(Z)-1,4-Diphenyl-2-phenylamino-2-butene-1,4-dione: Synthesis and Mechanizm of Formation

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Abstract—Heating of 1-phenyl-2-(phenylamino)ethanone in a water-ethanol solution of potassium carbonate gave rise to (Z)-1,4-diphenyl-2-phenylamino-2-butene-1,4-dione; it formed most probably by reaction of the initial aminoketone with its oxidation product, 1-phenyl-2-(phenylimino)ethanone.

In extension of our research in the field of diketones chemistry we started investigation of their heteroanalogs, 3-aza-1,5-diketones, that open the way to heterocycles with two heteroatoms. The main preparation method for 3-aza-1,5-diketones consists in reaction of α-haloketones with α-aminoketones [1]. Inasmuch as 2-[(2-oxo-2-phenylethyl)(phenyl)amino]cyclohexanone (**I**) was not described in the literature we attempted to prepare the compound by this procedure. To this end 2-chlorocyclohexanone (**II**) and 1-phenyl-2-(phenylamino)ethanone (**III**) were boiled in a saturated water-ethanol solution of potassium carbonate. As a result a bright yellow crystalline compound was obtained in a 64% yield; the substance turned out to be (Z)-1,4-diphenyl-2-phenyl-amino-2-butene-1,4-dione (**IV**). This procedure for preparation of diketone **IV** was not published before. The known methods afford lower yields of the reaction product [2, 3] or the reagents used are less accessible [4, 5]. We presumed that the compound obtained resulted from trans-

formations solely of aminoketone **III** and that chlorocyclohexanone (**II**) was not involved into the reaction. We proved this assumption by a control run without compound **II**, where product **IV** was obtained in the same yield.

The structure of diketone **IV** was confirmed by IR, ^{1}H and ^{13}C spectra, by GC-MS method and X-ray diffraction analysis. In the IR spectrum absorption bands were present belonging to vibrations of benzene ring (1605, 1506 cm^{-1}) and conjugated carbonyl group (1664 cm^{-1}). In contrast to [2] we did not observe stretching vibrations of the N–H bond in the high-frequency region at 3400 cm^{-1} because of a strong hydrogen bond (for reference, the N–H bond in compound **III** appeared in the spectrum as a strong absorption band at 3370 cm^{-1}). The same result was obtained in recording the IR spectrum in CHCl$_3$ at 5-fold dilution. The X-ray diffraction study revealed the stereochemistry of compound **IV** (see figure and table): the compound had the Z-configuration with a strong hydrogen bond C=O…HN.

The unexpected conversion of aminoketone **III** into unsaturated 1,4-diketone **IV** attracted our interest to the reaction mechanism. For this purpose we used the methods of GC and HPLC mass-spectrometry.

In the study of formation mechanism of compound **IV** we proceeded from the facts listed below. Oxygen significantly affected the reaction rate: the process hardly occurred in an argon atmosphere. Boiling of compound **III** under argon for 5.5 h provided less than 3% of diketone **IV,** and ~70% of unreacted initial aminoketone **III** remained in the reaction mixture, whereas in air, all other factors being the same, the reaction within 1.5 h afforded 64% yield of compound **IV**. Besides diketone
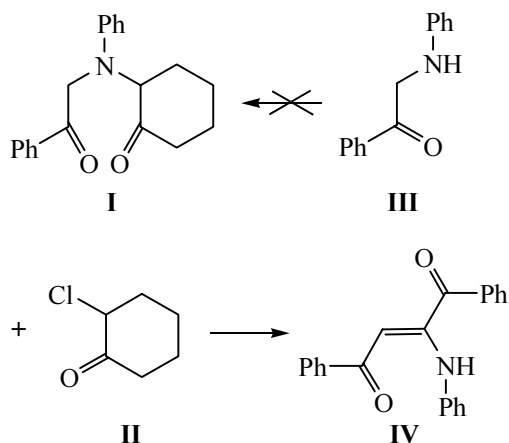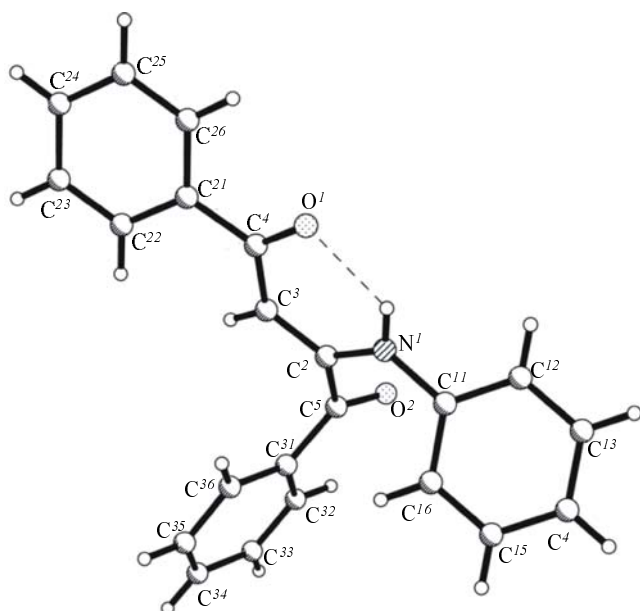
Structure of (*Z*)-1,4-diphenyl-2-phenyl-amino-2-butene-1,4-dione (**IV**).

IV one of the main products in the reaction mixture was aniline.

On the strength of this evidence we investigated three possible pathways of the process:

We assumed first that aniline arose in the first stage of the process and resulted from the hydrolysis of compound **III** (path *a*). Alongside aniline also ketoalcohol (A) formed in the reaction further oxidized by oxygen to phenylglyoxal (**V**); the latter enters into condensation with aminoketone **III** under the action of catalyst base to fur-

nish diketone **IV**. We tested the possibility of the process taking the pathway *a* by preparation of phenylglyoxal (**V**) [6] and bringing it into reaction with aminoketone **III** through boiling in water-ethanol solution of potassium carbonate in an argon atmosphere. As a result we recovered compound **III** (58%) and obtained diketone **IV** in ~6% yield. Obviously this yield was at the same level as at boiling aminoketone **III** under inert atmosphere, and no additional condensation with phenylglyoxal (**V**) occurred. Therefore the assumption of diketone **IV** formation along path *a* is wrong.

According to the second assumption the oxygen initiated formation of a radical (B) that on recombination provided dimer **VI**; the latter by aniline eliminating are diketone **IV** (path *b*). Preparation of compound **VI** in 30% yield by heating aminoketone **III** at reflux in ethanol in the presence of piperidine was described in [7]. It was reported that dimer **VI** formed only if the reaction mixture was kept in air for 12 h and failed to form under argon atmosphere. No diketone **IV** was revealed in the reaction mixture in this reaction. We reproduced the process described in [7] and on isolating dimer **VI** we subjected it to boiling in a water-ethanol solution of potassium carbonate under argon. Thus we obtained diketone **IV** in 77% yield. This result suggests that compound **VI** is an intermediate on the route aminoketone **III** → diketone **IV**. It also proved that in reaction carried out along procedure [7] in air compound **VI** could not be isolated, and the final product was diketone **IV**. We also established that preparation of dimer **VI** did not require boiling, and it was obtained in 40% yield by keeping aminoketone **III** in ethanol solution in the presence of catalytic amounts of
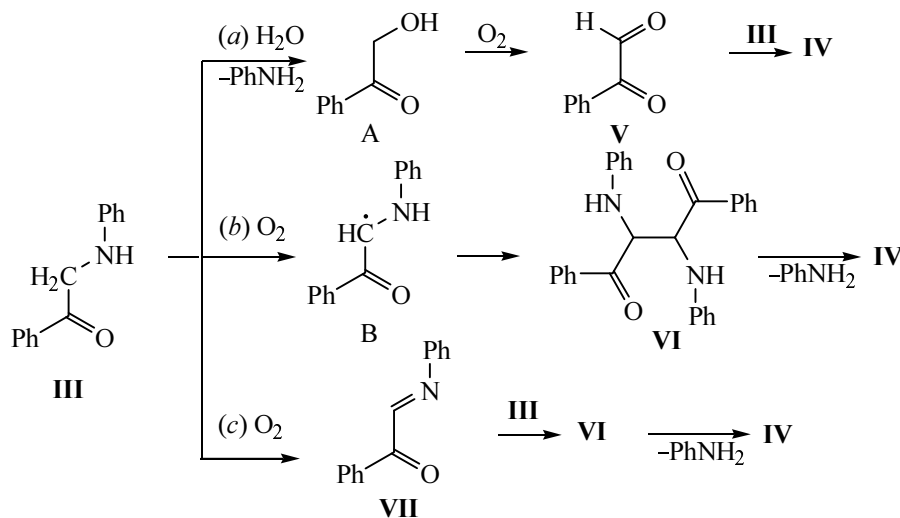
piperidine in air for 15 h; this process did not occur under inert atmosphere.

If the oxygen was necessary only to initiate radical (B) formation, then it would be possible to obtain diketone **IV** under inert atmosphere in the presence of the other radical initiators, like 2,2'-azobisisobutyronitrile (AIBN), hydrogen peroxide, potassium persulfate. Therewith the absence of a basic catalyst should not affect the formation of diketone **IV**. Therefore we investigated the reaction mixtures arising at boiling aminoketone **III** in the water-ethanol solution of potassium carbonate under argon in the presence of the mentioned initiators. It turned out that the yield of diketone **IV** in the presence of AIBN was similar to that in the control run performed in an inert atmosphere (less than 3%). In the presence of hydrogen peroxide and potassium persulfate the yield was higher and attained 35–47%. In the absence of potassium carbonate or piperidine the reaction did not occur even in air. This result invalidates the assumption of the intermediate generation of radical (B) and of the radical mechanism of dimer **VI** formation. As showed further studies, the considerable amounts of diketone **VI** arising in the presence of hydrogen peroxide or potassium persulfate originated from the oxidative properties of the latter favoring formation from aminoketone **III** of Schiff base **VII**.

We assumed in the study of the third path (*c*) leading to diketone **IV** that the oxygen oxidized aminoketone **III** giving Schiff base **VII** which further under catalysis with a base enters into condensation with aminoketone **III** yielding dimer **VI** and subsequently diketone **IV**. To test this assumption we attempted to prepare anil **VII** by procedure [8], but it proved that the target reaction product having the same melting point as reported did not correspond to Schiff base **VII** by IR and mass spectrum (double mass value). The required compound we prepared by mixing glyoxal **V** with aniline in ethanol solution at room temperature. Compound **VII** is yellow oily substance very unstable at storage. The freshly prepared reaction product **VII** that was an individual compound according to GC-MS data we brought into reaction with aminoketone **III** under argon, and succeeded to isolate from the reaction mixture diketone **IV** in a 75% yield. The reaction carried out at room temperature afforded dimer **VI**.

The results obtained suggest a conclusion that the most probable route of diketone **IV** formation from aminoketone **III** is path *c*. The latter adds across the C=N bond of compound **VII** affording dimer **VI** that at heating is converted into diketone **IV**. Aminoketone **III** in this reaction acts as a compound with an active methylene group.

Main bond lengths (*d*) and bond angles (ω) in diketone **IV** molecule

Bond	d, Å	Angle	ω, deg
O^1–C^4	1.2429(16)	$C^2N^1C^{11}$	126.73(11)
O^2–C^5	1.2228(16)	$N^1C^2C^3$	123.51(13)
N^1–C^2	1.3429(17)	$N^1C^2C^5$	117.46(12)
N^1–C^{11}	1.4110(17)	$C^3C^2C^5$	118.03(13)
C^2–C^3	1.3651(18)	$C^2C^3C^4$	123.39(13)
C^2–C^5	1.5134(18)	$O^1C^4C^3$	121.34(13)
C^3–C^4	1.4384(18)	$O^1C^4C^{21}$	118.81(12)
C^4–C^{21}	1.4859(18)	$C^3C^4C^{21}$	119.83(12)
C^5–C^{31}	1.4741(18)	$O^2C^5C^{31}$	121.76(12)
C^{11}–C^{12}	1.3802(19)	$O^2C^5C^2$	116.67(12)
C^{11}–C^{16}	1.3845(19)	$C^{31}C^5C^2$	121.53(12)
C^{12}–C^{13}	1.385(2)	$C^{12}C^{11}C^{16}$	119.29(13)
C^{13}–C^{14}	1.378(2)	$C^{12}C^{11}N^1$	119.51(12)
C^{14}–C^{15}	1.365(2)	$C^{16}C^{11}N^1$	121.17(12)
C^{15}–C^{16}	1.374(2)	$C^{11}C^{12}C^{13}$	120.09(14)
C^{21}–C^{22}	1.3785(19)	$C^{14}C^{13}C^{12}$	120.02(15)
C^{21}–C^{26}	1.3850(18)	$C^{15}C^{14}C^{13}$	119.72(15)
C^{22}–C^{23}	1.384(2)	$C^{14}C^{15}C^{16}$	120.81(15)
C^{23}–C^{24}	1.382(2)	$C^{15}C^{16}C^{11}$	120.04(14)
C^{24}–C^{25}	1.372(2)	$C^{22}C^{21}C^{26}$	118.20(13)
C^{25}–C^{26}	1.368(2)	$C^{22}C^{21}C^4$	122.94(12)
C^{31}–C^{36}	1.3844(18)	$C^{26}C^{21}C^4$	118.83(13)
C^{31}–C^{32}	1.3871(18)	$C^{21}C^{22}C^{23}$	121.27(14)
C^{32}–C^{33}	1.3760(19)	$C^{24}C^{23}C^{22}$	119.34(15)
C^{33}–C^{34}	1.376(2)	$C^{25}C^{24}C^{23}$	119.69(15)
C^{34}–C^{35}	1.366(2)	$C^{26}C^{25}C^{24}$	120.56(14)
C^{35}–C^{36}	1.3859(19)	$C^{25}C^{26}C^{21}$	120.93(15)
		$C^{36}C^{31}C^{32}$	119.44(12)
		$C^{36}C^{31}C^5$	122.19(12)
		$C^{32}C^{31}C^5$	118.35(12)
		$C^{33}C^{32}C^{31}$	120.35(14)
		$C^{32}C^{33}C^{34}$	119.82(14)
		$C^{35}C^{34}C^{33}$	120.35(14)
		$C^{34}C^{35}C^{36}$	120.43(15)
		$C^{31}C^{36}C^{35}$	119.59(14)

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Perkin Elmer Spectrum BX-II. ^1H and ^{13}C NMR spectra were registered on spectrometer Bruker AC-250 (operating frequencies 250 and 62.9 MHz respectively) from solutions in $CDCl_3$, internal reference TMS.

HPLC-mass spectra were measured on Agilent 1100 Series LC/MSD ("Hewlett-Packard", USA) instrument equipped with a column LiChroCART CN (4×250 mm, sorbent particles 5 μm) at thermostat temperature 40°C in linear gradient elution mode (30–70% aqueous acetonitrile) at a rate 2% per min. Elution rate 0.5 ml/min, detection by electron absorption spectra in the range 200–700 nm, ionization by electrospray at atmospheric pres-

sure, ionizing voltage 70 V, ionizing chamber voltage 4 kV, the gas-dryer flow (nitrogen) 6 l/min, the pressure of spraying gas (nitrogen) 50 kg cm^{-2}, the range of registered mass *m/z* 150–700. GC-MS spectra were taken on Agilent GC/MS 5973N ("Hewlett-Packard", USA) instrument, column HP5-MS, carrier gas helium, flow rate 1 ml/min, mass scanning in the range 50–500 *m/z*, detector temperature 230°C, oven temperature programmed as follows: 100°C (1 min), 20 deg/min; 250°C; 21.5 min.

Compounds **III, IV**, and **VII** were studied by GC-MS method, and compound **VI** that decomposed under GC-MS conditions was studied by HPLC-MS procedure.

The X-ray diffraction study of compound **IV** was performed on diffractometer SMART-1000 CCD (Bruker). Crystal of compound **IV** bright yellow prism, crystal habit 0.30×0.22×0.04 mm; at 293 (2) K *a* 5.9697(18), *b* 13.603 (4), *c* 21.260 (6) Å, β 94.077 (7)°, *V* 1772.1 (9) Å^3, ρ_{calc} 1.263 mg/m^3, µ 0.081 mm^{-1}, *F* 688, space group *P*2$_1$/*n*, *Z* 4. The structure was refined by full-matrix least-squares method along *F*^{2}. Number of refined parameters 227. GooF 0.746, R (*F*^{2}) [*F*^{2} > 2σ], R$_1$ 0.0431, wR$_2$ 0.0890, R using all reflections R$_1$ 0.1718, wR$_2$ 0.1193, extinction factor 0.0057(5), residual electron density (min/max.) –0.156/0.151 *ē*/Å^{-3}. From 12550 measured reflections 4814 were independent (*R*$_{int}$ 0.0676), 1548 had 2σ (*I*). The range of data collection θ 1.78–30.03°. The range of reflection indices 8 ≤ *h* ≤ 8, –18 ≤ *k* ≤ 18, –25 ≤ *I* ≤ 15. The structure was solved by the direct method and refined by the least-squares method in anisotropic approximation for nonhydrogen atoms. Collection and treating of the experimental data, refinement of parameters of the unit cell was performed by software SMART and SAINT Plus. All calculations in solving and refining of the structure were done by SHELXTL/PC programs. The X-ray abextinction in the sample was not taken into consideration.

The reaction progress was monitored and homogeneity of compounds was checked by TLC on Sorbfil plates, eluent petroleum ether–ethyl acetate (4:1), development in iodine vapor. Melting points were measured on Boëtius heating block.

1-Phenyl-2-phenylamino-1-ethanone (III) was prepared by procedure [7]. It is a yellow crystalline compound, after recrystallization from ethanol mp 93°C (publ.: mp 96–98°C [7]). According to GC-MS the compound is chromatographically homogeneous, retention time 8.96 min. IR spectrum (mull in mineral oil), ν, cm^{-1}: 3367

(N–H), 1693 (conjug. C=O), 1603, 1513 (Ph), 1579 (bending vibrations N–H), 1222, 1264 (C–N). Mass spectrum, *m/z* (*I*$_{rel}$, %): 211 [*M*]$^+$ (9.4), 106 (100), 77 (20.6).

(Z)-1,4-Diphenyl-2-phenylamino-2-butene-1,4-dione (IV). (a) A mixture of 0.5 g (2.37 mmol) of aminoketone **III**, 1.5 g of K$_2$CO$_3$, 1 ml of water, and 5 ml of ethanol was heated at reflux while stirring till complete consumption of aminoketone **III** (3.5 h; TLC monitoring). The mixture was cooled, diluted with water to complete dissolution of potassium carbonate, and the organic layer was separated. On cooling the solution yellow crystals precipitated of diketone **IV**, yield 0.25 g (64%). On recrystallization from ethanol mp. 126–127°C (publ.: mp 124–128°C [2–5]). IR spectrum (KBr), ν, cm^{-1}: 1664 (conjug. C=O), 1605, 1506 (Ph), 1575, 1552 (bending vibrations N–H), 1241, 1283 (C–N). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 6.12 s (1H, vinyl proton), 6.96–8.00 m (four groups of multiplets, aromatic protons), 12.5 s (1H, NH), the signal disappeared on adding CD$_3$OD. ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 190.9, 192.16 (2C=O), 121.7, 125.04, 127.4, 128.5, 128.7, 129.2, 129.7, 131.9, 134.3 (arom =CH), 134.6, 138.6, 138.9, 156.7 (arom =C–), 95.0 (CH=$\underline{C}$NH). GC-MS, *m/z* (*I*$_{rel}$, %): 327 [*M*]$^+$ (12), 222 (100), 105 (53), 77 (49). Retention time 22.20 min.

(b) The same mixture as used in the *a* run was boiled with passing air through the reaction mixture. The reaction completed within 1.5 h, yield of diketone **IV** 64%.

(c) The same mixture as used in the *a* run was boiled with passing argon through the reaction mixture. After 5.5 h the mixture was cooled, and from the organic layer separated the precipitate of unreacted aminoketonea **III** (0.27 g). The filtrate was diluted with water and extracted with ethyl ether. The extracts were dried on magnesium sulfate, and ethyl ether was distilled off to leave a semicrystalline red-brown mass (0.21 g). As revealed by GC-MS the residue contained the initial aminoketone **III**, 46%, anil **VII**, 6%, and diketone **IV**, 5%. The resulting recovery of compound **III** 73%, yield of compound **IV** 3%. No compound **VI** was present in the reaction product according to HPLC-MS data.

Conversion of aminoketone III in the presence of radical initiators. (a) A mixture of 0.5 g (2.37 mmol) of aminoketone **III**, 1.5 g of K$_2$CO$_3$, 1.5 ml (0.42 g, 12.35 mol) of H$_2$O$_2$, and 5 ml of ethanol was heated under reflux at stirring in an argon atmosphere for 5.5 h. After a workup carried out as in the run (c) from the alcohol layer was separated a yellow precipitate of diketone **IV**

weighing.12 g (31%). The extraction of filtrate furnished 0.26 g of red-brown oily substance that according to GC-MS was a multicomponent mixture with the following main components: compound of $[M]^+$ 225 (35%), aminoketone **III** (8%), and diketone **IV** (6%). The overall yield of compound **IV** reached 34%.

(b) A mixture of 0.5 g (2.37 mmol) of aminoketone **III**, 1.5 g of K_2CO_3, 1 ml of water, 0.64 g (2.35 mmol) of $K_2S_2O_8$, and 5 ml of ethanol was heated under reflux in an argon atmosphere for 5.5 h. After a workup carried out as in the run (c) from the organic layer was filtered off 0.3 g of yellow precipitate that according to GC-MS data was composed of diketone **IV** (55%), initial aminoketone **III** (44%), and anil **VII** (1%). After treating the filtrate we obtained 0.18 g of red-brown semicrystalline substance containing aminoketone **III** (70%), diketone **IV** (8%), and anil **VII** (5%). The overall yield of compound **IV** reached 47%.

Condensation of aminoketone III with phenyl-glyoxal (V). A mixture of 0.5 g (2.37 mmol) of amino-ketone **III**, 0.48 g (3.56 mmol) of phenylglyoxal (**V**), 1.5 g of K_2CO_3, 1 ml of water, and 5 ml of ethanol was heated under reflux at stirring in an argon atmosphere for 5.5 h. From the alcoholic layer on cooling separated a precipitate of the initial aminoketone **III**, 0.23 g (46%). After dilution with water and treatment of the filtrate as in the run (c), we obtained 0.56 g of red-brown oily substance that according to GC-MS contained the following main components: aminoketone **III** (11%), diketone **IV** (8%), Schiff base **VII** (17%), and a compound of $[M]^+$ 225 (36%). Yield of compound **IV** was ~6%, overall recovery of compound **III** 58%.

1,4-Diphenyl-2,3-diphenylaminobutane-1,4-dione (VI). (a_ A mixture of 0.6 g (2.85 mmol) of aminoketone **III** and 0.025 ml of piperidine in 8 ml of ethanol was boiled for 4 h on a steam bath, and then the reaction mixture was maintained in air for 12 h. The separated precipitate was filtered off and washed with ethanol, yield 0.15 g (25%), yellow crystalline substance, mp 183–184°C (from ethyl acetate) (publ.: mp 184–185°C [7]). IR spectrum, (KBr), ν, cm^{-1}: 3345 (N–H), 1664 (conjug. C=O), 1599, 1447 (Ph), 1579 (bending vibrations of N–H), 1269, 1295(C–N). By means of HPLC-MS was registered a pseudomolecular ion, m/z: 421 $[M + H]^+$ (calculated for $C_{28}H_{24}N_2O_2$ 420).

(b) A mixture of 0.1 g (0.47 mmol) aminoketone **III** and 0.01 ml of piperidine in 5 ml of ethanol was kept in air for 15 h. The precipitate of dimer **VI** was filtered off, washed with ethanol, yield 0.04 g (40%).

Conversion of dimer VI into diketone IV. A mixture of 0.08 g (0.19 mmol) of dimer **VI**, 0.2 g of K_2CO_3, 0.05 ml of water, 3 ml of ethanol was heated under reflux at stirring in an argon atmosphere for 5.5 h. After a workup carried out as in the run (c) from the organic layer was separated 0.02 g of diketone **IV** (32%). The treating of filtrate afforded a red-brown oily substance (0.04 g) that contained as the main component diketone **IV** (69%) (GC-MS data). According to HPLC-MS the reaction mixture contained no dimer **VI**. The overall yield of compound **IV** was 77%.

1-Phenyl-2-(phenylimino)ethanone (VII). A mixture of 4.15 g (31 mmol) of phenylglyoxal, 2.35 ml (26 mmol) of aniline, 20 ml of anhydrous ethanol was kept for 24 h at room temperature under argon, and then the reaction mixture was poured into 20 ml of water. The precipitated yellow oily Schiff base **VII** was several times washed with water, diluted with ethyl ether, the ether solution was dried on $MgSO_4$, ethyl ether was removed, yield 3.6 g (67%). According to GC-MS data the compound is homogeneous, retention time 8.14 min. Mass spectrum, m/z (I_{rel}, %): 209 $[M]^+$ (17), 104 (100), 77 (65.7).

Condensation of Schiff base VII with aminoketone III. (a) A mixture of 1 g (4.7 mmol) of aminoketone **III**, 1.2 g (5.7 mmol) of freshly prepared Schiff base **VII**, 6 g of potassium carbonate, 3 ml of water, and 20 ml of ethanol was heated under reflux at stirring in an argon atmosphere for 2.5 h (TLC monitoring). On cooling a precipitate separated (0.98 g) that by GC-MS data contained diketone **IV** (92.1%), anil **VII** (3%), and aminoketone **III** (4%). The filtrate was evaporated by half, and 0.25 g of bright yellow precipitate was additionally isolated. The precipitates were combined and recrystallized from ethanol to obtain 1.15 g of diketone **IV** (75%).

(b) In 10 ml of ethanol was dissolved at heating 0.25 g (1.2 mmol) of aminoketone **III**, and to the solution was added 0.3 g (1.4 mmol) of Schiff base **VII** and 0.05 ml of piperidine in 10 ml of ethanol. Through a homogeneous mixture argon was bubbled, and the reaction mixture was maintained at room temperature under argon for 36 h. The reaction progress was monitored by TLC, and after each sampling argon was again bubbled through the mixture. The separated yellow precipitate of dimer **VI** was filtered off, washed with ethanol, and dried; yield 0.2 g (40%).

REFERENCES

1. Lellmann, E. and Donner, A., *Ber.*, 1890, vol. 23, p. 166; Gabriel, S., *Ber.*, 1914, vol. 46, p. 3859; Mistryukov, E. A. and Katvalyan, G.T., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1969, vol. 12, p. 2800; Mistryukov, E. A. and Katvalyan, G.T., *Izv. Aakd. Nauk SSSR,. Ser. Khim.,* 1976, vol. 3, p. 671.

2. Moskalev, N. and Tartynova, M., *Mendeleev Commun.*, 1996, p. 72.

3. Paradisi, C., Prato, M., and Quintily, U., *J. Org. Chem.*, 1981, vol. 46, p. 5156.

4. Titova, E.I., Gavrilov, L. D., and Bol'shedvorskaya, R. L., *Zh. Org. Khim.*, 1969, vol. 5, 2113.

5. Hayashi, Y., Watanabe, T., and Oda, R., *Tetrahedron Lett.*, 1970, vol. 8, p. 605.

6. *Sint. Org. Prep.*, 1949, vol. 2, p. 507.

7. Correia, J., *J. Org. Chem.*, 1978, vol. 43, p. 3394.

8. Fraser, E., Paterson, W., and Proctor, G. R., *J. Chem. Soc.*, 1963, p. 510