androstene-3β,16α-diol (IIb) was hydrolyzed with hydrochloric acid in methanol to give 280 mg of ketol IIIb after recrystallization from aqueous methanol. One more crystallization brought the melting point to 177–180° (lit.[18] 177–181°). Its infrared spectrum shows absorption bands at 3400 (OH) and 1750 cm^{-1} (C=O).

3β,16α-Diacetoxy-5-androsten-17-one (IIIc).—Acetylation of ketol IIIb with acetic anhydride and pyridine at room temperature over night yielded IIIc, mp 167–168° (lit.[18] 166–168°).

Isomerization of Ketol IIIb to Ketol IVb.—A solution of 40 mg of 5-androstene-3β,16α-diol-17-one (IIIb) in 25 ml of aqueous methanol containing 150 mg of potassium hydroxide was let stand for 10 hr at room temperature. The mixture was poured into water, extracted with ether, washed, and dried to yield crude product (35 mg). Crystallization from aqueous ethanol gave ketol IVb. Its infrared spectrum and melting point were identical with those of an authentic sample prepared according to Stodola, *et al.*[19]

5-Androsten-3β-ol-16,17-dione Bisphenylhydrazone (Vb). From Ketol IIIb or IVb.—Following the procedure for V there was prepared the osazone Vb from 3β,16α-dihydroxy-5-androsten-17-one (IIIb) or from 3β,17β-dihydroxy-5-androsten-16-one (IVb). Recrystallization from ethanol water brought yellow crystals, mp 233–237°.

The infrared spectrum of this material was identical with that of the bisphenylhydrazone prepared from bromo ketone Ib.[18]

Attempted Reaction of 2α-Bromo-3-cholestanone with Methoxide.—2α-Bromo-3-cholestanone (1 g) was added to a solution of sodium methoxide prepared from 2 g of sodium and 100 ml of methanol. The mixture was heated under reflux for 45 min. Then it was poured into ice–water and worked up as for IIb. The crude product was obtained as an oily solid (850 mg), which resisted attempts of purification by chromatography or crystallization. The infrared spectrum of this compound indicated the presence of hydroxyl at 3500 and carbonyl at 1730 cm^{-1}. The nmr spectrum indicated that methoxy groups were absent. The same product mixture was obtained by heating the bromo ketone with potassium hydroxide in methanol.

Acknowledgment.—This investigation was supported by U. S. Public Health Service Grant CA-04474 from the National Cancer Institute. One of us (A. H.) also wishes to thank the Council on Research and Creative Work, University of Colorado, for a Faculty Fellowship.

(18) K. Fotherby, A. Colas, S. Atherden, and G. Marrian, *Biochem. J.*, **66**, 664 (1957).

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The Alkyl Nitration of Active Methylene Compounds. IV. The Mononitration of Ketones

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The mononitration of cycloalkanones with alkyl nitrates in the presence of potassium *t*-butoxide affords not only α-nitrocycloalkanones (A) but also ω-nitrocarboxylic esters (B). The latter arise from a fragmentation reaction which occurs (except in the case of cyclopentanone) during the nitration step and not during subsequent acidification, but cleavage is not caused by direct alkoxide attack except in the case where the resulting nitro ketone is tertiary. The relative amounts of compounds A and B formed vary with ring size, the fragmentation being most pronounced in the "middle ring region" and with α,α′-disubstituted cycloalkanones. Fragmentation also takes place with aliphatic and aryl alkyl ketones. Infrared, nmr, and ultraviolet spectra of α-nitrocyclanones and their potassium salts are reported. Spectral data of the six-, eight-, and ten-membered α-nitrocycloalkanones indicate a high degree of enolization.

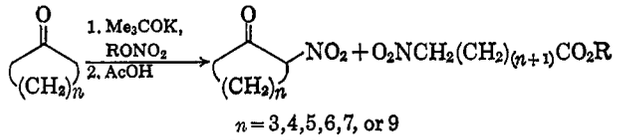
In continuation of our studies of the alkyl nitrate nitration of active methylene compounds,[2] we are now reporting on its application to the preparation of α-mononitro ketones.

Other general methods which have been employed for preparing α-nitro ketones are oxidation of the appropriate nitro alcohols[3] and the reaction between acyl cyanides and alkanenitronates, and of enol acetates or enol ethers with nitryl chloride.[4]

Attempts by Wieland and co-workers to prepare α-nitrocyclopentanone by treating cyclopentanone with ethyl nitrate in the presence of potassium ethoxide led only to the formation of dipotassium 2-ketocyclopentane-1,3-dinitronate; however, with cyclohexanone a low yield of 2-nitrocyclohexanone was obtained in addition to the dinitro compound.[5]

It has now been found that the procedure which led to high yields in the dinitration of ketones[2a] can be readily adapted to their mononitration by employing equivalent amounts of nitrate ester and ketone and a 50% excess of sublimed potassium *t*-butoxide in tetrahydrofuran (THF), and by acidifying the reaction mixture with glacial acetic acid prior to work-up.

However, the reaction did not only lead to α-nitro ketones but also to cleavage products which in the case of cyclic ketones were identified as ω-nitro carboxylic esters. Since it became apparent that the



amount of cleavage reaction was dependent on the structure of the starting ketone, a number of ketones were nitrated and the results are summarized in Table I.

(1) Dow Chemical Corp. Fellow, 1963–1964.

(2) For previous publications, see (a) H. Feuer, J. W. Shepherd, and C. Savides, *J. Am. 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).

(3) N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1103 (1946); L. Canonica and C. Cardani, *Gazz. Chim. Ital.*, **79**, 262 (1949); D. Hurd and M. E. Nilson, *J. Org. Chem.*, **20**, 927 (1959).

(4) G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4884 (1959); G. B. Bachman and T. Hokama, *J. Org. Chem.*, **25**, 179 (1960).

(5) H. Wieland, P. Garbsch and J. J. Chavan, *Ann.*, **461**, 295 (1928). Recently, A. A. Griswold and P. S. Starcher [*J. Org. Chem.*, **31**, 357 (1966)] reported the preparation of 2-nitrocyclohexanone in 40% yield from 1-cyclohexenol acetate and acetyl nitrate.

TABLE I

ALKYL NITRATE NITRATION OF KETONES

Ketone[a]	α-Nitro ketone yield, %	ω-Nitroalkyl ester yield, %
Cyclopentanone	0[b]	10
2,2,4-Trimethylcyclopentanone	82	trace
2,2,5-Trimethylcyclopentanone[c]	0	53
2,5-Dimethylcyclopentanone[c]	10	58
Cyclohexanone	20[d]	10
Cycloheptanone	65	4
Cyclooctanone	35, 25,[e] 3[f]	37, 20,[e] 2[f]
Cyclononanone	14	60
Cyclodecanone	14	58
Cyclododecanone	54	23
4-Heptanone	39	0[g]
2,4-Dimethyl-3-pentanone[c]	0	0[h]
α-Tetralone[c]	59	0
Propiophenone[c]	16	0[i]

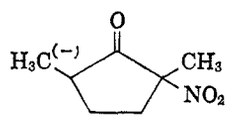
[a] Nitrations were carried out in the presence of potassium *t*-butoxide in THF at −50° with ethyl, *n*-propyl, or amyl nitrate except where noted. The amyl nitrate consisted of a mixture of *n*-amyl and isoemyl nitrate. About 10% of the starting ketone was recovered unless stated otherwise. [b] A 20% yield of dipotassium 2-ketocyclopentane-1,3-dinitronate and an 18% yield of aldol condensation product 2-(1′-hydroxycyclopentyl)cyclopentanone were obtained. [c] 40% 2,2,5-trimethylcyclopentanone, 21% 2,5-dimethylcyclopentanone, 16% 2,4-dimethyl-3-pentanone, 34% α-tetralone, and 59% propiophenone were recovered. [d] An 18% yield of potassium 2-keto-3-nitrocyclohexanenitronate and an 18% yield of aldol condensation product 2-(1′-hydroxycyclohexyl)cyclohexanone were obtained. [e] Nitration was carried out with isopropyl nitrate. [f] Nitration was carried out with *t*-butyl nitrate. [g] Two cleavage products, amyl butyrate (25%) and 1-nitropropane (20%) were obtained. [h] Two cleavage products, amyl isobutyrate (84%) and 2-nitropropane (66%) were obtained. [i] Ethyl benzoate (8%) and benzoic acid (7%) were obtained.

The α-nitro ketones and ω-nitro carboxylic esters were identified by their physical properties, correct elemental analyses, and where possible by conversion to suitable derivatives which gave correct elemental analyses; the data are summarized in Tables II, III, and IV.

Cyclic Ketones.—Nitration of cyclopentanone afforded mainly dipotassium 2-ketocyclopentane-1,3-dinitronate and the aldol condensation product, 2-(1′-hydroxycyclopentyl)cyclopentanone. Although no 2-nitrocyclopentanone was obtained, the presence of amyl 5-nitropentanoate indicated that some mononitration had taken place. Since no mononitro ketone was obtained in this reaction, it was of interest to nitrate a cyclopentanone which had one of the α positions blocked. Nitration of 2,2,4-trimethylcyclopentanone (I) gave an 82% yield of 2-nitro-3,5,5-trimethylcyclopentanone. In order to determine the course of the reaction with ketones having substituents in both α positions, 2,2,5-trimethylcyclopentanone (II) and 2,5-dimethylcyclopentanone (III) were nitrated. The results, which are summarized in Table I, show clearly that cleavage predominated with those ketones which cannot form nitro ketone salts.

The importance of salt formation can be readily seen by comparing the results from the nitration of I with those of II. In both ketones the α-methyl groups should offer steric hindrance to attack at the carbonyl group; however, with II where a tertiary nitro ketone was formed cleavage was the predominant reaction, whereas with I almost no cleavage occurred.

One unusual feature of the nitration of ketones II and III was that the more sterically hindered ketone II afforded only cleavage product while the less sterically hindered III gave about 10% nitro ketone. The reason for this difference might be that, after the initial nitration of III, proton abstraction competed with the cleavage reaction to give the anion IIIa which was stabilized to further attack at the carbonyl group.



IIIa

Nitration of cyclohexanone yielded potassium 2-keto-3-nitrocyclohexanenitronate (IV), 2-nitrocyclohexanone, amyl 6-nitrohexanoate, and the aldol condensation product, 2-(1′-hydroxycyclohexyl)cyclohexanone. With an increase in base concentration from 50 to 150%, aldol condensation was eliminated; however, dinitration predominated and an 87% yield of IV was obtained.

Nitration of cycloheptanone gave predominantly 2-nitrocycloheptanone but with the higher ring homolog cyclooctanone (V) equal amounts of 2-nitrocyclooctanone[6] (VI) and isomeric amyl 8-nitrooctanoates (VIII) were obtained.[7] With cyclononanone and cyclodecanone, cleavage predominated, probably owing to ring geometry, while, with the less strained cyclododecanone, 2-nitrocyclododecanone was again the major product.

Aliphatic and Aryl Alkyl Ketones.—The monitration of 4-heptanone afforded in addition to 3-nitro-4-heptanone, two cleavage products, amyl butyrate and 1-nitropropane. 2,4-Dimethyl-3-pentanone, a compound that could not lead to an α-nitro ketone salt, gave only cleavage products, amyl isobutyrate and 2-nitropropane.

Nitration of α-tetralone and propiophenone proceeded more slowly than with the other ketones, and, even though nitration of these ketones was carried out at higher temperatures (−30°) and for longer reaction times, large amounts of starting materials were recovered. It should also be noted that α-tetralone was the only ketone that did not undergo the cleavage reaction.

Study of the Cleavage Reaction.—There are two references in the literature in which cleavage reactions were reported to occur during the alkyl nitrate nitration. Wislicenus[8] found that the nitration of ethyl α-phenylacetate with ethyl nitrate gave potassium phenylmethanenitronate and ethyl carbonate; while the nitration of α-(*p*-mercaptotolyl acetophenone gave rise to two nitro compounds, α-(*p*-mercaptotolyl)-α-nitroacetophenone and (*p*-mercaptotolyl)nitromethane.[9] Since very little information was available about this fragmentation reaction, the course of the reaction was studied.

In the typical alkyl nitrate nitration, the alkyl nitrate is added to a mixture of ketone and base at

(6) Prepared and characterized by R. S. Anderson, Ph.D. thesis, Purdue University, 1960.

(7) A mixture of isomeric esters was obtained because the nitrating agent consisted of a mixture of *n*-amyl and isoamyl nitrate.

(8) W. Wislicenus and R. Grützner, *Ber.*, **42**, 1930 (1909).

(9) F. Arndt and J. D. Rose, *J. Chem. Soc.*, 1 (1935).

TABLE II

PHYSICAL PROPERTIES OF α-NITRO KETONES

α-Nitro ketone	Mp[a] or bp, °C (mm)	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2-Nitrocyclohexanone[b]	39.5–40.5		...		...			...	
2-Nitrocycloheptanone	37.5–38.0		$C_7H_{11}NO_3$	53.49	7.05	8.91	53.75	7.21	8.86
2-Nitrocyclooctanone[c]	73–74 (0.25)	1.5038	$C_8H_{13}NO_3$	56.12	7.65	8.18	56.05	7.57	8.19
2-Nitrocyclononanone	59–62 (0.1)	1.4990	$C_9H_{15}NO_3$	58.38	8.11	7.57	58.20	7.82	7.58
2-Nitrcyclodecanone	70–72 (0.1)	1.5191	$C_{10}H_{17}NO_3$	60.30	8.54	7.04	60.94	8.66	7.31
2-Nitrocyclododecanone	78–79.5		$C_{12}H_{21}NO_3$	63.45	9.25	6.17	63.45	9.35	6.42
2-Nitro-3,5,5-trimethylcyclopentanone	55–56		$C_8H_{13}NO_3$	56.12	7.65	8.18	55.98	7.79	8.27
2-Nitro-2,5-dimethylcyclopentanone[d]	45–46 (0.15)	1.4571	$C_7H_{11}NO_3$	53.49	7.05	8.91	54.88	7.71	8.22
3-Nitro-4-heptanone	72–75 (3.0)	1.4395	$C_7H_{13}NO_3$	52.83	8.17	8.80	53.00	8.09	8.82
2-Nitro-1-tetralone	72–73		$C_{10}H_9NO_3$	62.92	4.74	7.30	63.02	4.90	7.40
2-Nitro-1-propiophenone[e]	122 (0.7)	1.5432	...		...			...	

[a] Solid nitro ketones were recrystallized from 2-propanol. [b] Prepared by H. Wieland, *et al.*[5] [c] Prepared by R. S. Anderson.[6] [d] This nitro ketone could not be purified for a satisfactory elemental analysis. The structure was confirmed by its conversion to methyl 2-methyl-5-nitrohexanoate with sodium methoxide (*vide infra*, Table IV). [e] Prepared by G. B. Bachman and T. Hokama.[4]

TABLE III

PHYSICAL PROPERTIES OF α-NITRO KETONE DERIVATIVES

Derivative	Mp,[a] °C	Infrared spectra,[b] C=O	Infrared spectra,[b] C=NO_2^-	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % K	Found, % C	Found, % H	Found, % N	Found, % K
K 2-Ketocyclohexanenitronate	212–223	1608	1592	$C_6H_8NO_3K$	39.78	4.42	7.73	21.55	40.00	4.41	7.64	21.16
K 2-Ketocycloheptanenitronate	217–219	1666	1663	$C_7H_{10}NO_3K$	43.08	5.13	7.17	20.00	42.84	5.35	7.11	20.15
2-Nitrocycloheptanone-2,4-DNP	173–174	...	...	$C_{13}H_{15}N_5O_6$	46.29	4.45	20.77	...	46.45	4.28	20.84	...
K 2-Ketocyclooctanenitronate	202–205	1618	1600	$C_8H_{12}NO_3K$	45.93	5.74	6.70	18.66	45.33	5.97	6.74	19.10
2-Nitrocyclooctanone-2,4-DNP[c]	135–135.5	...	...	$C_{14}H_{17}N_5O_6$	47.86	4.88	19.48	...	47.55	5.03	19.36	...
2-Bromo-2-nitrocyclooctanone[c]	42–43	...	...	$C_8H_{12}BrNO_3$	38.42	4.84	5.60	[d]	38.29	4.89	5.33	[d]
K 2-Ketocyclononanenitronate	214–216	1639	1613	$C_9H_{14}NO_3K$	48.43	6.25	6.25	17.49	48.48	6.56	6.75	16.88
K 2-Ketocyclodecanenitronate	224–228	1613	1592	$C_{10}H_{16}NO_3K$	50.63	6.75	5.91	16.46	50.92	7.06	6.09	16.08
2-Nitrocyclodecanone-2,4-DNP	135–136	...	...	$C_{16}H_{21}N_5O_6$	50.66	5.54	18.47	...	50.86	5.71	18.42	...
2-Nitrocyclododecanone-2,4-DNP	197–198	...	...	$C_{18}H_{25}N_5O_6$	53.41	6.10	17.07	...	53.08	6.20	17.26	...
K 2-Keto-3,3,5-trimethylcyclopentanenitronate	228–231	1666	1639	$C_8H_{12}NO_3K$	45.93	5.74	6.70	18.66	46.28	6.00	6.57	18.93
3-Nitro-4-heptanonesemicarbazone	128–128.5	...	...	$C_8H_{16}N_4O_3$	44.44	7.41	25.92	...	44.41	7.44	25.82	...

[a] The nitronates melted with decomposition. [b] In Nujol mull. [c] Prepared by R. S. Anderson.[6] [d] Calcd for bromine, 31.95%. Found for bromine, 31.20%.

TABLE IV

PHYSICAL PROPERTIES OF ω-NITROCARBOXYLIC ESTERS[a]

ω-Nitrocarboxylic ester	Bp °C, (mm)	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ethyl 5-nitropentanoate	77–82 (0.8)	1.4398	$C_7H_{13}NO_4$	48.00	7.43	8.00	48.30	7.32	8.08
Methyl 6-nitrohexanoate		1.4429	$C_7H_{13}NO_4$	48.00	7.43	8.00	48.27	7.43	8.16
Ethyl 6-nitrohexanoate		1.4419	$C_8H_{15}NO_4$	50.79	7.94	7.41	50.90	8.05	7.69
Methyl 7-nitroheptanoate		1.4454	$C_8H_{15}NO_4$	50.79	7.94	7.41	51.09	8.23	7.32
Ethyl 8-nitrooctanoate	100–105 (0.6)	1.4445	$C_{10}H_{19}NO_4$	55.34	8.76	6.45	55.02	8.94	6.70
Isopropyl 8-nitrooctanoate[b]	92–94 (0.1)	1.4420	$C_{11}H_{21}NO_4$	57.14	9.09	6.06	57.46	9.02	5.86
t-Butyl 8-nitrooctanoate[c]		1.4432	$C_{12}H_{23}NO_4$	58.78	9.39	5.71	58.64	9.59	5.94
Methyl 9-nitrononanoate	87–89 (0.05)	1.4480	$C_{10}H_{19}NO_4$	55.34	8.76	6.45	55.66	8.60	6.67
n-Propyl 10-nitrodecanoate[d]	115–117 (0.1)	1.4484	$C_{13}H_{25}NO_4$	60.23	9.65	5.41	60.47	9.81	5.64
Methyl 12-nitrododecanoate	113–117 (0.1)	1.4522	$C_{13}H_{25}NO_4$	60.23	9.65	5.41	60.48	9.51	5.59
Methyl 2-methyl-5-nitrohexanoate	62–63 (0.15)	1.4385	$C_8H_{15}NO_4$	50.79	7.94	7.41	50.63	8.16	7.15
Methyl 2,2-dimethyl-5-nitrohexanoate		1.4414	$C_9H_{17}NO_4$	53.20	8.37	6.90	53.60	8.57	7.24
Methyl 2,2,4-trimethyl-5-nitropentanoate[e]		1.4448	$C_9H_{17}NO_4$	53.20	8.37	6.90	53.26	8.60	6.74

[a] The methyl or ethyl esters were prepared from the corresponding amyl esters which constituted mixtures of *n*-amyl and isoamyl ester (see ref 7). In the case in which no boiling point is indicated the ester was purified by vpc analysis. [b] Isopropyl nitrate was the nitrating agent. [c] *t*-Butyl nitrate was the nitrating agent. [d] *n*-Propyl nitrate was the nitrating agent. [e] This ester was obtained from the reaction of 2-nitro-3,5,5-trimethylcyclopentanone with acetic acid and methanol.

−50° and this is followed by acidification with glacial acetic acid at 0°. It appeared that fragmentation could have taken place either during the nitration or the subsequent acidification step.

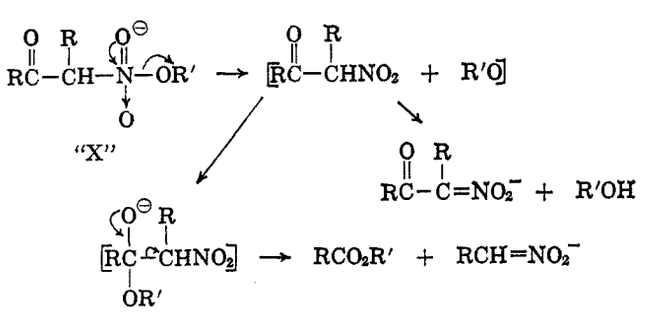
The possibility that cleavage occurred during acidification was easily ruled out by the following experiments.

(1) Subjecting the reaction mixture from the nitration of 4-heptanone with ethyl nitrate to vpc analysis *prior* to acidification showed the presence of ethyl butyrate, one of the expected fragmentation products. Moreover, the ester was readily obtained on distilling the reaction mixture *in vacuo*[10] at 0°. After acidification of the residue, the other cleavage product 1-nitropropane was obtained along with 3-nitro-4-heptanone.

$$(CH_3CH_2CH_2)_2CO \xrightarrow[Me_3COK]{EtONO_2} H_3C(CH_2)_2CO_2C_2H_5 + \text{"nitro salts"} \xrightarrow{HOAc} H_3CCH_2CH(NO_2)CO(CH_2)_2CH_3 + H_3C(CH_2)_2NO_2$$

(2) On nitration of cyclohexanone with amyl nitrate, addition of absolute ethanol to the reaction mixture at 0° *after* addition of glacial acetic acid had no effect on the cleavage reaction because only amyl 6-nitrohexanoate was formed. 2-Nitrocycloheptanone and 2-nitrocyclooctanone (VI) did not undergo cleavage in a refluxing methanolic acetic acid solution, while on similar treatment 2-nitrocyclohexanone and 2-nitro-3,5,5-trimethylcyclopentanone were only slowly converted to the corresponding ω-nitrocarboxylic esters.[11]

A possible reaction path proposed[2b] for the alkyl nitrate nitration involves the nucleophilic attack of a carbanion on the alkyl nitrate to give an intermediate "X" which collapses to a nitro ketone and an alkoxide ion. Further interaction then leads to the formation of the nitro ketone salt. This reaction path suggests that the cleavage reaction might be caused by a direct alkoxide attack on the carbonyl group of the nitro ketone. This mode of attack has been previously suggested to occur during nitrosation of α-alkylated ketones.[12]



Some support for this mechanism was obtained when it was established that addition of ethanol prior to amyl nitrate during the nitration of cyclooctanone (V) resulted in the formation of amyl 8-nitrooctanoate (VII) and ethyl 8-nitrooctanoate (VIII). The results of several experiments showed (see Table V) that with increase in ethanol concentration, both the amount of over-all nitration and the ratio of uncleaved to cleaved products decreased, while the ratio of ethyl ester VIII to amyl ester VII increased.[13]

TABLE V

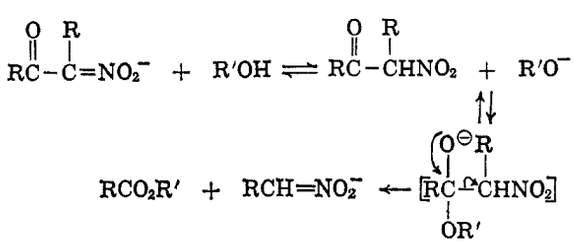
EFFECT OF ETHANOL CONCENTRATION ADDED PRIOR TO AMYL NITRATE ON PRODUCT DISTRIBUTION[a]

Ethanol equiv	Yield, %[b] VI	VII	VIII	VIII/VII	VII + VIII/VI	V
0.5[c]	29	34	16	0.47	1.72	21
1.0	14	29	26	0.90	3.93	31
1.5	10	20	25	1.25	4.50	45
5[d,e]	0	0	0	...	...	100

[a] In all experiments, 0.05 mole of cyclooctanone (V) was added to 0.085 mole of K-*t*-OBu at −50° in THF followed by absolute ethanol and 0.055 mole of amyl nitrate in 30 min; then the reaction mixture was acidified at −50° with 0.25 mole of glacial acetic acid dissolved in THF. [b] Based on vpc analyses. [c] Averages of duplicate experiments. [d] 90% amyl nitrate was recovered and no ethyl nitrate could be discovered. [e] Addition of 5 equiv of absolute ethanol after the amyl nitrate gave 2-nitrocyclooctanone (VI) (37%), amyl 8-nitrooctanoate (VII) (35%), ethyl 8-nitrooctanoate (VIII) (~1%), and V (27%).

However, the following experimental observations strongly suggested that direct alkoxide attack on the nitro ketone was not the mechanism involved in the cleavage: (1) no cleavage products were detected by vpc analysis, when 2-nitrocyclooctanone (VI) dissolved in THF was added at −50° to varying ratios of a potassium *t*-butoxide–potassium ethoxide mixture or when potassium ethoxide in THF was added to VI in THF and the reaction mixtures acidified with glacial acetic acid at 0°; (2) a similar experiment with 3-nitro-4-heptanone gave no evidence of formation of cleavage products; (3) potassium salts of nitro ketones were prepared in high yields by addition of the nitro ketone to an alcoholic potassium hydroxide solution at 0°.

While the results of these experiments exclude a cleavage *via* direct alkoxide attack at the nitro ketone, it is conceivable that the nitro ketone salt would be in equilibrium with the free nitro ketone, which is then cleaved by base.



Pearson, *et al.*,[14] have demonstrated that nitroacetone and ω-nitroacetophenone underwent cleavage in aqueous alkaline solutions and suggested formation of a nitro ketone salt in a prior equilibrium followed by

(10) This experiment was carried out to rule out the possibility that the ester could have arisen from an intermediate which might have decomposed at the high temperature of the vpc injector block.

(11) Subjecting cyclopentanone to the same reaction conditions as cyclohexanone resulted in the formation of both amyl and ethyl 5-nitropentanoates. Perhaps attempts to prepare 2-nitrocyclopentanone have been unsuccessful because of its facile cleavage in the presence of acetic acid and alcohol.

(12) R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.*, **67**, 866 (1943).

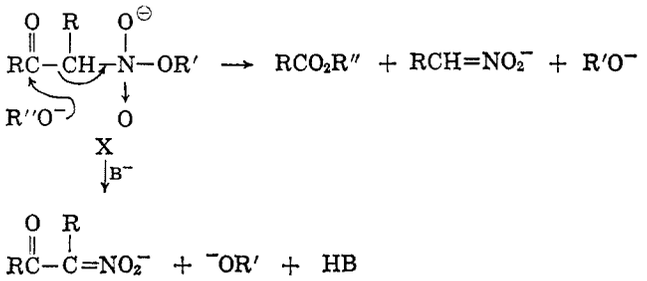
(13) We are indebted to R. W. Jans, Jr., for performing these experiments. Separately we ascertained that no transesterification occurs between ethoxide ion and amyl nitrate even at temperatures as high as 0°.

(14) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Am. Chem. Soc.*, **77**, 527 (1955).

hydroxide attack at the carbonyl in the rate determining step.[15]

However, the following experimental observations indicated that such an equilibrium with subsequent direct alkoxide attack could not account for the cleavage which was found to occur *rapidly* at $-50°$ upon addition of the alkyl nitrate: (1) when in a nitration of cyclooctanone (V) absolute ethanol was added immediately *after* the amyl nitrate, vpc analysis of the reaction mixture after acidification established that only a trace of ethyl 8-nitrooctanoate (VIII) was present while 37% of amyl 8-nitrooctanoate (VII) was obtained; (2) doubling the reaction times in the alkyl nitrate nitrations of cycloheptanone and V did not change the ratio of nitro ketone to cleavage product.

The fragmentation during the alkyl nitrate nitration must occur at a very fast rate, because in spite of addition of ethanol *after* the nitrate ester (amyl nitrate) only amyl ester VII formed. Also, experimental evidence indicates that fragmentation does not proceed *via* prior formation of a nitro ketone. Therefore, a mechanism consistent with all of our experimental observations involves alkoxide attack at the carbonyl group of intermediate X, which may have some stability at $-50°$. The same intermediate could also lead to the nitro ketone salt after abstraction of the



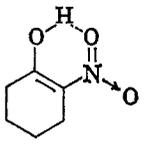
α hydrogen by base, such as potassium *t*-butoxide.[16]

As indicated in Table I, the nitration of ketones leading to tertiary α-nitro ketones gave rise to a high yield of cleavage product. This is not unexpected because salt formation which would stabilize such nitro ketones is not possible and fragmentation should prevail. Good evidence was obtained that in these cases the cleavage occurred *via* direct alkoxide attack at the carbonyl group.[12] Treatment of 2-bromo-2-nitrocyclooctanone with a mixture of potassium *t*-butoxide at $-50°$ gave ethyl 8-bromo-8-nitrooctanoate.[17] Also, treatment of 2-nitro-2,5-dimethylcyclopentanone with sodium methoxide at 0° followed by acidification with glacial acetic acid at 0° resulted in cleavage to methyl 5-nitro-2-methylhexanoate.

Enolization of α-Nitro Ketones.—Work by Schwarzenbach, Zimmerman, and Prelog[18] and Rhoads[19] has established that in α-carbethoxycyclanones the six-, eight-, and ten-membered rings are much more highly enolized than any of the other cyclic ketones.

It was of interest to determine whether any cyclic α-nitro ketones followed the same trend and consequently the infrared, nmr, and ultraviolet spectra of α-nitro ketones were studied (Table VI).

2-Nitrocyclohexanone, 2-nitrocyclooctanone, 2-nitrocyclononanone, and 2-nitrocyclodecanone showed, in addition to bands characteristic of the C=O and NO_2 groups, two other characteristic bands at 1613 cm^{-1} and 1515 cm^{-1}. In 2-nitro-1-tetralone these bands were masked by aromatic absorption bands, but nmr and ultraviolet spectra showed that this ketone was also highly enolized. The bands appeared as shoulders in 2-nitrocyclononanone indicating that this ketone was less highly enolized than the others.



The band at 1613 cm^{-1} was assigned to the C=C stretching vibration of the enol[19] and that at 1515 cm^{-1} was assigned to the conjugated nitro group of the enol.[19] The nitro band normally appears at 1563 cm^{-1}; hence there is a shift of about 50 cm^{-1} in the enol.[19] None of the α-nitro ketones showed the presence of an enolic OH band and this is also in agreement with the results of Rhoads[19] who observed that even the most highly enolized α-carbethoxycycloalkanones, determined by bromine titration, did not exhibit this band. The infrared data are summarized in Table VI.

As seen in Table VI the nmr spectrum of every α-nitro ketone except 2-nitro-2,5-dimethylcyclopentanone showed a characteristic doublet or triplet at 5.0–5.4 ppm due to $CHNO_2$. With a few of the cyclic α-nitro ketones the peak appeared as either a quartet or two doublets rather than a triplet and this may be due to ring geometry. The spectra of 2-nitro-3,5,5-trimethylcyclopentanone and its potassium salt (see Table VII) deserve special notation because the ring methylene protons in the 4 position *are not equivalent*, and the methyl groups in the 5 position of the potassium salt are not equivalent.

The enol structure was detected in 2-nitrocyclohexanone, 2-nitrocyclooctanone and 2-nitro-1-tetralone at 13.6, 14.3, and 14.6, ppm, respectively. The absence of the enol proton in 2-nitrocyclodecanone was surprising because both infrared and ultraviolet spectra indicated that this ketone was highly enolized. The difficulty in detecting the enol proton was probably due to its weak signal. If 30% of the nitro ketone were in the enol form, the ratio of intensity of this proton to the others would be only 1:48. Indirect proof for the enolization of this nitro ketone was obtained by comparison of the area of the $CHNO_2$ proton with the remaining ring methylene protons. The ratio which should be 1:16 was actually 1:27 and this suggests that about 30–40% of the $CHNO_2$ proton is present as the enol.

(15) Similarly, the potassium salts of 2-nitrocyclohexanone and 2-nitrocycloheptanone in methanol were cleaved slowly at room temperature to the corresponding ω-nitrocarboxylic ester salts, while the potassium salt of VI cleaved at reflux temperatures.

(16) Only ester VII was formed, even when a large excess (150%) of potassium *t*-butoxide was employed in the nitration of V with amyl nitrate. Apparently, the attack of the amyloxide ion (from the nitrating agent) on the carbonyl group of intermediate X occurs at a much faster rate than the attack of *t*-butoxide. This must certainly be due to steric factors, because *t*-butyl 8-nitrooctanoate was obtained, albeit in low yield, when V was nitrated with *t*-butyl nitrate in the presence of potassium *t*-butoxide (see Table I).

(17) A control experiment established that 2-bromo-2-nitrocyclooctanone did not undergo cleavage when treated at room temperature with an ethanol–glacial acetic acid mixture.

(18) G. Schwarzenbach, M. Zimmerman and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951).

(19) S. J. Rhoads, *et al.*, *Tetrahedron*, **19**, 1625 (1963).

TABLE VI

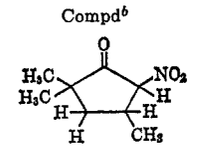
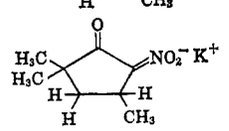
SPECTRAL DATA OF α NITRO KETONES

Ketone	Infrared Spectra, cm⁻¹ C=O	NO₂	C=C	C=CNO₂	Nmr spectra, ppm[a] CHNO₂[b]	Enol OH	Ultraviolet spectra[a] λmax mμ (log ε)
2-Nitrocyclohexanone	1739	1550	1618	1515	5.2 t (0.5)[c]	13.6 s (0.5)[c]	320 (3.6)
2-Nitrocycloheptanone	1718	1553	...	...	5.3 q (1.0)		
2-Nitrocyclooctanone	1739	1563	1613	1515	5.3 q (0.7)	14.3 s (0.3)	330 (3.45)
2-Nitrocyclononanone	1730	1558	1613 sh	1515 sh	5.2 t (0.9)		330 (3.23)
2-Nitrocyclodecanone	1739	1558	1592	1515	5.2 q (0.6)		328 (3.6)
2-Nitrocyclododecanone	1739	1550			5.05 q (1.0)		
2-Nitro-3,5,5-trimethylcyclopentanone	1770	1550			4.8 d (1.0)		315 (3.14)
2-Nitro-2,5-dimethylcyclopentanone	1704	1550					
3-Nitro-4-heptanone	1724	1550			5.0 t (1.0)		
2-Nitro-1-tetralone	1721	1560			5.4 m (0.7)	14.6 s (0.3)	370 (2.47)[d] (4.03)[e]

[a] Carbon tetrachloride was the solvent. [b] Multiplicity; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Intensity of proton signal. [d] In absolute ethanol. [e] In hexane.

TABLE VII

NMR SPECTRA OF 2-NITRO-3,5,5-TRIMETHYLCYCLOPENTANONE AND POTASSIUM 2-KETO-3,3,5-TRIMETHYLCYCLOPENTANENITRONATE[a]

Compd[b]	CHNO₂	CHCH₃	CHCH₃	CH₂	C(CH₃)₂
	4.82 d (1)[c]	3.00 m (1)	1.24 d (3)	2.16 m (1) 1.59 d (1)	1.2 s (6)
	...	2.92 m (1)	1.10 d (3)	1.84 m (1) 1.30 d (1)	0.83 s (3) 0.91 s (3)

[a] In ppm multiplicity; s = singlet, d = doublet, m = multiplet. [b] Carbon tetrachloride was the solvent for the nitro ketone, deuterium oxide for the nitro salt. [c] Proton area.

Savides[20] had noted earlier in a careful study of the ultraviolet spectrum of 2-nitro-1-tetralone that a band at 370 mμ varied in intensity from ε 294 in absolute ethanol to ε 10,800 in hexane. This band, not present in α-tetralone or 2-bromo-2-nitro-1-tetralone, was attributed to the enol form.

The ultraviolet spectra of the α-nitro ketones in carbon tetrachloride indicated that the six-, eight-, and ten-membered ring α-nitro ketones showed a strong enol band at 300 mμ while the five- and nine-membered ring ketones showed a weak enol band at 330 mμ.

The infrared spectra of a few mono- and dipotassium salts of α-nitro ketones have been reported by Feuer, Savides, and Rao.[21] The C=O stretching vibration for the nitro ketone salts appeared at 1639–1587 cm⁻¹. The C=N stretching frequency normally expected at about 1613 cm⁻¹ was not present and it was suggested that this band may have been imposed on the band attributed to the carbonyl vibration.

In contrast to these observations, examination of the infrared spectra of the mononitro ketone salts revealed the presence of both C=O and C=N bands at 1639 cm⁻¹ and 1613 cm⁻¹, respectively, as recorded in Table III.

The nmr spectra of the nitro ketone salts showed two characteristic bands at 2.6 ppm ($CH_2C{=}O$) and 2.9 ppm ($CH_2C{=}NO_2{-}$) while the ultraviolet spectra in absolute ethanol revealed a strong absorption band at 343 mμ (ε 12,000).

(20) Unpublished results from the Ph.D. thesis of C. Savides, Purdue University, 1958.

(21) H. Feuer, C. Savides, and C. N. R. Rao, *Spectrochim. Acta*, **19**, 431 (1963).

Experimental Section

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

Materials.—Amyl nitrate, a generous gift from the Ethyl Corporation, consisted of a mixture of *n*-amyl and isoamyl nitrate. THF was purified by the method of Feuer and Savides.[2b] 2,2,4-Trimethylcyclopentanone, 2,2,5-trimethylcyclopentanone, and 2,5-dimethylcyclopentanone, generous gifts from Professor H. C. Brown, were used as received.

Mononitration of Ketones.—The following experiment is typical of the procedure employed.[22] Cyclooctanone (V) (12.6 g, 0.10 mole) in 60 ml of THF[23] was added to a solution of 18.0 g (0.16 mole) of sublimed potassium *t*-butoxide in 90 ml of THF at −50° followed by dropwise addition of 14.4 g (0.11 mole) of amyl nitrate in 30 ml THF over 20 min at −45 to −50°. Acetic acid (30.0 g, 0.50 mole) in 100 ml of absolute ether was added rapidly and the reaction mixture was let stir at 0° for 12 hr. The potassium acetate was filtered and the filtrate was evaporated. Distillation of the residue at 0.2 mm gave 6.0 g (35%) of 2-nitrocyclooctanone (VI), bp 73–74°, and 9.6 g (37%) of isomeric amyl 8-nitrooctanoates (VII), bp 140–145°. The material in the Dry Ice trap contained 10% unreacted V as determined by vpc analysis. The over-all material balance was 82%.

Ethyl 8-Nitrooctanoate (VIII).—Isomeric amyl 8-nitrooctanoates (VII, 4.1 g) were converted to ethyl 8-nitrooctanoate by refluxing in 50 ml of absolute ethanol containing a few drops

(22) Aryl alkyl ketones were nitrated at −30° and the nitrate was added over a period of 90 min. In the case of cyclopentanone and cyclohexanone, the nitrate was added over a period of 5 min.

(23) Besides THF, dimethylformamide was found to be a convenient solvent for these reactions.

of concentrated sulfuric acid. After neutralization with sodium carbonate and filtration, distillation at 0.6 mm gave 3.4 g (100%) of VIII, bp 100–105°.

Potassium 2-Ketocycloalkanonenitronates.—The following experiment is typical of the procedure employed. To 0.6 g (0.01 mole) of potassium hydroxide in 20 ml of isopropyl alcohol at 0° was added 2-nitrocyclooctanone (1.0 g, 0.0058 mole) dissolved in 10 ml of isopropyl alcohol. Filtering, washing the salt with cold isopropyl alcohol until the filtrate was no longer basic, and then recrystallizing from a 1:1 mixture of ethanol–isopropyl alcohol gave 1.2 g (85%) of potassium 2-ketocyclooctanenitronate.

Treatment of 2-Nitrocyclooctanone (VI) with Base at Alkyl Nitrate Nitration Conditions. (a) **Adding VI to the Base.**—To a solution of potassium *t*-butoxide (2.2 g, 0.02 mole) in 40 ml of THF and absolute ethanol (9.2 g, 0.2 mole) at −50° was added VI (1.7 g, 0.01 mole) dissolved in 10 ml of THF over 15 min. The reaction mixture was allowed to stir for an additional 15 min and then glacial acetic acid (3.6 g, 0.06 mole) was added. Stirring for 18 hr at room temperature, filtering, adding ether to precipitate the remainder of potassium acetate, and refiltering was followed by evaporating the solvents. Vpc analysis of the residue indicated that only VI was present (recovery of 90% after distillation *in vacuo*).

The result was the same when the following amounts were employed: 6.7 g (0.06 mole) of potassium *t*-butoxide in 20 ml of THF, 0.45 g (0.01 mole) of absolute ethanol in 5 ml of THF, 1.0 g (0.006 mole) of VI in 10 ml of THF, and 15 g (0.25 mole) of glacial acetic acid.

(b) **Adding Base to VI.**—To a solution of VI (1.7 g, 0.01 mole) in 40 ml of THF was added at −50° potassium ethoxide (1.68 g, 0.02 mole) in 10 ml of THF over 15 min. Then proceeding as in experiment a and analyzing by vpc indicated that only VI was present and that no ethyl ester VIII had formed.[24]

Treatment of 3-Nitro-4-heptanone with Base at Alkyl Nitrate Nitration Conditions.—To a solution of potassium *t*-butoxide (6.7 g, 0.06 mole) in 50 ml of THF and absolute ethanol (0.45 g, 0.01 mole) was added over 15 min at −50° 3-nitro-4-heptanone (0.95 g, 0.006 mole) in 10 ml of THF. Then a large excess of glacial acetic acid was added all at once and the reaction mixture was allowed to stir at 0° for 1 hr. Filtering, removing the solvent *in vacuo*, and chromatographing the residue showed that only 3-nitro-4-heptanone was present. No 1-nitropropane or ethyl butyrate was detected.

Nitration of Cyclopentanone with Absolute Ethanol Added after Acidification.—The experimental procedure was the same as described in the nitration of V, except that cyclopentanone (8.4 g, 0.10 mole), potassium *t*-butoxide (18.5 g, 0.16 mole), and amyl nitrate (13.3 g, 0.01 mole) were employed. After acidifying with glacial acetic acid (30 g, 0.5 mole), 20 ml of absolute ethanol was added, and the mixture was stirred at 0° for 12 hr. Filtering and distilling at 0.8 mm gave 2.8 g (13%) of ethyl 5-nitropentanoate, bp 77–82°, and 1.3 g (7%) of amyl 5-nitropentanoates,[7] bp 82–90°.

The precipitate was washed with ether, dried *in vacuo*, and dissolved in a small amount of water. Addition of methanol to the aqueous solution precipitated 2.2 g of dipotassium 2-ketocyclopentane-1,3-dinitronate, explosion point 263–264°, lit.[2a] explosion point 259–261°.

Methyl 5-Nitro-2,2,4-trimethylpentanoate.—To 15 ml of absolute methanol and 5 ml of glacial acetic acid was added 2-nitro-3,5,5-trimethylcyclopentanone (1 g, 0.006 mole). After refluxing for 96 hr the solvent was evaporated and the residue distilled at 55–60° (0.15 mm) to give 1 g of a mixture consisting of 16% of ester and 80% of starting material. Purification of the ester was achieved by vpc on a SF-96 on Chromosorb column.

Under the same reaction conditions, 2-nitrocyclohexanone afforded 40% methyl 6-nitrohexanoate.

Nitration of 4-Heptanone without Subsequent Acidification.—4-Heptanone (11.4 g, 0.10 mole) was nitrated with ethyl nitrate (10.0 g, 0.11 mole) by the procedure described for V and the reaction mixture was distilled at 0° (0.5 mm). Vpc analysis of the distillate showed the presence of ethyl butyrate (20%) and 4-heptanone (10%).

After acidification of the residue at 0° with 30 g (0.5 mole) of glacial acetic acid, vpc analysis showed the presence of 1-nitropropane and 3-nitro-4-heptanone. Retention times of all compounds were compared with those of authentic samples. Distillation of the acidified residue at 3.0 mm gave 6.2 g (39%) of 3-nitro-4-heptanone, bp 72–75°.

2-Bromo-2-nitrocyclooctanone.—Bromine was added at room temperature to 2.4 g (0.011 mole) of potassium 2-ketocyclooctanenitronate in 70 ml of dry carbon tetrachloride until the color of bromine just persisted. After evaporation of the solvent, the residue was sublimed (0.05 mm) at room temperature to give 2.5 g (90%) of 2-bromo-2-nitrocyclooctanone, mp 42–43°.

Ethyl 8-Bromo-8-nitrooctanoate. (a) **From 2-Bromo-2-nitrocyclooctanone.**—2-Bromo-2-nitrocyclooctanone (1.0 g, 0.004 mole) dissolved in 10 ml THF was added to potassium *t*-butoxide (0.45 g, 0.004 mole) and absolute ethanol (0.1 g, 0.002 mole) in 15 ml THF at −50°. An excess of glacial acetic acid (1.2 g, 0.02 mole) was added at −40° and the reaction mixture stirred for 2 hr at 0°. After filtration and evaporation of the solvents the residue was distilled at 0.12 mm to give 0.20 g (~25%) of a mixture containing mostly 2-nitrooctanone[25] (VI), bp 58–62° and 0.50 g (82% based on absolute ethanol) of ethyl 8-bromo-8-nitrooctanoate, bp 100–104°. A considerable amount of tarry residue remained which did not distil at 180° (0.12 mm).

The analytical sample of the ester, $n^{20}D$ 1.4688, was obtained by vpc on a SF-96 on Chromosorb column at 170°.

Anal. Calcd for $C_{10}H_{18}BrNO_4$: C, 40.55; H, 6.13; N, 4.76; Br, 26.98. Found: C, 41.00; H, 6.34; N, 5.01; Br, 26.65.

(b) **From Ethyl 8-Nitrooctanoate (VIII).**—A small amount of VIII was dissolved in an ethanolic potassium hydroxide solution and an equivalent amount of bromine was added. After filtration and evaporation of the solvent the residue was subjected to vpc analysis. The retention time and the refractive index of the ethyl 8-bromo-8-nitrooctanoate were identical with those of the compound prepared from 2-bromo-2-nitrocyclooctanone.

Methyl 5-Nitro-2-methylhexanoate.—2,5-Dimethylcyclopentanone (11.2 g, 0.10 mole) was nitrated with amyl nitrate by the procedure described for V. The impure 2-nitro-2,5-dimethylcyclopentanone (0.15 g) was added at 0° to a small amount of sodium methoxide in 10 ml of methanol and the pH dropped from 11 to 7 (Hydrion B paper). More sodium methoxide was added to raise the pH to 9, then the solution was acidified at 0° with excess glacial acetic acid. Analysis of the crude reaction mixture by vpc revealed that the peak due to 2-nitro-2,5-dimethylcyclopentanone had disappeared and a new peak due to methyl 5-nitro-2-methylhexanoate was present. The compound was identified by comparison of vpc retention time and refractive index with an authentic sample of methyl 5-nitro-2-methylhexanoate prepared from the isomeric amyl esters.

Attempted Ester Exchange between Amyl Nitrate and Ethanol at Conditions of the Alkyl Nitrate Nitration.—To sublimed potassium *t*-butoxide (7.0 g, 0.063 mole) in 35 ml of purified THF was added all at once at −50°, absolute ethanol (2.8 g, 0.065 mole) in 5 ml of THF. Then at −50°, amyl nitrate (5.3 g, 0.04 mole) in 20 ml of THF was added dropwise in 30 min and the mixture neutralized with glacial acetic acid (6.0 g, 0.1 mole) dissolved in 10 ml of THF. After stirring at 0° for 18 hr, potassium acetate was filtered off and the filtrate was subjected to vpc analysis. By comparison of the retention times with those of authentic samples, it was found that no exchange had occurred. Neither ethyl nitrate nor amyl alcohol could be detected by using an SF-96 on Chromosorb W, 10-ft column at 83° and a flow rate of 85 ml/min.

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

(24) We are indebted to Mr. Melvin Auerbach for this experiment.

(25) The removal of a bromine atom from a bromonitro ketone with base has been noted previously: T. M. Lowry, *J. Chem. Soc.*, **73**, 986 (1898). Also see H. Feuer, J. W. Shepard, and C. Savides, *J. Am. Chem. Soc.*, **79**, 5768 (1957).