[Contribution from the Department of Chemistry, University of Missouri]

The Reaction of 2-(β-Cyanoethyl)-2-Ethylhexanal with Grignard Reagents

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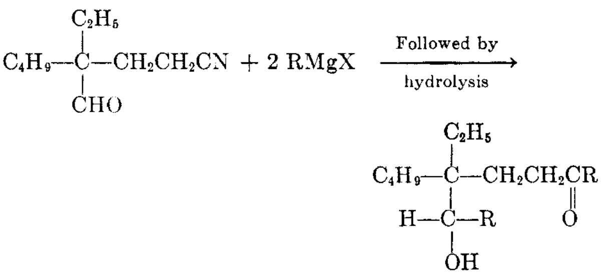
It has been shown that 2-(β-cyanoethyl)-2-ethylhexanal reacts with aliphatic Grignard reagents to give mixtures which contain 2,6-dialkyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyrans and hydroxynitriles.

The dihydropyrans which were prepared were reduced to the corresponding tetrahydropyrans and one of these was converted in low yield to a tetraalkylmethane.

The availability of 2-(β-cyanoethyl)-2-ethylhexanal suggested the possible use of this compound for the synthesis of hydroxy ketones according to the following equation.



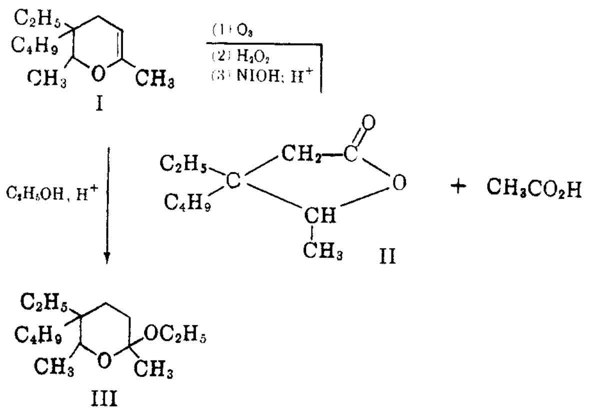
$$C_4H_9\text{—}\underset{CHO}{\overset{C_2H_5}{C}}\text{—}CH_2CH_2CN + 2\,RMgX \xrightarrow[\text{hydrolysis}]{\text{Followed by}} C_4H_9\text{—}\overset{C_2H_5}{\underset{H\text{—}\underset{OH}{C}\text{—}R}{C}}\text{—}CH_2CH_2\underset{O}{\overset{}{C}}R$$

It was hoped that the latter type compounds, or cyclic analogs which might result from them, could be converted then to certain desired unsymmetrical tetraalkylmethanes.

When 2-(β-cyanoethyl)-2-ethylhexanal was caused to react with 3 molar quantities of several different aliphatic Grignard reagents, it was found that fairly complex mixtures resulted. The separation of these mixtures by distillation was complicated by decomposition, but it was possible to obtain in each case a constant low-boiling fraction as well as a less pure higher-boiling fraction.

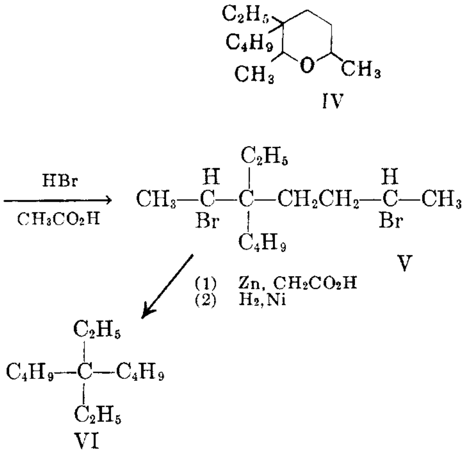
Analytical data and chemical examination of the low-boiling fractions showed that they possessed none of the properties expected of hydroxy ketones. Infrared spectra[2] indicated the presence of only very small amounts of carbonyl and hydroxyl functions. It was found that they gave tests for unsaturation, and were hydrogenated over a Raney nickel catalyst. Apparently, the hydroxy ketones which were formed initially suffered enolization and dehydration to give substituted dihydropyrans. In Table I are listed the dihydropyrans which were prepared as well as the related tetrahydropyrans which were obtained from them by reduction.

The dihydropyran structure was substantiated by the ozonization of 2,6-dimethyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyran (I). Oxidative cleavage of the ozonide afforded acetic acid and the lactone II, after hydrolysis of the reaction mixture.



Also, treatment of the dihydropyran (I) with ethanol, according to the procedure of Parham and Anderson,[3] gave the ethyl 2-tetrahydropyranyl ether (III).

The tetrahydropyran (IV) was cleaved by means of hydrogen bromide in acetic acid to a crude dibromide V which was reduced first with zinc and acetic acid and then with hydrogen and Raney nickel catalyst to produce the hydrocarbon VI. The over-all conversion from the tetrahydropyran to the hydrocarbon was quite low so that the process does not appear to possess much merit.



The higher-boiling fraction from the condensation

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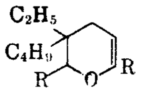
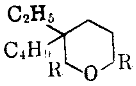
(1) Abstracted in part from the Ph. D. thesis of M. J. Latina, 1953. Lubrizol Corporation Fellow, 1951–1952.

(2) The authors are indebted to Dr. E. E. Pickett for the infrared data.

(3) Parham and Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).

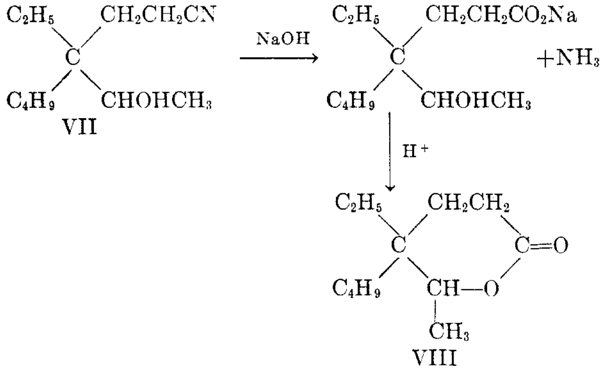
TABLE I

DIHYDROPYRANS, 

R	b.p., °C	mm.	n_D^{25}	Formula	Analyses Carbon Calc'd	Analyses Carbon Found	Analyses Hydrogen Calc'd	Analyses Hydrogen Found
CH_3	85–88°	1	1.4592	$C_{13}H_{24}O$	79.53	79.38	12.32	12.42
C_2H_5	98–100°	1	1.4602	$C_{15}H_{28}O$	80.29	80.59	12.58	12.13
C_6H_{13}(*n*-)	135–138°	1	1.4601	$C_{23}H_{44}O$	82.07	81.68	13.18	13.18
C_7H_{15}(*n*-)	133–135°	0.05	1.4600	$C_{25}H_{48}O$	82.34	82.16	13.27	13.01
Tetrahydropyrans, 								
CH_3	86–86.5	3.5	1.4480	$C_{13}H_{26}O$	78.72	78.94	13.21	13.25
C_2H_5	90–91	1	1.4514	$C_{15}H_{30}O$	79.57	79.82	13.36	13.39
C_6H_{13}(*n*-)	140–142	1	1.4542	$C_{23}H_{46}O$	81.58	81.36	13.69	13.78
C_7H_{15}(*n*-)	144–146	1	1.4546	$C_{25}H_{50}O$	81.89	81.79	13.75	13.59

of methylmagnesium iodide with 2-(β-cyanoethyl)-2-ethylhexanal failed to give a conventional test for nitrogen, but an infrared spectrum showed the presence of a nitrile grouping.

An hydroxynitrile structure (VII) was suggested for this material on the basis of the fact that it dissolved slowly when refluxed with strong alkali, and ammonia was evolved. Acidification of the reaction mixture and distillation of the product gave the lactone VIII-



VII

VIII

Cason[4] has prepared a similar hydroxynitrile from *n*-butylmagnesium bromide and the cyanoethylated 2-ethylhexanal. He has found likewise that it can be hydrolyzed to an hydroxy acid which lactonizes readily.

EXPERIMENTAL

Reaction of 2-(β-cyanoethyl)-2-ethylhexanal with Grignard reagents. The following procedure is representative. A solution of methylmagnesium iodide was prepared from 72 g. (3 gram-atoms) of magnesium and 500 g. (3.5 moles) of methyl iodide in a total volume of 1500 ml. of anhydrous ether. It was stirred while a solution of 181 g. (1 mole) of 2-(β-cyanoethyl)-2-ethylhexanal, b.p., 143–146°/1 mm.[5] in 250 ml. of dry ether was added at a rate sufficient to produce gentle refluxing. The reaction mixture was stirred for several hours and allowed to stand overnight. It was decomposed by pouring it onto a mixture of 500 ml. of concentrated hydrochloric acid and 500 g. of ice. The ether layer was separated, washed with concentrated hydrochloric acid, water, 10% sodium bicarbonate solution, water, and then was dried over sodium sulfate. After removing the ether, the residual oil was fractionated to give 67 g. (34%) of 2,6-dimethyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyran; b.p., 85–88°/1 mm., n_D^{25} 1.4592.

Anal. Calc'd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.38; H, 12.42.

A higher-boiling fraction was collected at 147–156°/1 mm., n_D^{25} 1.4680, which weighed 46 g. (23%).

Anal. Calc'd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75. Found: C, 72.87; H, 12.35.

Reduction of the dihydropyrans. The reduction of 2,6-dimethyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyran is illustrative. In a 125-ml. hydrogenation bomb were placed 50 g. of the dihydropyran and 2 g. of Raney nickel catalyst. Reduction began at 120° and 2200 p.s.i. and was completed within 30 minutes. The contents of the bomb were removed with the aid of ether and the catalyst was separated by filtration. After distilling the ether, the residue was fractionated to give 40 g. of product which boiled at 70–76°/1 mm. A sample was distilled through a Podbielniak Micro High Temperature Distillation Analyzer; b.p. 86–87°/3.5 mm., n_D^{25} 1.4480.

Anal. Calc'd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.94; H, 13.25.

Ozonization of 2,6-dimethyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyran. A solution of 5 g. of the dihydropyran in 75 ml. of carbon tetrachloride was ozonized with 2–3% ozone at ice-bath temperature. The reaction mixture was stirred with 75 ml. of water and gradually was heated to reflux. After heating for 1 hour, 5 ml. of 3% hydrogen peroxide was added and refluxing was continued 2 hours longer. The carbon tetrachloride layer was separated and extracted three times with 25-ml. portions of 5% sodium hydroxide solution. The latter was acidified with dilute sulfuric acid and extracted several times with small portions of ether. The combined ether extracts were washed with cold 2% sodium bicarbonate solution and dried over sodium sulfate.

The sodium bicarbonate washings were acidified with dilute sulfuric acid and steam-distilled. The distillate was neutralized with sodium hydroxide solution and evaporated to dryness. The sodium salt was converted to a *p*-nitrobenzyl ester, m.p. 76–77° and a *p*-bromophenacyl ester,

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(4) Cason, Private communication.

(5) Bruson and Riener, *J. Am. Chem. Soc.*, **66**, 56 (1944).

m.p. 83–85°. The corresponding esters of acetic acid are reported[6] to melt at 78° and 85°, respectively.

The ether solution from the above was evaporated and the residue was distilled to give 3 g. of a product which boiled at 135–136°/1 mm.; n_D^{25} 1.4454. It dissolved readily in warm sodium hydroxide solution.

Anal. Calc'd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; Sap. equiv., 184. Found: C, 71.42; H, 11.05; Sap. equiv., 187.

Ethyl 2,6-dimethyl-5-ethyl-5-butyl-2-tetrahydropyranyl ether. The method of Parham and Anderson[3] was followed. A mixture of 12.9 g. (0.066 mole) of 2,6-dimethyl-3-ethyl-3-butyl-3,4-dihydro-1,2-pyran, 3.0 g. (0.066 mole) of ethanol, and 6 drops of concentrated hydrochloric acid was shaken thoroughly and allowed to stand at room temperature for 24 hours. It was diluted with ether and the ether solution was washed several times with 10% sodium hydroxide solution. It was dried over sodium sulfate and the ether was removed by distillation. The residue was fractionated to give 8 g. (50%) of a colorless liquid; b.p. 100–101°/1 mm.; n_D^{25} 1.4470.

Anal. Calc'd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48. Found: C, 74.64; H, 12.58.

Preparation of 5,5-diethylnonane. A solution of 14 g. (0.07 mole) of 2,6-dimethyl-3-ethyl-3-butyltetrahydropyran in 14 ml. of glacial acetic acid was cooled in an ice-bath and saturated with anhydrous hydrogen bromide. The mixture was transferred to a Carius tube and heated at 150° for 4 hours. The contents of the tube were poured into ice-water and the heavy oil which separated was washed with an equal volume of concentrated sulfuric acid. It was allowed to stand for several hours over sodium carbonate and sodium sulfate. Upon filtration, there was obtained 14 g. of a yellow oil; n_D^{24} 1.4860.

The crude dibromide was dissolved in 35 ml. of glacial acetic acid, the solution was heated to reflux, and 14 g. of zinc dust was added over a period of 10 hours. The reaction mixture was filtered, diluted with a large volume of water and extracted with ether. The ether layer was separated, washed with 10% sodium bicarbonate solution and water, and dried over magnesium sulfate. After removing the ether, the residue was distilled to give a highly unsaturated liquid; b.p. 98–104°/15 mm., n_D^{26} 1.4490. This was hydrogenated over a Raney nickel catalyst at 175° and 1500 lbs. to yield 2 g. (15%) of a colorless liquid; b.p. 98–102°/15 mm., n_D^{24} 1.4438.

Anal. Calc'd for $C_{13}H_{28}$: C, 84.69; H, 15.31. Found: C, 84.48; H, 15.03.

Hydrolysis of 4-ethyl-4-butyl-5-hydroxyhexanonitrile. A mixture of 15 g. (0.076 mole) of 4-ethyl-4-butyl-5-hydroxyhexanonitrile and 25 ml. of 20% sodium hydroxide solution was refluxed for 3 hours after which time the odor of ammonia was no longer perceptible and the nitrile had dissolved. The reaction mixture was cooled, extracted twice with ether, and the water layer was acidified with concentrated hydrochloric acid. The oil layer which separated was removed and the aqueous portion was extracted three times with 15-ml. portions of ether. The combined oil and ether extracts were washed with 10% sodium bicarbonate solution and were dried over sodium sulfate. After removing the ether, the residual oil was distilled to yield 13 g. (73%) of 4-ethyl-4-butyl-5-hydroxyhexanoic acid lactone, b.p. 134–136°/2 mm., n_D^{25} 1.4690.

Anal. Calc'd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.63; H, 11.24.

COLUMBIA, MISSOURI

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(6) Shriner and Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, New York, 1948, p. 222.