 30 min at −33°, 100 ml of anhydrous ether was added, and the ammonia was allowed to evaporate in a stream of nitrogen. After the mixture was recooled to 0°, glacial acetic acid (23.1 g, 0.384 mol) was added, and stirring was continued at 0° for 12 hr. Filtering and distilling the residual oil at 0.2 mm gave 14.2 g (79%) of 2-nitrocycloheptanone, bp 100–105°, and 0.32 g (1.1%) amyl 7-nitroheptanoates, bp 120°. About 7% cycloheptanone was present in the Dry Ice trap as determined by glpc.

On cooling, 2-nitrocycloheptanone solidified and, after recrystallizing from isopropyl alcohol, had mp 38–38.5° (lit.[1d] mp 37.5–38°).

Reaction of Potassium Amide with Amyl Nitrate in Liquid Ammonia.—Amyl nitrate (14.63 g, 0.11 mol) was added dropwise to a solution of potassium amide (0.1 mol) (prepared from 4.03 g of potassium in the presence of ferric nitrate decahydrate) in 300 ml of liquid ammonia at −33°. The mixture was stirred 30 min and acidified with ammonium chloride (8.5 g, 0.14 mol) at −33°. Then anhydrous ether was added while the ammonia was allowed to evaporate slowly. Filtering the reaction mixture and distilling the filtrate at 0.6 mm gave 5.91 g (40%) of recovered amyl nitrate and 4.78 g (49.5%) of isomeric amyl alcohols.[12] The identity of the compounds was established by glpc comparison of retention times with those of authentic samples.

Registry No.—Ammonia, 7664-41-7; dipotassium 2-keto-1,3-cyclopentanedinitronate, 12286-73-6; dipotassium 2-keto-1,3-cyclohexanedinitronate, 12286-74-7; dipotassium 2-keto-1,3-cycloheptanedinitronate, 12286-75-8; 2,6-dibromo-2,6-dinitrocycloheptanone, 17202-33-4.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of the work.

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[9] C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

[10] *Caution!* The first few drops of alkyl nitrate *must* be added *slowly* because a considerable exotherm might develop.

[11] H. Feuer and G. Leston, *Org. Syn.*, **34**, 37 (1954).

[12] A mixture of isomeric alcohols was obtained because amyl nitrate consisted of a mixture of *n*-amyl and isoamyl nitrate.