[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE SYNTHESIS OF β-HYDROXY-γ-NITROCARBONYL COMPOUNDS

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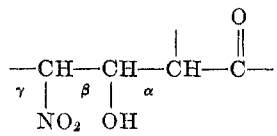
The development of general methods for the preparation of γ-nitroesters (1) and γ-nitroketones (2) has led to the adoption of these compounds as versatile synthetic intermediates (2, 3). We felt that an additional parameter for subsequent synthetic operations would be provided by the presence of a hydroxyl group along with the nitro and carbonyl functions. Accordingly, we have devised a method for the preparation of β-hydroxy-γ-nitro-esters and -ketones of type I from the corresponding nitroparaffins and hydroxymethylenecarbonyl



I

compounds. One novelty of the method lies in the fact that the sodium salt of the aldehyde (hydroxymethylenecarbonyl compound) was brought together with the active methylene compound (nitroparaffin), thus constituting an ostensible transposition of the salt combination in the usual aldol condensation (4).

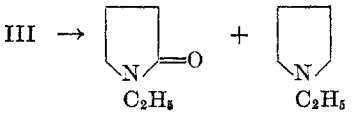
The use of the sodium salt (II) of ethyl malonaldehydate, for example, was directed because the free aldehydoester has never been isolated (5, 6), due to its tendency to self-condensation with the formation of ethyl α-formylglutaconate (5) and triethyl trimesate (6, 7). Furthermore, attempts (6, 8) to bring about the condensation of ethylmalonaldehydate with aldehydes and ketones have been frustrated by the preferential self-condensation of this reagent. The only previous reports of the formation of a carbon-carbon bond between ethyl malonaldehydate and another compound [ethyl cyanoacetate (9), resorcinol (10)] succeeded through the use of the sodium salt (II). Ethyl β-hydroxy-γ-nitrobutyrate (IIIa), the first member in our series, was prepared by the addition of the crude sodium salt (6, 11) of ethyl malonaldehydate to a benzene solution containing ten mole-equivalents of nitromethane, followed by stirring for about three days. The mild, heterogeneous conditions were employed with the hope of obtaining a slow equilibration between the anions of ethyl malonaldehydate and nitromethane, so that condensation of ethyl malonaldehydate with sodionitromethane would supersede self-condensation of the former. Isolation of the salt product and treatment with 5 % hydrochloric acid gave ethyl β-hydroxy-γ-nitrobutyrate (IIIa) in quantitative yield, based on the estimate of McElvain and Clarke (11) as to the purity (*ca.* 39–40%) of the sodium salt of ethyl malonaldehydate as initially prepared. The over-all yield calculated from ethyl acetate suffers from a poor first step, the preparation of sodio-ethyl malonaldehydate.

$$Na^+[OCH{=}CHCOOC_2H_5]^- + RCH_2NO_2 \rightarrow \rightarrow \underset{\displaystyle NO_2}{\underset{|}{RCH}}\!-\!\underset{\displaystyle OH}{\underset{|}{CH}}CH_2COOC_2H_5$$

II III

(a) R = H; (b) R = CH_3; (c) R = C_2H_5

The assignment of structure IIIa to the product was based on elementary analysis, molar refractivity, and infrared absorption bands indicative of nitro, hydroxyl, and ester carbonyl groups (see Table I). The skeletal structure of IIIa was confirmed by its reductive cyclization to N-ethyl-α-pyrrolidone (IV) and N-ethylpyrrolidine (V). The hydrogenolysis of the hydroxyl group was expected (12) under the conditions used, namely, hydrogenation over copper



IV V

chromite at high temperature and pressure in dioxane containing a small amount of ethanol. For success in preparing ethyl β-hydroxy-γ-nitrovalerate (IIIb) and ethyl β-hydroxy-γ-nitrocaproate (IIIc) by condensation of II with nitroethane and 1-nitropropane, two modifications were employed. The crude sodium salt of ethyl malonaldehydate, prepared by the method of Cogan (6), was not isolated, but the solution in which it was formed was treated directly with an excess of the nitroparaffin. The second modification was in the method employed for the isolation of the β-hydroxy-γ-nitroester from its sodium salt. The procedure of Kornblum and Graham (13), using urea in dilute acetic acid, was followed in isolating IIIb and IIIc, as well as some of the other compounds described below. The structures of the products (IIIb, IIIc) were assigned on the basis of homology with the first member of the series (IIIa) and satisfactory analyses, molar refractivities, and infrared absorption spectra. Application of the method to the preparation of a β-hydroxy-γ-nitroester substituted by an α-alkyl group was exemplified by the condensation of nitromethane with the sodium salt (VI) of ethyl methylmalonaldehydate, obtained from ethyl formate and ethyl propionate.

$$\begin{matrix} HCOOC_2H_5 \\ + \\ CH_3CH_2COOC_2H_5 \end{matrix} \xrightarrow{Na} Na^+[OCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}COOC_2H_5]^- \xrightarrow{CH_3NO_2} \longrightarrow$$

VI

$$CH_2\!-\!\underset{\displaystyle NO_2}{\underset{|}{CH}}\!-\!\underset{\displaystyle OH}{\underset{|}{CH}}\!-\!\underset{\displaystyle CH_3}{\underset{|}{CH}}COOC_2H_5$$

VII

The product was ethyl α-methyl-β-hydroxy-γ-nitrobutyrate (VII), isomeric with IIIb.

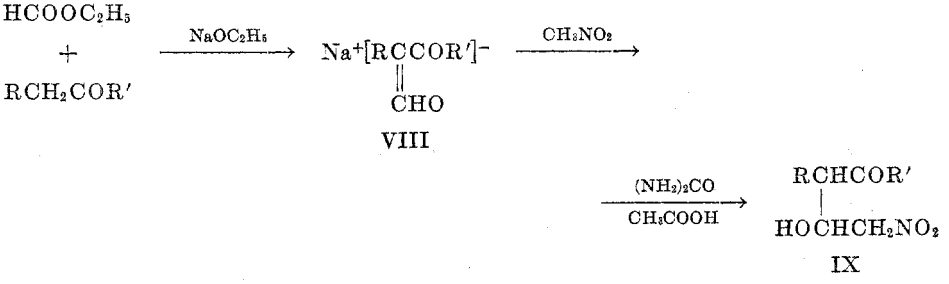
TABLE I

β-Hydroxy- γ-nitrocarbonyl Compounds

PRODUCT	B.P., °C.	MM.	n_D^{20}	d_4^{20}	OVER-ALL YIELD, %[b]	FORMULA	ANALYSIS								SELECTED INFRARED ABSORPTION MAXIMA, CM.$^{-1}$				
							C		H		N		MR_D						
							Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found					
Ethyl β-hydroxy-γ-nitrobutyrate (IIIa)	118–119	0.9	1.4559	1.2349	24	$C_6H_{11}NO_5$	40.68	40.61	6.26	5.98	7.91	8.01	38.68	38.91	3476[d]	1726[e]	1560,	1377[f]	1420
Ethyl β-hydroxy-γ-nitrovalerate (IIIb)	95	.15	1.4536	1.1916	16	$C_7H_{13}NO_5$	43.97	44.39	6.85	6.85	7.33	7.66	43.33	43.44	3477	1726	1554,	1395–1363	
Ethyl β-hydroxy-γ-nitrocaproate (IIIc)	95	<.1	1.4534	1.1530	10	$C_8H_{15}NO_5$	46.82	47.55	7.48	7.48	6.83	6.66	47.95	48.13	3483	1725	1554,	1376	
Ethyl α-methyl-β-hydroxy-γ-nitrobutyrate (VII)	94–97.5	<.1	1.4539	1.2029	16	$C_7H_{13}NO_5$	43.97	43.82	6.85	6.82	7.33	7.47	43.33	43.06	3476	1724	1556,	1383–1376	1420
4-Hydroxy-5-nitro-2-pentanone (IXa)	97–98	<.1	1.4679	1.2507	6	$C_5H_9NO_4$	40.81	41.84	6.16	6.35	9.52	9.50	32.45	32.71	3434	1710	1556,	1375–1363	1420
4-Methyl-5-hydroxy-6-nitro-3-hexanone (IXb)	98	<.1	1.4658	1.1615	54	$C_7H_{13}NO_4$	47.99	48.24	7.48	7.53	8.00	7.76	41.69	41.68	3464	1705	1557,	1382	1420
β-Hydroxy-γ-nitrobutyrophenone (IXc)	78–79.5[a]	—			3	$C_{10}H_{11}NO_4$	57.41	57.56	5.30	5.54	6.70	6.72			3500[c]	1671	1547,	1372	*ca.* 1412[g]

[a] Melting point (corr.) [b] Calculation of the yield on an over-all basis from the original ester or ketone reflects a low conversion (6, 11) to the sodium salt on the hydroxymethylene compound, which is the first step. The second step, in certain instances, may be as good as quantitative. [c] Determined in Nujol mull. [d] Hydroxyl. [e] Carbonyl. [f] Nitro. [g] Addition bands attributable to the aromatic nucleus: 1598, 1580, 760, 688 cm.$^{-1}$

The method was extended to the hydroxymethylene derivatives of ketones. The sodium salts of α-hydroxymethyleneacetone (VIIIa), diethyl ketone (VIIIb),



(a) R = H, R′ = CH_3; (b) R = CH_3, R′ = C_2H_5; (c) R = H, R′ = C_6H_5

and acetophenone (VIIIc) were condensed *in situ* with nitromethane, and 4-hydroxy-5-nitro-2-pentanone (IXa), 4-methyl-5-hydroxy-6-nitro-3-hexanone (IXb), and β-hydroxy-γ-nitrobutyrophenone (IXc) were obtained in varying yields (see Table I). Characterization of the β-hydroxy-γ-nitroketones was made by analysis, molar refractivity, and infrared absorption bands indicative of hydroxyl, nitro, and ketone carbonyl functions. In general, the degree of success in the preparation of β-hydroxy-γ-nitrocarbonyl compounds (such as III, VII, IX) by this method appears to be dependent upon the reactants selected and upon the conditions employed for each combination.

EXPERIMENTAL[1]

The sodium salt of ethyl malonaldehydate (ethyl α-formylacetate) was prepared from 88.8 g. (1.2 mole) of ethyl formate and 88 g. (1.0 mole) of ethyl acetate in the presence of one mole of alcohol-free sodium ethoxide, according to the procedure of Cogan (6) as modified by McElvain and Clarke (11). The yield was 73–80 g. of salt of stated 39–40% purity (11).

Ethyl β-hydroxy-γ-nitrobutyrate (IIIa). To a stirred solution of 73 g. (1.2 mole) of nitromethane in 1 l. of dry benzene was added slowly (one hour) 36 g. of the crude sodium salt of ethyl malonaldehydate, by means of a solid-addition attachment. The suspension was stirred at 28° for 67 hours. A shorter reaction period, *e.g.*, one or two days, resulted in a diminished yield of the desired product. The insoluble material was collected, pressed dry, and washed with ether. The cake was dissolved in 300 cc. of 5% hydrochloric acid overlayered with 100 cc. of ether. The aqueous phase was separated and extracted with four additional 100-cc. portions of ether. The combined ether extracts were dried and the solvent was removed. The residue was distilled through a Claisen head, and the material boiling at 113–119° (0.9 mm.), n_D^{20} 1.4559–1.4591, was collected. The pot residue was transferred to a short-path apparatus for distillation. Additional material was collected at 110–115° (0.45–0.75 mm.), n_D^{20} 1.4552–1.4577. The combined distillates (18.8 g.) were redistilled through the short-path apparatus to give very light yellow ethyl β-hydroxy-γ-nitrobutyrate (see Table I for properties, analysis, and infrared absorption bands).

Reductive cyclization of ethyl β-hydroxy-γ-nitrobutyrate. A solution of equimolar portions of ethyl β-hydroxy-γ-nitrobutyrate and ethanol in purified dioxane was hydrogenated in

[1] The authors are indebted to Mr. and Mrs. Maurice Dare, Miss Emily Davis, Mrs. Esther Fett, Mrs. Jean Fortney, and Mrs. Katherine Pih for microanalyses and to Miss Elizabeth M. Petersen and Miss Helen P. Miklas for determination of the infrared absorption spectra.

the presence of 20 g. of copper chromite catalyst at 260° and 260 atm. during 6.5 hours. After removal of the catalyst, the solvent was removed by distillation at reduced pressure, leaving an oily residue (A). Since the solvent distillate was basic and had an amine odor, hydrochloric acid was added to acidity and the solvent was again distilled. The residue (B) was made strongly alkaline with 20% sodium hydroxide and extracted with ether. The picrate was prepared from the ether solution and recrystallized from ethanol, and was identified directly as the picrate of *N-ethylpyrrolidine*, m.p. 185° (14).

When residue A was fractionally distilled in a vacuum, extensive decomposition occurred, but a clear distillate was collected at 61–66° (2–3 mm.) and redistilled at 93–97° (16 mm.); n_D^{20} 1.4640. The elementary analysis was consistent with the formulation of this product as *N-ethyl-α-pyrrolidone*.

Anal. Calc'd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38.

Found: C, 63.58; H, 9.80; N, 12.28.

The infrared absorption spectrum (strong carbonyl band at 1680 cm.$^{-1}$) of the product was identical with that of an authentic sample of N-ethyl-α-pyrrolidone, n_D^{27} 1.4629, prepared from butyrolactone and ethylamine after the directions of Adams and Mahan (15) for N-*n*-butyl-α-pyrrolidone.

Ethyl β-hydroxy-γ-nitrovalerate (IIIb). To a stirred suspension of the sodium salt of ethyl malonaldehydate, prepared from 22 g. (0.30 mole) of ethyl formate and 22 g. (0.25 mole) of ethyl acetate with sodium ethoxide according to the directions of Cogan (6), was added 56 g. (0.50) mole of nitroethane in one portion. The suspension was stirred at 25–28° for 109 hours, and the free nitro compound was generated with a solution of a slight molar excess of urea in 10% acetic acid (13). The phases were separated, and the aqueous phase was extracted with two 50-cc. portions of ether. The combined organic layers were washed with 150 cc. of saturated saline and then dried. After distillation of the low-boiling components under reduced pressure, the residual oil was distilled using a short-path apparatus to give 7.4 g. of light yellow ethyl β-hydroxy-γ-nitrovalerate.

Ethyl β-hydroxy-γ-nitrocaproate (IIIc). The procedure followed was similar to that described for IIIb, with the exception that 1-nitropropane was employed in place of nitroethane. The yield was 4.9 g. from 22 g. (0.25 mole) of ethyl acetate.

Ethyl α-methyl-β-hydroxy-γ-nitrobutyrate (VII). Using sodium sand, 222 g. (3.0 mole) of ethyl formate was caused to condense with 204 g. (2.0 mole) of ethyl propionate according to the directions of Harkins and Johnson (16). To the stirred suspension of the sodium salt of ethyl methylmalonaldehydate was added, in small portions, 246 g. (4.0 moles) of nitromethane. After about one-third of the nitromethane had been added, 500 cc. of anhydrous ether was added in order to facilitate stirring. The suspension was stirred at 25–28° for two days. The reaction mixture was then treated with 1 l. of water, the phases were saturated with carbon dioxide by addition of Dry Ice, and after separation of the phases the aqueous phase was extracted repeatedly with ether. The combined organic layers were dried, the solvent was removed, and the residual oil was distilled at 90–106° (0.12–0.28 mm.) through a short Claisen head, giving 59.5 g. of product. Two further distillations furnished VII in analytical purity but having a yellow cast.

4-Hydroxy-5-nitro-2-pentanone (IXa). By the procedure of Frank and Varland (17), 111 g. (1.5 moles) of ethyl formate was caused to condense with 87 g. (1.5 moles) of acetone in the presence of sodium ethoxide. Three hours after the addition, 184 g. (3.0 moles) of nitromethane in 250 cc. of ether was added with stirring over one-half hour, while the reaction flask was chilled in an ice-salt bath. The mixture was stirred at 0° for five hours, then at 25–28° for 13 hours. After the suspension was concentrated to about 2 l., water (1 l.) was added, and the phases were saturated with carbon dioxide and separated. The aqueous phase was extracted with four 250-cc. portions of ether and one 250-cc. portion of chloroform. The combined organic layers were dried and the solvent was removed. The residue was twice distilled from a short-path apparatus to give 14.1 g. of pure 4-hydroxy-5-nitro-2-pentanone. Upon acidification of the aqueous phase (see above) with hydrochloric acid,

followed by heating and working up according to the directions of Frank and Varland (17), 35 g. (35%) of 1,3,5-triacetylbenzene, m.p. 162–163°, was obtained.

4-Methyl-5-hydroxy-6-nitro-3-hexanone (IXb). To the suspension obtained by stirring 19 g. (0.25 mole) of ethyl formate and 22 g. (0.25 mole) of diethyl ketone with sodium ethoxide (17) for six hours was added 31 g. (0.50 mole) of nitromethane in one portion. Stirring was continued for 1½ days, after which the nitro product was generated by a modification of the procedure of Kornblum and Graham (13). A chilled solution of 33 g. (0.55 mole) of urea in 16.8 g. (0.28 mole) of glacial acetic acid diluted with 151 ml. of water was added slowly (20 min.) to the cooled reaction mixture. The phases were separated, and the aqueous layer was extracted with two 100-cc. portions of ether. The combined organic solution was dried, the solvent was removed, and the residue was distilled twice through a short-path apparatus to give 23.6 g. of analytically pure 4-methyl-5-hydroxy-6-nitro-3-hexanone having a slight yellow cast.

β-Hydroxy-γ-nitrobutyrophenone (IXc). To the suspension obtained by stirring 37 g. (0.50 mole) of ethyl formate and 60 g. (0.50 mole) of acetophenone with sodium ethoxide (17) for two hours was added 61 g. (1.0 mole) of nitromethane in four portions. Stirring had to be stopped after two hours because of solidification of the reaction mixture. (This factor may have influenced the yield unfavorably). The mass was allowed to stand for 36 hours, 600 cc. of water was added, and the organic layer was separated. The aqueous phase was extracted with two 300-cc. portions of ether and one 300-cc. portion of benzene. The combined organic layers were dried, and the solvent was removed. Distillation in a vacuum enabled the recovery of 8.8 g. of acetophenone and left a residual oil which solidified on standing. Recrystallization from carbon tetrachloride gave lustrous white plates of β-hydroxy-γ-nitrobutyrophenone, m.p. 78–79.5°. Treatment of the aqueous layer (see above) with urea in 10% acetic acid, followed by ether and benzene extractions, did not result in the isolation of any further quantity of crystalline material.

SUMMARY

A method has been devised which is applicable, with a varying degree of success, to the preparation of β-hydroxy-γ-nitro-esters and -ketones. The products result from the combination of the sodium salt of the hydroxymethylene-carbonyl compound and the nitroparaffin under heterogeneous reaction conditions.

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