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Synthesis of 2-*iso*-Propyl-3-methyl-buten-(3)-ol-(1)*

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The title compound was synthesized in the following way: Reformatsky condensation of ethyl α-bromo-*iso*-valerate with acetone and zinc to ethyl 3-hydroxy-2-*iso*-propyl-3-methyl-butyrate (I), dehydration to the mixture of ethyl 2-*iso*-propyl-3-methyl-buten-(3)-oate (II) and 2-*iso*-propyl-3-methyl-buten-(2)-oate (IV), and lithium aluminum hydride reduction to 2-*iso*-propyl-3-methyl-buten-(3)-ol-(1) (VI). The mixture of esters was hydrolysed to 2-*iso*-propyl-3-methyl-buten-(3)-oic acid (III) which gave on reduction with lithium aluminum hydride the same alcohol VI. Proof of the structure of the acid III was accomplished by means of chemical and physical methods.

During the investigation of certain relationships between chemical structures and odours we nedeed as intermediates 2-*iso*-propyl-3-methyl-buten-(3)-ol-(1) (VI) and the isomeric 2-*iso*-propyl-3-methyl-buten-(2)-ol-(1). Both compounds have not yet been described, and in this paper a relatively simple synthesis of alcohol VI is reported. As starting material ethyl *α*-bromo-*iso*-valerate was used and subjected to the Reformatsky reaction with acetone. The reaction was caried out in benzene solution and ethyl 3-hydroxy-2-*iso*-propyl-3-methyl-butyrate (I) obtained in $46^{0}/_{0}$ yield. In such a manner the basic carbon skeleton of alcohol VI was obtained in the first stage of the synthesis. In subsequent steps it was necessary to accomplish dehydration followed by reduction of carbethoxy group.

Dehydration of I with thionyl chloride in pyridine[1,2] gave a mixture of unsaturated esters II and IV as evident from UV- (λ_{max} 217 mμ, $\varepsilon = 1210$)[3] and IR- (896 cm^{-1} and 1645 cm^{1-} bands)[1,4,5,6] absorption spectra. The dehydration with *p*-toluenesulfonic acid (azeotropic distillation with toluene) afforded the same mixture but with a little higher content of ester IV (λ_{max} 217 mμ, $\varepsilon = 2260$)[3].

The mixture of esters was hydrolysed with sodium hydroxide and the pure crystalline 2-*iso*-propyl-3-methyl-buten-(3)-oic acid (III) was obtained.

Detailed proof of the structure for acid III was accomplished as follows. The acid binds one mole of hydrogen by catalytic hydrogenation over Adams' platinum catalyst and reveals no UV-absorption in the range 200—350 $m\mu$[3]. The IR-spectrum gives, *inter alia* peaks at 900 cm^{-1} (ethylenic C-H out-of-plane bending vibration) and 1642 cm^{-1} (C=C streching vibration)[1,4,5,6]. NMR-spectrum (40 Mc, CH_2Cl_2 as standard) shows signals for olefinic protons (-5 cps), methyl protons of the $CH_3\text{-}\overset{|}{C}{=}$group (+120 cps) and methyl protons of *iso*-propyl group

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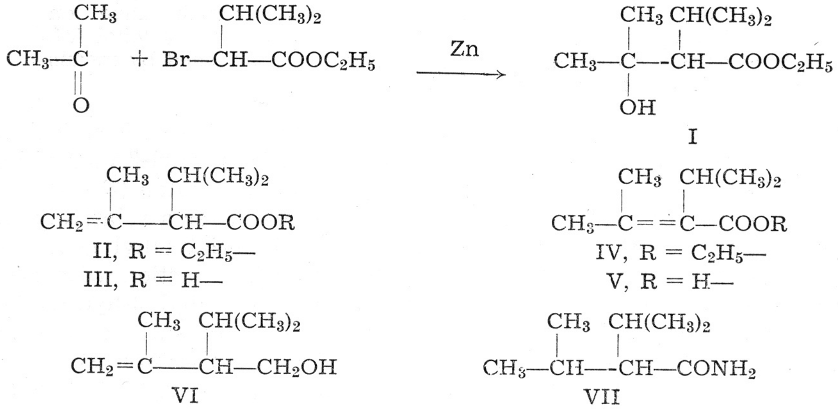
(+154 cps)[5,7]. The ratio of the areas under the peaks was roughly 2:3:6 as to be expected from formula III. Chemical shifts expressed as δ are —0.12, +3.0 and +3.85[7]; and the calculated τ-values are 5.19, 8.31, and 9.16[8], respectively.*

By catalytic hydrogenation of acid III, di-*iso*-propyl acetic acid was obtained and characterized as amide VII identical in all respects with the amide prepared by an unequivocal way (according Sarel and Newman[9]) as evident from m.p., mixed m.p., and IR absorption spectra.

Pure, sublimed acid III was reduced with lithium aluminum hydride to alcohol VI in 64% yield. Identical compound was obtained in 90% yield by reduction the mixture of esters II and IV. Identity of both preparations was confirmed by m.p. and mixed m.p. of 3,5-dinitrobenzoates. Compound VI absorbs one mole of hydrogen by catalytic hydrogenation, and the IR-absorption spectrum exhibits bands at 889 cm^{-1} (ethylenic C-H bending vibration, attributable to $\rangle C=CH_2$) and 1645 cm^{-1} (C=C streching vibration)[1,4,5,6].

Alcohol VI is a colourless liquid with a strong camphorlike odour.



$$CH_3-\underset{\underset{O}{\|}}{\overset{\overset{CH_3}{|}}{C}} + Br-\overset{\overset{CH(CH_3)_2}{|}}{CH}-COOC_2H_5 \xrightarrow{Zn} CH_3-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-\overset{\overset{CH(CH_3)_2}{|}}{CH}-COOC_2H_5$$

I

$$CH_2=\overset{\overset{CH_3}{|}}{C}-\overset{\overset{CH(CH_3)_2}{|}}{CH}-COOR$$

II, R = C_2H_5—
III, R = H—

$$CH_3-\overset{\overset{CH_3}{|}}{C}=\overset{\overset{CH(CH_3)_2}{|}}{C}-COOR$$

IV, R = C_2H_5—
V, R = H—

$$CH_2=\overset{\overset{CH_3}{|}}{C}-\overset{\overset{CH(CH_3)_2}{|}}{CH}-CH_2OH$$

VI

$$CH_3-\overset{\overset{CH_3}{|}}{CH}-\overset{\overset{CH(CH_3)_2}{|}}{CH}-CONH_2$$

VII

EXPERIMENTAL

Ultraviolet spectra were recorded on Beckman Model DU spectrophotometer, infrared spectra on Perkin-Elmer Mod. 134 and 21, and NMR spectrum on a Varian Associates Instrument.

Melting points are uncorrected.

*Ethyl 3-hydroxy-2-*iso*-propyl-3-methyl-butyrate* (I)

Ethyl α-bromo-*iso*-valerate (b. p. 73—74°/10 mm.) (104.5 g., 0.5 mole) and dry acetone (29 g., 0.5 mole) were dissolved in 150 ml. of dry benzene. Approximately 1/6 of this mixture was added to fresh zinc turnings (32.7 g., 0.5 mole) and 50 ml. of dry benzene. It was protected from moisture and heated with stirring until the vigorous reaction started. The reaction was controlled by cooling with tap water and afterwards the rest of the above mixture was added at such a rate that the reaction mixture gently boiled (in case the reaction subsided it was warmed up again). The addition required about 1.5 hour and then the mixture was refluxed for 1 hour, until all zinc was dissolved. While cooling with ice, 50 ml. of water was

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* These data show that this acid is not identical with α-*iso*-propil-senecioic acid (V), see R. B. Wagner and J. A. Moore, *J. Am. Chem. Soc.* **72** (1950) 974.

added to the mixture and the resulted precipitate was dissolved with cold diluted sulfuric acid (17 ml. of concd. sulfuric acid and 100 g. of ice). The layers were separated, the benzene layer washed with water, sodium carbonate solution and finally with water to neutral reaction. The water layer was extracted with ether and after washing, the ether and the benzene solutions were mixed and dried over magnesium sulfate. After evaporating the solvents the residue was distilled under reduced pressure through a 20 cm. Vigreux-column. The main fraction distills between 89—94°/13 mm. as pale yellow oil. The yield was 43.4 g. (46%). Repeated distillation over a Widmer-type column gave 33 g. of the pure ester, b.p. 89—91°/10 mm.

For analysis the sample was redistilled at 92°/14 mm.; n_D^{20} 1.4352.

Anal. $C_{10}H_{20}O_3$ (188.26) calc'd.: C 63.79; H 10.71%
found : C 63.59; H 10.49%

*Mixture of ethyl 2-*iso*-propyl-3-methyl-buten-(3)-oate* (II) *and ethyl 2-*iso*-propyl-3-methyl-buten-(2)-oate* (IV)

A) Dehydration of ester I with thionyl chloride in pyridine[1]. Ester I (37.6 g., 0.2 mole; b.p. 89—91°/10 mm.), dry pyridine (27 g., 27.5 ml., 0.34 mole) and 96 ml. of dry chloroform were cooled to —10°. To this solution a mixture of dry pyridine (27 g., 27.5 ml., 0.34 mole), dry chloroform (80 ml.) and thionyl chloride (28.6 g., 17.5 ml., 0.24 mole) was added with stirring within one hour. After keeping for 1 hour at room temperature the mixture was distilled (evolution of sulfur dioxide) until the temperature reached 128° (thermometer in the liquid). The residue was poured on approximately 200 g. of ice and 100 ml. of ether, the resulting mixture filtered through a G-3 glass filter in order to remove the tarry material and the water layer extracted repeatedly with ether (5×50 ml.). The combined ether solutions were washed with 10% hydrochloric acid, water, 10% sodium hydrocarbonate and water in turn and dried over magnesium sulfate. Ether was evaporated and the residue distilled under reduced pressure through a short Vigreux-column. B.p. 64—66°/13 mm. Yield 24 g. (71%).

It is important for the success of the preparation that the starting material is freshly distilled, as otherwise quite a lot of tarry material is formed which complicates the isolation of the product.

The analytical sample was distilled twice *in vacuo* at 64.5—65°/14 mm., n_D^{20} 1.4295

The ultraviolet absorption spectrum showed maximum at 217 mμ (ε = 1210)[3]; the IR spectrum exhibits *inter alia* peaks at 896 cm^{-1} and 1645 cm^{-1} [1,4,5,6].

Anal. $C_{10}H_{18}O_2$ (170.24) calc'd.: C 70.54; H 10.66%
found : C 70.68; H 10.33%

B) Dehydration of ester I with *p*-toluenesulfonic acid. Ester I (15 g., 0.074 mole), 1 g. of *p*-toluenesulfonic acid hydrate and 50 ml. of toluene were boiled for 7 hours in a flask with a water separator[10]. As soon as water separation ceased the mixture was cooled and washed successively with water, sodium hydrocarbonate and water and dried over magnesium sulfate. By distillation *in vacuo* 8.2 g. (65%), b.p. 62—64°/10 mm. was obtained. The higher boiling fraction: b.p. 69.5—70°/12 mm., λ_{max} 217 mμ, ε = 2260[3].

2-iso-*Propyl-3-methyl-buten-(3)-oic acid* (III)

Mixture of the unsaturated esters II and IV (18.4 g., 0.108 mole, b.p. 62.5—63.5°/10 mm.), 6.5 g. of sodium hydroxide, 15 ml. of water and 60 ml. of ethanol were boiled under reflux for 4 hours. Ethanol was evaporated, the residue dissolved in 50 ml. of water and extracted with ether to remove the unhydrolysed material. The water layer after boiling with charcoal and filtering was acidified with concd. hydrochloric acid (ca. 18 ml.). The precipitated crystalline acid III was separated by suction and dried. Yield: 11.5 g. (75%).

Recrystallization from 60 ml. of methanol after addition of 60 ml. of water and seeding gave 10 g. of the pure acid m.p. 64.5—66°.

The analytical sample was twice sublimed *in vacuo* at 60°/12 mm.

UV-spectrum showed no absorption maximum in the region 200—350 mμ[3]; IR-spectrum[1,4,5,6] showed peaks at 900 cm^{-1} and 1642 cm^{-1}; NMR-spectrum had the signals at —306, —5, +90, +120, and +154 cps[5] relative to water (carbon tetrachloride solution, methylene chloride as standard, 40 Mc); corresponding δ-values: —7.65, —0.12, +2.25, +3.0, and +3.85[7].

Anal. $C_8H_{14}O_2$ (142.19) calc'd.: C 67.57; H 9.93%
found : C 67.54; H 9.79%

Hydrogenation: 97.7 mg. (0.687 mmole) of acid III was hydrogenated over Adams' platinum catalyst in alcohol at 25° and 750 mm. It was absorbed 13.35 ml. of hydrogen (S.T.P.). Theoretical amount 15.35 ml.

Di-iso-*propylacetamide* (VII)

2-*iso*-Propyl-3-methyl-buten-(3)-oic acid (III) (1.47 g., 10.33 mmoles) was hydrogenated with 100 mg. of Adams' platinum catalyst in 15 ml. of ethanol at 23° and 755 mm. During about 60 min. 233.5 ml. of hydrogen (S.T.P.) was absorbed. After removing the catalyst, the filtrate was evaporated *in vacuo* and 5 ml. of thionyl chloride was added to the oily residue. The mixture was refluxed for 3 hrs., the excess of thionyl chloride evaporated *in vacuo* and the oily residue poured into 15 ml. of concd. ammonia. The crystalline product was extracted with ether, the solution washed with water and dried over magnesium sulfate. Ether was evaporated and the white crystaline residue recrystallized from benzene; 0.55 g. m.p. 147—148°. For IR-spectrophotometry it was twice recrystallized from benzene and dried during two hours *in vacuo* (0.06 mm.) at 75°. M.p. 149—150°. It was identical with the amide prepared according to the procedure reported by Sarel and Newman[9] (as evident by m.p., mixed m.p. and IR-spectra).

2-iso-*Propyl-3-methyl-buten-(3)-ol-(1)* (VI)

A) Reduction of ester II. Ethyl 2-*iso*-propyl-3-methyl-buten-(3)-oate (19.6 g., 0.115 mole) was dissolved in 60 ml. of dry ether and added to the solution of lithium aluminum hydride (3.2 g., 0.069 mole, 80%) in 100 ml. of dry ether at such a rate that ether gently boiled. Then additional 0.5 g. of lithium aluminum hydride was added and the boiling continued for half an hour. The hydrolysis was effected with 20 ml. of wet ether and then with a concentrated solution of sodium potassium tartrate. After the whole precipitate was dissolved, the layers were separated and the water layer extracted with ether. The ether solution was washed with water until neutral and dried over magnesium sulfate.

After evaporation of ether the residual oil was distilled *in vacuo:* b.p. 64—65°/10 mm.; 13.2 g., 90%.

For analysis the sample was redistilled; n_D^{20} 1.4326

Anal. $C_8H_{16}O$ (128.21) calc'd.: C 74.94; H 12.58%
found : C 74.81; H 12.35%

3,5-dinitrobenzoate: 400 mg. of alcohol VI and 1,2 g. of 3,5-dinitrobenzoyl chloride were mixed with 2 ml. of pyridine and heated on a water bath for 30 minutes. The mixture was poured into a solution of sodium hydrocarbonate and extracted with petroleum ether. Leafy crystals, m. p. 61—62°, were obtained.

Anal. $C_{15}H_{18}N_2O_6$ (322.31) calc'd.: N 8.69%
found : N 8.79%

B) Reduction of acid III. A solution of 2-*iso*-propyl-3-methyl-buten-(3)-oic acid (3.5 g., 0.0246 mole) in 25 ml. of dry ether was added to a solution of lithium aluminum hydride (1.5 g., 0.03 mole) in 50 ml. of dry ether during one hour with stirring. At the end of the addition the mixture became viscous. The heating was continued for two hours. A few ml. of water was added whilst cooled and then a concd. solution of sodium potassium tartrate. The ether solution was washed with water until neutral and dried over magnesium sulfate. The solvent was evaporated and the residual oil distilled *in vacuo* at 64.5—65°/10 mm. The yield was 2 g. (64%). The analytical sample was redistilled *in vacuo* b.p. 64°/10 mm.

IR-spectrum showed *inter alia* peaks at 889 cm^{-1} and 1645 cm^{-1}.

Hydrogenation: 113.8 mg. of alcohol VI was hydrogenated over Adams' platinum catalyst in ethanol at 23° and 752 mm. There was absorbed 18.25 ml. of hydrogen (S.T.P.); calc'd. 19.9 ml.

3,5-dinitrobenzoate, prepared as above, m.p. 61—62°, showed no depression of melting point when mixed with previous specimen.

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IZVOD

Sinteza 2-*izo*-propil-3-metil-buten-(3)-ol-(1)-a

K. Šestanj

2-*izo*-Propil-3-metil-buten-(3)-ol-(1) (VI) je sintetiziran slijedećim putem: kondenzacijom etilnog estera α-brom-*izo*-valerijanske kiseline s acetonom i cinkom po Reformatskome u etilni ester 3-hidroksi-2-*izo*-propil-3-metil-maslačne kiseline (I), dehidratacijom estera I u smjesu etilnih estera 2-*izo*-propil-3-metil-buten-(3) kiseline (II) i 2-*izo*-propil-3-metil-buten-(2) kiseline (IV) i redukcijom s litijevim aluminijevim hidridom u alkohol VI. Isti alkohol dobiven je i iz čiste kiseline III, a njena je struktura dokazana fizikalnim i kemijskim metodama.

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