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CONVERSION OF 3-BENZOYL-1-METHYL-4-PHENYL-γ-PIPERIDOL BY ARYLAMINES AND ARYLHYDRAZINES. SYNTHESIS OF 3-ARYLAMINO-1-OXO-1-PHENYL-PROPANES AND 1,3-DIARYLPYRAZOLES AND THEIR FRAGMENTATION UNDER ELECTRON IMPACT

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It has been established that on heating, 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine is ring-opened in the presence of arylamines by a type of retroaldol reaction, with subsequent transamination of the intermediate Mannich base and the formation of 3-arylamino-1-oxo-1-phenylpropanes. When using arylhydrazines this γ-piperidol is recyclized with the formation of 1,3-diarylpyrazoles and their 4,5-dihydro derivatives. The mass spectral behavior of a series of 3-arylamino-substituted 1-phenylpropanones has been studied.

Keywords: arylamines, arylhydrazines, 3-arylamino-1-oxo-1-phenylpropanes, 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine, 1,3-diarylpyrazoles, mass spectra.

Previously [1], in attempting the synthesis of Schiff's bases from 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine (**1**) [2] and *o*-phenylenediamine, we established an unusual direction for their interaction under conditions standard for that type of condensation (boiling in toluene in the presence of catalytic amounts of *p*-toluene-sulfonic acid). In place of the expected imine we isolated from the reaction mixture mono- and di-N-benzoylethyl-substituted *o*-phenylenediamine and a benzo-annelated macrocycle, 1,4,8-triazacycloundecane. The structure of the compounds obtained in this case indicated the occurrence of a complex cascade of reactions the, chief of which may be: ring-opening of piperidol **1**, transamination of the opened products, and intramolecular cyclocondensation of the new Mannich bases. In the present report results are presented of a systematic study of the reactions of piperidol **1** with *p-, m-,* and *o*-substituted anilines and arylhydrazines. In all cases the interaction of 2 equiv. arylamine with 1 equiv. piperidol **1** under the conditions indicated above form the expected (in agreement with the results of [1]) N-monobenzoylethylated anilines **2a-u** (Tables 1 and 2). On using unsubstituted aniline the yield of aminopropanone **2a** was 49%. The introduction of electron-donating substituents (alkyl or methoxyl groups), reducing the NH-acidity of arylamines, into the position 4 of aniline led to a significant reduction in the yield of the corresponding aminopropanones **2b-e**.

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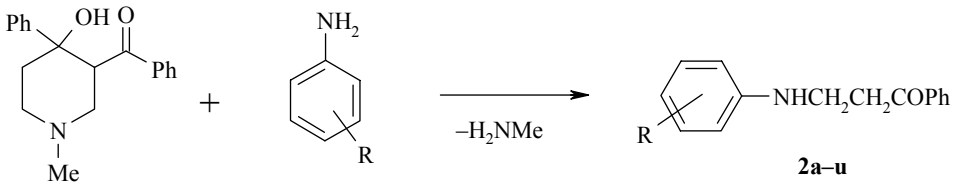


1 **2a–u**

2 a R = H, **b** R = 4-Me, **c** R = 4-Et, **d** R = 4-*i*-Pr, **e** R = 4-OMe, **f** R = 4-Br, **g** R = 4-Cl, **h** R = 4-I, **i** R = 4-COOEt, **j** R = 4-NO_2, **k** R = 3-Cl, **l** R = 3-COMe, **m** R = 3-CF_3, **n** R = 3-NO_2, **o** R = 2-COOMe, **p** R = 2-F, **q** R = 2-Cl, **r** R = 2-Br, **s** R = 2-NH_2 [1], **t** R = $HNCH_2CH_2COPh$ [1], **u** R = 2-Cl, 4-Br

However the presence of halogen or ethoxycarbonyl groups in the *para* position provides an increase in the yield of analogous products up to 63-74%. It might be assumed that such a strong electron-withdrawing substituent as a nitro group at the C(4) atom of the aniline would increase further the yield of the expected 3-aminopropanone **2j**. However this product was formed only in trace amounts and was identified only on chromatomass-spectral analysis of the reaction mixture. The reason for the inactivity of 4-nitroaniline in this reaction may probably be transition of the primary amino group into imine with the formation of an iminoquinonoid tautomer which is incapable of partaking in the transamination reaction. If the nitro group is present in the *meta* position of the nitroaniline then reaction occurs smoothly and compound **2n** is formed in high yield (82%).

On going to *ortho*-substituted anilines, the yields of 3-aminopropanones as a rule fell (compounds **2o-u**), which is probably linked with an increase in the role of steric factors.

Intense absorption bands were present in the IR spectra of the obtained 3-(N-arylamino)propanones **2** for the C=O (at 1655-1686 cm^{-1}) and NH groups (3210-3410 cm^{-1}). The ^1H NMR spectra of these compounds (Table 2) were characterized by the presence of two triplet signals for the protons of the O=C–CH_2–CH_2–N grouping, which were recorded in the region of 3.46-3.70 and 3.05-3.33 ppm with coupling constant 5.7-6.9 Hz. The proton of the secondary amino group resonates at 3.8-4.8 ppm and is displayed as a broadened signal. The aromatic protons in the positions *ortho* to the amino group of the aniline fragment afford diagnostic signals from their high field disposition (at 6.6-6.8 ppm). At the same time the three groups of signals at low field (at 7.27-7.45, 7.46-7.65, and 7.93-7.97 ppm with ratio of integral intensities 2:1:2), belonging to the *meta*, *para*, and *ortho* protons of the benzoyl fragment, are characteristic for the identification of all compounds **2**.

A detailed analysis of the mass spectra of compounds **2a-i,k-q,t**, obtained under electron ionization conditions (Table 3), enabled assessment of the relative stability of their molecular ions and the finding of general pathways for the fragmentation of the latter.

Analysis of the obtained mass spectra of compounds **2** (Tables 3 and 4) shows that the stability of these molecular ions (W_M) varies from 1.9 to 17.9% of the total ion current, however it was not possible to clarify the influence of the electronic properties of the substituents in the aniline portion of the molecule on the stability of the molecular ion.

Nonetheless the character of the fragmentation of the molecular ions of all compounds **2** has much in general (which is evident from the scheme given below) and is determined first of all by the fission of the C–C bond in the benzoylethyl fragment of the molecule with the formation of ion $\mathbf{F_1}$, the intensity of the peak of which in the majority of cases is maximal or close to maximal (Table 4). Fission of the benzoyl fragment with the formation of ions $\mathbf{F_4}$, $\mathbf{F_5}$, and $\mathbf{F_6}$ is the second decomposition pathway of significance. Finally, decomposition of the molecular ion by the third main pathway is accompanied by transfer of a hydrogen atom from the benzoylethyl fragment to the nitrogen atom with the formation of the rearranged odd-electron ions $\mathbf{F_2}$

TABLE 1. ^{1}H NMR Spectra of the Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm. (SSCC, *J*, Hz)					
	NCH_2 (2H, t)	$O{=}CCH_2$ (2H, t)	O=CPh	$H_{arom,}$ in N–Ar	R, substituent in N–Ar	NH (1H, br. c)
2a	3.30 (*J* = 6.1)	3.63 (*J* = 6. 1)	7.47 (2H, m, H-3,5); 7.58 (1H, m, H-4); 7.96 (2H, d, *J* = 7.5, H-2,6)	6.60 (2H, d, *J* = 7.6, H-2,6); 7.19 (2H, t, *J* = 7.6, H-3,5)	6.72 (1H, t, *J* = 7.4, H-4)	4.14
2b	3.28 (*J* = 6.0)	3.60 (*J* = 6.0)	7.46 (2H, m, H-3,5); 7.57 (1H, m, H-4); 7.95 (2H, d, *J* = 7.6, H-2,6)	6.58 (2H, d, *J* = 8.1, H-2,6); 7.00 (2H, t, *J* = 8.1, H-3,5)	2.24 (3H, s, 4-CH_3)	4.01
2c	3.26 (*J* = 6.07)	3.59 (*J* = 6.07)	7.45 (2H, m, H-3,5); 7.56 (1H, m, H-4); 7.94 (2H, d, *J* = 7.4, H-2,6)	6.56 and 6.99 (2H each, system, AA'BB', *J* = 8.2, H-2,6 and H-3,5)	1.20 and 2.54 (3H, t and 2H, q resp., *J* = 7.55, CH_2CH_3)	3.98
2d	3.26 (*J* = 6.2)	3.60 (*J* = 6.2)	7.45 (2H, m, H-3,5); 7.56 (1H, m, H-4); 7.95 (2H, d, *J* = 7.4, H-2,6)	6.58 and 7.04 (2H each, system AA'BB', *J* = 8.3, H-2,6 and H-3,5)	1.26 (6H, d, *J* = 5.0) and 2.83 (1H, m, $H(CH_3)_2$)	4.02
2e	3.28 (*J* = 6.2)	3.56 (*J* = 6.2)	7.27, 7.46 and 7.95 (2H, 1H and 2H resp., all m, H-3,5, H-4 and H-2,6 resp.)	6.63 and 6.78 (2H each, system AA'BB', *J* = 8.9, H-2,6 and H-3,5)	3.75 (3H, s, 4-OCH_3)	3.75
2f	3.27 (*J* = 5.9)	3.58 (*J* = 5.9)	7.47 and 7.57 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.94 (2H, d, *J* = 7.6, H-2,6)	6.51 and 7.24 (2H each, system AA'BB', *J* = 8.7, H-2,6 and H-3,5)	4-Br	4.18
2g	3.24 (*J* = 5.7)	3.46 (*J* = 5.7)	7.45 and 7.54 (2H and 1H, both m, H-,5- and H-4 resp.); 7.93 (2H, d, *J* = 7.5, H-2,6)	6.52 and 7.08 (2H each, system AA'BB', *J* = 8.1, H-2,6 and H-3,5)	4-Cl	4.14
2h	3.23 (*J* = 5.7)	3.57 (*J* = 5.7)	7.46 and 7.56 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.93 (2H, d, *J* = 7.5, H-2,6)	6.40 and 7.38 (2H each, system AA'BB', *J* = 8.6, H-2,6 and H-3,5)	4-I	4.18
2i	3.28 (*J* = 5.8)	3.67 (*J* = 5.8)	7.45 and 7.54 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.93 (2H, d, *J* = 7.4, H-2,6)	6.55 and 7.84 (2H each, system AA'BB', *J* = 8.6, H-2,6 and H-3,5)	1.36 (3H, t, *J* = 7.10) and 4.31 (2H, q, *J* = 7.10); OCH_2CH_3	4.54
2j*	3.33 (*J* = 5.8)	3.71 (*J* = 5.8)	7.47 and 7.58 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.95 (2H, d, *J* = 7.5, H-2,6)	6.71 and 8.1 (2H each, system AA'BB', *J* = 8.6, H-2,6 and H-3,5)	4-NO_2	4.85

TABLE 1. (continued)

1	2	3	4	5	6	7
2j*	3.33 (J = 5.8)	3.71 (J = 5.8)	7.47 and 7.58 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.95 (2H, d, J = 7.5, H-2,6)	6.71 and 8.1 (2H each, system AA'BB', J = 8.6, H-2,6 and H-3,5)	4-NO_2	4.85
2k	3.26 (J = 6.0)	3.59 (J = 6.0)	7.47 and 7.57 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.95 (2H, d, J = 7.6, H-2,6)	6.49 (1H, d. d, J = 8.2 and J = 1.6, H-6); 6.61 (1H, d, J = 1.7, H-2); 6.65 (1H, d, J = 8.0, H-4); 7.06 (1H, t, J = 8.0, H-5)	3-Cl	4.27
2l	3.28 (J = 5.7)	3.65 (J = 5.7)	7.45 and 7.54 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.94 (2H, d. d, J = 7.6 and J = 1.3, H-2,6)	6.78 (1H, d. d, J = 7.3 and J = 1.9, H-6); 7.19–7.26 (2H, m H-4,5); 7.23 (1H, s, H-2)	2.56 (3H, s, $COCH_3$)	4.33
2m	3.28 (J = 5.6)	3.64 (J = 5.6)	7.45-7.60 (3H, m, H-3,4,5); 7.94 (2H, d, J = 7.8, H-2,6)	6.74 (1H, d. d, J = 8.1 and J = 1.5, H-6); 6.8 (1H, t, J = 1.5, H-2); 6.91 (1H, d, J = 7.6, H-4); 7.23 (1H, m H-5)	3-CF_3	4.38
2n	3.17 (J = 5.9)	3.66 (J = 5.9)	7.45-7.61 (3H, m, H-3,4,5); 7.96 (2H, d, J = 7.8, H-2,6)	6.88 (1H, d. d, J = 8.1 and J = 1.8, H-6); 7.26 (1H, m H-5); 7.43 (1H, t, J = 1.8, H-2); 7.46 (1H, m H-4)	3-NO_2	4.59
2o	3.35 (J = 6.9)	3.70 (J = 6.9)	7.45-7.90 (3H, m, H-3,4,5); 7.96 (2H, d, J = 7.1, H-2,6)	6.54 (1H, m H-6); 6.74 (1H, d, J = 8.4, H-3); 7.3-7.9 (2H, m H-4,5)	3.85 (3H, s, OCH_3)	3.86
2p	3.30 (J = 6.0)	3.64 (J = 6.0)	7.46 and 7.55 (2H and 1H, both m, H-3,5 and H-4 resp.); 7.95 (2H, d, J = 7.2, H-2,6)	6.60, 6.75 and 6.93 (1H, 1H and 2H resp., all m, H-6, H-4 and H-3,5)	2-F	4.28
2q	3.24 (J = 6.2)	3.63 (J = 6.2)	7.40-7.52 (3H, m, H-3,4,5); 7.92 (2H, d. d, J = 7.1, H-2,6)	6.62 and 7.12 (1H each, m H-4 and H-5); 6.71 (1H, d. d, J = 7.9 and J = 1.1, H-6); 7.23 (1H, d. d, J = 7.8 and J = 1.0, H-3)	2-Cl	4.70
2r	3.05 (J = 6.3)	3.46 (J = 6.3)	7.27-7.37 (3H, m, H-3,4,5); 7.78 (2H, d.d, J = 7.4, H-2,6)	6.45 and 7.07 (1H each, both m, H-4 and H-5); 6.58 (1H, d. d, J = 8.5 and J = 1.2, H-6); 7.28 (1H, d, J = 8.2, H-3)	2-Br	4.70
2u	3.29 (J = 5.9)	3.64 (J = 5.9)	7.47 and 7.57 (2H and 1H resp., H-3,5- and H-4); 7.95 (2H, d, J = 7.0, H-2,6)	6.58 (1H, d, J = 8.5, H-6); 7.21 (1H, d, J = 8.5, H-5); 7.36 (1H, s, H-3)	2-Cl + 4-Br	4.70

* The spectrum was obtained by deducting the spectrum of the initial 4-nitroaniline from the spectrum of its mixture with product **2j**.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, ºC	IR spectrum, ν, cm^{-1}		Yield, %
		C	H	N		NH	C=O	
2a	$C_{15}H_{15}NO$	79.80 80.00	6.88 6.67	6.25 6.22	109-110	3400, 3410	1686	49
2b	$C_{16}H_{17}NO$	80.15 80.33	7.35 7.11	6.01 5.86	110-111	3381, 3400	1681	37
2c	$C_{17}H_{19}NO$	79.88 80.63	7.62 7.51	5.47 5.53	94-95	3375	1678	44
2d	$C_{18}H_{21}NO$	80.30 80.90	7.43 7.87	5.12 5.24	108-109	3378	1679	46
2e	$C_{16}H_{17}NO_2$	75.41 75.29	6.55 6.67	5.62 5.49	104-105	3361	1673	30
2f	$C_{15}H_{14}BrNO$	59.14 59.21	4.39 4.61	4.50 4.61	138-140	3400	1681	65
2g	$C_{15}H_{14}ClNO$	70.00 69.37	5.70 5.39	5.82 5.39	132-133	3390	1677	63
2h	$C_{15}H_{14}INO$	51.36 51.28	3.89 3.99	4.07 3.99	140-141	3388	1667	74
2i	$C_{18}H_{19}NO_3$	72.12 72.73	6.80 6.40	5.00 4.71	139-140	3366	1670, 1678	66
2j	$C_{15}H_{14}N_2O_3$							<1
2k	$C_{15}H_{14}ClNO$	70.01 69.37	5.64 5.39	5.73 5.39	112-113	3371	1670	75
2l	$C_{17}H_{17}NO_2$	75.90 76.40	6.53 6.37	5.63 5.24	81-82	3378	1678	79
2m	$C_{16}H_{14}F_3NO$	65.63 65.53	4.63 4.78	4.83 4.78	105-106	3378	1670	84
2n	$C_{15}H_{14}N_2O_3$	66.78 66.67	5.31 5.19	10.24 10.37	116-117	3394	1673*	82
2o	$C_{17}H_{17}NO_3$	72.01 72.09	6.09 6.01	5.11 4.95	110-112	3353	1680, 1673	60
2p	$C_{15}H_{14}FNO$	73.61 74.10	5.48 5.76	5.51 5.76	95-96	3390	1680	60
2q	$C_{15}H_{14}ClNO$	69.94 69.37	5.76 5.39	5.02 5.39	Oil	3385	1675	23
2r	$C_{15}H_{14}BrNO$	59.45 59.21	4.26 4.61	4.85 4.61	Oil	3400	1655	17
2u	$C_{15}H_{13}BrClNO$	53.57 53.25	3.57 3.84	4.43 4.14	Oil	3392	1687	35

*IR spectrum, ν, cm^{-1}: 1530, 1334 (NO_2).

and **F_3**. As follows from the data of Table 4, the total intensity of the peaks of the molecular ion and the six fragment ions listed above is from 33 to 70% of the total ion current, which indicates the high selectivity of the fragmentation process of the investigated compounds. In all probability, in the molecular ions of all compounds **2** the positive charge is localized predominantly on the aminoethylbenzoyl portion of the molecule. Confirmation of this conclusion is the very low intensity (or even absence) of ion peaks linked with the primary fission or breakdown of substituent R.

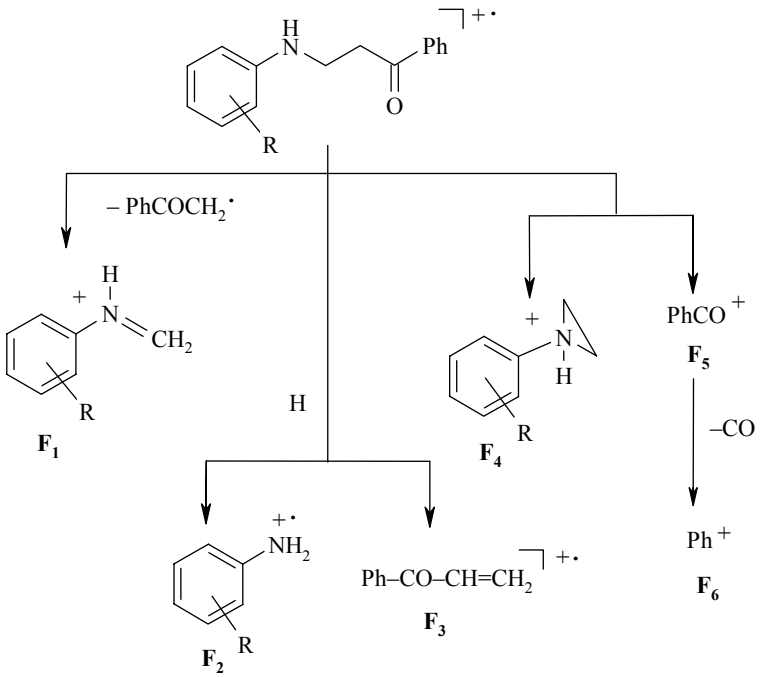
For example, the $[M\text{-}Me]^+$ ion, so characteristic of acetylarenes [3], was absent in the mass spectrum of acetyl-substituted **2l**. The ions caused by loss of methyl (or ethoxcarbonyl group respectively), typical of the mass spectra of 4-methoxy (or ethoxycarbonyl) anilines [3-5], were absent from the mass spectra of the

TABLE 3. Mass Spectra of Compounds **2a-i,k-q,t**

Compound	*m/z* ($I_{отн}$, %)*
2a	225 [M] (27), 120 (5), 118 (5), 105 (100), 93 (6), 91 (6), 77 (47), 65 (10), 52 (15)
2b	239 [M] (28), 238 (25), 120 (100), 118 (20), 105 (31), 91 (26), 77 (63), 65 (14), 51 (20)
2c	253 [M] (100), 238 (14), 148 (13), 134 (85), 119 (15), 118 (21), 105 (48), 91 (15), 77 (70)
2d	267 [M] (13), 252 (15), 148 (35), 136 (37), 132 (49), 120 (100), 105 (82), 91 (20), 77 (81)
2e	255 [M] (59), 136 (100), 135 (27), 123 (24), 120 (38), 108 (36), 105 (80), 77 (59), 51 (22)
2f	303 [M] (40)*[2], 184 (100)*[2], 171 (9)*[2], 155 (6)*[2], 118 (12), 105 (58), 91 (19), 77 (87), 51 (21)
2g	259 [M] (34)*[2], 140 (100)*[2], 132 (15), 127 (17)*[2], 111 (8), 105 (39), 77 (56), 65 (8), 51 (16)
2h	351 [M] (56), 232 (88), 219 (25), 105 (100), 92 (19), 91 (23), 77 (29), 65 (23), 51 (35)
2i	297 [M] (27), 178 (74), 165 (35), 132 (48), 120 (100), 105 (28), 77 (98), 65 (34), 51 (45)
2k	259 [M] (56)*[2], 140 (72)*[2], 127 (10)*[2], 118 (11), 111 (13)*[2], 105 (54), 99 (19)*[2], 77 (100), 51 (40)
2l	267 [M] (27), 162 (11), 148 (100), 135 (13), 120 (17), 105 (13), 77 (55), 51 (23), 43 (40)
2m	293 [M] (37), 274 (10), 174 (100), 161 (18), 145 (10), 120 (8), 105 (21), 77 (22), 51 (8)
2n	270 [M] (29), 151 (53), 138 (34), 132 (18), 120 (21), 105 (100), 92 (25), 77 (84), 51 (25)
2o	233 [M] (42), 164 (56), 151 (8), 146 (20), 132 (100), 119 (6), 105 (24), 77 (30), 51 (6)
2p	243 [M] (26), 132 (21), 124 (100), 111 (67), 105 (69), 83 (20), 77 (98), 55 (21), 51 (42)
2q*[3]	273 [M] (6)*[2], 140 (89)*[2], 134 (100), 133 (66), 127 (12)*[2], 119 (15), 103 (20), 91 (14), 77 (51)
2t	372 [M] (75), 240 (13), 147 (14), 133 (51), 132 (35), 119 (44), 105 (94), 92 (14), 77 (100)

*[M] and the eight most abundant ion peaks are given.
*[2]Ions containing the ^{35}Cl or ^{79}Br isotopes .
*[3]As hydrazone.

4-methoxy (**2e**)- and 4-ethoxycarbonyl (**2i**)-substituted derivatives. Such processes however (frequently to an insignificant extent) occur only after the formation of ions $\mathbf{F_1}$ and $\mathbf{F_2}$. Intense peaks for the $\mathbf{F_1}$-$\mathbf{F_4}$ and $\mathbf{F_6}$ ions are observed even in the mass spectrum of compound **2q**, but in the case of 1,2-bis(2-benzoylethylamino)benzene

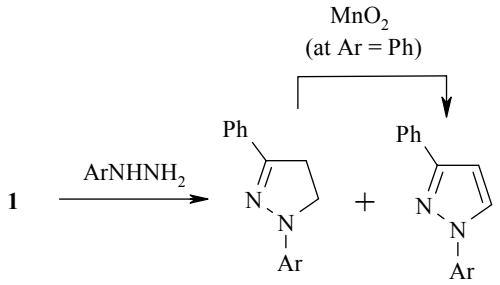


(**2t**) the molecular ion initially loses a molecule of phenyl vinyl ketone, but the resulting odd-electron (pseudo-molecular) ion of 2-amino-substituted **2s** eliminates a phenacyl radical with the formation of ion $\mathbf{F_1}$.

On replacing arylamines by arylhydrazines a more complex chain of sequential conversions of piperidol **1** occurs. In reality, analysis of the ^{1}H NMR spectra of the reaction mixture and chromato-mass spectrometric analysis of it showed that, in the case of phenylhydrazine, the final products of this interaction were 1,3-diphenyl-substituted 4,5-dihydropyrazole **3a** and pyrazole **4a**.

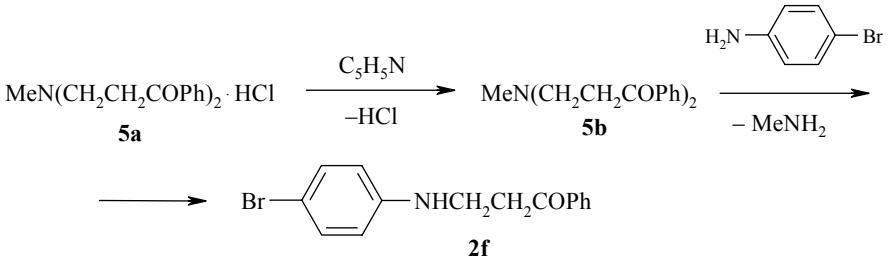
Both substances have close chromatographic mobilities and were isolated by column chromatography only as mixtures in a total yield of 55% (in a ratio of 1:2 according to NMR data).

On oxidation of this mixture with manganese dioxide individual pyrazole **4a** was obtained in high yield. The use in place of phenylhydrazine of its 2,4-dinitro derivative led, as assumed, to complete dehydrogenation of the intermediate dihydro-pyrazole **3b** *in status nascendi*.



3,4 a Ar = Ph, **b** Ar = $C_6H_3(NO_2)_2$-2,4

Proceeding from the hypothesis that 3-benzoyl-substituted γ-piperidol **1** undergoes a retroaldol reaction at the first stage of its conversion into 3-aminopropanones **2**, we studied the interaction of 4-bromoaniline with Mannich base **5b**. The reaction proceeded in the presence of an equimolar amount of pyridine with conversion of the Mannich salt **5a** [2] into the free base **5b**. As a result the expected aminopropanone **2f** was isolated in 60% yield.



On the basis of the results obtained in the previous [1] and the present communications it is possible to offer a scheme for the sequential conversions of piperidol **1** under the action of arylamines and arylhydrazines in the following form.

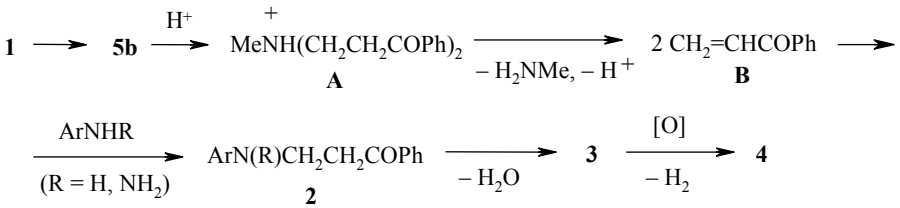


TABLE 4. Intensities of Peaks of Characteristic Ions in the Mass Spectra of Compounds **2a-i,k-q,t** (Σ*I*, %)

Com-pound	W_M	F_1	F_2	F_3	F_4	F_5	F_6	$\sum_{M+Fi\%}$
2a	11.0	—	2.0	—	1.8	37.6	17.3	69.7
2b	6.6	22.1	0.9	0.9	1.0	6.4	15.4	58.3
2c	17.9	15.4	0.5	2.3	1.3	7.7	11.8	60.0
2d	1.9	3.8	3.1	6.2	—	8.9	8.5	32.4
2e	9.5	15.2	4.4	2.1	0.4	5.4	8.0	59.2
2f	12.0	26.6	2.2	—	0.8	8.5	11.6	61.7
2g	8.2	24.6	6.1	1.7	1.0	8.6	11.0	61.2
2h	8.3	12.2	3.7	1.0	0.3	15.7	13.1	54.3
2i	3.3	8.1	3.8	4.3	0.2	9.5	10.5	39.7
2k	11.6	13.6	2.0	—	1.7	7.8	13.8	50.2
2l	5.3	18.8	3.0	2.5	2.2	6.6	9.3	47.7
2m	13.1	33.0	5.0	0.8	2.2	5.9	6.7	68.9
2n	5.7	8.1	5.1	3.7	0.6	13.3	8.9	45.4
2o	11.0	14.4	2.1	25.8	0.4	6.2	7.8	51.8
2p	4.0	14.0	8.7	2.6	0.6	9.1	12.6	67.7
2q	1.4	18.3	1.8	1.7	0.7	2.1	8.2	44.2
2t	12.4	6.8	1.7	4.7	1.9	14.5	7.4	60.7

The Mannich base **5b** resulting from the retroaldol decomposition gives intermediate cation **A** after protonation, which in its turn is decomposed to methylamine and phenyl vinyl ketone **B**. The latter then undergoes a Mannich reaction with arylamines and forms new bases **2**, which usually are difficult to synthesize by the Mannich method. In the case of R=NH_2 the amino ketones readily undergo heterocyclization and are converted into dihydropyrazoles **3**.

According to the predictions of the internet programs PASS [6] 3-(N-arylamino) ketones **2a-c,e,g,k,n,o,q** may possess antileishmanial activity with a probability of 66-78%. Vasodilator action on heart vessels may be displayed by compounds **2e,n,o** (probability 60-71%). Antiviral activity (against herpes) (probability 61-67%) may be expected for **2c,d,g,h,p,r,u** and also amino ketone hydrazone **2q**. The trifluorophenyl amino ketone **2m** is promising for testing as an inhibitor of tyrosine phosphatase (74% probability), and N-(2-fluorophenyl)amino ketone **2p** as an agonist of interferon (59%) and the GABA receptor (61%). There is a particularly high probability of bioactivity for amino ketone **2r** as an agonist of interferon (70%) and an antagonist of interleukin (90%).

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WP 400 (400 MHz) spectrometer in $CDCl_3$, internal standard was TMS. Mass spectra were obtained on a Finnigan MAT Incos 50 (70 eV) mass spectrometer. The IR spectra were recorded on an IR 75 spectrometer in KBr disks. Silufol UV 254 plates were used for TLC (visualization with iodine vapor). The characteristics of the synthesized compounds are given in Tables 1-4.

Preparation of 3-Aminopropanones 2 (General Method). A. A solution of piperidol **1** (2 mmol), arylamine (4 mmol), and TsOH (10 mg) in toluene (30 ml) was boiled for 3-5 h with a Dean – Stark trap. The solvent was evaporated to ½ volume, and cooled. The isolated crystals were separated, and recrystallized from an appropriate solvent. Oily products **2q,r,u** were isolated by column chromatography on silica gel, eluting with hexane–chloroform, 5:1. Compound **2q** was also characterized as the hydrazone, which was obtained in 36% yield as light yellow crystals by boiling a methanolic solution of amino ketone (2.8 g; 10 mmol) with

hydrazine hydrate (2 ml). Mp 86-88°C. IR spectrum, ν, cm^{-1}: 1593 (C=N), 3210 (NH), 3330 (NH_2). ^1H NMR spectrum, δ, ppm: 2.99 and 3.45 (2H each, both m, NCH_2 and $N=CCH_2$), 4.51 (1H, br. s, NH); 5.51 (2H, s, NH2), 6.65, 7.11, and 7.25 (total 4H, all m, NC_6H_4Cl), 7.40-7.76 (5H, m, C_6H_5). Mass spectrum, see Table 3.

Amino Ketone 2a is described in [7], mp 111-112°C.

Compounds 2s,t, and also the diacetate of compound **2s** were obtained previously in [1].

B. Pyridine (2 mmol), 4-bromoaniline (0.71 g, 4.1 mmol), and TsOH (10 mg) were added to a suspension of Mannich salt **5a** (0.66 g, 2 mmol) in toluene (30 ml). The mixture was boiled for 3 h, the solvent evaporated, and the residue recrystallized from ether. Aminopropanone **2f** (0.36 g, 60%) was obtained.

Preparation of 1,3-Diphenyl-4,5-dihydropyrazole (3a) and 1,3-Diphenyl-pyrazole (4a). A mixture of piperidol **1** (1.2 g, 4 mmol), phenylhydrazine hydrochloride (0.6 g, 4 mmol), pyridine (0.32 g, 4 mmol), and TsOH (10 mg) was boiled for 5 h. The solvent was distilled, and the residue separated on a chromatographic column of silica gel, eluting with hexane. A mixture (0.5 g, 55%) of compounds **3a** and **4a** (in a ratio of 1:2 according to data of NMR and chromato-mass spectra) was isolated. ^1H NMR spectrum of dihydropyrazole **3a**, δ, ppm (*J*, Hz) (obtained by deducting signals of the pyrazole **4a** spectrum from the spectrum of a mixture of it with dihydropyrazole **3a**): 3.25 and 3.90 (2H each, both t, $J = 10.5$, 3-CH_2 and 2-CH_2 respectively); 6.85 (1H, t, $J = 7.4$, H-4 NPh fragment); 7.1 (2H, d, $J = 8.0$, H-2,6 NPh fragment); 7.25-7.80 (7H, m, H arom.).

Oxidation of a Mixture of 3a compounds and 4a. Manganese dioxide (0.7 g, 8 mmol) was added to a solution of the mixture (0.1 g, 0.4 mmol) of compounds **3a** and **4a** in toluene (30 ml) and the suspension obtained was boiled for 3 h. The solid phase was filtered off and washed on the filter with hot toluene (10 ml), the combined filtrates were evaporated to ¼ the initial volume, and cooled. 1,3-Diphenylpyrazole **4a** (80 mg, 80%) was obtained as grayish white crystals, mp 82°C (lit. mp 84-85°C [8]).

1-(2,4-Dinitrophenyl)-3-phenylpyrazole) (4b) was obtained analogously to the synthesis of the compounds **3a** and **4a** mixture from piperidol **1** (0.6 g, 2 mmol) and 2,4-dinitrophenylhydrazine (0.8 g, 4 mmol). Following resolution of the reaction mixture by column chromatography on silica gel, compound **4b** (0.45 g, 60%) was isolated as yellowish crystals; mp 159-160°C (lit. mp 162-163°C [9]).

REFERENCES

1. A. T. Soldatenkov, S. V. Kutyakov, S. V. Volkov, Zh. A. Mamyrbekova, and K. B. Polyanskii, *Khim. Geterotsikl. Soedin.*, 1731 (2004). [*Chem. Heterocycl. Comp.*, **40**, 1499 (2004)].
2. J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).
3. P. B. Terentiev and A. P. Stankevicius, *Mass Spectrometric Analysis of Biologically Active Nitrogen Compounds* [in Russian], Mokslas, Vilnius (1981).
4. A. T. Lebedev, *Mass Spectrometry in Organic Chemistry* [in Russian], Binom, Moscow (2003).
5. V. G. Zaikin, A. V. Varlamov, A. I. Mikaya, and N. S. Prostakov, *Principles of Mass Spectrometry of Organic Compounds* [in Russian], MAIK Nauka, Moscow (2001), p. 286.
6. A. V. Sadym, A. A. Lagunin, D. A. Filimonov, and V. V. Poroikov, *Khim.-farm. Zh.*, **36**, No. 10, 21 (2002).
7. Beilstein, Vol. 14, 62 (1931).
8. *Dictionary of Organic Compounds* [Russian translation], Vol. 1, Izd. Inostr. Lit., Moscow (1949), p. 1041.
9. J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2832 (1966).