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SYNTHESIS OF 1-ARYL-4-AZOLYLBUTANONES

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A convenient method was developed for the synthesis of substituted 4-azolyl-1-arylbutanones from the available γ-chlorobutyrophenones by successive stages of transformation into ketals, alkylation of sodium imidazolate or 1,2,4-triazolate by the ketals in DMF, and removal of the ketal protection.

Keywords: 1-aryl-4-azolyl-1-butanones, dioxolanes, *p*-substituted γ-chlorobutyrophenones, imidazole, ketals, 1,2,4-triazole, alkylation of azoles.

Many imidazole and 1,2,4-triazole derivatives of aliphatic-aromatic ketones have fungicidal (antimycotic) activity [1, 2]. Most of them are derivatives of alkanophenones, in which the azolyl group is at the α-position to the carbonyl group, e.g., such fungicides as etaconazole and antimycotic agents fluconazole and ketoconazole [3]. At the same time substituted butyrophenones and isobutyrophenones with nitrogen-containing heterocycles at the ω-position, used as neuroleptics (haloperidol, droperidol) and antispasmodic preparations (midocalm), are known [4]. Unknown ω-azolylalkanophenones and their derivatives are therefore of interest as subjects for investigation of biological activity.

Descriptions of the alkylation of azoles by various halo-substituted compounds are quite often found in the literature [5-7]. There are also examples of the alkylation of saturated nitrogen-containing heterocycles by substituted γ-chlorobutyrophenones: Substituted piperazines [8], compounds of the tropine series [9], and most often substituted piperidines [10]. However, data on 4-azolylbutyrophenones and their analogs are extremely limited. The production of γ-imidazolylpropyl 3-fluorenyl ketone by opening 3-fluorenyl cyclopropyl ketone was mentioned [11]. A single example* of the production of γ-imidazolylbutyrophenone with a yield of 50% by the reaction of 4-bromo-γ-chlorobutyrophenone with an excess of imidazole in DMF is known [12]. Prolonged heating of the reaction mass (48 h) at 95-100°C leads to the formation of a mixture of alkylation products, from which the required product can be isolated by column chromatography. In addition, as shown by our investigations, triazole derivatives cannot be obtained by this method. In the present work we describe a convenient method for the production of substituted γ-azolylbutyrophenones.

Whereas the alkylation of 4-hydroxy-4-phenylpiperidine with γ-chlorobutyrophenone leads to γ-(4-hydroxy-4-phenylpiperidin-1-yl)butyrophenone with a yield of 70% [10], the direct alkylation of azoles with the corresponding γ-chlorobutyrophenones by the analogous method did not give satisfactory results.

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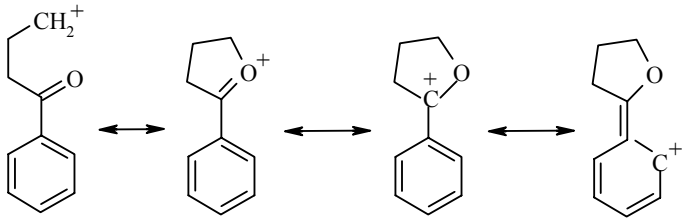
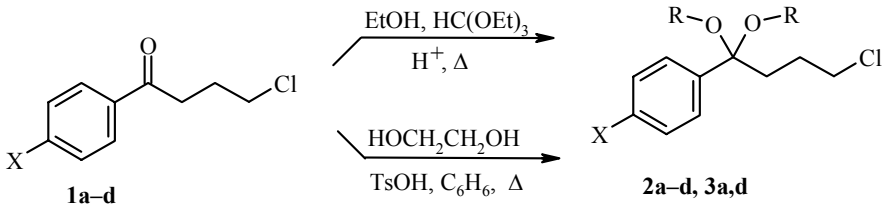
The prototype of the procedure for the reaction of γ-chlorobutyrophenone with imidazole was the method for the production of ε-dimethylaminocaprophenone [13]. A mixture of the chloro ketone with a fourfold excess of imidazole in methanol was heated at 120°C for 24 h. The alkylation product was isolated through the hydrochloride with subsequent purification by column chromatography (eluant 9:1 chloroform–2-propanol). As a result it was possible to obtain the required γ-imidazolylbutyrophenone, but the yield amounted to only 10%.

It was possible to obtain γ-triazolylbutyrophenone by a method similar to the production of triadimefon [14]. γ-Chlorobutyrophenone was boiled with a fourfold excess of triazole in acetonitrile for 50 h. Potassium iodide was used as catalyst. After isolation by column chromatography (eluant 9:1 chloroform–2-propanol) γ-(1,2,4-triazol-1-yl)butyrophenone was obtained with a yield of 12%.

The low yields are probably due to the occurrence of side reactions involving the carbonyl group under the proposed conditions (basic medium, elevated temperature) together with the insufficient activity of the chlorine at the γ-position to the carbonyl group. In addition, the low alkylating ability of the γ-chlorobutyrophenone may be due to the formation of the intermediate stable phenyltetrahydrofuran carbocation first proposed in [15].



We therefore chose a scheme of transformations with prior protection of the carbonyl group for the production of the required compounds, and this made it possible to realize the alkylation of the azole under fairly "rigorous" conditions. For this purpose we chose the method for the production of ketals widely used in laboratory practise and described in detail in the literature [16, 17]. The diethyl ketals **2a-d** were synthesized with yields of 77-87% by the reaction of the corresponding ketones **1a-d** with alcohol. The ethylene ketals (dioxolanes) **3a**,**d** were obtained with yields of 64 and 94% by the reaction of the ketones **1a**,**d** with ethylene glycol (Table 1).



1-3 a X = H, **d** X = Br; **1**, **2 b** X = F, **c** X = Cl; **2a-d** R = Et, **3a**,**d** 2R = CH_2CH_2

The obtained ketals were used to alkylate sodium azolates in DMF. Here the reaction with the triazolate **4b** was conducted at a higher temperature and for a longer time than with the imidazolate **4a**, since the product from 4-substitution of the triazole was converted by prolonged heating into the main thermodynamically stable product from 1-substitution of 1,2,4-triazole [18]. For purification from the nonpolar impurities the obtained ketals **5-8** were isolated in the form of hydrochlorides, and here during extraction with hydrochloric acid the diethyl ketals **5a-d** and **6a-d** were hydrolyzed to the corresponding γ-azolylbutyrophenones **9a-d** and **10a-d**. The dioxolanes **7d** and **8a**,**d** proved considerably more stable, and their hydrolysis therefore required boiling in a water–alcohol solution of hydrochloric acid for several hours. At the stage of isolation of the free bases the yield

TABLE 1. The Characteristics of Compounds **2a-d**, **3a**,**d**, **9a-d**, and **10a-d**

Compound	Empirical formula	Found, % / Calculated, %				bp, °C (mm Hg), mp, °C	Yield, %
		C	H	N	Hal*		
2a	$C_{14}H_{21}ClO_2$	—	—		13.57 / 13.81	103-105 (0.2)*[2]	84
2b	$C_{14}H_{20}ClFO_2$	—	—		12.74 / 12.90	95-97 (0.06)	77
2c	$C_{14}H_{20}Cl_2O_2$	—	—		12.05 / 12.18	118-120 (0.2)*[2]	78
2d	$C_{14}H_{20}BrClO_2$	—	—		10.29 / 10.56	138-140 (0.2)	87
3a	$C_{12}H_{15}ClO_2$	63.50 / 63.58	6.83 / 6.70		15.52 / 15.64	97-100 (0.18), 47-48	64
3d	$C_{12}H_{14}BrClO_2$	46.93 / 47.16	4.75 / 4.62		37.58 / 37.75	138-143 (0.2)	94
9a	$C_{13}H_{14}N_2O$	72.53 / 72.87	6.83 / 6.59	12.91 / 13.07		77-79 167-170*[3]	80
9b	$C_{13}H_{14}ClFN_2O$	58.05 / 58.11	5.39 / 5.25	10.39 / 10.43		132-134*[3]	62*[3]
9c	$C_{13}H_{14}Cl_2N_2O$	54.78 / 54.75	5.20 / 4.95	9.95 / 9.82	24.62 / 24.86	163-165*[3]	77*[3]
9d	$C_{13}H_{13}BrN_2O$	53.33 / 53.26	4.55 / 4.47	9.54 / 9.56	27.03 / 27.26	84-86 167-169*[3]	44 61*[4]
10a	$C_{12}H_{13}N_3O$	67.19 / 66.96	6.17 / 6.09	19.66 / 19.52		80–82	70 49*[4]
10b	$C_{12}H_{13}ClFN_3O$	53.53 / 53.44	5.08 / 4.86	15.63 / 15.58		120-122*[3]	78*[3]
10c	$C_{12}H_{12}ClN_3O$	50.20 / 50.37	4.66 / 4.58	14.75 / 14.68	24.49 / 24.78	63-64 122-124*[3]	63
10d	$C_{12}H_{12}BrN_3O$	49.23 / 49.00	4.38 / 4.11	14.35 / 14.35	26.88 / 27.16	87-89 148-150*[3]	64 60*[4]

* For compounds **2a-d** the content of mineralized Cl after boiling with EtONa is given.

*[2] n_D^{20} 1.4947 (**2a**), 1.5106 (**2c**).

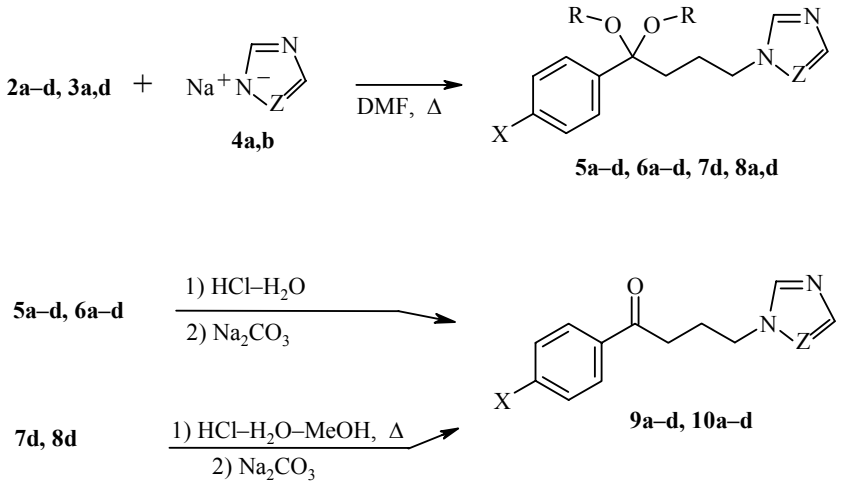
*[3] In the form of the hydrochloride.

*[4] The yield during production through the dioxolanes **3a**,**d**.

was almost quantitative (90-95%). Most of the compounds were isolated with yields of 44-80% and were characterized in the form both of the free γ-azolylbutyrophenones **9a**,**c**,**d** and **10a**,**c**,**d** and of the respective hydrochlorides, while the fluorine derivatives **9b** and **10b**, which were low-melting substances, were characterized only in the form of the hydrochlorides (Scheme 1).

During the formation of the ketals from the chlorobutyrophenones **1a-d** the signals for the protons of the chloromethylene groups in the ^{1}H NMR spectra of compounds **2a-d** and **3a**,**d** (Table 2) are shifted upfield from 3.7 to 3.4 ppm. If the chlorine is replaced by an azole ring, on the other hand, there is a downfield shift of 0.9 ppm in the signal for the γ-methylene group, which is observed at ~4.4 ppm in both the imidazole and triazole derivatives. Mass-spectrometric investigations of the substituted azolylbutyrophenones **9a**,**b** and **10b** made it possible to conclude that the main direction of fragmentation under electron impact is accompanied by the elimination of vinylazoles, as shown by the fragment ion with *m*/*z* 95 or 96 for the derivatives of imidazole and 1,2,4-triazole respectively, which has maximum intensity in the mass spectra of the investigated alkylazoles.

Scheme 1



4 a Z = CH, **b** Z = N; **5, 6, 8–10 a** X = H, **5**, **6**, **9**, **10 b** X = F, **c** X = Cl, **5–10 d** X = Br;

5a–d, 6a–d R = Et; **7d, 8a,d** 2R = CH_2CH_2; **5a–d, 7d, 9a–d** Z = CH;

6a–d, 8a,d, 10a–d Z = N

TABLE 2. The Spectral Characteristics of Compounds **2a-d**, **3a**,**d**, **9a-d**, and **10a-d**

Com-pound*	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*[2]
1	2	3
2a	1045, 1070, 1095 (C–O–C–O–C)	1.22 (6H, t, *J* = 7.0, $2CH_3$); 1.43-1.50 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.03-2.11 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.34-3.44 (6H, m, CH_2Cl, $2OCH_2$); 7.33 (3H, t, *J* = 8.0, C_6H_5); 7.51 (2H, d, *J* = 7.0, C_6H_5)
2b	1012, 1045, 1065, 1095 (C–O–C–O–C)	1.21 (6H, t, *J* = 7.1, $2CH_3$); 1.39-1.53 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.00-2.11 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.30-3.48 (6H, m, CH_2Cl, $2OCH_2$); 7.03 (2H, d, *J* = 8.4, FC_6H_4); 7.46 (2H, dd, ^3J = 8.8, ^4J = 5.5, FC_6H_4)
2c	1015, 1045, 1055, 1080 (C–O–C–O–C)	1.21 (6H, t, *J* = 7.0, $2CH_3$); 1.40-1.51 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.01-2.12 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.30-3.51 (6H, m, $\underline{CH_2}CH_2CH_2Cl$, $2OCH_2$); 7.33 (2H, m, *J* = 8.4, ClC_6H_4); 7.45 (2H, m, *J* = 8.4, ClC_6H_4)
2d	1010, 1055, 1070, 1090 (C–O–C–O–C)	1.22 (6H, m, *J* = 7.0, $2CH_3$); 1.38-1.52 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.99-2.10 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.28-3.48 (6H, m, $\underline{CH_2}CH_2CH_2Cl$, $2OCH_2$); 7.37 (2H, d, *J* = 8.6, BrC_6H_4); 7.49 (2H, d, *J* = 8.6, BrC_6H_4)
3a	1010, 1030, 1040, 1095 (C–O–C–O–C)	1.83-1.93 (2H, m, $CH_2\underline{CH_2}CH_2Cl$); 2.02-2.09 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.55 (2H, t, *J* = 6.0, $\underline{CH_2}Cl$); 3.77 (2H, t, *J* = 6.0, $OCH_2\underline{CH_2}O$); 4.05 (2H, t, *J* = 6.0, $OCH_2\underline{CH_2}O$); 7.25-7.38 (3H, m, C_6H_5); 7.46 (2H, d, *J* = 6.0, C_6H_5)
3d	1008, 1040, 1070, 1100 (C–O–C–O–C)	1.75-1.93 (2H, m, $CH_2\underline{CH_2}CH_2Cl$); 1.93-2.08 (2H, m, $\underline{CH_2}CH_2CH_2Cl$); 3.54 (2H, t, *J* = 6.3, $\underline{CH_2}Cl$); 3.76 (2H, t, *J* = 6.9, $OCH_2\underline{CH_2}O$); 4.03 (2H, t, *J* = 7.0, $OCH_2\underline{CH_2}O$,); 7.33 (2H, *J* = 8.4, $BrC_6\underline{H_4}$); 7.48 (2H, *J* = 8.4, $BrC_6\underline{H_4}$)
9a	1660 (C=O), 1575 (C=N)	2.12 (2H, q, *J* = 6.5, $CH_2\underline{CH_2}CH_2$); 3.15 (2H, t, *J* = 6.9, $CH_2\underline{CH_2}CO$); 4.31 (2H, t, *J* = 6.3, $CH_2\underline{CH_2}N$); 6.95 (1H, s, CH Im); 7.09 (1H, s, CH Im); 7.40-7.56 (3H, m, C_6H_5); 7.59 (1H, s, CH Im); 7.99 (2H, d, *J* = 7.5, C_6H_5)

TABLE 2 (continued)

1	2	3
9b	1670 (C=O), 1580 (C=N)	2.17 (2H, q, J = 7.0, $CH_2\underline{CH_2}CH_2$); 3.11 (2H, t, J = 7.1, $CH_2\underline{CH_2}CO$); 4.28 (2H, t, J = 7.0, $CH_2\underline{CH_2}N$); 7.36 (2H, t. d, ^3J = 8.8, ^4J = 2.0, FC_6H_4); 7.69 (1H, t, ^3J = 1.7, CH Im); 7.84 (1H, t, ^3J = 1.7, CH Im); 8.05 (2H, dd, ^3J = 8.9, ^4J = 5.6, ^4J = 2.1, FC_6H_4); 9.25 (1H, s, CH Im)
9c	1675 (C=O), 1575 (C=N)	2.15 (2H, q, J = 7.0, $CH_2\underline{CH_2}CH_2$); 3.11 (2H, t, J = 7.0, $CH_2\underline{CH_2}CO$); 4.29 (2H, t, J = 6.9, $CH_2\underline{CH_2}N$); 7.57 (2H, d, J = 8.5, ClC_6H_4); 7.69 (1H, s, CH Im); 7.86 (1H, s, CH Im); 7.98 (2H, d, J = 8.5, ClC_6H_4); 9.28 (1H, s, CH Im)
9d	1670 (C=O), 1570 (C=N)	2.23 (2H, q, J = 7.0, $CH_2\underline{CH_2}CH_2$); 2.90 (2H, t, J = 6.8, $CH_2\underline{CH_2}CO$); 4.34 (2H, t, J = 6.9, $CH_2\underline{CH_2}N$); 6.94 (1H, s, CH Im); 7.08 (1H, s, CH Im); 7.53 (1H, s, CH Im); 7.59 (2H, d, J = 8.5, BrC_6H_4); 7.76 (2H, d, J = 8.5, BrC_6H_4)
10a	1660 (C=O), 1580 (C=N)	2.35 (2H, q, J = 6.6, $CH_2\underline{CH_2}CH_2$); 3.00 (2H, t, J = 6.5, $CH_2\underline{CH_2}CO$); 4.32 (2H, t, J = 6.5, $CH_2\underline{CH_2}N$); 7.43-7.59 (3H, m, C_6H_5); 7.92 (2H, d, J = 7.5, C_6H_5); 7.95 (1H, s, CH triaz.); 8.07 (1H, s, CH triaz.)
10b	1670 (C=O), 1585 (C=N)	2.15 (2H, q, J = 7.0, $CH_2\underline{CH_2}CH_2$); 3.09 (2H, t, J = 7.0, $CH_2\underline{CH_2}CO$); 4.32 (2H, t, J = 7.0, $CH_2\underline{CH_2}N$); 7.35 (2H, t, ^3J = 8.7, FC_6H_4); 8.02 (2H, dd, ^3J = 8.4, ^4J = 5.6, FC_6H_4); 8.45 (1H, s, CH triaz.); 9.21 (1H, s, CH triaz.)
10c	1660 (C=O), 1575 (C=N)	2.34 (2H, q, J = 6.8, $CH_2\underline{CH_2}CH_2$,); 2.97 (2H, t, J = 6.5, $CH_2\underline{CH_2}CO$); 4.22 (2H, t, J = 6.6, $CH_2\underline{CH_2}N$); 7.44 (2H, d, J = 8.4, ClC_6H_4); 7.89 (2H, d, J = 8.4, ClC_6H_4); 7.95 (1H, s, CH triaz.); 8.08 (1H, s, CH triaz.)
10d	1670 (C=O), 1578 (C=N)	2.34 (2H, t, J = 6.7, $CH_2\underline{CH_2}CH_2$); 2.97 (2H, t, J = 6.7, $CH_2\underline{CH_2}CO$); 4.33 (2H, t, J = 6.7, $CH_2\underline{CH_2}N$); 7.61 (2H, d, J = 8.5, BrC_6H_4); 7.77 (2H, d, J = 8.5, BrC_6H_4); 7.95 (1H, s, CH triaz.); 8.08 (1H, s, CH triaz.)

* Mass spectrum, *m/z* (*I*, %), **9a**: 214 $[M]^+$ (24), 147 (11), 120 (39), 105 (75), 95 (100); **9b**: 232 $[M–36]^+$ (34), 165 (11), 138 (42), 123 (74), 95 (100); 10b: 233 $[M–36]^+$ (1), 164 (17), 138 (21), 123 (100), 96 (78); compounds **9b**,**c** and **10b** in the form of the hydrochloride.

*[2] Im = imidazole, triaz. = triazole.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument in thin films (liquids) and in Vaseline oil (solids). The ^{1}H NMR spectra were obtained on Bruker AC-200 (200 MHz) and Bruker AM-300 (300 MHz) spectrometers with deuterochloroform as solvent and in DMSO-d_6 for the hydrochlorides of azolyl ketones **9b**,**c** and **10b**. The mass spectra were obtained on a Kratos MS-30 instrument (Great Britain) with 70-eV electrons. The reactions and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates in the 10:1 chloroform–ethanol system (development in UV light, treatment with a solution of 2,4-dinitrophenylhydrazine and the azoles with modified Dragendorf reagent [19]). The melting points were determined on a Boetius bench.

The initial 1-aryl-4-chloro-1-butanones **1a-d** were obtained by the acylation of substituted benzenes with 4-chlorobutyryl chloride by the Friedel–Crafts reaction [10].

Ketals of γ-Chlorobutyrophenones 2a-d and 3a,d. A. To a solution of the ketone **1a-d** (32 mmol) and triethyl orthoformate (96 mmol) in absolute ethanol (19 ml) we added conc. hydrochloric acid (1 ml). The reaction mixture was stirred for 24 h, the acid was neutralized with triethylamine (12 mmol), the low-boiling

components were evaporated, the residue was distilled under the vacuum of an oil pump, and 1-aryl-4-chloro-1,1-diethoxybutanes **2a-d** were obtained.

B. A solution of the ketone **1a-d** (87 mmol), ethylene glycol (131 mmol), and *p*-toluenesulfonic acid (4.4 mmol) in dry benzene (100 ml) was boiled with a Dean–Stark tube until the release of water had stopped. After cooling the reaction mass was washed with sodium carbonate solution (3 × 30 ml) and with water, and dried with magnesium sulfate. The solvent was evaporated, the residue was distilled under the vacuum of an oil pump, and the 2-aryl-1-(3-chloropropyl)-1,3-dioxolanes **3a**,**d** were obtained.

Alkylation of Imidazole (General Procedure). We dissolved metallic sodium (100 mmol) in absolute ethanol (40 ml) and added imidazole (100 mmol). The mixture was stirred, the ethanol was evaporated to dryness under vacuum under the vacuum of a water-jet pump, and the sodium imidazolate **4a** was obtained. We dissolved the azolate **4a** (100 mmol) by heating and stirring in DMF (90 ml) and added dropwise a solution of the ketal **2a-d** or **3a**,**d** (83 mmol) in DMF (10 ml) over 30 min at 70°C. The reaction mass was stirred at the same temperature for 24 h. The course of the reaction was monitored by TLC. After cooling the reaction mass was filtered, the solvent was evaporated under vacuum, and the residue was dissolved in 100 ml of benzene and washed with aqueous sodium carbonate solution (30 ml). The organic phase was extracted with 10% hydrochloric acid solution (5 × 40 ml), and the extract was evaporated. The residue was recrystallized from absolute 2-propanol, and 2-(4-bromophenyl)-2-[3-(1-imidazolyl)propyl]-1,3-dioxolane **7d** (from the initial ketal **3d**) or the hydrochlorides of the 1-aryl-4-(1-imidazolyl)-1-butanones **9a-d** were obtained.

Alkylation of 1,2,4-Triazole (General Procedure). The reaction was carried out by a similar procedure to the alkylation of imidazole with the exception that after the addition of the solution of the ketals **2a-d** and **3a**,**d** to the solution of sodium triazolate **4b** the reaction mixture was stirred at 110-120°C for 30-40 h. The hydrochlorides of 2-aryl-2-[3-(1,2,4-triazol-1-yl)propyl]-1,3-dioxolanes **8a**,**d** (from the initial ketals **3a,d**) or the hydrochlorides of 1-aryl-4-(1,2,4-triazol-1-yl)-1-butanones **10a-d** were obtained.

Hydrolysis of Dioxolanes of γ-Azolylbutyrophenones 7d and 8a,d. A solution of the hydrochloride of the dioxolane **7d** or **8a**,**d** (20 mmol) in a mixture of methanol (75 ml) and 2 N hydrochloric acid (75 ml) was boiled for 3-4 h. The solvents were evaporated, the residue was recrystallized from absolute 2-propanol, and the hydrochlorides of the azolyl ketones **9d** or **10a**,**d** were obtained.

The Free Bases of γ-Azolylbutyrophenones 9a-d and 10a-d. The hydrochlorides of the azolyl ketones **9a-d** or **10a-d** were dissolved in water, sodium carbonate solution was added to a basic reaction, and the product was extracted with toluene. The extract was dried with magnesium sulfate, the solvent was evaporated under vacuum, the residue was recrystallized from diisopropyl ether, and the γ-azolylbutyrophenones **9a-d** or **10a-d** were obtained.

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