TABLE VI

PHYSICAL PROPERTIES OF CYCLOHEXYLIDENE PRODUCTS FROM THE KNOEVENAGEL CONDENSATION OF CYCLOHEXANONE WITH VARIOUS CYANO ACTIVE METHYLENE COMPOUNDS

Active Methylene	B.P./P., Mm.	M.P.	n_D^t	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Ref.
Malononitrile	98–101/0.08–0.09	−3.5 to −4.5	$1.5091^{26.6}$	73.94	73.80	6.89	6.71	19.16	19.32	23
Cyanoacetamide	—	110.5–111.5[a]	—	65.83	65.77	7.37	7.37	17.06	17.08	30
Pivaloylacetonitrile	103–105/0.13–0.14	<−35	$1.4911^{19.4}$	76.05	76.00	9.33	9.31	6.82	6.70	—
Benzoylacetonitrile	145–147/0.05	69–71.5[a]	$1.5687^{30.5}$	79.97	79.25	6.71	6.64	6.22	6.35	—

[a] Corrected.

reaction mixture was cooled, filtered to separate the resin, and vacuum distilled to give ethyl cyclohexylidenecyanoacetate in 95–100% yield. See Tables V and VI for the physical properties of the products of the reactions cited in this work.

Fresh catalyst was used in each experiment described in this work. All the Dowex 3 used was from the same lot. The amine acetate catalysts were formed *in situ* from equimolar quantities of the amine and acetic acid. Blank runs were made with all resins as well as with the ammonium acetate and the cyanoacetic acid to determine their water content, so as to correct for it.

CLEVELAND 6, OHIO

(30) M. Nakamura, Japan. Pat. 2,176 (April 23, 1954); *Chem. Abstr.*, 49, 14802 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

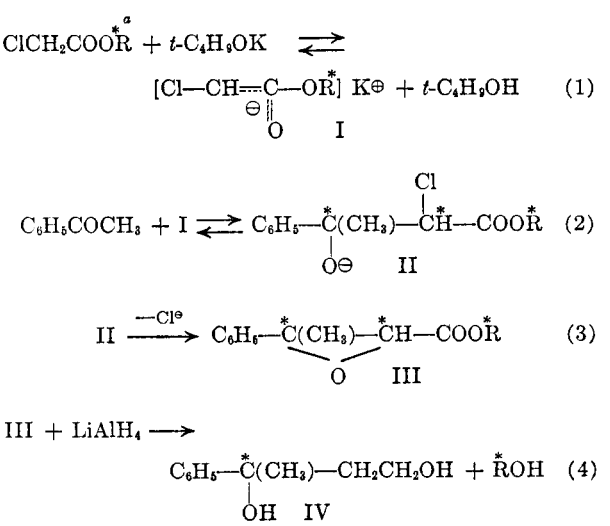
Partial Asymmetric Synthesis in the Darzens Reaction

KEIITI SISIDO, OSAMU NAKANISI, AND HITOSI NOZAKI

Received June 22, 1961

The Darzens reaction of either (−)-menthyl or (+)-bornyl chloroacetate with acetophenone is accompanied by a partial asymmetric synthesis, as this is shown by reduction of the resulting ester with lithium aluminum hydride to (−)-3-phenylbutane-1,3-diol of varying optical activities. Interestingly the predominant configuration of the asymmetric center newly formed has been found to be the same in both cases. Ethanolysis of menthyl or bornyl glycidate thus prepared affords the corresponding ethyl ester, which is dextrorotatory and can be transformed into (−)-3-phenylbutane-1,3-diol in optical yields comparable to those in direct hydride reduction. Possible mechanism leading to this asymmetric synthesis is discussed.

Evidence has been accumulated in favor of the aldolization mechanism of the Darzens reaction between α-halo esters and aldehydes or ketones, involving the initial formation of halohydrin anions (I) (Equations 1 and 2) followed by the loss of halide anion (Equation 3).[1,2] On the other hand the aldol type condensation of ketones and esters[3] has been shown to afford optically active β-hydroxy acids, when (−)-menthyl or (+)-bornyl acetate is allowed to react with unsymmetrically substituted ketones and the resulting β-hydroxy esters are hydrolyzed.[4] This paper comprises the Darzens reaction of optically active chloroacetates and the subsequent removal of asymmetric carbons initially introduced. These reactions are accompanied by partial asymmetric syntheses and are summarized as follows:



(1) (a) M. Ballester, *Chem. Reviews*, 55, 283 (1955); (b) M. Ballester and D. Pérez-Blanco, *J. Org. Chem.*, 23, 652 (1958).

(2) (a) H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, 82, 5459 (1960); (b) H. Kwart and L. G. Kirk, *J. Org. Chem.*, 22, 116 (1957); (c) J. Munch-Petersen, *Acta Chem. Scand.*, 7, 1041 (1953).

(3) (a) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, 73, 2972 (1951); (b) K. Sisido, H. Nozaki, and O. Kurihara, *J. Am. Chem. Soc.*, 74, 6254 (1952); (c) For a recent publication on this problem see W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, 25, 1693 (1960).

(4) K. Sisido, K. Kumazawa, and H. Nozaki, *J. Am. Chem. Soc.*, 82, 125 (1960).

$$\text{III} + C_2H_5OH \xrightarrow{C_2H_5ONa}$$

$$C_6H_5\text{—}\overset{*}{C}(CH_3)\text{—}\overset{*}{C}H\text{—}COOC_2H_5 + \overset{*}{R}OH \quad (5)$$

$$\underset{O \quad V}{\diagdown\diagup}$$

$$V + LiAlH_4 \longrightarrow IV + C_2H_5OH \quad (6)$$

$$C_6H_5\text{—}\underset{OH}{\overset{*}{C}}(CH_3)\text{—}CH_2COOR + LiAlH_4 \longrightarrow IV + ROH \quad (7)$$

VI

[a] An asterisk indicates an asymmetric carbon

The condensation of either (−)-menthyl or (+)-bornyl chloroacetate with acetophenone in the presence of potassium *t*-butoxide was carried out under standardized conditions[5] and the crude reaction products were treated with an excess of lithium aluminum hydride. Chromatographic separation of the resulting mixture on a silica gel column afforded 3-phenylbutane-1,3-diol (IV), whose infrared spectrum was superimposable in every fine detail with an authentic sample prepared from acetophenone and ethyl bromoacetate by the Reformatsky reaction and the following reduction with lithium aluminum hydride (Equation 7).[6] The specific rotation ($[\alpha]_D$) of IV prepared from (−)-menthyl chloroacetate had values of −8.2° and −8.5° in duplicated experiments, while the one of IV obtained from (+)-bornyl chloroacetate values of −2.3° and −2.6°, respectively.[7] Practically no change of the rotation values was observed upon repeated chromatography.

In order to exclude the possibility of this asymmetric synthesis occurring during the hydride reduction of glycidic esters (III), III was treated with an excess of ethanol containing sodium ethoxide as a catalyst (Equation 5) and the resulting ethyl (+)-β-phenyl-β-methylglycidate (V) was reduced with lithium aluminum hydride. Chromatographic separation of the reaction product afforded 3-phenylbutane-1,3-diol (IV), whose purity was again checked by infrared spectrum. The specific rotation of IV prepared from (−)-menthyl chloroacetate by this route (Equations 1–3, 5, and 6) showed values of −6.2° and −6.4° in duplicated experiments, while that of IV obtained similarly from (+)-bornyl chloroacetate was −1.8° and −1.9°, respectively.[8]

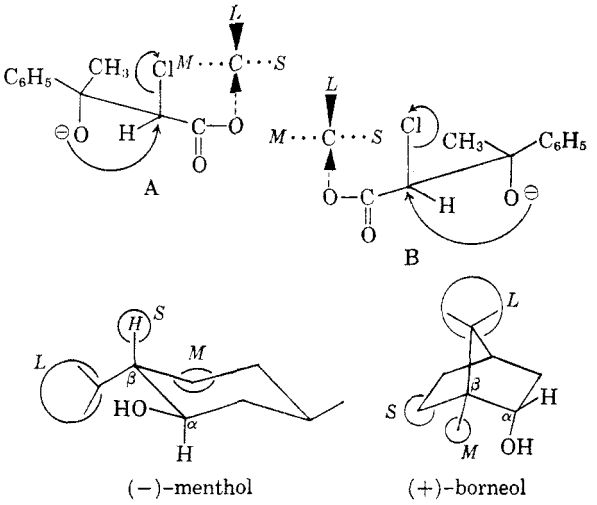
(5) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953). See also M. S. Newman and B. J. Magerlein, *Organic Reactions*, **5**, 413 (1949).

(6) M. H. Palmer and J. A. Reid, *J. Chem. Soc.*, 931 (1960).

(7) As Palmer and Reid (ref. 6) have recorded $[\alpha]_D$ −56.82° for (−)-3-phenylbutane-1,3-diol (IV) obtained by the hydride reduction of (−)-menthyl (+)-β-hydroxy-β-phenylbutyrate, these specific rotation values may be converted in optical yields of 14.4 and 15.0% for the one obtained from (−)-menthyl chloroacetate and 4.0 and 4.5% for the one from (+)-bornyl chloroacetate.

(8) Optical yields (see ref. 7) are 10.9 and 11.3% for the diol (IV) prepared from (−)-menthyl chloroacetate, while 3.2 and 3.3% for the one from (+)-bornyl chloroacetate.

Therefore the asymmetric synthesis does arise in the formation of glycidic esters (III) and possibly in the aldolization step (equations 2 and 3). The cause of this asymmetry may be visualized by assuming the diastereomeric intermediate stages A and B, the plausible difference in thermodynamic stabilities between them controlling the asymmetry.[9]



Similarly, as recorded in the aldol-type asymmetric synthesis of β-hydroxy acids,[4] the Prelog's rule[10] covering the McKenzie-type synthesis is not applicable to the present reaction, as both (−)-menthyl and (+)-bornyl chloroacetates have afforded the diol (IV) predominantly of the same (−) sign of rotation. Reid and associates recorded the asymmetric synthesis of (+)-β-hydroxy-β-phenylbutyric acid (VI) by the Reformatsky reaction of (−)-menthyl bromoacetate with acetophenone,[11] while they obtained predominantly (−)-β-hydroxy-β-phenylbutyric acid by the analogous reaction of (−)-bornyl bromoacetate.[6] They also described the reduction of esters of (+)-VI with lithium aluminum hydride affording (−)-diol (IV). So far as these findings are concerned, one can conclude that the configuration of 3-phenylbutane-1,3-diol (IV) is determined solely by the configuration of alcohol components (menthol and borneol) of haloacetates, being irrespective of the route of preparation either through Darzens glycidates or Reformatsky β-hydroxy esters. In view of the inconsistence of the Prelog's rule in both cases,

(9) The stereochemistry of an alkyl β-phenyl-β-methylglycidate appears to have not been determined as yet. In accord with the concept of overlap control as advanced by Zimmerman and associates (see ref. 2) the intermediate stages A and B have been indicated as having *trans* configuration with respect to alkoxycarbonyl group and phenyl residue which would be more bulky than methyl group. Since the asymmetry of α-carbon in the glycidate is washed out by the subsequent hydride reduction, *cis-trans* isomerism of the glycidate has not been examined in any further details.

(10) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

(11) J. A. Reid and E. E. Turner, *J. Chem. Soc.*, 3365 (1949); 3694 (1950).

the configuration of the α-asymmetric carbon attached directly to the hydroxy group of menthol or borneol should have little, if any, effect of controlling the stereochemistry of the aldol—*viz.*, II or similar intermediate stages in the Reformatsky reaction. It is postulated, as a working hypothesis, that the configuration of the β-asymmetric carbon is particularly determinant with respect to this point, the L, M, S-relationship being same on each β-carbon both of (−)-menthol and (+)-borneol as indicated in the formulas.[12]

EXPERIMENTAL[13]

(−)-Menthyl and (+)-bornyl chloroacetates. (−)-Menthyl chloroacetate was prepared from (−)-menthol and chloroacetyl chloride in the presence of dimethylaniline[14] and had a b.p. of 104–105° (4 mm.), m.p. 37–38°, α_D^{16} 9.42°, $[\alpha]_D^{16}$ −81.07° (*c* 11.62, chloroform).

(+)-Bornyl chloroacetate[15] was obtained similarly from (+)-borneol in 82–86% yields, b.p. 105–107° (4 mm.), α_D^{22} −42.89° (neat).

Darzens condensation of acetophenone with (−)-menthyl chloroacetate. To a mixture of 15 g. (0.13 mole) of acetophenone and 19 g. (0.082 mole) of (−)-menthyl chloroacetate, a solution of potassium *t*-butoxide prepared from 3.2 g. (0.082 g.-atom) of potassium and 70 ml. of anhydrous *t*-butyl alcohol was added dropwise with vigorous stirring over 1 hr., the temperature being kept at 10–13°. The red-colored reaction mixture was then treated with cold water and extracted with ether. The combined ethereal solutions were washed with 10% sulfuric acid, water, sodium bicarbonate solution, and again with water, and dried over anhydrous sodium sulfate. Distilling of the solvent and the excess of acetophenone under reduced pressure afforded 20 g. (78%) of crude (−)-menthyl β-methyl-β-phenylglycidate as a residue, which formed a yellowish viscous oil. No attempt was made to purify the condensation product, but this was subjected to the ethanolysis and to the reduction directly.

Darzens condensation of acetophenone with (+)-bornyl chloroacetate. The condensation of 15 g. (0.13 mole) of acetophenone and 19 g. (0.082 mole) of (+)-bornyl chloroacetate was carried out similarly as above and 20 g. (78%) of crude (+)-bornyl β-methyl-β-phenylglycidate was obtained as a viscous oil.

Ethanolysis of (−)-menthyl β-methyl-β-phenylglycidate.[16] To a solution of sodium ethoxide prepared from 0.5 g. (0.022 g.-atom) of sodium and 200 ml. of anhydrous ethanol, 20 g. (0.063 mole) of crude (−)-menthyl β-methyl-β-phenylglycidate was added. The solution was kept at about 40° over 12 hr. with stirring, then cooled to room temperature, and the catalyst was destroyed with an equivalent amount of acetic acid. After removal of ethanol at reduced pressure, the residue was treated with water and extracted with ether. Upon working up the solution solid menthol separated from the evaporation residue and was removed by filtration. Fractional distillation of the residue under reduced pressure gave 4.5 g. (35%) of ethyl β-methyl-β-phenylglycidate, b.p. 106° (3.5 mm.), n_D^{25} 1.4994, α_D^{18} +0.05°, $[\alpha]_D^{18}$ +0.5° (*c* 10.22).[17] The infrared spectrum was essentially superimposable with that of racemic ethyl β-methyl-β-phenylglycidate.[18]

Ethanolysis of (+)-boronyl β-methyl-β-phenylglycidate. Ethanolysis of 15 g. of the (+)-bornyl ester was carried out similarly as above to afford 2.0 g. (20%) of ethyl β-methyl-β-phenylglycidate, b.p. 96° (2 mm.), n_D^{25} 1.4990, α_D^{18} +0.13°, $[\alpha]_D^{18}$ +2.9° (*c* 4.53).[17] The infrared spectrum was practically identical with that of racemic ethyl β-methyl-β-phenylglycidate.

Reduction of (−)-menthyl β-methyl-β-phenylglycidate with lithium aluminum hydride. To a vigorously stirred mixture of 1.0 g. (0.026 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether a solution of 6.4 g. (0.020 mole) of the crude (−)-menthyl glycidate in 100 ml. of anhydrous ether was added dropwise over 30 min. The mixture was stirred at room temperature for 2 hr. and then worked up in the usual way. The evaporation residue of ethereal extracts was taken up in benzene, and this solution was subjected to chromatography on a silica-gel column. A sharp separation of the desired 3-phenylbutane-1,3-diol from (−)-menthol could easily be attained by eluting the latter with benzene and then the former with methanol. Concentration of this methanolic solution, followed by removal of the last trace of solvent under reduced pressure, afforded 1.5 g. (45%) of an oil, n_D^{28} 1.5220, α_D^{24} −1.20°, $[\alpha]_D^{24}$ −8.5° (*c* 14.12). The infrared spectrum (neat) was completely superimposable with that of an authentic sample of racemic 3-phenylbutane-1,3-diol[19] throughout the rock-salt prism region including following bands: 695, 761, 831, 880, 900, 963, 1027, 1046, 1070, 1090, 1143, 1180, 1240, 1264, 1290, 1310, 1340, 1370, 1440, 1490, 1580, 1605, 1750, 1810, 1890, 1960, 2920, 2960, 3020, 3040, and 3340 cm.$^{-1}$

Duplicate experiment on a 0.022-mole scale: yield 1.0 g. (27%), n_D^{20} 1.5187, α_D^{12} −0.48°, $[\alpha]_D^{12}$ −8.2° (*c* 5.87).

Reduction of (+)-bornyl β-methyl-β-phenylglycidate with lithium aluminum hydride. Similar reduction of 8.6 g. (0.027 mole) of crude (+)-bornyl β-methyl-β-phenylglycidate with 1.5 g. (0.39 mole) of lithium aluminum hydride and the succeeding chromatographic separation afforded 1.5 g. (33%) of 3-phenylbutane-1,3-diol, n_D^{25} 1.5273, α_D^{24} −0.16°, $[\alpha]_D^{24}$ −2.3° (*c* 6.83). The infrared spectrum was again superimposable in every fine detail with those of the racemic 3-phenylbutane-1,3-diol and of the sample obtained from (−)-menthyl chloroacetate as described above.

(12) L, M, and S indicate large, medium, and small groups, respectively, in accordance with common usuage. See for example D. J. Cram, *J. Chem. Education*, **37**, 317 (1960). Ring methylene group of borneol was considered less bulky than methyl group, as this appeared plausible on inspecting the molecular model.

(13) All temperatures are uncorrected. Analyses were carried out by Miss Kenko Ogawa. Optical rotations were determined with 1-dm. length tubes and in 95% ethanol unless otherwise stated.

(14) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers, *Org. Syntheses*, Coll. Vol. III, 142 (1955). Palmer and Reid (ref. 6) reported $[\alpha]_D^{25}$ −80.0° in chloroform, while J. B. Cohen [*J. Chem. Soc.*, 1058 (1911)] recorded $[\alpha]_D^{20}$ −75.1°.

(15) T. Takahashi, M. Hori, and Y. Suzuki, *J. Pharm. Soc. Japan*, **75**, 1377 (1955). These authors did not describe the rotatory values.

(16) For the alcoholysis of glycidates see P. S. Starcher, F. C. Frostick, Jr., and B. Philips, *J. Org. Chem.*, **25**, 1420 (1960).

(17) As difficulties were encountered in removing (−)-menthol or (+)-borneol completely from the ethanolysis products, the specific rotation values cannot be regarded as representing the degree of predominance of an enantiomeric glycidate over the other. The possibility of the contaminated (−)-menthol or (+)-borneol causing the asymmetric reduction of ethyl β-methyl-β-phenylglycidate was, however, excluded by the following observations. The reduction of optically inactive ethyl β-methyl-β-phenylglycidate was carried out in the presence of (−)-menthol or (+)-borneol by means of excess lithium aluminum hydride, but the resulting 3-phenylbutane-1,3-diol was completely inactive.

(18) Prepared from acetophenone and ethyl acetate in a 72% yield according to the method of Johnson and others (ref. 5).

(19) The authentic sample was prepared according to the method of Palmer and Reid (ref. 6) by lithium aluminum hydride reduction of the Reformatsky ester obtained from acetophenone and ethyl bromoacetate.

Duplicate experiment on a 0.016-mole scale: yield 0.82 g. (30%), n_D^{17} 1.5335, α_D^{14} −0.21°, $[\alpha]_D^{14}$ −2.6° (*c* 8.23).

Reduction of the partially active ethyl (+)-β-methyl-β-phenylglycidate with lithium aluminum hydride. Reduction of the ethyl glycidate obtained by ethanolysis of (−)-menthyl β-methyl-β-phenylglycidate gave on a 0.021-mole scale 1.2 g. (35%) of (−)-3-phenylbutane-1,3-diol, n_D^{18} 1.5310, α_D^{17} −0.74°, $[\alpha]_D^{17}$ −6.2° (*c* 11.89). Duplicate experiment on a 0.015-mole scale: yield 1.0 g. (41%) n_D^{20} 1.5240 α_D^{12} −0.62°, $[\alpha]_D^{12}$ −6.4° (*c* 9.71).

Reduction of the ethyl glycidate obtained by ethanolysis of (+)-bornyl β-methyl-β-phenylglycidate afforded on a 0.046-mole scale 1.3 g. (17%) of 3-phenylbutane-1,3-diol, n_D^{17} 1.5290, α_D^{14} −0.25°, $[\alpha]_D^{14}$ −1.9° (*c* 13.29). Duplicate experiment on a 0.024-mole scale: yield 1.6 g. (40%), n_D^{18} 1.5329, α_D^{12} −0.28°, $[\alpha]_D^{12}$ −1.8° (*c* 15.88).

The infrared spectra of these products were completely identical with those of racemic 3-phenylbutane-1,3-diol and of the partially active samples described above. The diol gave correct analyses for carbon and hydrogen.

Addendum. According to the private communication of Professors M. Ohno and H. M. Walborsky, which has reached to us after completion of writing this paper, the Darzens condensation of (−)-menthyl chloroacetate with acetophenone and the following hydride reaction have been investigated independently in their laboratories. The formation of a mixture of glycols consisting of 95% 3-phenylbutane-1,3-diol and 5% 3-phenylbutane-1,2-diol was observed. Removal of the 1,2-glycol by periodate oxidation yielded the pure 1,3-glycol, $[\alpha]_D^{24}$ −9.1° (*c* 4.2, chloroform).[20] The possibility of the 1,3-diol samples obtained in our experiments being contaminated by the 1,2-diol was excluded by periodate titration. Apparently the 1,2-diol had been eliminated by chromatographic purification of the glycol over silica-gel column.

KYÔTO, JAPAN

(20) Y. Inouye, S. Inamasu, M. Ohno, T. Sugita, and H. M. Walborsky, *J. Am. Chem. Soc.*, **83**, 2962 (1961).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE LABORATORY]

Reaction of 1,1,1,3-Tetranitropropane with Bases

MORTIMER J. KAMLET, JOSEPH C. DACONS, AND JOHN C. HOFFSOMMER

Received March 17, 1961

A product obtained in the reaction of the title compound with bases, reported by previous workers to be the potassium salt of 1,1,3-trinitropropane (II), is shown to be the potassium salt of 1,1,3-trinitro-2-propene (IV). Authentic II was synthesized by two independent methods. Evidence bearing on the mechanisms of the reactions is presented.

Novikov and co-workers[1] have recently reported that the reaction of 1,1,1,3-tetranitropropane (I) with dimethylamine in aqueous alcohol yielded as the main product a dimethylammonium salt which, on subsequent treatment with aqueous potassium chloride, was converted to a monopotassium salt. For this compound the Russian workers suggested the structure of the potassium salt of 1,1,3-trinitropropane (II), offering as evidence elemental analyses for potassium and nitrogen. The over-all yield in the transformation of I to the potassium salt was 74%. I was also purported to yield II as the main product on treatment with potassium acetate in acetone-ethanol.[2]

With aqueous ethanolic ammonia the reaction took a different course.[1] The major product obtained after treatment with aqueous potassium chloride was the dipotassium salt of 1,1,3,3-tetranitropropane (III), and only minor amounts of monopotassium salt were isolated. With the two higher homologs of I and dimethylamine, potassium acetate or potassium methoxide, only the potassium salts of 1,1,3,3-tetranitrobutane and 1,1,3,3-tetranitropentane were isolated and no trinitro derivatives corresponding to II were reported.[2]

We wish now to record the synthesis by two independent methods of the authentic potassium salt of 1,1,3-trinitropropane (II) whose properties differed markedly from those of the compound thought by Novikov to be II. We wish also to suggest evidence that the latter compound has the structure of the potassium salt of 1,1,3-trinitro-2-propene (IV).

$C(NO_2)_3CH_2CH_2NO_2$ (I) $\quad K^+\,\bar{C}(NO_2)_2CH_2CH_2NO_2$ (II)

$K^+\,\bar{C}(NO_2)_2CH_2C(NO_2)_2^-\,K^+$ (III) $\quad K^+\,\bar{C}(NO_2)_2CH{=}CHNO_2$ (IV)

Our separate preparations of authentic II involved (a) the direct reduction of I with potassium iodide in methanol and (b) the reaction of the potassium salt of 2,2-dinitroethanol with nitroethylene in absolute methanol containing a slight excess of acetic acid. The products in both instances showed comparable ultraviolet and infrared spectra and similar crystal habits and melting behavior. Elemental analyses for both samples corresponded to II (Table I).

Method (a) is general for the conversion of 1,1,1-trinitroalkanes to salts of the corresponding 1,1-dinitro compounds. Under similar conditions, for example, methyl 4,4,4-trinitrobutyrate may be

(1) S. S. Novikov, A. A. Feinsil'berg, S. A. Shevelev, I. S. Korsakova, and K. K. Babievskii, *Doklady Akad. Nauk S.S.S.R.*, **124**, 589 (1959).

(2) S. S. Novikov, A. A. Feinsil'berg, S. A. Shevelev, I. S. Korsakova, and K. K. Babievskii, *Doklady Akad. Nauk S.S.S.R.*, **132**, 846 (1960).