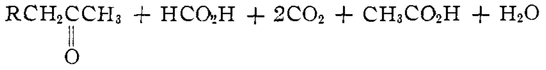

$$RCH_2\overset{\displaystyle CCH_3}{\underset{\underset{\displaystyle O}{\|}}{}} + HCO_2H + 2CO_2 + CH_3CO_2H + H_2O$$

The scheme outlined here is consistent with all known features of the reaction. The postulated end groups on the severed hydrocarbon chains are in reasonable agreement with published analyses[17] of highly oxidized hevea, and the known rapid oxidation of aldehydes at the temperature used here.[18] The yields of volatile materials are in the proportions found by experiment. The scheme requires six molecules of oxygen for each scission of the hydrocarbon chain, in good agreement with the limiting value found on rapid oxidation of dry rubber at high temperatures.[16]

The total amount of oxygen consumed (18.5 moles/mole of scissions) at the temperature of these experiments is much larger than that required for the scission reaction. Most of the additional oxygen appears in hydroxyl[17] and, probably, ether[18] groups. It is not clear whether the ratio of oxygen required for scission to the total is a measure of the relative amount of hydroperoxide having the structure assumed by Bolland and Hughes to predominate, or if this structure decomposes by alternate paths of which only one involves thermal scission of the tertiary alkoxy group with consequent scission of the hydrocarbon as a whole. In view of the good agreement between the postulated mechanism and the oxygen requirements at high temperature and of the decreasing yield of scission as the temperature is lowered,[8,16] the second alternative may be correct.

PASSAIC, NEW JERSEY

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[17] R. F. Naylor, *Trans. Inst. Rubber Ind.*, **19**, 45 (1944).

[18] G. R. Mitchell and J. Reid Shelton, *Ind. Eng. Chem.*, **45**, 386 (1953).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

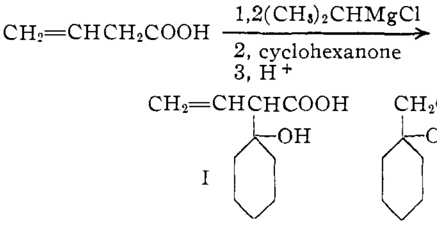
The Reaction of Isopropylmagnesium Chloride with Vinylacetic and Crotonic Acids

BY F. F. BLICKE AND HAROLD ZINNES[1,2]

RECEIVED MAY 24, 1955

The Ivanov reagent, obtained from vinylacetic acid and isopropylmagnesium chloride, reacted with cyclohexanone to yield γ-(1-hydroxycyclohexyl)-crotonic acid. The 1,4-addition of isopropylmagnesium chloride to crotonic acid was observed.

It was found that after reaction of isopropylmagnesium chloride with vinylacetic acid, with the expectation that an Ivanov reagent, $CH_2{=}CHCH(MgCl)COOMgCl$, might be formed, and addition of cyclohexanone to the reaction mixture, an acid (m.p. 127–129°) was obtained which we thought might be the unknown α-(1-hydroxycyclohexyl)-vinylacetic acid (I). The analytical data and the neutralization equivalent found corresponded to the calculated data for this compound. If the product did not possess structure I, it seemed that the only other structure which it might possess would be that of γ-(1-hydroxycyclohexyl)-crotonic acid (II). It was reported[3] that the crotonic acid, which Dreiding and Pratt had obtained by another procedure, melted at 127–128.5°. We synthesized II by the described process[3] and found that the mixed melting point of the two acids was 127–129°.



Presumably the formation of II in the Ivanov reaction was the result of an allylic rearrangement of the Ivanov reagent. Rearrangements of this type

$$CH_2{=}CHCH(MgCl)COOMgCl \rightleftharpoons CH_2(MgCl)CH{=}CHCOOMgCl$$

which involve other Grignard reagents are well known.[4] In view of the equilibrium which may exist between the two forms of the Ivanov reagent, it is not impossible that compound I may have been produced to some extent; compound II was isolated in only 22% yield.

The interaction of crotonic acid with two molecular equivalents of isopropylmagnesium chloride resulted in the formation of an intermediate IV which yielded β-isopropylbutyric acid (V), α-(1-hydroxycyclohexyl)-β-isopropylbutyric acid (VI)[5] and α-(phenylcarbamyl)-β-isopropylbutyric acid (VII) when it was treated with water, cyclohexanone and phenyl isocyanate, respectively. The formation of IV probably took place through the 1,4-addition of isopropylmagnesium chloride to the chloromagnesium salt III followed by a tautomeric rearrangement.[6]

The boiling point of the liquid acid V corre-

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[1] This paper represents part of a dissertation submitted by Harold Zinnes in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1955.

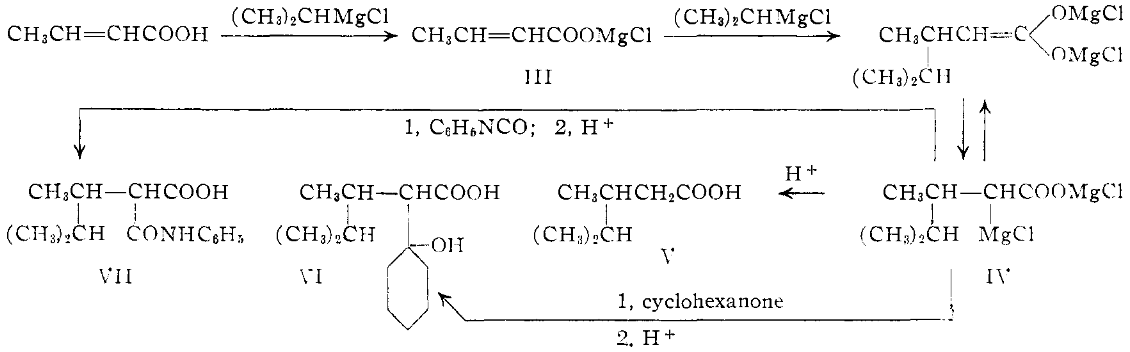
[2] American Foundation for Pharmaceutical Education Fellow.

[3] A. S. Dreiding and R. J. Pratt, THIS JOURNAL, **75**, 3717 (1953).

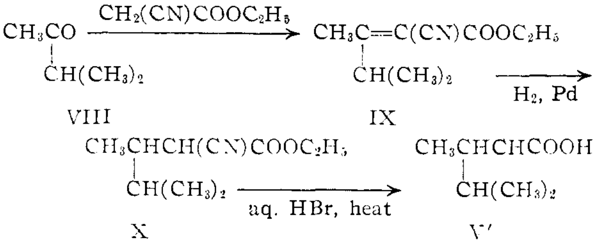
[4] See E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 287–292; M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 1133–1158.

[5] Two acids were obtained. The analytical data and the neutralization equivalent obtained in the case of each acid corresponded to that calculated for VI. We believe that the acids were diastereoisomers.

[6] A similar explanation was offered by C. D. Nenitzescu (*Bull. soc. chim. Romania*, **12**, 48 (1930); *C.A.*, **25**, 1509 (1931)) to account for the formation of N-ethyl-α-acetyl-β,β-diphenylpropioanilide. In order to obtain this substance, phenylmagnesium bromide was allowed to react with N-ethylcinnamanilide, and acetyl chloride then was added to the reaction mixture.



sponded to that mentioned in the literature.[7,8] The amide and anilide melted at 137–138° and 110–111°, respectively. Since different melting points for these derivatives have been reported,[9] the amide and anilide were prepared again from β-isopropylbutyric acid (V′) which we synthesized from X. Compounds IX and X had been prepared previously[10] from VIII in the manner indicated below.



$$\underset{\text{VIII}}{\underset{\mathrm{CH(CH_3)_2}}{\mathrm{CH_3CO}}} \xrightarrow{\mathrm{CH_2(CN)COOC_2H_5}} \underset{\text{IX}}{\underset{\mathrm{CH(CH_3)_2}}{\mathrm{CH_3C{=}C(CN)COOC_2H_5}}} \xrightarrow[\mathrm{H_2,\ Pd}]{}$$

$$\underset{\text{X}}{\underset{\mathrm{CH(CH_3)_2}}{\mathrm{CH_3CHCH(CN)COOC_2H_5}}} \xrightarrow[\text{aq. HBr, heat}]{} \underset{\text{V}'}{\underset{\mathrm{CH(CH_3)_2}}{\mathrm{CH_3CHCHCOOH}}}$$

Simultaneous hydrolysis and partial decarboxylation converted X into V′. The infrared spectra of V and V′ were found to be identical. The amide and anilide obtained from V′ were shown by mixed melting points to be identical with the corresponding derivatives of V.

When V was converted into the acid chloride and the latter substance was treated with diethylamine, an amide, N,N-diethyl-β-isopropylbutyramide, was obtained which was found to be identical with the amide prepared by 1,4-addition of isopropylmagnesium bromide to N,N-diethylcrotonamide.[11]

The structure of VII was established by its conversion, by decarboxylation, into the anilide of V.

Experimental

γ-(1-Hydroxycyclohexyl)-crotonic Acid (II).—To the stirred Grignard reagent, prepared from 5.4 g. of magnesium, 25 cc. of isopropyl chloride and 50 cc. of ether, there was added 8.6 g. of vinylacetic acid[12] dissolved in 150 cc. of ether. More ether (100 cc.) was added and the mixture was refluxed for 18 hours. After the addition of 11.8 g. of cyclohexanone, dissolved in 50 cc. of ether, the material was refluxed for 4 hours.

The mixture was poured into 200 cc. of ice-cold, 10% ammonium chloride solution. The layers were separated and the organic layer was extracted with water. The combined aqueous solutions were washed with ether, cooled in an ice-bath, 10% sulfuric acid added and the precipitated oil extracted with ether. The solvent was removed from the dried extract under an air jet, the oily residue was triturated with petroleum ether (40–60°) and refrigerated for several days. The gummy, yellow material (10 g.) was crystallized from 50 cc. of diisopropyl ether; yield 4 g. (22%) of colorless crystals, m.p. and mixed m.p.[3] 127–129° after several recrystallizations from diisopropyl ether.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; neut. equiv., 184.2. Found: C, 65.20; H, 8.75; neut. equiv., 185.1.

β-Isopropylbutyric Acid (V).—A solution of isopropylmagnesium chloride was prepared from 27.0 g. of magnesium, 125 cc. of isopropyl chloride and 250 cc. of ether. Ether (250 cc.) was added, the mixture was stirred and 43.0 g. of crotonic acid, dissolved in 250 cc. of ether, was added slowly. After the material had been refluxed for 18 hours, it was poured into an ice-cold solution of 55 cc. of concentrated sulfuric acid in 1000 cc. of water. The aqueous layer was extracted with ether, the combined ether solutions were washed with water and then concentrated to a volume of about 400 cc. The solution was extracted with sodium bicarbonate solution, the extract was washed with ether and then made acidic to congo red with dilute sulfuric acid. The precipitated oil was separated and the aqueous layer was extracted with ether. The combined oil and extract were dried, the solvent was removed and the residue distilled; b.p. 77–78° (2 mm.),[13] 209–211° (740 mm.)[12]; yield 31.0 g. (48%).

Anal. Calcd. for $C_7H_{14}O_2$: neut. equiv., 130.2. Found: neut. equiv., 132.4.

The following acid derivatives were prepared from the acid chloride, b.p. 161–165° (745 mm.): The amide melted at 137–138°[14] after recrystallization from petroleum ether (90–100°). *Anal.* Calcd. for $C_7H_{15}ON$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.17; H, 11.64; N, 10.72.

The anilide melted at 110–111°[15] after recrystallization from petroleum ether (90–100°). *Anal.* Calcd. for $C_{13}H_{19}ON$: N, 6.82. Found: N, 6.72.

The N,N-diethylamide boiled at 115–116° (11 mm.).

Anal. Calcd. for $C_{11}H_{23}ON$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.24; H, 12.67; N, 7.40.

The N,N-diethylamide also was obtained in the following manner. After isopropylmagnesium bromide had been prepared from 8.8 g. of magnesium, 40 cc. of isopropyl bromide and 200 cc. of ether, 42.3 g. of N,N-diethylcrotonamide,[11] dissolved in 300 cc. of ether, was added. The mixture was refluxed for 4 hours, poured into cold, dilute hydrochloric acid, the organic layer was separated, washed with water, dried and the solvent removed. The amide boiled at 115–116° (11 mm.), yield 23.0 g. (41%). The infrared spectra of the N,N-diethyl amides prepared by the two methods were identical. *Anal.* Calcd. for $C_{11}H_{23}ON$: N, 7.56. Found: N, 7.38.

β-Isopropylbutyric Acid (V′).—Ethyl isopentylidenecyanoacetate[16] (63.0 g.), dissolved in 100 cc. of absolute ethanol,

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[7] R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1950).

[8] A. A. Morton, F. D. Marsh, R. D. Coombs, H. E. Ramsden, V. B. Baker, E. L. Little and R. L. Letsinger, THIS JOURNAL, **72**, 3785 (1950).

[9] The melting points reported for the amide and anilide were 95.5 and 67,[7] respectively; for the anilide 110.3–111.2°.[8]

[10] British Patent 613,705; *C.A.*, **43**, 4692 (1949).

[11] N. Maxim (*Bull. soc. chim. Romania*, **10**, 97 (1928); *C.A.*, **23**, 2697 (1929)) showed that N,N-diethyl-β-ethylbutyramide and N,N-diethyl-β-phenylbutyramide could be obtained by 1,4-addition of ethylmagnesium bromide and phenylmagnesium bromide, respectively, to N,N-diethylcrotonamide.

[12] E. Rietz, *Org. Syntheses*, **24**, 96 (1944).

[13] Ref. 8, b.p. 75° (2 mm.), ref. 7, b.p. 210°.

[14] Ref. 7 m.p. 95.5°.

[15] Ref. 8, m.p. 110.3–111.2°. Ref. 7, m.p. 67°.

[16] Obtained in 60% yield by the described method.[10]

was hydrogenated[10] in the presence of 0.3 g. of palladium-on-charcoal (5%) catalyst[17] under an initial pressure of 30 pounds until the required amount of hydrogen had been absorbed. The residue, obtained after removal of the catalyst and the solvent, was mixed with 500 cc. of 48% hydrobromic acid and was stirred and refluxed for 48 hours. The mixture was poured into ice-water, the layers were separated and the aqueous layer was extracted with ether. The combined organic layer and ether extract were washed with water and then extracted with sodium bicarbonate solution. The alkaline solution was washed with ether, cooled in an ice-bath and made strongly acidic with dilute sulfuric acid. The oily precipitate was separated and the aqueous layer was extracted with ether. From the combined dried oil and extract, 31 g. of product was obtained, b.p. 208–210° (732 mm.). *Anal.* Calcd. for $C_7H_{14}O_2$: neut. equiv., 130.2. Found: neut. equiv., 131.2. The infrared spectrum was identical with that of the product V obtained from crotonic acid and isopropylmagnesium chloride.

The amide (m.p. and mixed m.p. 137–138°) and the anilide (m.p. and mixed m.p. 110–111°) were prepared from the acid chloride.

α-(1-Hydroxycyclohexyl)-β-isopropylbutyric Acids (VI).—Crotonic acid (17.2 g.), dissolved in 400 cc. of ether, was added slowly to isopropylmagnesium chloride prepared from 10.7 g. of magnesium, 50 cc. of isopropyl chloride and 100 cc. of ether. After the addition of a solution of 23.5 g. of cyclohexanone in 100 cc. of ether, the mixture was refluxed for 4 hours. The material was poured into cold ammonium chloride solution and treated in the usual manner. Strong acidification of the aqueous layer yielded a white solid (18.2 g.) which was triturated with 150 cc. of ice-cold petroleum ether (30–40°). The material was extracted with 200 cc. of boiling petroleum ether (90–100°) and then filtered. After this process had been repeated, the residue (8.9 g.) was recrystallized from methyl ethyl ketone; m.p. 194–196° dec.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; neut. equiv., 228.3. Found: C, 68.10; H, 10.41; neut. equiv., 227.8.

The combined petroleum ether extracts were refrigerated whereupon 6.4 g. of product precipitated, m.p. 131–135° dec. after recrystallization from petroleum ether (90–100°).

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; neut. equiv., 228.3. Found: C, 68.23; H, 10.69; neut. equiv., 227.3.

α-(Phenylcarbamyl)-β-isopropylbutyric Acid (VII).—After the preparation of isopropylmagnesium chloride from 5.4 g. of magnesium, 25 cc. of isopropyl chloride and 50 cc. of ether, the solution was stirred and 8.6 g. of crotonic acid, dissolved in 300 cc. of benzene, was added. The mixture was refluxed for 18 hours, a solution of 14.4 g. of phenyl isocyanate in 50 cc. of benzene was added and the mixture was refluxed for 4 hours. The material was poured into an ice-cold solution of 20 cc. of concentrated sulfuric acid in 250 cc. of water. The aqueous layer was extracted with ether, the extract was combined with the organic layer, the solution was washed with water and then extracted with 400 cc. of 10% potassium carbonate solution. The alkaline extract was washed with ether, cooled in an ice-bath, stirred and 15 cc. of concentrated sulfuric acid dissolved in 150 cc. of water was added. The gummy precipitate was extracted with ether and the solvent was removed from the dried extract under an air jet. The residue was washed with cold petroleum ether (30–40°) and crystallized from 150 cc. of benzene; yield 9.0 g. The product sintered at 128° and melted at 134° dec. after recrystallization from benzene.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 67.44; H, 7.68; N, 5.62; neut. equiv., 249.3. Found: C, 67.34; H, 7.84; N, 5.56; neut. equiv., 247.8.

When the acid (1.5 g.) was heated for 1 hour in an oil-bath (200°), a gas was evolved. The solidified residue, β-isopropylbutyranilide, was recrystallized from petroleum ether (90–100°); yield 1.0 g., m.p. and mixed m.p. 110–111°.

ANN ARBOR, MICH.

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(17) Purchased from Wilkens-Anderson Company, Chicago, Ill.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XXII. β-Diethylaminoethyl Esters of β-Substituted α-Phenyl-β-hydroxypropionic Acids

BY F. F. BLICKE AND R. H. COX[1,2]

RECEIVED JUNE 9, 1955

Eighteen salts of β-diethylaminoethyl β-substituted α-phenyl-β-hydroxypropionates have been described. The required acids were obtained by the Ivanov reaction. The antispasmodic activity has been reported.

A number of investigators[3-5] have shown that basic alkyl esters of β-substituted α-phenyl-β-hydroxypropionic acids are potent antispasmodics. The required acids were obtained from phenylacetic acid by the use of the Ivanov reaction.

During this investigation, we prepared a number of β-substituted α-phenyl-β-hydroxypropionic acids (Table I) by interaction of the Ivanov reagent, $C_6H_5CH(MgCl)COOMgCl$, with the following aldehydes and ketones: hexaldehyde,[6] anisaldehyde, 2-methyl- and 3-methylcyclohexanone, cycloöctanone,[7] propiophenone and 2-acetylthiophene. By the Horenstein and Pählicke procedure[8] some of the acids were converted into hydrochlorides of their β-diethylaminoethyl esters; a variety of quaternary bromides of the esters were also prepared (Table II).

An attempt to obtain β-diethylaminoethyl α,β-diphenyl-β-hydroxyvalerate from the required acid and β-diethylaminoethyl chloride, by the Horenstein and Pählicke process, yielded only β-diethylaminoethyl phenylacetate and propiophenone. β-Diethylaminoethyl α-phenyl-α-(1-hydroxycyclooctyl)-acetate was obtained in 73% yield from the required acid and the basic alkyl halide; however, a small amount of cycloöctanone was present in the reaction mixture which showed that some cleavage of the acid or ester had occurred.

When α-phenyl-α-(1-hydroxycyclohexyl)-acetic acid was distilled under 15 mm. pressure, cyclohexanone was present in the distillate; however, the bulk of the acid distilled unchanged.

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[1] This paper represents part of a dissertation submitted by R. H. Cox in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1954.

[2] Sterling-Winthrop Fellow.

[3] A. W. Weston and R. W. DeNet, THIS JOURNAL, **73**, 4221 (1951).

[4] G. R. Treves and F. C. Testa, *ibid.*, **74**, 46 (1952).

[5] F. F. Blicke and H. Raffelson, *ibid.*, **74**, 1730 (1952).

[6] Purchased from Matheson, Coleman and Bell, Norwood, Ohio.

[7] F. F. Blicke, J. Aznara, N. Doorenbos and E. B. Hotelling, *ibid.*, **75**, 5418 (1953).

[8] H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).