Hydrolysis of the three *tert*-alkylcyanoacetate esters by long heating with potassium hydroxide in ethylene glycol resulted in high yields of the anticipated quaternary acids (Table II).

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The Preparation of 2,2-Dialkyl-3-nitropropionic Acids

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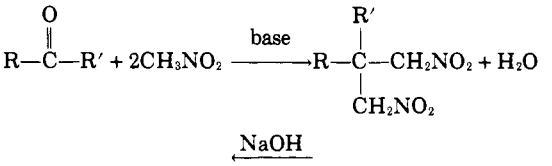
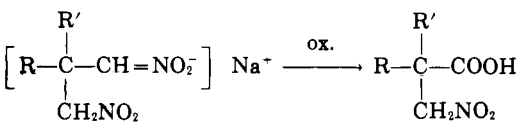
Several 2,2-dialkyl-3-nitropropionic acids were prepared by the nitric acid oxidation of the monoalkali salts of 2,2-dialkyl-1,3-dinitropropanes. The dinitro compounds were obtained conveniently by the base-catalyzed condensation of aliphatic ketones with nitromethane.

NITROPIVALIC ACID, 2,2-dimethyl-3-nitropropionic acid, has been reported in the literature once (*9*), but there appears to be no mention of any other 2,2-dialkylnitropropionic acid. The preparation noted for nitropivalic acid (*9*) consisted of the addition of hydrogen cyanide to 2-methyl-1-nitropropene followed by hydrolysis of the nitronitrile. No experimental details were given nor was there any mention of yields or physical properties.

Since nitro acids of this type were needed, consideration was given to alternate routes which might be more convenient or more general. Among these were the liquid-phase nitration of pivalic acid and the reaction of iodo- or bromopivalic esters with silver nitrite or sodium nitrite (*5*), but both were rejected as being infeasible, the first because of the known difficulty of nitrating neopentane (*4*) and aliphatic acids (*10*), and the second because of the reported inability to obtain nitro compounds from the reaction of neopentyl iodide with silver nitrite (*6*).

The method finally chosen was the oxidation of monosalts of 2,2-dialkyl-1,3-dinitropropanes:





Many 2,2-dialkyl-1,3-dinitropropanes can be obtained readily by the reaction of ketones with nitromethane (*1, 2, 7, 8*). Preparation of the monosalts is relatively straightforward using stoichiometric amounts of sodium hydroxide. The authors thought, at first, that Nef reaction (*11, 13*) on the salts might lead to nitroaldehydes which then could be oxidized further to the acids. However, treatment of the nitrosalts with hydrochloric or sulfuric acid, under a variety of conditions, invariably led to regeneration of the dinitro compounds as the principal reaction. This result is clearly in agreement with the mechanism of the Nef reaction postulated by van Tamelen (*17*) and by Hawthorne (*3*) where the slow step in the reaction is attack by water on the carbon bonded to a protonated acinitro group. In the case of a neopentyl nitro compound, isomerization of the acinitro to the nitro would be expected to be much faster than a sterically hindered nucleophilic attack by solvent.

Since Shechter has studied the effect of many oxidizing agents on salts of mononitro compounds (*15, 16*), and has reported that such salts can be oxidized with potassium permanganate to acids (*16*), then, the use of strong oxidizing agents was considered. A brief investigation of potassium permanganate led only to inconclusive results. However, when nitric acid was used as the oxidant, the nitrosalts were converted smoothly into the desired acids. Table I lists the melting points and analyses of the compounds isolated. The oxidation appears to be general and probably can be used to convert any primary nitroparaffin containing no other readily oxidizable groups to the corresponding acid.

The reaction of cyclohexanone with nitromethane is reported (*7*) to give a very low yield of 1,1-bis(nitromethyl)-cyclohexane with the principal product being a condensed product (*12*), which has recently been identified by Noland and Sundberg (*14*). The use of diethylamine as the condensing agent and long reaction times at room temperature made it possible to obtain a crude material which gave an infrared spectrum consistent with 1,1-bis(nitromethyl)-cyclohexane, but all attempts to obtain a pure dinitro compound failed. However, the conversion of the crude material to a salt, followed by oxidation, gave a low yield of 1-nitromethylcyclohexane carboxylic acid.

EXPERIMENTAL

Condensation of Ketones with Nitromethane. In a typical preparation, 2 moles of nitromethane, 1 mole of ketone, and 1 mole of diethylamine were mixed together and allowed to stand for a week or more over magnesium sulfate in a

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Table I. β-Nitroacids

Acid	Yield, %	M.P., °C.	Analysis, Calcd./Found % C	% H	% N
2-Methyl-2-nitromethylpropionic acid	66	86–7	40.8/40.7	6.12/6.22	9.52/9.34
2-Methyl-2-nitromethylbutyric acid	57	63	44.7/45.0	6.83/6.96	8.70/8.55
2-Methyl-2-nitromethylpentanoic acid	57	72–3	48.1/48.4	7.43/7.52	8.00/8.05
1-Nitromethyl-1-cyclohexane carboxylic acid		79–80	51.3/51.3	6.95/7.06	

Table II. 2,2-Dialkyl-1,3-dinitropropanes

Compound	Yield, %	B.P., °C.	Analysis, Calcd./Found % C	% H	% N
1,3-Dinitro-2,2-dimethylpropane	71	110–15/1 mm.	37.03/37.30	6.21/6.51	17.28/17.68
2-Methyl-2-nitromethyl-1-nitrobutane	64	136–40/12 mm.	36.58/36.42	7.37/7.22	17.07/16.88
2-Methyl-2-nitromethyl-1-nitropentane	71	138–40/1 mm.	44.20/44.30	7.42/7.83	14.73/15.02
2-Ethyl-2-nitromethyl-1-nitrobutane	55	57–59°	44.20/44.21	7.42/7.86	14.73/14.77

° M.p.

stoppered flask at room temperature. The reactions conveniently were followed daily by change in refractive index. When the refractive index was constant, indicating no further reaction, the drying agent was filtered and washed with ethyl ether which was added to the filtrate. The product solution then was washed several times with 5% sulfuric acid and then with water. After drying, the solvent was removed under vacuum and the residue distilled.

Data on the dinitro compounds prepared are given in Table II.

Preparation of Monosodium Salt of 1,3-Dinitro-2,2-dimethylpropane. A solution of 30 grams (0.18 mole) of 1,3-dinitro-2,2-dimethylpropane dissolved in 50 ml. of methanol was added dropwise with stirring over a 25-minute period to an ice-cooled solution of 6.6 grams (0.16 mole) of 97% sodium hydroxide in 150 ml. of methanol. After the addition was complete, the solution was filtered to remove a fine white precipitate which had formed. The clear filtrate then was concentrated on a rotary evaporator at aspirator pressure until the first crystals of the sodium salt appeared. At this point, the solution was removed from the evaporator, and 400 ml. of 30° to 60° C. petroleum ether and 100 of ethyl ether were added. The resulting slurry was stirred for 3 hours. The precipitate was separated by filtration, washed with 150 ml. of ethyl ether, and dried at room temperature under vacuum. The yield of fine white crystalline salt was 23 grams (78%).

The other monosalts were prepared in a similar manner.

Caution. Salts of nitro compounds are thermally unstable. The pure salts prepared by the above procedure should not be dried in an oven or subjected to heat in any other way. Some of these compounds will decompose rapidly when heated, but they appear to be quite stable to storage at room temperature.

2-Methyl-2-nitromethylpropionic Acid (Nitropivalic Acid). A solution of 20 grams (0.108 mole) of the monosodium salt of 1,3-dinitro-2,2-dimethylpropane in 50 ml. of water was added dropwise with stirring to 100 ml. of 70% nitric acid heated initially to 95° C. on a steam bath. The rate of addition was such that the temperature of the oxidation could be maintained > 90° C. with no heat from the steam bath. When addition of the salt solution was completed (80 minutes), the solution was heated on the steam bath for one additional hour. As the solution cooled, nitrogen was bubbled through it until all traces of nitrogen oxides were gone. The green reaction solution then was extracted four times with 40-ml. portions of ethyl ether. The combined ether extracts were dried overnight over anhydrous $MgSO_4$ and then evaporated on a rotary evaporator to give 15.3 grams of crude nitropivalic acid. Recrystallization twice from cyclohexane gave 9.8 grams (66%) of nitropivalic acid, m.p. 86–7° C. The NMR spectrum showed three singlet peaks at 1.46 (methyl), 4.77 (methylene), and 12.56 p.p.m. (carboxyl), with peak area ratios 6:2:1.

2-Methyl-2-nitromethylbutyric Acid. The oxidation was run in the same manner as above. The product solution was extracted continuously for 2 days with chloroform. This solution was concentrated and, in turn, extracted with 5% $NaHCO_3$ solution. The $NaHCO_3$ solution was extracted once with ethyl ether and then acidified. The oil which separated on acidification was taken up in chloroform. The chloroform solution was dried and then evaporated under vacuum to leave a yellow oil which solidified slowly. This solid was dissolved in a minimum amount of ethyl ether, and the solution was diluted about sixfold with petroleum ether and cooled in a dry ice bath. The solid which precipitated was filtered off, washed with petroleum ether, and dried.

2-Methyl-2-nitromethylpentanoic Acid. The oxidation procedure was as above. The product solution was extracted several times with chloroform. This extract was extracted, in turn, with 5% $NaHCO_3$ solution. The product was obtained on acidification of the $NaHCO_3$ solution. Purification was by crystallization from a mixed ethyl ether–petroleum ether solution cooled in a dry ice bath.

1-Nitromethylcyclohexane Carboxylic Acid. Crude sodium salt of 1,1-bis(nitromethyl)cyclohexane was oxidized and isolated by $NaHCO_3$ solution extraction as described above. The product was recrystallized from chloroform to give colorless crystals of 1-nitromethylcyclohexane carboxylic acid, m.p. 79–80° C. The infrared and NMR spectra were consistent with the assigned structure. The yield could not be calculated, since the starting material was of unknown purity, but the over-all yield from cyclohexanone was low.

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Synthesis of a New Analog of Chloramphenicol

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DL-*threo*-2-Dichloroacetamido-1-(4-methylsulfonyl-3-fluorophenyl)-1,3-propanediol and its *erythro*-isomer were synthesized. 4-Methylsulfonyl-3-fluoroacetophenone, α-bromo-4-methylsulfonyl-3-fluoroacetophenone and its hexamethylenetetramine salt, α-amino-4-methylsulfonyl-3-fluoroacetophenone hydrochloride, α-dichloroacetamido-4-methylsulfonyl-3-fluoroacetophenone, and racemic α-dichloroacetamido-β-hydroxy-4-methylsulfonyl-3-fluoroacetophenone were new intermediates for this synthesis.

AMONG the analogs of chloramphenicol, DL-*threo*-2-dichloroacetamido-1-(4 - methylsulfonylphenyl)-1,3-propanediol (*3*) has significant antifungal activity. DL-*threo*-Dichloroacetamido-1-(4-methylsulfonyl - 3-fluorophenyl)-1,3 - propanediol was synthesized by using general methods of syntheses of chloramphenicol and its analogs (*1*, *3*), with some modifications which are described in the footnote of Table I.

The starting materials for this synthesis, *o*-fluorothiophenol, *o*-fluorothioanisole, and 4-methylmercapto-3-fluoroacetophenone were reported previously by two of the authors (*2*). The antimicrobial activity of the analog of chloramphenicol obtained are under investigation. Preliminary assays showed antibacterial activity against some pathogenic and nonpathogenic strains. The chloramphenicol analog and the intermediates and congeners which were synthesized are listed in Table I.

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Table I. Synthesis and Analysis of Chloramphenicol Analogs

Compound	M.P., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4-Methylsulfonyl-3-fluoroacetophenone	90	95	$C_9H_9FO_3S$	50.00	49.85	4.16	4.18
α-Bromo-4-methylsulfonyl-3-fluoroacetophenone	95	92	$C_9H_8BrFO_3S$	35.93	36.07	2.71	2.80
Hexamethylenetetramine salt of α-bromo-4-methylsulfonyl-3-fluoroacetophenone[a]	198	90	$C_{15}H_{20}BrFN_4O_3S$	41.37	41.70	5.59	4.63
α-Amino-4-methylsulfonyl-3-fluoroacetophenone hydrochloride[b]	...	80	$C_9H_{11}ClFNO_3S$	...	...	...	...
α-Dichloroacetamido-4-methylsulfonyl-3-fluoroacetophenone	115	36	$C_{11}H_{10}Cl_2FNO_4S$	38.59	38.46	2.92	3.06
Racemic α-dichloroacetamido-β-hydroxy-4-methylsulfonyl-3-fluoroacetophenone	103	23	$C_{12}H_{12}Cl_2FNO_5S$	38.70	39.02	3.22	3.41
DL-*threo*-2-Dichloroacetamido-1-(4-methylsulfonyl-3-fluorophenyl)-1,3-propanediol[c]	206	44	$C_{12}H_{14}Cl_2FNO_5S$	38.50	38.62	3.74	3.62
DL-*erythro*-2-Dichloroacetamido-1-(4-methylsulfonyl-3-fluorophenyl)-1,3-propanediol[c]	80	11	$C_{12}H_{14}Cl_2FNO_5S$	38.50	38.71	3.74	3.90

[a] This salt was made in chlorobenzene at a temperature below 5° C. and, after being retained at this temperature for 2 hours, was kept overnight at room temperature. At higher temperatures, orange gummy materials were obtained. [b] The α-amino-4-methylsulfonyl-3-fluoroacetophenone hydrochloride, obtained by acid hydrolysis of the hexamethylenetetramine salt, contained a large amount of ammonium chloride and, being water soluble, was dichloroacetylated without previous purification. [c] The assignment of *threo*- and *erythro*- configurations was made by analogy with a large number of synthesized chloramphenicol analogs, supported by the infrared spectroscopy (*4*).