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REDUCTION OF SOME CYCLIC DERIVATIVES OF DIPHENIC ACID WITH SODIUM BORANE IN ALCOHOLS

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Reduction of heptamerous cyclic imides with sodium borane has been carried out for the first time by the example of some imides of diphenic acid. In this case for the first time amides of 2'-hydroxymethylxenyl-2-carboxylic acid which are potentially valued bioactive compounds were obtained. It was shown that the nature of substituent at nitrogen atom influences the reaction products yields and composition. The reduction of diphenic acid anhydride with sodium borane in simple alcohols occurs with the formation of reduction products – 7H-dibenzyl[c,e] oxepin-5-on (36...46 %) as well as products of diphenic acid alcoholysis-monoester (29...36 %). In this case the nature of alcohol influences weakly reaction products ratio.

Imides of diphenic (biphenyl-2,2′-dicarboxylic) acid are of practical interest as semi-products for obtaining new nitrogen-containing biologically active substances – derivatives 2,2′-substituted biphenyls [1]. Recently new synthesis methods of these compounds based on reaction of diphenic acid with ureas were proposed [2, 3]. For further functionalisation of the above stated imides their reduction with sodium borohydride in methanol medium was studied in the given paper.

The analysis of literary data showed that reduction of dicarboxylic acid cyclic imides with alkalis borohydrides is known only by the example of penta- and hexamerous cycles [4–8] in this case succinimide, phtalimide, glutharimide and their derivatives served as a rule as substrates. There is no information about similar reactions for heptamerous cyclic imides in scientific literature.

Earlier unsubstituted imide of diphenic acid **Ia** was reduced with zinc amalgam in hydrochloric acid and with lithium aluminum hydride in ether. In the first case 6,7- dihydrodibenzo[c,e]azepine-5-on was obtained, in the second – 6,7-dihydro-5*H*-dibenzo[c,e]azepine (with outputs of 13 and 29 % respectively) [9].

We studied sodium borohydride influence on some imides of diphenic acid in methanol. For this purpose a number of imides containing substituents of different nature at nitrogen atom was selected. They are: hydrogen (R=H, **Ia**), alkyl (R=CH_3, **Ib**), aryl (R=Ph, **Ic**), aralkyl (R=CH_2Ph, **Id**), halogenalkyl (R=CH_2CH_2Cl, **Ie**) and hetaryl (R=antipyryl-4, **If**).

It was revealed that reduction starts at room temperature (20...25 °C) and finishes for 20...25 min.

It was shown that reduction of unsabstituted imide of diphenic acid **Ia** by 2 moles of $NaBH_4$ in methanol results in forming mixture of four products. Only the main reaction product which is the amide of 2′-hydroxymethylbiphenil-2-carboxylic acid **IIa** was extracted individually (Fig. 1). Compound **IIa** was obtained with the output (32 %).

One more product of this reaction by the data of thin-layer chromatography (TLC), is probably 7*H*-dibenzo[c,e]oxepine-5-on **III**. The rest products could not be identified by the moment.

N-substituted imides **Ib-e** are reduced with 2 moles of $NaBH_4$ in methanol exclusively to acyclic *N*-substituted amides of 2′-hydroxymethylbiphenil-2-carboxylic acid **IIb-e**. Yields of reduction products with such substituents as methyl **IIb**, phenyl **IIc** and benzyl **IId** amount to 84, 85 and 88 % respectively. *N*-(2-chloroethan)imide **Ie** forms respective amide **IIe** only with the yield of 63 %. Reduced yield of the product **IIe**, may be evidently explained by the fact that imide **Ie**, in comparison wit imides **IIb-d** contains reactive substituent – CH_2CH_2Cl, the chlorine atom in which may undergo various reactions of substitution or removal in the given

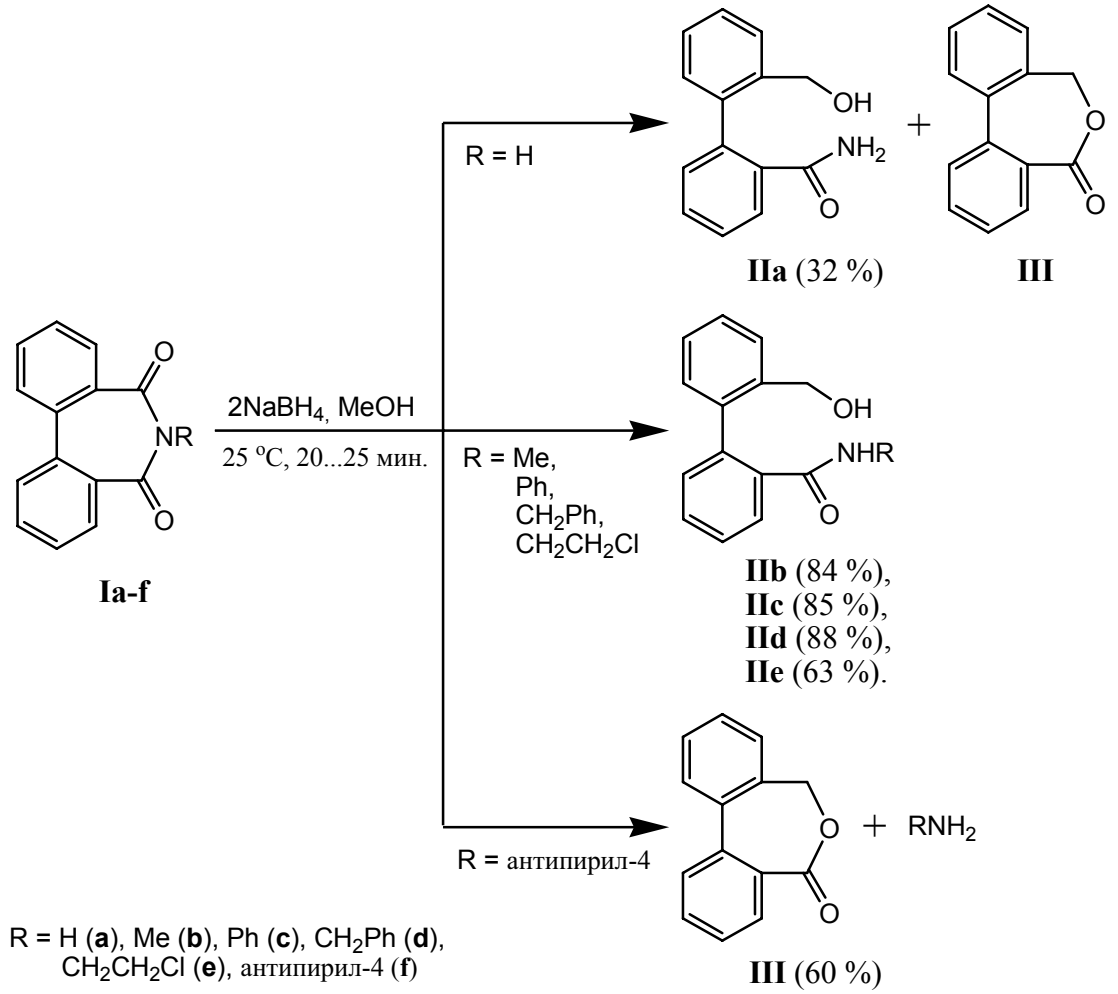

Fig. 1. *Diagram of reduction of imides of diphenic acid $NaBH_4$*

conditions. Earlier, for example, at reduction of *N*-chloromethyphtalimide $NaBH_4$ in MeOH the formation of N-methoxymethyl-3-hydroxyisoindolin-1-on (72 %) was observed [7].

Reduction of *N*-(antipyryl-4)imide of diphenic acid **If** in similar conditions results in removal of the molecule of 4-aminoantipyrin and accompanied with formation of 7*H*-dibenzo[c,e]oxepine-5-on **III** with the yield of 60 %. It is obvious that relative *N*-(antipyryl-4)amid is formed nevertheless during the reaction, however, its existence turns out to be energy unfavorable may be owing to steric problems; then it dissociates forming two more stable molecules of 4-aminoantipyrin and 7*H*-dibenzo[c,e]oxepine -5-on **III**.

Amides of 2′-hydroxymethylbiphenil-2-carboxylic acid **IIa-e** were obtained for the first time. Compounds of the given group are of interest as new potentially valued biologically active substances.

Another cyclic derivative of diphenic acid – its anhydrate **IV** was earlier reduced in dimethylformamide (DMF) to 7*H*-dibenzo[c,e]oxepine-5-on **III** with the yield of 87 % [10].

It was shown that carrying out this reaction in the medium of proton solvents such as elementary alcohols in comparison with aproton DMF is also accompanied with significant alcoholyses of initial anhydride **IV** to the relative alkylmonoethers of diphenic acid **Va-c** besides reduction process (Fig. 2). Reaction was carried out in such alcohols as methanol, ethanol (96 %) and propanol-2 in the conditions similar to reduction of imides **Ia-f**.

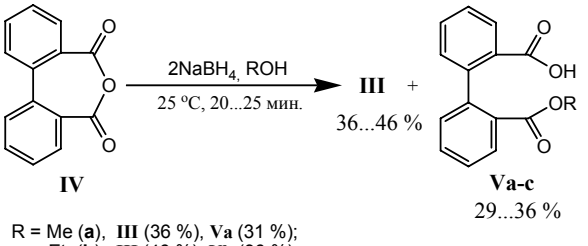

Fig. 2. *Diagram of reduction of anhydride of diphenic acid $NaBH_4$*

It is known that $NaBH_4$ decays with alcohols forming relative sodium alcoholates [4]. Most probably it is alcoholate appearance in reaction mass results in anhydride **IV** alcoholysis

The analysis of the obtained data on product yield shows that alcohol nature influences weakly both the yi-

eld of oxepinon **III** and the yield of corresponding ethers **Va-c**. Maximal spread of yields of oxepinon **III** amounts to 10 % and ethers **Va-c** – 7 % and ratio of the products for all cases is close to 1. It may indicate the fact that the ratio of recovery rate to alcoholysis rate for all these alcohols is approximately equal.

Reaction of reduction and alcoholysis occur simultaneously therefore, the ratio of rates of these reactions should determine final ratio of the products.

Alcoholysis rate depends on alcoholate concentration and its basicity and recovery rate depends on equilibrium concentration of $NaBH_4$ in solution.

Current concentration of alcoholate is determined by $NaBH_4$ decay rate and will be maximal in methanol as the strongest acid [4]. However, the formed sodium methylate is the weakest base for the given series. At the same time $NaBH_4$ solubility in methanol is considerably higher than in other alcohols [4] therefore, concentration of dissolved borohydride is the highest in the given case. Thus, there is a high alcoholysis and recovery rate in methanol.

The opposite picture is observed in propanol-2: alcoholate current concentration is not high however, sodium isopropylate is the strongest base; $NaBH_4$ equilibrium concentration is also comparatively low. Thus, alcoholysis and reduction occur relatively slowly in propanol-2. The ratio of these reactions rates both for methanol and propanol-2 remains almost equal.

Ethanol, probably, takes intermediate position in this series.

Thus, by the example of some imides of diphenic acid **Ia-f** heptamerous cyclic imides were firstly reduced with sodium borohydride; and in this case amides of 2′-hydroximethylbiphenil-2-carboxylic acid **IIa-e** which are potentially valued biologically active compounds were firstly obtained. It was shown that the nature of substituent at nitrogen atom influences the yields and composition of reaction products. So unsubstituted imide **Ia** gives four products the main of which is amide of 2′-hydroximethylbiphenil-2-carboxylic acid **IIa** (32 %), *N*-alkyl-, aryl-, aralkyl- and halogenalkyl substituted imides **Ib-e** form exclusively proper amides **IIb-e** (63...88 %), *N*-(antipyryl-4)imide **If** undergoes deamination during reduction process; end products in this case are 7*H*-dibenzo[c,e]oxepine-5-on **III** (60 %) and 4-aminoantipyrine.

Reduction of anhydride of diphenic acid **IV** with sodium borohydride in elementary alcohols occurs forming cyclic reduction product – 7*H*-dibenzo[c,e]oxepine-5-on **III** (36...46 %) as well as alcoholysis products – monoethers of diphenic acid **Va-c** (29...36 %). In this case, it was stated that alcohol nature influences weakly the ratio of reaction products.

Experimental part

Reaction and identity of the obtained compounds were controlled with the help of TLC at plates «Sorbfil» PTSH-AF-V-UV, eluent benzene-ethanol (9:1 by volume), spot detection in UV-light (254 nm). Spectra NMR were obtained at spectrometer Avance-300 (300 MHz), solvent – $CDCl_3$. IR spectra were obtained at the device Avatar Nicolett 5700 in tablets KBr.

Original compounds, agents and solvents

Unsubstituted imide **Ia** and substituted **IIb-d** were obtained from diphenic acid and relative ureas by the methods described in [2] and [3] correspondingly. Anhydride **IV** was obtained by heating diphenic acid in acetic anhydride according to [9].

Imide **Ie** was obtained from anhydride of diphenic acid **IV** in two stages by the diagram, Fig. 3.

10 g (0,045 mole) **IV**, 150 ml of acetonitrile and 2,7 ml (0,045 mole) of monoethanolamine was put into a bulb supplied with blackflow condenser. Reaction mixture was boiled during 2...3 h. At the end of reaction acetonitril was distilled off the bulb; filled up with 30 ml of ethyl acetate and excess of 7 % NaOH. In this case product transferred into liquid phase in a form of salt. Liquid phase was separated, acidated with 10 % HCl to subacid reaction of the medium. The obtained emulsion was settled while liquid phase became transparent. Water layer was drained from the formed oil; oil was dried under the vacuum, obtained about 9 g (70 %) of the product **VI**. *N*-(2-hydroxyethyl)monamide of diphenic acid **VI**, $C_{16}H_{15}NO_4$, oil. Spectra NMR ^1H, δ, ppm: 3,06 with broadness (1H, OH), 3,25 m (4H, CH_2CH_2), 7,08...7,78 m (8H, arom.), proton signal of NH-group falls most probably under the signals of aromatic protons, therefore, was not identified. Signal of proton of COOH-group was not also revealed.

9 g (0,0315 mole) **VI** was loaded into the bulk and filled up with 25 ml $SOCl_2$ (0,126 mole). The mixture was heated at water bath at 40...50 °C to gas extraction cease and oil complete dissolution. After that the reaction mixture was cooled, poured with 60 ml of water and neutralized with 3 % solution of NaOH. The lade-down sediment was filtered washing with water excess at filter, dried and recrystallized from propanol-2. 8 g of the pro-

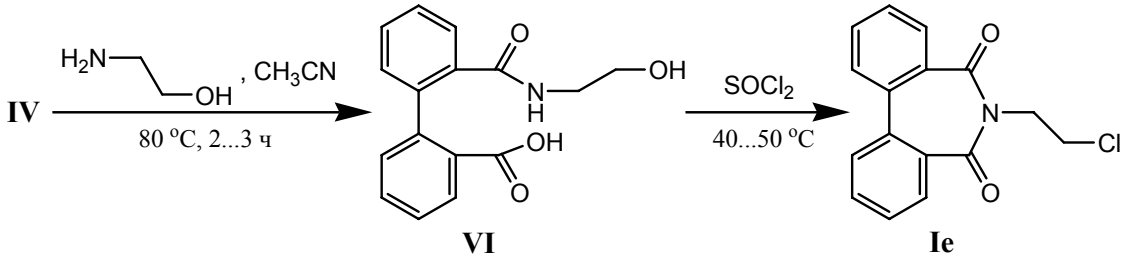

Fig. 3. *Diagram of obtaining N-(2-chlorethyl) of imide of diphenic acid* ***Ie***

duct **Ie** (90 %) was obtained. *N*-(2-chlorethyl) imide of diphenic acid **Ie**, $C_{16}H_{12}ClNO_2$, colorless needle crystals, $T_{mlt.}$=130 °C. IR-spectrum, δ, cm^{-1}: 1700, 1640 (C=O). Spectrum NMR ^1H, δ, ppm: 3,84 t (2H, CH_2-N, J=5,5 Hz), 4,45 t (2H, CH_2-Cl, J=5,4 Hz), 7,52...7,89 m (8H, arom.).

Sodium borohydride, solvents and other aids were used commercially available.

Reduction of imide Ia

0,02 mole (0,76 g) of atomized sodium borohydride was added by small portions during 3...5 min to the suspension 0,01 mole (2,23 g) of imide **Ia** in 30 ml of methanol at room temperature and intensive mixing. After that the reaction mixture was stirred during 15...20 min up to borhydride sediment disappearance and gas extraction cease. The reaction mixture was poured into 150 ml of water and acidated with 10 % solution of HCl to subacid reaction of the medium. The products were extracted by three portions of chloroform 20 ml each. The extracts were combined and shaken with 50 ml of 3 % NaOH. After sedimentation chloroform layer was segregated, solvent was distilled off at water bath. The obtained solid mixture of products was ground and treated with two portions of hot benzene 10 ml each. Solid residual was filtered, dried and recrystallized from the mixture ethanol-water (2:1 by volume) and obtained **IIa** (32 %). Amid of 2′-hydroxymethylbiphenil-2-carboxylic acid **IIa**, $C_{14}H_{13}NO_2$, colorless prismatic crystals, $T_{mlt.}$=137...138 °C. Spectra NMR ^1H, δ, ppm: 2,63 s with broadness (1H, OH), 4,48 dd (2H, CH_2, J_1=74,4 Hz, J_2=11,4 Hz), 5,65 s, 6,37 s (2H, NH_2), 7,11...7,58 m (8H, arom.). Spectrum NMR ^{13}C, δ, ppm: 63,403 (CH_2), 127,774...140,127 (arom.), 171,721 (C=O).

Reduction of imides Ib-e. General technique

The reaction is similar to reduction of **Ia**. The reaction mixture was poured into 60 ml of water, acidated with 10 % solution of HCl to subacid reaction of the medium. After that the solution clouded owing to formation of emulsion or suspension which was allowed settling during 12 h. The formed solid sediment was filtered, washed at filter first with 1 % solution of NaOH, then with a large water excess. The residue at filter was dried and recrystallized form benzene.

***N*-methylamide of 2′-hydroxymethylbiphenil -2-carboxylic acid IIb**, $C_{15}H_{15}NO_2$, colorless prismatic crystals. Yield is 84 %. $T_{mlt.}$=119...120 °C. IR-spectrum, ν, cm^{-1}: 3265, 3191 (NH), 3103, 3052 (CH arom.), 2934, 2897, 2871 (CH_3, CH_2), 1629 (C=O). Spectrum NMR ^1H, δ, ppm: 2,56 d (3H, CH_3, J=4,8 Hz), 3,89 with broadness (1H, OH), 4,45 dd (2H, CH_2, J_1=78,3 Hz, J_2=11,1 Hz), 6,55 c (1H, NH), 7,04...7,58 m (8H, arom.). Spectrum NMR ^{13}C, δ, ppm: 26,475 (CH_3), 63,296 (CH_2), 127,686...140,116 (arom.), 170,309 (C=O).

***N*-phenylamide of 2′-hydroxymethylbiphenil -2-carboxylic acid IIc**, $C_{20}H_{17}NO_2$, colorless prismatic crystals. Yield is 85 %. $T_{mlt.}$=131...132 °C. IR-spectra, ν, cm^{-1}: 3215 (NH), 3060 (CH arom.), 2937, 2884 (CH_2), 1632 (C=O). Spectrum NMR ^1H, δ, ppm: 2,65 with broadness (1H, OH), 4,67 dd (2H, CH_2, J_1=111,0 Hz, J_2=10,8 Hz), 7,00...7,79 m (13H, arom.), 8,52 s (1H, NH). Spectrum NMR ^{13}C, δ, ppm: 63,773 (CH_2), 119,929...140,299 (arom.), 167,570 (C=O).

***N*-benzeneamide of 2′-hydroxymethylbiphenil-2-carboxylic acid IId**, $C_{21}H_{19}NO_2$, colorless prismatic crystals. Yield is 88 %. $T_{mlt.}$=110...111 °C. IR-spectrum, ν, cm^{-1}: 3433 (OH), 3323 (NH), 3064, 3028 (CH arom.), 2954, 2898, 2827 (CH_2), 1622 (C=O). Spectrum NMR ^1H, δ, ppm: 3,03 with broadness (1H, OH), 4,26 d (2H, CH_2, J=5,4 Hz), 4,45 dd (2H, CH_2O, J_1=83,7 Hz, J_2=11,1 Hz), 6,73 s (1H, NH), 6,84...7,66 m (13H, arom.). Spectrum NMR ^{13}C, δ, ppm: 43,851 (CH_2), 63,479 (CH_2), 127,234...140,180 (arom.), 169,480 (C=O).

***N*-(2-chlorethyl) amide of 2′-hydroxymethylbiphenil -2-carboxylic acid IIe**, $C_{16}H_{16}ClNO_2$, colorless prismatic crystals. Yield is 63 %. $T_{mlt.}$=89...90 °C. IR-spectrum, ν, cm^{-1}: 3252, 3180 (NH), 3089 (CH arom.), 2954, 2934, 2915, 2860 (CH_2), 1642 (C=O). Spectrum NMR ^1H, δ, ppm: 3,06...3,53 m (4H, CH_2CH_2), signal of proton of OH-group is in the range of 3,20...3,60 ppm and falls under the signals of protons of the group CH_2Cl, therefore it was not identified, 4,50 dd (2H, CH_2, J_1=82,2 Hz, J_2=11,1 Hz), 6,92 s (1H, NH), 7,09...7,64 m (8H, arom.). Spectrum NMR ^{13}C, δ, ppm: 41,379 (CH_2N), 42,916 (CH_2Cl), 63,503 (CH_2O), 127,779...140,130 (arom.), 169,795 (C=O).

Reduction of imide If

Reaction is similar to reduction **Ia**. Reaction mixture was poured into 60 ml of water, acidated with 10 % solution of HCl to subacid reaction of the medium. After that the solution clouded owing to emulsion forming. Emulsion was allowed being settled during 12 h. Water layer was drained from the formed oil. Oil was dried under the vacuum; 15 ml of propanol-2 was added and boiled to complete dissolution. The mixture was slowly cooled, precipitated crystals were recrystallized again from propanol-2, obtained **III** (60 %). 7*H*-dibenzo[c,e]oxepine-5-on **III**, $C_{14}H_{10}O_2$, colorless prismatic crystals, $T_{mlt.}$=127...128 °C. IR-spectra, ν, cm^{-1}: 1705 (C=O). Spectrum NMR ^1H, δ, ppm: 5.02 d (2H, CH_2, J=13,5 Hz), 7,45...8,00 m (8H, arom.)

Reduction of anhydride IV. General technique

0,02 mole (0,76 g) of atomized sodium borohydride was added by small portions during 3...5 min to suspension of 0,01 mole (2,24 g) of anhydride of diphenic acid **IV** in 30 ml of corresponding alcohol at room temperature and intensive mixing. After that the reaction mixture was stirred 15...20 min up to disappearance of borohydride sediment and cease of gas extraction. Reaction mixture was poured into 120...150 ml of water and left for 12 h. Water-alcohol mixture was decanted from the lade-down sediment which may represent oil or the mixture of crystals and oil. 20 ml of $CHCl_3$ and 50 ml of 5 % water solution of Na_2CO_3 was added to the sediment. The obtained mixture was thoroughly shaken up to complete sediment dissolution. The mixture was allowed being settled. Chloroform layer was segregated;

solvent was distilled off at water bath, the obtained solid residue **III** was recrystallized from propanol-2.

Water-alkaline layer was acidated with 10 % HCl to subacid reaction, and solution was clouded. The obtained solution was allowed settling during 12 h, water layer was drained from precipitated oil. Oil was dried under vacuum, recrystallized from the mixture ethanol-water (1:1 by volume), obtained relative ether **Va-c**.

IV reduction in methanol

Yield of **III** is 36 %. Yield of **Va** is 31 %. Monomethyl ether of diphenic acid **Va**, $C_{15}H_{12}O_4$, colorless prismatic crystals, $T_{mlt.}$=98...99 °C. Spectrum NMR ^{1}H, δ, ppm: 3,61 s (3H, CH_3), 7,16...8,06 m (8H, arom.), 10,30 with broadness (1H, COOH).

IV reduction in 96 % ethanol

Yield of **III** is 46 %. Yield of **Vb** is 36 %. Monoethyl ether of diphenic acid **Vb**, $C_{16}H_{14}O_4$, colorless prismatic crystals, $T_{mlt.}$=87...88 °C. Spectrum NMR ^{1}H, δ, ppm: 0,98 t (3H, CH_3, J=7 Hz), 4,05 q (2H, CH_2, J=7 Hz), 7,05...8,07 m (8H, arom.), 10,55 with broadness (1H, COOH).

IV reduction in propanol-2

Yield of **III** is 44 %. Yield of **Vc** is 29 %. Monoisopropyl ether of diphenic acid **Vc**, $C_{17}H_{16}O_4$, colorless prismatic crystals, $T_{mlt.}$=81...82 °C. Spectrum NMR ^{1}H, δ, ppm: 1,27 d (6H, CH_3, J=6 Hz), 4,85 m (1H, CH), 7,12...8,03 m (8H, arom.), 9,15 with broadness (1H, COOH).

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