The catalyst (50–100 mg.) was added and the reduction was carried out in a Parr low-pressure hydrogenation apparatus, the total volume of which had been reduced to 545 ml. All hydrogenations were carried out for 30–120 min. at room temperature and 50–60 p.s.i.g. hydrogen pressure. Samples of the filtered reduction mixture were evaporated under a stream of nitrogen to approximately one-tenth their original volume and analyzed by gas–liquid chromatography.

Catalytic Hydrogenations in Aqueous HCl.—The catalyst (50–100 mg.) was added to a solution of the ketone (0.12–0.15 ml.) in 5 ml. of 0.2 *N* hydrochloric acid giving a pH of 1–2. The hydrogenation was carried out using the apparatus and conditions described for the ethanolic hydrogenations. Dilute sodium hydroxide (10%) was added to the filtered reduction mixture until the pH rose to 13. The alkaline solution was extracted with four 10-ml. aliquots of chloroform. From the combined chloroform aliquots approximately 90% of the solvent was removed by distillation through a small Vigreux column. The remaining solution was then concentrated with a stream of nitrogen and analyzed by gas–liquid chromatography.

Alkali Metal–Ethanol Reductions.—In 3 ml. of anhydrous reagent grade benzene was placed the metal (0.6 g. of sodium or 0.9 g. of potassium). To this was added dropwise a solution of 0.12–0.15 ml. of the ketone in 2.0 ml. absolute ethanol. After 2 hr. of reflux, distilled water (5 ml.) was added to the mixture. The aqueous phase was extracted with two 5-ml. aliquots of benzene to quantitatively remove the amino alcohols. The benzene aliquots were combined, concentrated, and analyzed by gas–liquid chromatography.

Sodium Borohydride Reductions.—The ketone (0.12–0.15 ml.) was added dropwise to a solution of sodium borohydride (0.10 g.) in distilled water (5.0 ml.). The mixture was permitted to stand overnight. Concentrated ammonium hydroxide (1.0 ml.) was added and the mixture was allowed to stand for an additional 1–2 hr. The solution was saturated with sodium chloride and extracted with five 10-ml. aliquots of benzene to remove quantitatively the mixture of amino alcohols. The benzene aliquots were combined, concentrated, and then analyzed by g.l.c.

Lithium Aluminum Hydride Reductions.—To 0.10 g. of lithium aluminum hydride in 5.0 ml. of anhydrous ether in an ice bath was added dropwise 0.12–0.15 ml. of ketone; the mixture was warmed to room temperature. Thirty minutes later 0.25 ml. of distilled water was added followed by 0.20 ml. of sodium hydroxide (10%). After standing overnight, the ethereal solution was decanted, filtered, and then analyzed by g.l.c.

Gas–Liquid Chromatographic Analysis.—All g.l.c. analyses were carried out with a 10 ft. × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support.[2] Column temperatures of 208–212° and helium flow rates of 120–150 ml./min. were used. Symmetrical peaks were obtained with a minimum of tailing. Peaks corresponding to the epimeric racemates, parent ketone, and quinolizidine were identified by infrared and g.l.c. comparison with known samples of each. In the catalytic and metal hydride reductions, no other products resulted. Preparative scale catalytic reductions gave yields which were essentially quantitative. Some of the alkali metal–alcohol reductions gave small but appreciable proportions (3–12%) of foreign products which were not identified.

Quantitative determinations of the relative amounts of amino alcohols were made by measuring their relative peak areas on the gas–liquid chromatograms. These measurements were normally made with a disk integrator. Check measurements made by cutting out the peaks and weighing them on an analytical balance or by taking the product of the peak height (h) times the peak width at $h/2$ gave results which were identical with those of the disk integrator within 2%. The detector response of the Aerograph A-90-P apparatus used for all analyses was shown to be the same for racemates A and B of each set of amino alcohols. This was accomplished by analyzing mixtures containing known amounts of pure A and pure B.

In order to demonstrate that the work-up procedures used for the various reductions did not alter the relative amounts of racemates resulting from the reductions themselves, mixtures containing known amounts of quinolizidine and each of the 3-hydroxyquinolizidines were subjected to each of the work-up procedures and then analyzed by g.l.c. In all cases the relative amounts of the constituents were not altered by the work-up to an extent greater than 2%. Since the ratio of 3-hydroxyquinolizidines is more susceptible to alteration during work-up than either of the other sets of amino alcohol racemates,[25] it may be concluded that the methods of work-up of the other reduction mixtures have not altered the epimeric ratios by any significant amount.

The A–B racemate ratios from the various chemical and catalytic reductions were found to be reproducible within ±3%, which is the approximate limit of the error resulting from the work-up procedures and the g.l.c. analyses. This is the same limit of experimental error as has resulted[19] from infrared analyses of tropine–pseudotropine reduction mixtures.

(25) Preliminary experiments using a different work-up procedure revealed the difference in volatility to be the greatest potential source of A–B alteration during the work-ups. This difference is greatest for the 3-hydroxyquinolizidines.

Michael Additions of Nitroform. III. The C_9 Precursor, Potassium Methyl 4,4-Dinitro-2-hydroxybutyrate

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From the examination of the changes in the ultraviolet spectra with time of the nitroform–methyl acrylate system and methyl 4,4,4-trinitrobutyrate decomposition in aqueous dioxane (pH ≃5), it was shown that potassium methyl 4,4-dinitro-2-hydroxybutyrate is the precursor of dimethyl 4,4-dinitro-2-hydroxypimelate (C_9). The only path for the formation of potassium methyl 4,4-dinitro-2-butenoate was found to be the elimination of the elements of nitrous acid from methyl 4,4,4-trinitrobutyrate. The isolation and characterization of potassium methyl 4,4-dinitro-2-hydroxybutyrate and the potassium salt of 5,5-dinitro-3-hydroxypentan-2-one, the methyl vinyl ketone analog, are described. With acrylonitrile as the augend, spectral evidence for the presence in solution of the potassium salt of 3,3-dinitropropionaldehyde was obtained.

The addition of nitroform (pK ≈0)[1] to methyl acrylate in moderately to strongly acidic aqueous solutions was found to give excellent yields of methyl 4,4,4-trinitrobutyrate (MeTNB). The first evidence of competing side reactions was found in a study of the effect of pH upon the yield of MeTNB.[2] In a methanol–water system at pH 1 to ≈3.5, the yield of MeTNB varied between 80 and 90%. On increasing the pH to ≈4.2, the yield of MeTNB fell sharply to 65%. Another sharp decrease in yield occurred on increasing the pH to ≈5, where the yield of MeTNB obtained was only 21%. Under the low yield conditions, it was not possible to recover substantial quantities of unreacted nitroform. This indicated that the low yields were not caused by a pH-dependent equilibrium reaction.

(1) S. S. Novikov, V. I. Slovetski, S. A. Shevelev, and A. A. Fainzil'berg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 598 (1956).

(2) Private communication, M. E. Hill of these laboratories.

This observation remained untouched until a kinetic investigation of the addition of nitroform to methyl acrylate was undertaken. Lack of constancy of the specific rate constants throughout a given run, determined by the rate of formation of MeTNB in an acetate buffer, once again suggested the presence of competing reactions. The kinetic experiments were abandoned in favor of synthetic studies.

When the reaction of equimolar quantities of nitroform and sodium acetate with a 200% molar excess of methyl acrylate was carried out in 33% aqueous methanol, the expected adduct MeTNB was isolated in 56.5% yield. In addition, there was obtained a 24.7% yield of a denitrosation product, dimethyl 4,4-dinitro-2-hydroxypimelate (C_9).[3]

$$HC(NO_2)_3 + CH_2{=}CHCO_2CH_3 \xrightarrow[MeOH\text{-}H_2O]{OAc^-} C(NO_2)_3CH_2CH_2CO_2CH_3 + C(NO_2)_2(CH_2CH_2CO_2CH_3)(CH_2CHOHCO_2CH_3)$$

MeTNB; C_9

Under somewhat more alkaline conditions, potassium trinitromethide and methyl acrylate in 50% methanol yielded a third product, potassium methyl 4,4-dinitro-2-butenoate (DNU). The results are summarized by the following equation.

$$K^+{}^-C(NO_2)_3 + CH_2{=}CHCO_2CH_3 \xrightarrow[H_2O]{MeOH} \text{MeTNB (10.9\%)} + C_9\ (31.1\%) + K^+{}^-C(NO_2)_2CH{=}CHCO_2CH_3$$

DNU (34.5%)

The isolation of the unsaturated ester, DNU, at first suggested that it could be the precursor of C_9 by undergoing hydration to the α-hydroxydinitro ester[4] which would add to another mole of methyl acrylate to yield C_9. However, the ester DNU was found to be unreactive under the reaction conditions. In addition, the ester DNU did not add to methyl acrylate under Michael conditions to yield dimethyl 4,4-dinitro-2-heptenedioate. This ruled out the possibility that this diester could be the precursor of C_9 by adding the elements of water to its double bond.

The first evidence for a logical precursor for C_9 came from the reaction of acrylamide with potassium trinitromethide in "absolute" methanol. Under these conditions, the potassium salt of 4,4-dinitro-2-hydroxybutyramide was obtained.[5] Unlike the ester DNU, this saturated amide readily added to methyl acrylate under Michael conditions to yield the C_9 analog, 6-carbomethoxy-4,4-dinitro-2-hydroxyhexanamide.

Attempts to prepare the potassium salt of methyl 4,4-dinitro-2-hydroxybutyrate (DNS) by this procedure gave a 50% yield of the unsaturated ester DNU together with a 23% yield of MeTNB and only a 4.4% yield of C_9. Therefore, it appeared that the α-hydroxydinitro ester DNS was the precursor of C_9, but under a variety of reaction conditions it successfully evaded capture and seemed to be a rather reactive intermediate.

Spectrophotometric Studies.—From the above results, it seemed that the best approach to follow for the detection of the C_9 precursor DNS was to study the changes in the total ultraviolet spectrum of the reaction of nitroform with methyl acrylate. Based upon previous synthetic results,[3,5] a 1:1 acetic acid–acetate buffer system in 50 vol. % dioxane was selected as the reaction medium.

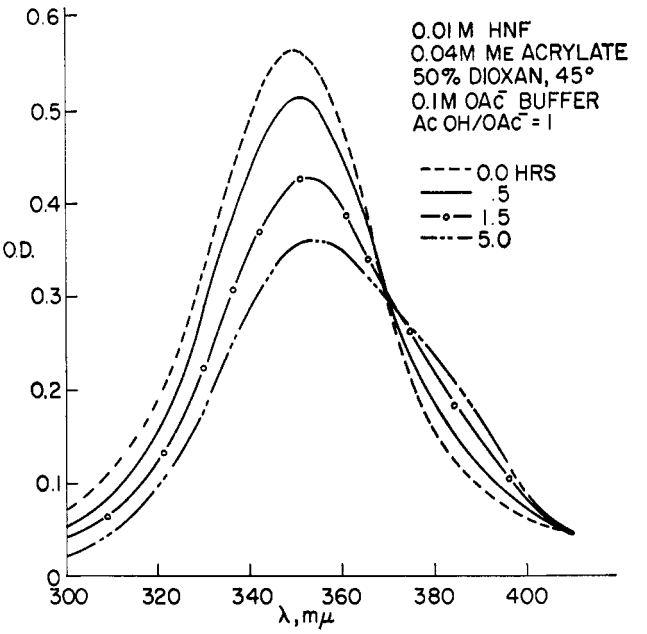


Fig. 1.—Spectral changes *vs.* time for 0.01 *M* HNF, 0.04 *M* methyl acrylate, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ----, 0.0 hr.; ———, 0.5 hr.; —O—, 1.5 hr.; —·—·—, 5.0 hr.

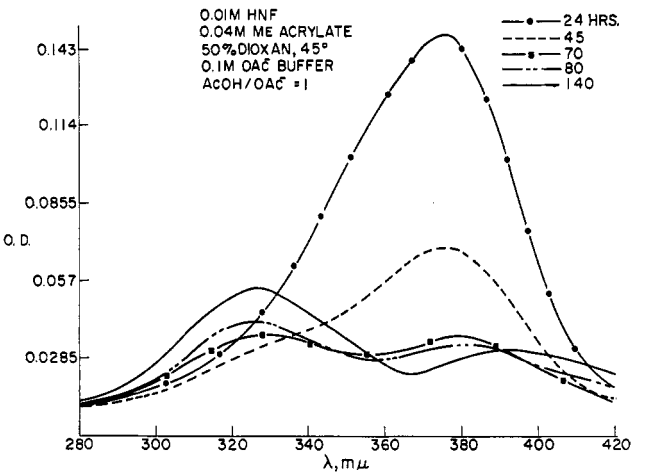


Fig. 2.—Spectra changes *vs.* time, reactants as in Fig. 1.: —●—, 24 hr.; ----, 45 hr.; —■—, 70 hr.; —·—·—, 80 hr.; ———, 140 hr.

Figures 1 and 2 give the total spectrum of the nitroform–methyl acrylate system at various times. Inspection of the spectra in Fig. 1 shows that as the reaction progresses the absorption maximum at 350 mμ for nitroform[6] decreases. Although this was expected, the increased absorption on the long wave-length side of the maximum, coupled with the shift of this absorption maximum to longer wave lengths with time, indicated that a new polynitro anion was being formed. The regular decrease in the absorption with time on the short wave-length side of the absorption maximum was taken as evidence for the fact that this new polynitro

(3) L. A. Kaplan and M. J. Kamlet, *J. Org. Chem.*, **27**, 780 (1962).

(4) This possibility was thought to be extremely remote since the unsaturated ester DNU would be expected to yield the β-hydroxy derivative.

(5) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **28**, 2128 (1963).

(6) J. Hine and L. A. Kaplan, *J. Am. Chem. Soc.*, **82**, 2915 (1960).

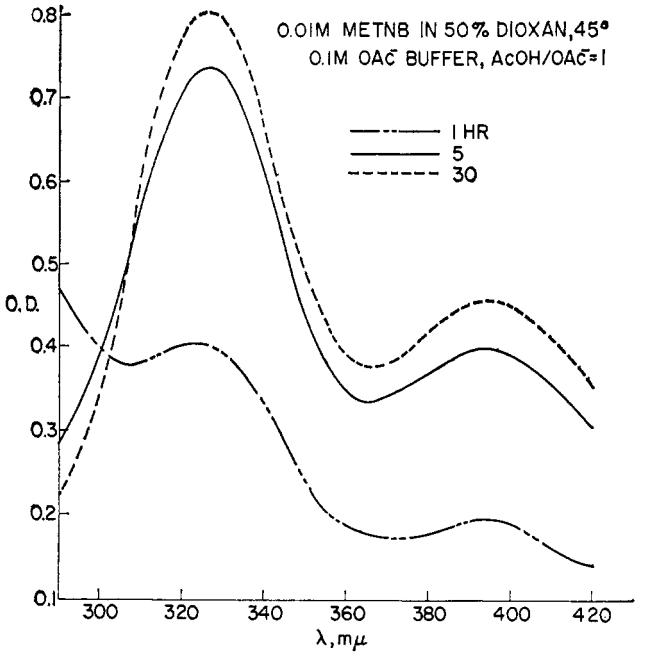


Fig. 3.—Spectral changes *vs.* time for 0.01 *M* MeTNB, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ——, 1 hr.; ———, 5 hr.; – – – –, 30 hr.

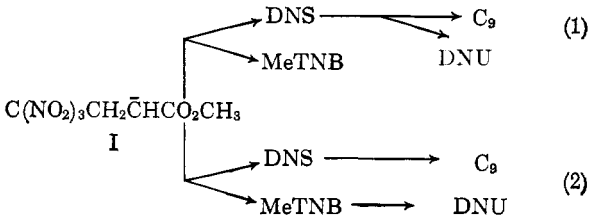
anion was *not* the unsaturated ester DNU, as this anion has twin maxima: $\lambda_{max}^{dil\ KOH}$ 326 mμ (log ε 4.24), 396–402 (3.98).[5] The observed spectrum shift is best correlated with the presence of the heretofore undetected precursor of C_9, potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS). This polynitro anion would be expected to have an absorption maximum at about 380 mμ.[7]

Allowing the reaction to proceed further (Fig. 2) shows that at the end of 24 hr. the original nitroform maximum at 350 mμ has not only shifted out to 380 mμ, but it has also undergone a considerable decrease in intensity.[8] This is consistent with the DNS reacting further with methyl acrylate to yield C_9. The appearance of a slight inflection at ≈330 mμ in this spectrum is indicative of the formation of the unsaturated ester DNU (*vide supra*). After 45 hr., both the decrease in the absorption of the 380-mμ maximum and the increased absorption of the inflection at ≈330 mμ are more pronounced.

The remaining spectra in Fig. 2 show that, with increasing time, the inflection at ≈330 mμ increases in intensity and becomes a true absorption maximum at ≈325 mμ and, as the 380-mμ absorption maximum disappears, a new long wave-length band at ≈400 mμ takes its place. This observation is consistent with the slow formation of the unsaturated ester DNU.

By analogy with the nitroform–β-nitrostyrene system,[6] the anion I would be formed by the addition of trinitromethide ion to methyl acrylate. On the basis of the above spectral data, two schematic paths seemed reasonable (eq. 1 and 2).

Inspection of the two paths shows that, in path 1, DNS is the common precursor for C_9 and DNU and, under the reaction conditions, the normal Michael



adduct MeTNB is stable. Path 2 predicts that the adduct MeTNB is not stable under the reaction conditions, and that its decomposition is responsible for the formation of DNU. It should be noted that there was no evidence of reversal of the adduct MeTNB to trinitromethide ion found in the spectra of the forward reaction[9] compared with the nitroform–β-nitrostyrene system where the adduct is quantitatively converted to trinitromethide ion and β-nitrostyrene in a pyridine–pyridinium ion buffer system.[6]

It appeared that it would be relatively simple to differentiate between the two possible paths by measuring the spectral changes with time of a MeTNB solution under the identical reaction conditions. Fig. 3 shows that, after 1 hr., this spectrum is vastly different from that of the forward reaction (Fig. 1) in that it exhibits absorption maxima at ≈323 and 400 mμ,[10] but no inflections at 350 and/or 380 mμ.[9]

After 5 hr., the spectrum (Fig. 3) exhibits the typical twin maxima of DNU at ≈323 and ≈395–400 mμ. The ratio, $O.D._{325}/O.D._{390}$ was found to be 1.79. For an authentic sample of DNU, this ratio equals 1.85. A comparison of the spectrum after 30 hr. with that of the forward reaction after 24 hr., Fig. 2, showed the complete absence of the 380-mμ absorption maximum due to DNS in the reverse reaction. Allowing this reaction to proceed for a period of better than 100 hr. produced no change in the shape of the spectral envelope. The decomposition of MeTNB under these conditions, therefore, gives essentially quantitative yields of the unsaturated ester DNU.

The almost complete absence of DNU in the forward reaction until 24 to 45 hr. and the absence of DNS in the reverse reaction suggest that DNS is not the precursor of DNU. It will be shown that the reaction of DNS with methyl acrylate under these conditions yields C_9 as the sole product. The spectrum of this reaction at various times showed no evidence of DNU formation (*vide infra*). This observation, together with the one that MeTNB is essentially quantitatively decomposed to DNU under these conditions, made path 2 the best representation of the over-all reaction.

Synthetic Studies.—The above spectral data (Fig. 1 and 2) also suggest that the α-hydroxydinitro ester

(7) For the corresponding amide, $\lambda_{max}^{dil\ KOH}$ 380 mμ (log ε 4.22).[5] See too, M. J. Kamlet and D. J. Glover, *J. Org. Chem.*, **27**, 537 (1962).

(8) All spectra in Fig. 1 and 2 are converted to equivalent dilutions so that the relative concentrations of the intermediates and products at various time intervals may be compared.

(9) Work now in progress on the effect of substituents on the course of the reverse reaction indicates that there is some reversal of MeTNB to nitroform[6] and possibly DNS under these conditions. These reaction paths represent about 5% of the total reaction under these conditions. The significance of this result will be reported in a future communication.

(10) The spectra in Fig. 3 have *not* been normalized to account for dilutions of the reaction mixture, and the relative concentrations at the various times can *not* be compared. The spectrum measured after 1 hr. is that of the undiluted reaction mixture, 0.01 *M* MeTNB. Calculations based on $O.D._{395}$ show that less than 0.2% of the MeTNB has reacted during this time interval. After 1.5 hr., 35% of the nitroform has reacted to form MeTNB and DNS (Fig. 1). The decomposition of the product MeTNB under these conditions is too slow to interfere with the spectrophotometric study of the addition of nitroform to methyl acrylate. The presence of end absorption in the 1-hr. spectrum (Fig. 3) is due to carbonyl and nitro group absorption as this solution is essentially 0.01 *M* in MeTNB.

DNS was present as a stable intermediate in moderate concentrations during the earlier stages of the forward reaction and should be able to be isolated from the reaction mixture. This hypothesis was tested by treating methyl acrylate with an excess of potassium trinitromethide in an aqueous dioxane solution containing 1 equiv. of potassium acetate. Under these conditions, the competing reactions, Michael addition of DNS to methyl acrylate to form C_9 and the protonation of the anion I to form MeTNB, would be minimized. The reaction was followed spectrophotometrically and when the ratio $O.D._{380}/O.D._{350}$ reached a maximum, the reaction was stopped. This point corresponded to a maximum yield of DNS.

After extraction with ether and removal of the unchanged potassium trinitromethide, a lemon yellow salt was obtained in 36% yield. The salt analyzed well for potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS) and had $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.23).[7] In the infrared, the spectrum exhibited the expected absorption bands for the functionality present: 1730 for ester carbonyl,[11] 3250–3470 and 3540 for hydroxyl,[12] and 1167 and 1242 cm.$^{-1}$ for nitro groups in $-C(NO_2)_2^-$.[13]

Spectrophotometric analysis of the mother liquors from the isolation of DNS did not indicate that any other polynitro anions [DNU or $C(NO_2)_3^-$] were present. Work-up of the ether extracts of the reaction mixture gave the expected by-products, MeTNB and C_9. The absence of DNU in the reaction products of this short-stopped reaction confirmed the conclusions reached in the preliminary spectral comparison experiments as to its mode of formation.

$$C(NO_2)_3^- + CH_2{=}CHCO_2CH_3 \xrightarrow[\text{aq. dioxane}]{OAc^-}$$

MeTNB (12.6%) + C_9 (23.2%) + DNS (36%)

The preliminary spectroscopic and analytical evidence points to the fact that DNS was indeed the α-hydroxydinitro ester. This structural assignment was readily confirmed by treating DNS with methyl acrylate in an aqueous dioxane acetic acid–acetate buffer. The previously characterized C_9[3] was obtained in 78% yield. The lack of side reactions in this Michael addition was shown initially by the total ultraviolet spectrum of the reaction mixture determined at various times throughout the course of the reaction. These spectra, Fig. 4, show a regular decrease in the optical density at the absorption maximum which corresponds to the formation of C_9. Additionally, there is a regular decrease in the optical density on both sides of the absorption maximum, thus precluding the formation of such by-products as DNU or other polynitro anions in this reaction.

Other evidence for the singular path that this reaction takes came from kinetic measurements.[14] The specific rate constants calculated for several runs, followed to about 99% completion, exhibited no downward drift. This would not be the expected result if other polynitro anions were being produced in concurrent side reactions.

(11) R. N. Jones in "Chemical Applications of Spectroscopy in Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 203, *et. seq.*

(13) L. A. Kaplan, *J. Org. Chem.*, **29**, 1638 (1964).

(14) The complete results will be reported in a future communication.

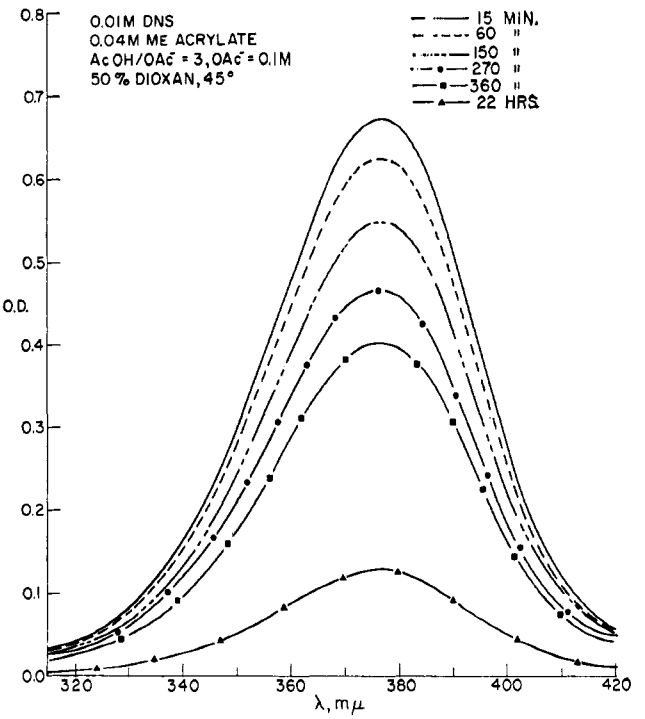


Fig. 4.—Spectral changes *vs.* time for 0.01 *M* DNS, 0.04 *M* methyl acrylate, 0.1 *M* OAc^-, AcOH–OAc^- (1:1), 50% dioxane at 45°: ———, 15 min.; – – – –, 60 min.; —·—·—, 150 min. —●—, 270 min.; —■—, 360 min.; —▲—, 22 hr.

The synthetic procedure for the preparation of DNS was extended to other acrylic systems to see if analogous α-hydroxydinitro derivatives could be isolated. Under similar conditions, the reaction of potassium trinitromethide with methyl vinyl ketone gave the expected product, 5,5-dinitro-3-hydroxypentan-2-one, as the potassium salt (II). This salt had the characteristic ultraviolet absorption spectrum, $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.22), and in the infrared had absorption bands at 1700, 3375, and 1160 and 1243 cm.$^{-1}$ for the carbonyl, hydroxyl, and nitro groups in the $-C(NO_2)_2^-$ function, respectively.

$$C(NO_2)_3^- + CH_2{=}CHCOCH_3 \longrightarrow {}^-C(NO_2)_2CH_2CHOHCOCH_3$$

II (33.9%)

With acrylonitrile as the acrylic augend, it was predicted that the potassium salt of 3,3-dinitropropionaldehyde (IV) would be obtained by the following sequence.

$$C(NO_2)_3^- + CH_2{=}CHCN \longrightarrow \underset{\text{III}}{{}^-C(NO_2)_2CH_2CHOHCN} \longrightarrow {}^-C(NO_2)_2CH_2CHO + HCN$$

IV

The α-hydroxydinitro derivative III produced in this reaction would be the cyanohydrin of 3,3-dinitropropionaldehyde. Under the reaction conditions the cyanohydrin equilibrium should be shifted in the direction of the aldehyde IV. When this reaction was followed spectrophotometrically, the 350-mμ absorption maximum for nitroform shifted to ≈357 mμ compared with the methyl acrylate or methyl vinyl ketone systems where the shift was generally to 370 to 375 mμ. After removing the unchanged potassium trinitromethide, the residual solution exhibited an absorption maximum at ≈360 mμ as compared with the methyl acrylate or

methyl vinyl ketone products which had absorption maxima at ≈380 mμ.

Utilizing similar isolation procedures, it was not possible to obtain a solid potassium salt from the acrylonitrile reaction. However, the presence of an absorption maximum at ≈365 mμ is characteristic of the chromophore system $^{-}C(NO_2)_2$-CH_2-Y, where Y is an electron-attracting substituent.[7] Thus, for 3,3-dinitropropionitrile, 2,2-dinitroethanol, and 2,2-dinitroethylamine, $\lambda_{max}^{dil\ KOH}$ is 362.5, 365, and 362 mμ, respectively.[7] Based upon the ultraviolet spectrum of the reaction mixture after removal of unchanged potassium trinitromethide, it appeared that the product remaining in solution was 3,3-dinitropropionaldehyde.

Experimental[15,16]

Spectrophotometric Studies.—The nitroform–methyl acrylate system was studied by thermostating 10 ml. of 0.400 *M* methyl acrylate in dioxane, 10 ml. of 1.00 *M* acetic acid in dioxane, 10 ml. of 1.00 *M* sodium acetate in water, and about 50 to 55 ml. of 50 v./v. % dioxane at 45° in a 100-ml., low actinic volumetric flask for at least 20 min. At the end of this time, 10 ml. of 0.100 *M* nitroform in water was added; the resulting solution was made up to volume with 50 v./v. % dioxane at 45°, thoroughly mixed by shaking, and returned to the thermostat. At appropriate times, 5-ml. aliquots of this solution were taken and diluted to 50 ml. with water to quench the reaction. A 4-ml. aliquot of the resulting solution was then diluted to 100 ml. with water after first adding 5 ml. of 20% sodium acetate solution. The spectrum of this dilution was then determined on the Cary Model 14 recording spectrophotometer, scanning at a rate of 15 mμ/min. For the spectra determined after 5 hr., dilutions were chosen to give optical density readings between 0.3 and 1.0 at the absorption maxima. These values were then normalized to the 5- to 50-ml., 4- to 100-ml. dilution to obtain the data plotted in Fig. 2.

For the decomposition of methyl 4,4,4-trinitrobutyrate, Fig. 3, a similar procedure was followed using 0.100 *M* methyl 4,4,4-trinitrobutyrate in dioxane in place of nitroform and methyl acrylate. The spectra in Fig. 3 have *not* been normalized for different dilution factors.

For the reaction of DNS with methyl acrylate, the procedure was identical with that used in studying the nitroform–methyl acrylate system, using 10 ml. of 0.100 *M* DNS in water in place of the aliquot of nitroform stock solution. For all of the spectra in Fig. 4 except the 22-hr. spectrum, the dilution procedure was the same as that described for the early part of the nitroform–methyl acrylate runs. For the spectrum after 22 hr., the dilution was 5 to 50 ml., then 10 to 100 ml. The data for this spectrum have been divided by 2.5 before plotting in Fig. 4.

Synthetic Studies. Potassium methyl 4,4-dinitro-2-hydroxybutyrate (DNS) was prepared by dissolving 0.12 mole (22.7 g.) of potassium trinitromethide and 0.1 mole (9.8 g.) of potassium acetate in 200 ml. of 50% dioxane. To the resulting solution, heated to 45 to 50°, was added 0.1 mole (8.6 g.) of methyl acrylate. The spectrum of this reaction mixture was followed with a Cary Model 14 spectrophotometer by making appropriate dilutions of small samples of the reaction mixture at various times. These spectra were not unlike those in Fig. 1. After 180 min., calculations based upon optical density measurements at 350 and 380 mμ showed that there was 0.025 mole of trinitromethide ion and 0.034 mole of the α-hydroxydinitro ester, DNS, present in the reaction mixture. As the $O.D._{380}/O.D._{350}$ ratio had reached a maximum at this time, the reaction was stopped by cooling to ambient temperature.

The dark red solution was extracted with three 100-ml. portions of ether and the combined extracts were washed with water until the washings were essentially colorless. The organic phase was then dried over Drierite and saved for C_9 and MeTNB isolation (*vide infra*).

The dark red aqueous phase was warmed on the steam bath to expel the residual ether and then cooled in ice. A yellow crystalline solid separated which was collected on a Büchner funnel, washed with methanol then ether, and air-dried. This procedure yielded 4.58 g. (20.8%) of a dark yellow product, $\lambda_{max}^{H_2O}$ 350 mμ. The ultraviolet spectrum of this material was identical with that of potassium trinitromethide. This salt was unchanged starting material.

The filtrate, but not the washings, from the above procedure was diluted with twice its volume of absolute methanol and cooled to about −10° in a Dry Ice–acetone bath. A microcrystalline yellow solid separated. This was collected on a Büchner funnel, washed with cold methanol and ether, and air-dried to yield 3.89 g. of material having $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.24.

The mother liquors from the preceding crop were diluted with an additional 100 ml. of absolute methanol and cooled in Dry Ice–acetone as previously. An additional 1.85 g. of lemon yellow crystals were obtained, $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.16.

The addition of 400 ml. of absolute methanol to the mother liquors followed by cooling to −20 to −30° in Dry Ice–acetone gave a final crop of 1.80 g. of the yellow salt, $\lambda_{max}^{dil\ KOH}$ 378 mμ, $O.D._{380}/O.D._{350}$ = 2.09. An analytical sample of the salt was prepared by recrystallization from a large volume of methanol.

Anal. Calcd. for $C_5H_7KN_2O_7$: C, 24.4; H, 2.9; K, 15.9; N, 11.4. Found: C, 24.1, 23.2, 23.7; H, 3.3, 3.0, 2.8; K, 15.3, 15.4; N, 11.7, 11.1, 11.1.

Principal infrared absorption bands were carbonyl, 1730; hydroxyl, 3250–3470 and 3540; $-C(NO_2)_2^-$, 1167 and 1242 cm.$^{-1}$. The ultraviolet absorption maximum was $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ε 4.23).

The mother liquors from the final crop were subjected to analysis by ultraviolet absorption spectroscopy. The filtrates were made up to 1000 ml. and then diluted by a factor of 2500, with a small amount of dilute potassium hydroxide added to the final dilution. The optical density of this final dilution was determined at 380 mμ: $O.D._{380}$ = 0.306, 0.304; 10^5[DNS] = 1.81 *M*, 10^3[DNS] = 4.5 *M*. The total yield of the α-hydroxydinitro ester DNS was 36% based upon methyl acrylate.

The combined dried ether extracts were treated with Darco decolorizing charcoal and evaporated to dryness. The residual oil was slurried with a mixture of 20 ml. of *n*-hexane and 5 ml. of ether. By this procedure there was obtained 3.40 g. of a white crystalline solid melting at 71.5–4.5° (authentic C_9, m.p. 73–74°). This corresponded to 0.0116 mole of C_9 or a 23.2% yield based upon methyl acrylate.

The solvent phase from this work-up was evaporated to yield 2.98 g. of a colorless, viscous oil melting at 15–20° (authentic MeTNB, m.p. 27–28°). This represents a 12.6% yield based upon methyl acrylate. The total materials balance based upon methyl acrylate is therefore 71.8%.

5,5-Dinitro-3-hydroxypentan-2-one (potassium salt) was prepared by treating 0.12 mole (22.7 g.) of potassium trinitromethide, 0.1 mole (9.8 g.) of potassium acetate, and 0.1 mole (7.0 g.) of methyl vinyl ketone in 200 ml. of 50% dioxane at 50° as described previously. The reaction in this case was quite exothermic and the solution turned very dark almost immediately upon the addition of the methyl vinyl ketone. After 30 min., a constant ultraviolet spectrum was obtained ($\lambda_{max}^{H_2O}$ 370 mμ), and the solution was cooled to room temperature. The solution was extracted with three 100-ml. portions of ether.

The aqueous phase, after the residual ether had been removed on the steam bath, was cooled to 0 to −5°, whereupon a yellow solid separated. This product was collected by filtration, washed with absolute methanol (washings discarded) and ether, and dried. There was obtained 3.73 g. of a yellow salt, $\lambda_{max}^{H_2O}$ 350 mμ. This was unchanged potassium trinitromethide.

The mother liquors ($\lambda_{max}^{H_2O}$ 375 mμ) were diluted with 50 ml. of absolute methanol and cooled to about −10°. A yellow-orange solid separated. It was collected by filtration, washed with absolute methanol and ether, and dried. This procedure gave 3.70 g. of a crystalline solid, $\lambda_{max}^{dil\ KOH}$ 378 mμ.

The mother liquors were cooled to −20° and a second crop of 4.10 g. of a yellow-orange salt was obtained, $\lambda_{max}^{dil\ KOH}$ 377 mμ. On cooling the mother liquors to as low as −40°, only small amounts of material separated which could not be collected on a Büchner funnel.

(15) Many of the compounds described are explosive in nature and quite sensitive to impact or grinding. Appropriate precautions should be taken in their handling.

(16) Microanalyses were performed by Dr. Mary Aldridge, Department of Chemistry, American University, Washington, D. C. Infrared spectra were determined in Nujol mulls with a Beckman IR-4 spectrophotometer

An analytical sample was obtained by recrystallization of the combined crops from a large volume of methanol as small yellow-orange plates.

Anal. Calcd. for $C_3H_7KN_2O_6$: C, 26.1; H, 3.1; K, 17.0; N, 12.2. Found: C, 26.2, 25.9; H, 3.1, 3.4; K, 16.9, 16.7; N, 12.5, 12.2.

Principal infrared absorption bands were carbonyl, 1690; hydroxyl, 3375; $-C(NO_2)_2^-$, 1160 and 1243 cm.$^{-1}$. The ultraviolet absorption maximum was $\lambda_{max}^{dil\ KOH}$ 378 mμ (log ϵ 4.22).

3,3-Dinitropropionaldehyde (potassium salt) was prepared by treating 0.1 mole (22.7 g.) of potassium trinitromethide, 0.1 mole (9.8 g.) of potassium acetate, and 0.1 mole (5.3 g.) of acrylonitrile in 200 ml. of 50% dioxane at about 60°. Samples of the reaction mixture were analyzed spectrophotometrically throughout the 150-min. reaction period. During this time there was a gradual shift of λ_{max} from 350 to about 357 mμ.

At the end of 150 min., the mixture was cooled to ambient temperature and extracted with three 100-ml. portions of ether. The aqueous phase was cooled to about −5°, whereupon a yellow crystalline solid separated. This product after washing with methanol and ether weighed 5.28 g. and proved to be unchanged potassium trinitromethide, λ_{max} 350 mμ.

Diluting the mother liquors with an equal volume of methanol and cooling to about −30 to −40° in Dry Ice–acetone gave only small amounts of a gummy solid. This material had λ_{max} 368 mμ while the mother liquors after removal of the unchanged potassium trinitromethide had λ_{max} 360 mμ.

Reaction of Potassium Methyl 4,4-Dinitro-2-hydroxybutyrate (DNS) with Methyl Acrylate.—Fifteen thousandths of a mole (3.69 g.) of DNS, 0.03 mole (2.58 g.) of methyl acrylate, 25 ml. of 1 *M* acetic acid in dioxane, and 50 ml. of water were heated on the steam bath for 3 hr. The resulting mixture was diluted with 200 ml. of water and extracted with five 100-ml. portions of ether, after first adjusting the pH of the solution to between 7 and 8 with sodium carbonate. The combined ether extracts were dried over calcium sulfate and the ether was removed on the steam bath to leave a viscous oil. This oil solidified on cooling to yield 3.42 g. of a white solid melting at 72–75°.

After recrystallization from ether, this product melted at 74–75° and did not depress the melting point of an authentic sample of dimethyl 4,4-dinitro-2-hydroxypimelate (C_9). Spectrophotometric analysis of the residual aqueous phase showed that less than 10^{-4} moles of DNS remained in solution.

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Cyclization of Isothiocyanates as a Route to Phthalic and Homophthalic Acid Derivatives[1,2]

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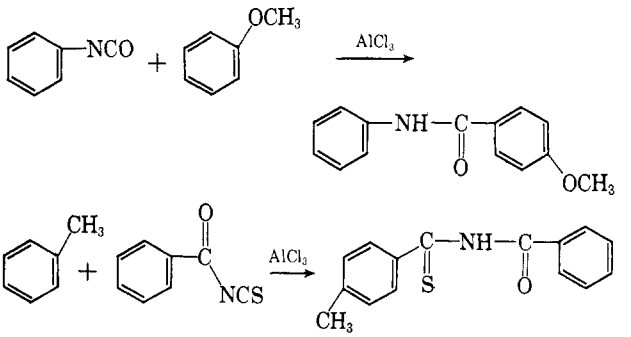
Under Friedel–Crafts conditions, benzoyl isothiocyanates undergo cyclization to monothiophthalimides, and phenylacetyl isothiocyanates give monothiohomophthalimides. The thioimides may be converted to their oxygen analogs, reduced to isoquinoline derivatives, or hydrolyzed to the dicarboxylic acids. The cyclization shows great selectivity when two different *ortho* positions are open for ring closure.

Although there exist numerous methods for the introduction of a carboxyl group into an aromatic ring, they are almost exclusively limited to bimolecular electrophilic substitution reactions, with concomitant uncertainty about the site of introduction, the *para* position usually being favored over the *ortho* position. Prominent examples of such methods include the Gattermann and the Gattermann–Koch reactions,[3,4] the Hoesch reaction,[5] the Vilsmeier–Haack reaction,[6] the Reimer–Tiemann reaction,[7] the Kolbe reaction,[8] bromination followed by the Grignard reaction with carbon dioxide, and the Friedel–Crafts acylation reaction. The use of isocyanates as acylating agents has been studied intermittently since 1885, when Leuckart first produced *p*-methoxybenzanilide by treatment of anisole with phenyl isocyanate and aluminum chloride,[9] but the yields in these and other studies were often low owing in part to the rapid decomposition of the reagents. The use of acyl isothiocyanates was first reported by Wheeler[10] in the reaction of toluene with benzoyl isothiocyanate.



It occurred to us that aromatic acyl and alkyl isothiocyanates would possess sufficient reactivity to serve as intramolecular acylating agents in order to provide a synthetic route to phthalic acids from benzoic acids and to homophthalic acids from phenylacetic acids. This paper reports the results of these studies.[11]

(1) Taken in part from the doctoral thesis of R. O. Kan, University of Michigan, 1961.

(2) For a preliminary communication describing some of the results reported here, see P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 4753 (1960).

(3) (a) L. Gattermann, *Ber.*, **31**, 1149 (1898); (b) N. O. Calloway, *Chem. Rev.*, **17**, 327 (1935).

(4) (a) L. Gattermann and J. A. Koch, *Ber.*, **30**, 1622 (1897); (b) N. N. Crounse, *Org. Reactions*, **5**, 290 (1949).

(5) (a) J. Houben and W. Fischer, *Ber.*, **66**, 339 (1933); (b) P. E. Spoerri and A. S. DuBois, *Org. Reactions*, **5**, 387, 1949.

(6) L. F. Fieser, J. L. Hartwell, J. E. Jones, J. H. Wood, and R. W. Frost, *Org. Syn.*, **20**, 11 (1940).

(7) K. Reimer and F. Tiemann, *Ber.*, **9**, 824 (1876).

(8) (a) H. Kolbe, *J. prakt. Chem.*, [2]**10**, 89 (1874); (b) R. Schmitt, *ibid.*, [2]**31**, 397 (1885).

(9) R. Leuckart and M. Schmidt, *Ber.*, **18**, 2338 (1885).

(10) H. L. Wheeler, *Am. Chem. J.*, **26**, 345 (1901).

(11) One such example had been previously reported in the conversion of α-naphthyl isothiocyanate to thionaphthacarbostyril [N. S. Dokunikhin and L. A. Gaeva, *Zh. Obshch. Khim.*, **24**, 1871 (1954)], but, in view of our results, the structure of the product should be reinvestigated.