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Abstract

Full Text

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SYNTHESIS OF ESTERS OF -HYDROXY- -NAPHTHYLPROPIONIC ACIDS BY THE REFORMATSKY REACTION

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Esters of β-hydroxy-β-arylaliphatic carboxylic acids are of interest as starting products for the synthesis of substances from the group of sympathomimetics. To study similar physiologically active substances containing a naphthyl ring in their molecule, it was necessary to find methods for the synthesis of certain esters of β-hydroxy-β-naphthylpropionic acids. The required compounds have not been described in the literature. We found that the above-mentioned β-hydroxy esters are conveniently obtained by the Reformatsky reaction, starting from unsubstituted 1- or 2-naphthaldehyde. Until now, the Reformatsky reaction has been applied only to certain substituted naphthaldehydes, and in the corresponding publications (1) the yields are not reported.

The condensation of unsubstituted naphthaldehydes with esters of α-bromoacetic and α-bromopropionic acids was carried out by us using activated zinc powder, at the molar ratios of ester and aldehyde and with the yields given in Table 1. The condensation proceeds under continuous

Table 1

$$\text{naphthyl-CH(OH)} \cdot \text{CH(R)} \cdot \text{CO} \cdot \text{OR'}$$

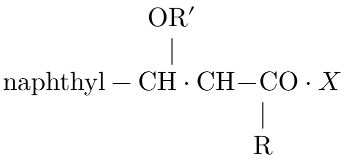
Position of the substituent in the naphthyl ring	R	R	B.p., °C	M.p., °C	n_D^{20}	Yield, %	Gross formula	Mol. wt.	C, % found	C, % calculated	H, % found	H, % calculated
1	H —	C H —	188—192/0.4 mm	54—56 (from benzene, *n*-hexane)		63	C H O	244.28	73.77	73.75	6.45	6.60
1	CH —	C H —	168—179/0.1 mm	—	1.5748	81	C H O	258.31	73.22	74.39	6.91	7.03
2	H —	C H —	198—8/0.15 mm	35—37 (from toluene, *n*-hexane)		50	C H O	244.28	73.84	73.75	6.73	6.60
1	H —	H —		164—165 (from benzene, acetic ester)		87	C H O	216.23	71.05	72.20	5.50	5.59

Position of the substituent in the naphthyl ring	R	R	B.p., °C	M.p., °C	n_D^{20}	Yield, %	Gross formula	Mol. wt.	C, % found	C, % calculated	H, % found	H, % calculated
2	H —	H —		168 — 169 (from benzene, acetic ester)		80	C H O	216.23	71.92	72.20	5.65	5.59
2	CH —	C H —	175 — 185/0.1 mm	—	1.5760	59	C H O	258.31	73.08	74.39	6.78	7.03

external heating, since naphthaldehydes exhibit low reactivity. Hydroxy esters with a methyl group in the α-position relative to the carbethoxy group are a diastereomeric mixture. All the esters were obtained only in the form of racemates. Esters with a branched chain, in accordance with the data on the Reformatsky reaction (²), were obtained in better yields than esters with a straight chain. Since 2-naphthaldehyde reacts with greater difficulty, in its condensation it was necessary to use a more high-boiling solvents (benzene—toluene 1:1) and zinc treated under more severe conditions. The hydroxy esters distilled under reduced pressure almost without decomposition.

Hydroxy esters containing a 1-naphthyl substituent were characterized through derivatives of their β-hydroxyl group (see Table 2).

Table 2



$$\text{naphthyl}-\underset{}{\overset{\mathrm{OR'}}{\overset{|}{\mathrm{CH}}}}\cdot\underset{\underset{\mathrm{R}}{|}}{\mathrm{CH}}-\mathrm{CO}\cdot X$$

Position of the substituent in the naphthyl ring	R	R'	X	M.p., °C	Yield, %	Empirical formula	Mol. wt.	N, %, found	N, %, calc.
1	H	*n*-$O_2N\cdot C_6H_4\cdot CO$—	C_2H_5O—	104–105 (from methanol)	31	$C_{22}H_{19}NO_6$	393.38	3.61	3.56
1	CH_3	*n*-$O_2N\cdot C_6H_4\cdot CO$—	C_2H_5O—	110–111 (from methanol)	30	$C_{23}H_{21}NO_6$	407.41	3.17	3.44
1	CH_3	$C_6H_5\cdot NH\cdot CO$—	C_2H_5O— (substance I)	144–145 (from benzene, *n*-hexane)	71	$C_{23}H_{23}NO_4$	377.42	3.70	3.71
1	CH_3	$C_6H_5\cdot NH\cdot CO$—	C_2H_5O— (substance II)	101–102 (from benzene, *n*-hexane)	71	$C_{23}H_{23}NO_4$	377.42	3.66	3.71
1	H	$C_6H_5\cdot NH\cdot CO$—	C_2H_5O—	115–116 (from benzene, petroleum ether)	61	$C_{22}H_{21}NO_4$	363.39	3.71	3.85
1	H	H	$NH_2\cdot NH$—	201–202 (from methanol)		$C_{13}H_{14}N_2O_2$	230.26	12.27	12.16

Position of the substituent in the naphthyl ring	R	R'	X	M.p., °C	Yield, %	Empirical formula	Mol. wt.	N, %, found	N, %, calc.
2	H	H	$NH_2 \cdot NH$ –	203–204 (from dioxane)		$C_{13}H_{14}N_2O_2$	230.26	12.09	12.16
1	CH_3	H	$NH_2 \cdot NH$ – (substance I)	191–192 (from water)		$C_{14}H_{16}N_2O_2$	244.29	11.56	11.46
1	CH_3	H	$NH_2 \cdot NH$ – (substance II)	131–132 (from abs. ether)		$C_{14}H_{16}N_2O_2$	244.29	11.30	11.46
2	CH_3	H	$NH_2 \cdot NH$ – (substance I)	205–206 (from methanol)		$C_{14}H_{16}N_2O_2$	244.29	11.74	11.46
2	CH_3	H	$NH_2 \cdot NH$ – (substance II)	160–161 (from acetic ethyl ester)		$C_{14}H_{16}N_2O_2$	244.29	11.46	11.46

n-Nitrobenzoates were obtained by the Schotten–Baumann method with pyridine from *n*-nitrobenzoyl chloride and the given ester at 20°. At elevated temperature, dehydration of the hydroxy ester into the ester of a $\Delta^{\alpha,\beta}$-unsaturated acid probably occurs. This is indicated by the formation of *n*-nitrobenzoic anhydride from the corresponding chloride in the anhydrous reaction mixture.

Addition of β-hydroxy esters to phenyl isocyanate leads to the corresponding N-phenylurethanes and proceeds in almost 60% yield at 130–150° without solvent. On heating above 170° under pressure, resinification is observed.

In esters containing a 2-naphthyl radical, the reactivity of the hydroxyl group is lower, as a result of which n-nitrobenzoates or N-phenylurethanes could not be isolated from them.

From the diastereomeric mixture of ethyl esters of β-hydroxy-β-(1-naphthyl)-α-methylpropionic acids, both expected diastereomeric N-phenylurethanes were obtained, but instead of two diastereomeric n-nitrobenzoates only one was obtained. That the latter is a pure individual substance is also confirmed by its chromatographic properties on paper.

By means of alkaline hydrolysis in alcohol, the hydroxy esters gave the corresponding acids; however, since isolation of the four diastereomeric acids corresponding to two diastereomeric ester mixtures proved rather difficult, to date only two α-unsubstituted β-hydroxy-β-naphthylpropionic acids, also listed in Table 1, have been isolated in pure form.

β-Hydroxy esters, under the action of alcoholic hydrazine hydrate, were converted into hydrazides of hydroxycarboxylic acids. In a definite way, from two diastereomeric ester mixtures both pairs of diastereomeric hydrazides were obtained and isolated. We regard the synthesis of the latter compounds as proof that the β-hydroxy esters obtained do indeed contain a β-hydroxyl group, since otherwise, on dehydration of the hydroxy esters to esters of a $\Delta^{\alpha,\beta}$-unsaturated acid, one would have expected the formation of pyrazolidones, which do not possess a reducing-active $NH \cdot NH_2$ group.

The 2-naphthaldehyde required for the synthesis was obtained according to Stephen(3). On reproducing the literature directions it was found that the aldehyde is obtained in a maximum yield of 30%, and with an admixture of the starting nitrile in a ratio of 1 : 1. Separation of the two substances by distillation is difficult because of the closeness of their boiling points. With the modification introduced by us, the aldehyde is obtained in 85% yield relative to the nitrile that reacted.

Experimental part

1. 2-Naphthaldehyde. 100 g of anhydrous tin dichloride is saturated in 280 ml of abs. ether at 10° for 3 hours with dry hydrogen chloride. 20.4 g of 2-naphthonitrile in 200 ml of abs. ether is added, and, with stirring, the mixture is saturated for another 3 hours with hydrogen chloride. The mixture is left overnight, after which it is again saturated at 10° with hydrogen chloride. The yellow powdery precipitate is filtered off, washed with ether, and hydrolyzed for 1 hour with 450 ml of water and 2 ml of sulfuric acid on a steam bath. After cooling, 25 ml of hydrochloric acid is added and the aldehyde obtained is extracted with ether. The ethereal solution, washed with water to pH 6, is shaken for one hour with 150 ml of a 40% solution of sodium bisulfite. The mixture is filtered; the white precipitate is washed with ether and dried in air. From the filtered and water-washed ethereal solution, 7.4 g of unreacted nitrile, m.p. 61–63°, is isolated, while the crystalline bisulfite compound (25.3 g) is heated for 2.5 hours on a water bath with 60 ml of 8% hydrochloric acid and at the same time air is blown through. To prevent entrainment of the aldehyde by sulfur dioxide, a reflux condenser 1.5 m long is used. The mixture is extracted with boiling ether, and the ethereal solution is washed to pH 7 and evaporated to dryness; 11.2 g of naphthaldehyde is obtained, m.p. 61–62° (85% of theory relative to the nitrile that reacted).

2. *threo*-Erythro ethyl ester of -hydroxy- -(1-naphthyl)- -methylpropionic acid. A mixture of 31.2 g of 1-naphthaldehyde, 36.2 g of ethyl α-bromopropionate, 40 ml of dry benzene, and 10 ml of abs. ether is added dropwise over 1 hour at 75° to a mixture of 0.2 g of iodine and 19.2 g of freshly activated zinc powder (50 g is stirred for 5 min with 120 ml of 5% hydrochloric acid, filtered off, thoroughly washed with water and ethanol, then dried at 120° and evacuated at 1 mm). After the addition, the mixture is stirred for 2 hours at 80° and cooled. The organozinc complex is decomposed, with stirring, with 75 ml of 15% sulfuric acid and 75 g of crushed ice over the course of an hour. The unreacted zinc is filtered off, and the organic solution is washed successively with 10% sulfuric acid, with sodium carbonate solution, and then shaken for 1 hour with a saturated solution of sodium bisulfite to remove traces of naphthaldehyde. The bisulfite complex is filtered off, and the washed benzene-ether solution, after twofold rectification, gives 41.9 g of ethyl ester of β-hydroxy-β-(1-naphthyl)-α-methylpropionic acid with b.p. 168–179°/0.1 mm, i.e., 81% of theory.

3. Ethyl ester of -(*p*-nitrobenzoyloxy)- -(1-naphthyl)propionic acid. 1.20 g of ethyl ester of β-hydroxy-β-(1-naphthyl)propionic acid is dissolved in 5 ml of dry benzene and mixed at 20° with a solution of 1.10 g of *p*-nitrobenzoyl chloride in 15 ml of dry benzene. To the solution is added 3 ml of pyridine, and after 24 hours the mixture is poured onto ice and dilute sulfuric acid. With vigorous shaking, it is extracted with 100 ml of chloroform. The chloroform extracts are washed with dilute sulfuric acid, water, and then three times with a 5% solution of sodium carbonate. The solution, washed to neutrality, is dried and evaporated, and the resulting oil, after treatment with ether, gives crystalline ethyl ester *p*-nitrobenzoate of β-hydroxy-β-(1-naphthyl)propionic acid. After recrystallization from methanol, 0.63 g of colorless rhombic crystals is obtained, m.p. 104-105°.

4. **N-Phenylurethanes of threo-erythro ethyl ester of -hydroxy- -(1-naphthyl)- -methylpropionic acid.** 10.3 g of a diastereomeric mixture of ethyl ester of β-hydroxy-β-(1-naphthyl)-α-methylpropionic acid is heated for 6 hours with 6.0 g of phenyl isocyanate, cooled, and boiled with 35 ml of benzene to dissolve the oil. After cooling, the insoluble triphenyl isocyanurate is filtered off and 70 ml of *n*-hexane is added. The

separated crude crystals (6.5 g) are one of the N-phenylurethanes (substance I, white druses with m.p. 144–145°, after recrystallization from ethyl acetate and *n*-hexane). The other diastereomer precipitates from the mother liquor after an additional addition of *n*-hexane. This gives 4.3 g of crude phenylurethane (substance II, colorless needles with m.p. 101–102°, recrystallized from ethyl acetate, *n*-hexane 1:10). The total yield of N-phenylurethanes from the diastereomeric mixture is 71%.

5. **-Hydroxy- -(2-naphthyl)propionic acid.** It is obtained from 2.44 g of ethyl ester of β-hydroxy-β-(2-naphthyl)propionic acid after two hours' heating with 0.80 g of caustic soda dissolved in 2.0 ml of water and 10 ml of methanol at 60°. After dilution with water and acidification to pH 3, 1.52 g of the hydroxy acid precipitates, recrystallized from benzene (acetic acid). Crystals with a pale-yellow tint, m.p. 168–169°.

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Note: Figure translations are in progress. See original paper for figures.