

## THE REACTION OF CYANOHYDRINS WITH $\alpha,\beta$ -UNSATURATED ALDEHYDES

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(Received 9 June 1966)

**Abstract**—Cyanohydrins react with  $\alpha,\beta$ -unsaturated aldehydes carrying electron-attracting groups forming saturated esters of the type  $RCH_2CH(R_1)COOC(R_2)(R_3)CN$ .

WE HAVE recently studied the action of acetone cyanohydrin on *trans*-4,4-dimethoxy-2-butenal for obtaining cyanohydrins of some  $\alpha,\beta$ -unsaturated aldehydes. The reaction was carried out according to the method developed earlier for saturated and aromatic aldehydes (and ketones).<sup>1-3</sup>

This method was applied to 4-(2,2,6-trimethyl-1-cyclohexen-1-yl)-2-methyl-2-butenal, and a normal cyanohydrin was obtained in high yield.<sup>4</sup>

*trans*-4,4-Dimethoxy-2-butenal did not react with acetone cyanohydrin in the presence of saturated methanolic solution of  $K_2CO_3$ . In the presence of triethylamine (equimolar quantity for optimum yield) an exothermic reaction took place and the product I having composition  $C_{10}H_{17}NO_4$  corresponded to a reaction of one molecule of acetone cyanohydrin with one molecule of 4,4-dimethoxy-2-butenal.

Compound I was a high boiling oil, gave one peak on GLC (column 2 m with 1% silicon elastomer on NaCl,  $N_2$  carrier gas, 30–35 ml/min, 145°) and one stain on thin layer plate ( $Al_2O_3$ ) in different systems of solvents (n-hexane–benzene, n-hexane–ether). I did not absorb UV, and its IR spectrum showed a strong carbonyl band at 1767  $cm^{-1}$  and a weak band at 3454  $cm^{-1}$ . There were no bands at 2210–2260  $cm^{-1}$  which are typical of CN group. I had one active hydrogen atom. It slowly dissolved in 5N KOH and formed the dimethyl acetal of aldehydosuccinic acid. On boiling with HCl, I splitted off ammonia. Taking into consideration these data a structure of dimethyl acetal lactone of 3-carboxy-4-imino-5-hydroxy-5-methylpentanal was ascribed to I.<sup>5</sup> But further detailed investigation of product II from the reaction of cinnamic aldehyde with acetone cyanohydrin established the structure of these products as saturated esters of the type  $RCH_2CH_2COOC(R_1)(R_2)CN$ .

Compound II had a composition  $C_{13}H_{18}NO_3$ ; it was a high boiling oil which crystallized on long standing or cooling. It gave also one peak on GLC and one stain on thin layer plate. Its IR-spectrum (liquid film) showed a strong carbonyl band at 1752  $cm^{-1}$ , a weak band at 3463  $cm^{-1}$  and bands at 1603 (m), 1634 (m),

<sup>1</sup> I. N. Nazarov, A. A. Achrem and A. V. Kamernitzky, *Zhur. Ob. Khim.* 25, 1345 (1955).

<sup>2</sup> F. E. Küng, U. S. Pat. 2,259,167; *Chem. Abstr.* 36, 494 (1942).

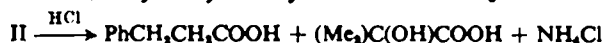
<sup>3</sup> A. Ercoli and P. de Ruggieri, *J. Amer. Chem. Soc.* 75, 650 (1953).

<sup>4</sup> G. I. Samochvalov, L. I. Zacharkin, L. P. Davydova and I. M. Chorlina, *Dokl. Akad. Nauk SSSR* 126, 1013 (1959).

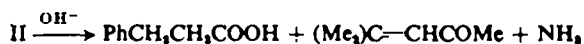
<sup>5</sup> L. A. Yanovskaya, R. N. Stepanova and V. F. Kutcherov, *Izvest. Akad. Nauk SSSR Ser. Khim.* 1509 (1965).

1714 (m)  $\text{cm}^{-1}$ ; its IR spectrum (crystals in liquid paraffin) showed bands at 1596 (m), 1702 (m), 1743 (s), 3448 (w)  $\text{cm}^{-1}$ . II contained also one active hydrogen atom.

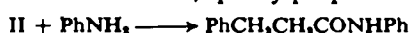
Compound II did not hydrolyse with dil. acids even on heating for many hours, but on boiling with conc. HCl acid it hydrolyzed completely within few hours forming  $\beta$ -phenylpropionic acid,  $\alpha$ -hydroxyisobutyric acid and  $\text{NH}_4\text{Cl}$ :



Compound II dissolved in 5N KOH after stirring for a few hours at room temperature, forming  $\beta$ -phenylpropionic acid, mesityl oxide (on self-condensation of acetone) and ammonia:



When heated with aniline, II formed  $\beta$ -phenylpropionanilide:



Boiling the ethanolic solution of II in the presence of HCl or  $\text{H}_2\text{SO}_4$  resulted in ethyl  $\beta$ -phenylpropionate:

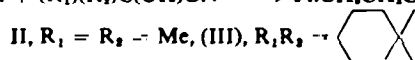


These properties pointed rather to the ester structure of II than to the imino- $\gamma$ -lactonic structure.

NMR spectra of II and the product III from the reaction of cyclohexanone cyanohydrin with cinnamic aldehyde showed peaks of  $-\text{CH}_2\text{CH}_2-$  chain. There were no peaks corresponding to CH or NH groups which must be in the imino- $\gamma$ -lactonic form.

On the basis of these data we concluded that II and III and also I have the structure of esters of the type  $\text{RCH}_2\text{CH}_2\text{COOC}(\text{R}_1)(\text{R}_2)\text{CN}$ .

In order to confirm this assumption we independently synthesized II and III. Thus acetone cyanohydrin and cyclohexanone cyanohydrin were acylated with  $\beta$ -phenyl-propionyl chloride:



The crystalline  $\alpha$ -( $\beta$ -phenylpropionyloxy)-isobutyronitrile and  $\alpha$ -( $\beta$ -phenylpropionyloxy)-cyclohexylnitrile obtained in this way proved to be identical with II and III respectively.

The absence of absorption of CN group in IR spectra of these compounds are typical and might be explained by the influence of the neighbouring CO group which leads to strong reduction in the intensity of the absorption of the CN group.

The displacement of the absorption of the CO group in the IR spectra of these compounds might be explained by the influence of the neighbouring CN group.

Table I shows characteristic absorption of the CO group in some esters of acetone cyanohydrin in comparison with ethyl  $\beta$ -phenylpropionate.

TABLE I. ABSORPTION OF THE CO GROUP IN THE IR SPECTRA OF SOME ESTERS

Compound	$\nu$ $\text{cm}^{-1}$ (liquid film)	Compound	$\nu$ $\text{cm}^{-1}$ (liquid film)
$\text{PhCH}_2\text{CH}_2\text{COOEt}$	1738	$\text{PhCH}_2\text{CH}_2\text{COOCMe}_2\text{CN}$	1752
$\text{PhCH}_2\text{COOCMe}_2\text{CN}$	1751	$\text{MeCOOCMe}_2\text{CN}$	1751





The presence of one active hydrogen atom in I-III might be explained as a result of enolization of CO group which is facilitated by the influence of the two neighbouring electron-attracting groups (CN and Ph). Partial enolization takes place even in  $\alpha$ -acetoxisobutyronitrile (Table 2).

TABLE 2. NUMBER OF ACTIVE HYDROGEN ATOMS IN SOME ESTERS

Compound	Number of active H	Compound	Number of active H
MeCOOC(Me) <sub>2</sub> CN	0.38	PhCH <sub>2</sub> COOC(Me) <sub>2</sub> CN	1
PhCH <sub>2</sub> CH <sub>2</sub> COOEt	0.40	PhCH <sub>2</sub> CH <sub>2</sub> COOC(Me) <sub>2</sub> CN	1

This new peculiar reaction was further studied by the action of cyanohydrins on different unsaturated aldehydes. It was found that aldehydes with electron-donating substituents did not react at all and were recovered from the reaction mixture (crotonaldehyde, citral,  $\alpha$ -methyl- $\beta$ -benzoyloxyacrolein,  $\beta$ -N,N-dimethylaminoacrolein), some of these aldehydes polymerized ( $\omega$ -N,N-dimethylamino-2,4-pentadienal,  $\beta,\beta$ -dichloroacrolein). On the contrary aldehydes with electron-accepting substituents such as  $\alpha$ -methylcinnamic aldehyde,  $\beta$ -furylacrolein,  $\alpha$ -methyl- $\beta$ -furylacrolein,  $\beta$ -carbethoxyacrolein react with acetone cyanohydrin forming esters with rather high yields (Table 3).

TABLE 3. YIELDS AND CONSTANTS OF OBTAINED ESTERS OF CYANOHYDRINS

Compound		Yield %	B.p. °C/mm or m.p.	$n_D^{20}$
PhCH <sub>2</sub> CH <sub>2</sub> COO 	III	59	61-62.5	
PhCH <sub>2</sub> CH <sub>2</sub> COOCH <sub>2</sub> CN	IV	74	115-117/0.33	1.5122
PhCH <sub>2</sub> CH <sub>2</sub> COOCH(Et)CN	V	67	90/0.1	1.4995
PhCH <sub>2</sub> CH <sub>2</sub> COOCH(Ph)CN	VI	80	132-135/0.1	1.5512
PhCH <sub>2</sub> CH <sub>2</sub> COO 	VII	66	64.5-66.5	
PhCH <sub>2</sub> CH(Me)COOC(Me) <sub>2</sub> CN	VIII	53	89-90/0.09	1.5000
 -CH <sub>2</sub> CH <sub>2</sub> COOC(Me) <sub>2</sub> CN	IX	60	105-107/0.85	1.4747
 -CH <sub>2</sub> CH(Me)COOC(Me) <sub>2</sub> CN	X	56	75-77/0.09	1.4650
(MeO) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> COOCH(Et)CN	XI	50	89-92/0.25	1.4320
(MeO) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> COOCH(Ph)CN	XIII	36	124/0.1	1.4952

Different cyanohydrins react in this way. For instance, aliphatic cyanohydrins (formaldehyde and propanal cyanohydrins), alicyclic cyanohydrins (cyclohexanone and 2-methylcyclohexanone cyanohydrins), aromatic cyanohydrins (benzaldehyde cyanohydrin) react with 4,4-dimethoxy-2-butenal and cinnamic aldehyde, forming esters (data in Table 3).

## ANALYTICAL DATA

Compd	C%		H%		M.W.		Active H Found	$\nu_{CO}cm^{-1}$ (film)
	Found	Calc.	Found	Calc.	Found	Calc.		
III	74.58	74.68	7.41	7.44	252	257	0.94	1751 (in chf)
IV	69.80	69.89	6.06	5.86	192	189	1.20	1760
V	72.07	71.86	7.06	6.96	—	—	—	1760
VI	76.84	76.95	5.07	5.28	259	265	1.00	1760
VII	75.62	75.22	7.89	7.80	270	271	—	1752 (in chf)
VIII	72.72	72.70	7.47	7.41	—	—	1.05	1718, 1754
IX	62.97	63.75	6.68	6.32	—	—	—	1715, 1760
X	64.47	65.24	6.86	6.83	—	—	—	1704, 1760
XI	56.32	55.80	8.12	7.96	—	—	—	1760
XII	63.41	63.86	6.45	6.51	—	—	—	1760

Cyanohydrins of the high aliphatic ketones especially branched ketones (butyrone and isobutyrono cyanohydrins) react with unsaturated aldehydes forming complex mixtures from which it was impossible to isolate any products in analytically pure state.

TABLE 4. REACTION TIME AND YIELDS OF THE PRODUCT  
(Molar ratio aldehyde:cyanohydrin:triethylamine = 1:2:2)


Aldehyde	Cyanohydrin	Reaction time hr	Product	Yield %
PhCH=CHCHO	(Me <sub>3</sub> C(OH)CN	0.5	II	57
		72		67
	EtCH(OH)CN	0.5	V	52
		96		65
 -CH=CHCHO	(Me <sub>3</sub> C(OH)CN	24	X	56
		72		58
	PhCH=CHCHO	168	VIII	38
		240		53

TABLE 5. ALDEHYDE:CYANOHYDRIN:TRIETHYLAMINE (A:C:T) RATIO AND YIELDS OF PRODUCTS (TIME 24 HR)


Aldehyde	Cyanohydrin	Molar ratio A:C:T	Product	Yield %
PhCH=CHCHO	H <sub>3</sub> C(OH)CN	1:2:1	IV	47
		1:2:2		74
	EtCH(OH)CN	1:1:1	V	69
		1:2:2		65
	PhCH(OH)CN	1:1:1	VI	40
		1:2:2		80
	Me <sub>3</sub> C(OH)CN	1:1:1	II	45
		1:2:1		56
		1:2:2		65

The optimum conditions of the reaction were found out. Increasing the reaction time as a rule has a small influence on the yield of the product (Table 4). The ratio of aldehyde:cyanohydrin:triethylamine often has a strong influence on the yield (Table 5). Decreasing the quantity of triethylamine leads to unstable and low yields of the products. Maximum yields were obtained by the ratio of 1:2:2.

Pyridine and diethylaniline do not catalyse the reaction between aldehydes and cyanohydrins.

#### EXPERIMENTAL

*Reaction of acetone cyanohydrin with cinnamic aldehyde.* 6.6 g (0.05 M) cinnamic aldehyde were mixed with 8.5 g (0.1M) acetone cyanohydrin and 10 g (0.1M) triethylamine were added. After 1–2 min an exothermic reaction took place and the mixture darkened. The reaction mixture was cooled and distilled *in vacuo*. 7.2 g  $\alpha$ -( $\beta$ -phenylpropionyloxy)-isobutyronitrile (II) was obtained, b.p. 105°/0.3 mm,  $n_D^{20}$  1.5032; crystallized on standing, m.p. 33–34° (from pet. ether); M.W. 207, calc. 217. (Found: C, 71.81; H, 6.91; N, 6.55.  $C_{13}H_{15}NO_2$  requires: C, 71.86; H, 6.96; N, 6.45%; Found: active H 0.96). NMR (in  $CCl_4$ , TMS standard): 1.57 ( $Me_2C$ ), 2.69 ( $-CH_2CH_2-$ ), 7.06 ppm (Ph.)

Compounds III–XII were similarly obtained (data are given in Table 3). NMR of III (in  $CCl_4$ , TMS standard): 2.13 () , 2.70 ( $-CH_2CH_2-$ ), 7.06 ppm (Ph).

*Hydrolysis of II with conc. HCl.* 2.8 g (II) were boiled by intensive stirring with 7 ml conc. HCl during 6 hr. Next day the product was extracted with ether. The ether extract was dried ( $Na_2SO_4$ ) and the ether distilled off. A crude product (1.8 g) was obtained which was crystallized from n-hexane, m.p. 46–47.5°, and was identical with  $\beta$ -phenylpropionic acid (m.p. and m. m.p.). The aq. layer was filtered (0.4 g  $NH_4Cl$  was obtained) and evaporated to dryness *in vacuo*. The crude product (1 g) was crystallized from benzene, m.p. 77–78.5°, and was identical with 2-hydroxyisobutyric acid (m.p. and m. m.p.).

Similar hydrolysis of III produces  $\beta$ -phenylpropionic acid, m.p. 46–47°, and a product, m.p. 106–108°, which was identical with  $\alpha$ -hydroxycyclohexanecarbonic acid (m.p. and m. m.p.).

*Hydrolysis of III with 5N KOH.* 2.57 g III were stirred with 5 ml KOH for some hours. The clear soln was carefully extracted with ether. On acidifying the aq. with  $H_2SO_4$ ,  $\beta$ -phenylpropionic acid was obtained (yield 1 g), m.p. 46–47.5° (from n-hexane). The ether extract was dried and the ether evaporated off. A part of the residue was treated with HCl soln. of 2,4-dinitrophenylhydrazine. An orange 2,4-dinitrophenylhydrazone was obtained, m.p. 156–158° (from AcOH), which was identical with cyclohexanone 2,4-dinitrophenylhydrazone (m.p. and m. m.p.). Another part of the residue gave one peak on GLC (for conditions see above, 140°), and was identified as cyclohexanone.

Similar hydrolysis of 2.8 g VI produces 1.8 g  $\beta$ -phenylpropionic acid and 0.8 g benzaldehyde which was identified by GLC (for conditions see above, 158°) and as 2,4-dinitrophenylhydrazone, m.p. 235–237° (from AcOH) undepressed on admixture with an authentic specimen.

From 2.17 g II 1.6 g  $\beta$ -phenylpropionic acid and mesityl oxide were obtained which were identified by GLC (for conditions see above, 60°).

From 4.2 g IX 2.4 g  $\beta$ -(2-furyl)-propionic acid, m.p. 54.5–56, was obtained.

*Reaction with aniline.* 0.5 g IV and equimolar quantity of aniline were boiled for 3 hr. Next day a crystalline mixture was obtained which was recrystallized from isopentane and ether. 0.45 g  $\beta$ -phenylpropionanilide was obtained, m.p. 96–97° undepressed on admixture with an authentic specimen.

In similar conditions II and VI gave also  $\beta$ -phenylpropionanilide.

*Alcoholysis of IV.* 1.9 g (0.01M) IV were dissolved in 25 ml EtOH, 4 ml conc. HCl and 5 ml water were added and the mixture was boiled for 4 hr. After completion of the reaction (its course was followed on thin layer plate:  $Al_2O_3$ , n-hexane-ether, 1:1 by volume) the mixture was neutralized by stirring with  $CaCO_3$ , and the liquid filtered and evaporated. The residue was extracted with ether, and the extract dried ( $Na_2SO_4$ ) and distilled. The main fraction (1.3 g), b.p. 130°/20 mm,  $n_D^{20}$  1.4078, was identified (GLC, for conditions see above, 116°) as ethyl  $\beta$ -phenylpropionate.

In the same manner 2.4 g II produced 2 g of ethyl  $\beta$ -phenylpropionate.

*Synthesis of II.* 4.6 g (0.03M)  $\beta$ -phenylpropionyl chloride were heated with 4.25 g (0.05 M) acetone cyanohydrin at 60–70° for 2 hr. The reaction mixture was distilled. The main fraction

(4.8 g) boiled at 114–116°/0.35 mm, m.p. 33–34.5° undepressed on admixture with II prepared by reaction of acetone cyanohydrin with cinnamic aldehyde.

In a similar manner there were obtained:  $\alpha$ -( $\beta$ -phenylpropionyloxy)-cyclohexylnitrile (from  $\beta$ -phenylpropionylchloride and cyclohexanone cyanohydrin), b.p. 151–152°/0.027 mm, m.p. 60–62.5° undepressed on admixture with III prepared by reaction of cyclohexanone cyanohydrin with cinnamic aldehyde);  $\alpha$ -(phenylacetoxy)-isobutyronitrile (from phenylacetylchloride and acetone cyanohydrin), b.p. 104–106°/0.3 mm,  $n_D^{20}$  1.4955, m.p. 36–37.5° (Found: C, 70.90; H, 6.70.  $C_{13}H_{18}NO_2$  requires: C, 70.91; H, 6.45%);  $\alpha$ -(phenylacetoxy)-cyclohexylnitrile (from phenylacetyl chloride and cyclohexanone cyanohydrin), b.p. 148–150°/0.06 mm,  $n_D^{20}$  1.5155, m.p. 29–30.5°. (Found: C, 73.98; H, 7.01.  $C_{14}H_{17}NO_2$  requires: C, 74.05; H, 7.04%.)