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 pent- and hexamers cycles [4–8] in this case succinimide, phthalimide, glutarimide and their derivatives served as a rule as substrates. There is no information about similar reactions for heptamers 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-5H-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=CH3, Ib), aryl (R=Ph, Ic), aralkyl (R=CH2Ph, Id), halogenalkyl (R=CH2CH2Cl, Ie) and hetaryl (R=antipyril-4, If).

It was revealed that reduction starts at room temperature (20...25 °С) and finishes for 20...25 min. It was shown that reduction of unsubstituted imide of diphenic acid Ia by 2 moles of NaBH4 in methanol results in forming mixture of four products. Only the main reaction product which is the amide of 2'-hydroxymethylbiphenyl-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 7H-dibenzo[c,e]oxepin-5-on III. The rest products could not be identified by the moment.

N-substituted imides Ib-e are reduced with 2 moles of NaBH4 in methanol exclusively to acyclic N-substituted amides of 2'-hydroxymethylbiphenyl-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 IIE forms respective amide IIF only with the yield of 63 %. Reduced yield of the product IIE, may be evidently explained by the fact that imide IIE, in comparison with imides IIB-d contains reactive substituent — CH2CH2Cl, the chlorine atom in which may undergo various reactions of substitution or removal in the given

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conditions. Earlier, for example, at reduction of N-chloromethylphthalimide NaBH$_4$ in MeOH the formation of N-methoxymethyl-3-hydroxyisoindolin-1-one (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 7H-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 7H-dibenzo[c,e]oxepine-5-on III.

Amides of 2'-hydroxymethylbiphenil-2-carboxylic acid Ila-e were obtained for the first time. Compounds of the given group are of interest as new potentially valuable biologically active substances.

Another cyclic derivative of diphenic acid – its anhydrate IV was earlier reduced in dimethylformamide (DMF) to 7H-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 aprotion 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.

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 NaBH₄ in solution.

Current concentration of alcoholate is determined by NaBH₄ 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 NaBH₄ 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; NaBH₄ equilibrium concentration is also comparatively low. Thus, alcoholysis and reduction occur relatively slowly in propanol-2. The ratio of these reactions rates both for alcoholysis and reduction 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-(antipyril-4)-imide If undergoes deamination during reduction process; end products in this case are 7H-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 – 7H-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 «Sorfil» 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 – CDCl₃. 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 acetonitrile 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, acidified 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, C₁₅H₁₂NO₄, oil. Spectra NMR 1H, δ, ppm: 3,06 with broadness (1H, OH), 3,25 m (4H, CH₂), 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 SOCl₂ (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-chlorothyl) imide of diphenic acid Ie, C16H14ClNO2, colorless needle crystals, Tm = 119...120 °C. IR-spectrum, ν, cm–1: 3265, 3191 (NH), 3103, 3052 (CH arom.), 2934, 2897, 2871 (CH3, CH2), 1629 (C=O). Spectrum NMR 1H, δ, ppm: 2,56 d (3H, CH3), J=4,8 Hz, 3,89 with broadness (1H, OH), 4,45 dd (2H, CH2, J=78,3 Hz, J=11,1 Hz), 6,55 c (1H, NH), 7,04...7,58 m (8H, arom.), 127,686...140,116 (arom.), 170,309 (C=O).

N-methylamid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIb, C18H16NO2, colorless prismatic crystals.

Yield is 84 %. Tm = 119...120 °C. IR-spectrum, ν, cm–1: 3265, 3191 (NH), 3103, 3052 (CH arom.), 2934, 2897, 2871 (CH3, CH2), 1629 (C=O). Spectrum NMR 1H, δ, ppm: 2,56 d (3H, CH3), J=4,8 Hz, 3,89 with broadness (1H, OH), 4,45 dd (2H, CH2, J=78,3 Hz, J=11,1 Hz), 6,55 c (1H, NH), 7,04...7,58 m (8H, arom.), 127,686...140,116 (arom.), 170,309 (C=O).

N-phenylamid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIc, C16H13NO2, colorless prismatic crystals.

Yield is 85 %. Tm = 131...132 °C. IR-spectra, ν, cm–1: 3215 (NH), 3060 (CH arom.), 2937, 2884 (CH3), 1632 (C=O). Spectrum NMR 1H, δ, ppm: 2,65 with broadness (1H, OH), 4,67 dd (2H, CH2, J=111,0 Hz, J=10,8 Hz), 7,00...7,79 m (13H, arom.), 8,52 s (1H, NH). Spectrum NMR 13C, δ, ppm: 63,773 (CH2), 119,929...140,299 (arom.), 167,570 (C=O).

N-benzeneamid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIa, C20H17NO2, colorless prismatic crystals.

Yield is 85 %. Tm = 130 °C. IR-spectrum, ν, cm–1: 3252, 3180 (NH), 3089 (CH arom.), 2954, 2941, 2860 (CH), 1642 (C=O). Spectrum NMR 1H, δ, ppm: 3,06...3,53 m (4H, CH2CH2), signal of proton of the group CH2Cl, 7,09...7,64 m (8H, arom.) 127,779...140,130 (arom.), 169,795 (C=O).

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 borohydride sediment disappearance and gas extraction cease. The reaction mixture was poured into 150 ml of water and acidified 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 residue was filtered, dried and recrystallized from the mixture ethanol–water (2:1 by volume) and obtained IIa (32 %). Amid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIa, C16H15NO2, colorless prismatic crystals, Tm = 137...138 °C. Spectra NMR 1H, δ, ppm: 2,63 m with broadness (1H, OH), 4,48 dd (2H, CH2, J=74,4 Hz, J=1,1 Hz), 5,65 s, 6,37 t (2H, NH2), 7,11...7,58 m (8H, arom.) 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, acidified 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 large water excess. The residue at filter was dried and recrystallized from benzene.

N-methylamid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIb, C18H16NO2, colorless prismatic crystals.

Yield is 84 %. Tm = 119...120 °C. IR-spectrum, ν, cm–1: 3265, 3191 (NH), 3103, 3052 (CH arom.), 2934, 2897, 2871 (CH3, CH2), 1629 (C=O). Spectrum NMR 1H, δ, ppm: 2,56 d (3H, CH3), J=4,8 Hz, 3,89 with broadness (1H, OH), 4,45 dd (2H, CH2, J=78,3 Hz, J=11,1 Hz), 6,55 c (1H, NH), 7,04...7,58 m (8H, arom.), 127,686...140,116 (arom.), 170,309 (C=O).

N-phenylamid of 2'-hydroxymethylbiphenyl-2-carboxylic acid IIc, C16H13NO2, colorless prismatic crystals.

Yield is 85 %. Tm = 131...132 °C. IR-spectra, ν, cm–1: 3215 (NH), 3060 (CH arom.), 2937, 2884 (CH3), 1632 (C=O). Spectrum NMR 1H, δ, ppm: 2,65 with broad-
solvent was distilled off at water bath, the obtained solid residue III was recrystallized from propanol-2.

Water-alkaline layer was aciditated 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 %. Monoethyl ether of diphenic acid Vb, C_{16}H_{14}O_{4}, colorless prismatic crystals, T_mît.=81...82 °C. Spectrum NMR 1H, δ, ppm: 0,98 t (3H, CH₃, J=7 Hz), 4,05 q (2H, CH₂, J=7 Hz), 7,12...8,03 m (8H, arom.), 9,15 with broadness (1H, COOH).

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