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REACTION OF 3-BENZOYL-1-METHYL-4-PHENYL-γ-PIPERIDOL WITH ARYLAMINES AND ARYLHYDRAZINES. SYNTHESIS OF 3-ARYLAMINO-1-OXO-1-PHENYLPROPANES AND 1,3-DIARYL-PYRAZOLES AND THEIR FRAGMENTATION UNDER ELECTRON IMPACT

S. V. Volkov[1], S. V. Kutyakov[1], A. N. Levov[1], E. I. Polyakova[1], Le Tuan Anh[1], S. A. Soldatova[1], P. B. Terentiev[2], and A. T. Soldatenkov[1]

Upon heating in the presence of arylamines 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine decyclizes via a retroaldol type reaction with subsequent transamination of the intermediate Mannich base to give 3-arylamino-1-oxo-1-phenylpropanes. In the case of the use of arylhydrazines this γ-piperidol recyclizes to give 1,3-diarylpyrazoles and their 4,5-dihydro derivatives. The mass spectroscopic behavior of a series of 3-arylamino-substituted 1-phenylpropanones has been studied.

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

In previous [1] attempts to synthesize a Schiff base from 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine (**1**) [2] and 1,2-diaminobenzene we identified an unusual route for their condensation under standard type conditions (refluxing in toluene in the presence of a catalytic amount of *para*-toluenesulfonic acid). In place of the expected imine the mono- and di-N-(benzoylethyl)-substituted *ortho*-phenylenediamines and benzo derivative of the macrocycle 1,4,8-triazacycloundecane were separated from the reaction mixture. The structure of the compounds obtained in this case pointed to a complex reaction cascade, of which the principal might be decyclization of piperidol **1**, transamination of the decyclization products and intramolecular cyclocondensation of the novel Mannich bases. We now present the results of a systematic study of the reaction of piperidol **1** with *para*-, *meta*-, and *ortho*-substituted anilines and arylhydrazines. In all cases the reaction of two equivalents of the arylamines with one equivalent of the piperidol **1** under the conditions indicated above gave the expected N-monobenzoylethyl aniline derivatives **2a-u** (in agreement with the results of [1]), the charcteristics of which are given in Table 1. For the unsubstituted aniline the yield of the aminopropanone **2a** was 49%. Introduction of electron-donor substituents into the *para*-position of the aniline lowers the NH-acidity of the arylamines leading to a marked decrease in the yield of the corresponding aminopropanones **2b-e**.

[1]Russian People's Friendship University, Moscow 117198; e-mail: swelfen@mail.ru. [2]M. V. Lomonosov State University, Moscow 119899, Russia; e-mail: petr_terentev@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 544-554, April, 2007. Original article submitted February 17, 2006.

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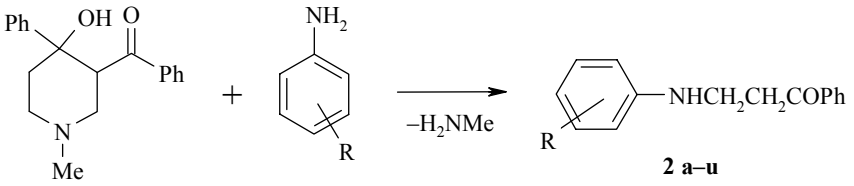
TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	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	$C_{15}H_{14}ClNO$	70.10 / 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	$C_{15}H_{14}ClNO$	70.11 / 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 / —	4.63 / —	4.83 / —	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 (1530, 1334, NO_2)	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				23
2r	$C_{15}H_{14}BrNO$	59.45 / 59.21	4.26 / 4.61	4.85 / 4.61		3400	1655	17
2u	$C_{15}H_{13}BrClNO$	3.57 / 3.25	3.57 / 3.84	4.43 / 4.14				35

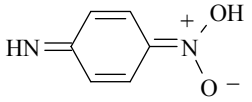
The presence of halogens or carbethoxy groups in the *para* position leads to an increase in the yield of the analogous products to 63-74%. It might be expected that such a strong electron-acceptor substituent as the nitro group on the $C_{(4)}$ position of the aniline would increase the yield of the expected 3-aminopropanone **2j** even



1 **2 a–u**

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 = $HNCH_2CH_2COPh$, **u** R = 2-Cl + 4-Br

further. However this product is formed only in trace amounts and was identified only by chromatomass-spectrometric analysis of the reaction mixture. The reason for the unreactivity of the 4-nitroaniline in this reaction can evidently derive from a change of the primary amine to an imino group with formation of an iminoquinoid tautomer structure which cannot then take part in the transamination reaction. If the nitro group is present in the *meta* position of the nitroaniline the reaction occurs smoothly with a high yield (82%) of the compound **2n**.



The yields of the 3-aminopropanones formed on going to the *ortho*-substituted anilines generally fall (compounds **2o-u**) and this is evidently associated with the increased steric factor.

The IR spectra of the 3-(N-aryl)propanones **2** obtained show strong absorption bands for the C=O groups (at 1655-1686 cm^{-1}) and NH group (3210-3410 cm^{-1}). The ^1H NMR spectra of these compounds (Table 2) show the characteristic presence of two triplet signals for the protons of the O=C–CH_2–CH_2–N– group in the regions 3.46-3.7 and 3.05-3.33 ppm with a spin-spin coupling of 5.7-6.9 Hz. The secondary amino group proton absorbs at 3.8-4.8 ppm as a broadened signal. The aromatic protons *ortho* to the amino group of the aniline fragment give a typically high field positioned signal (6.6-6.8 ppm). An identifier for these compounds **2** is the presence of three groups of signals to low field (7.27-7.45, 7.46-7.65, and 7.93-7.97 ppm) in the integrated ratio 2 : 1: 2 for the *meta*, *para*, and *ortho* protons of the benzoyl fragment.

A detailed analysis of the mass spectra of compounds **2a-i,k-q,t** recorded under electron ionization conditions (Table 3) allowed us to assign the relative stability of their molecular ions and to find an overall route for the fragmentation of the latter.

Analysis of the mass spectra of compounds **2** shows that the stability values of their molecular ions (W_M) occurs in the range form 1.9 to 17.9% of the total ion current but explaining the effect of the electronic properties of the substituent in the aniline part of the molecule to the molecular ion stability value did not prove possible, probably because the mass spectra were recorded over an extended time and often under differ conditions. None the less, the nature of the fragmentation of the molecular ions of all of the compounds **2** have much in common (as evident in the Scheme) and are determined mostly by cleavage of the C–C bond in the benzoylethyl fragment of the molecule to give the ion F_1, the intensity of whose peak is maximal or close to in most cases (Table 4).

The second most important route for decomposition is cleavage of the benzoyl fragment to form the ions F_4, F_5, and F_6. Finally, the third basic cleavage route for the molecular ion involves transfer of a hydrogen atom from the benzoylethyl fragment to the nitrogen atom with formation of the rearranged, odd electron ions F_2 and F_3.

As seen in Table 4, the overall peak intensity of the molecular ion peaks and the six fragmentation ions listed above from 33 to 70% of the total ion current point to a high selectivity of the process in the fragmentation of the compounds investigated. In all probability, the positive charge in the molecular ions of all of the compounds **2** are localized principally in the aminoethylbenzoyl part of the molecule. The conclusion is confirmed by the very low intensity (or even absence) of ion peaks associated with primary cleavage or cleavage of the R substituent. Hence in the mass spectrum of the acetyl-substituted **2l** the $[M–Me]^+$ ion (so characteristic of acetylarenes [3]) is absent. In the mass spectra of the 4-methoxy (**2e**) and 4-carbethoxy (**2i**) derivatives the ions for primary loss of methyl (correspondingly carbethoxy) which are so typical of the mass spectra of 4-methoxy(carbethoxy)anilines [3-5] are absent. Such processes (often to a minor degree) occur only after formation of the ions F_1 or F_2. The strong peaks for the F_1-F_4 and F_6 ions are even observed in the mass

TABLE 2. ^{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)	$O{=}CC_6H_5$	H_{arom} in N-Ar	R (substituent in N-Ar)	NH (1H, br. s)
1	2	3	4	5	6	7
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, AA'BB' system, *J* = 8.2, H-2,6 and H-3,5)	1.20 and 2.54 (3H, t and 2H, q corr., *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, AA'BB' system, *J* = 8.3, H-2,6 and H-3,5)	1.26 (6H, d, *J* = 5.0) and *J* = 2.83 (1H, m, $CH(CH_3)_2$)	4.02
2e	3.28 (*J* = 6.2)	3.56 (*J* = 6.2)	7.27, 7.46 and 7.95 (2H, 1H and 2H corr., all m, H-3,5,4 and H-2,6 corr.)	6.63 and 6.78 (2H each, AA'BB' system, *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 corr.); 7.94 (2H, d, *J* = 7.6, H-2,6)	6.51 and 7.24 (2H each, AA'BB' system, *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-3,5 and H-4 corr.); 7.93 (2H, d, *J* = 7.5, H-2,6)	6.52 and 7.08 (2H each, AA'BB' system, *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 corr.); 7.93 (2H, d, *J* = 7.5, H-2,6)	6.40 and 7.38 (2H each, AA'BB' system, *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 corr.); 7.93 (2H, d, *J* = 7.4, H-2,6)	6.55 and 7.84 (2H each, AA'BB' system, *J* = 8.6, H-2,6 and H-3,5)	1.36 (3H, t) and 4.31 (2H, q, 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 corr.); 7.95 (2H, d, J = 7.5, H-2,6)	6.71 and 8.1 (2H each, AA'BB' system, J = 8.6, H-2,6 and H-3,5)	4-NO_2	4.85

TABLE 2 (continued)

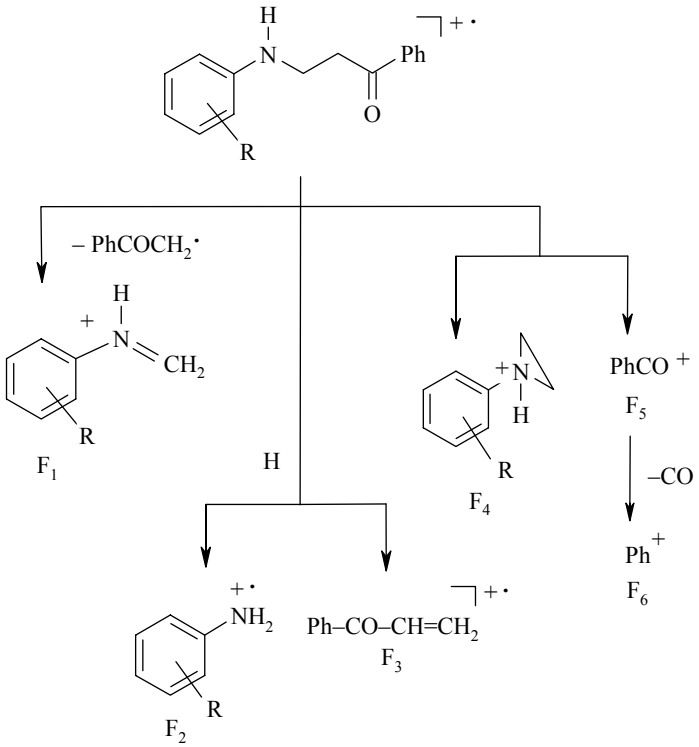
1	2	3	4	5	6	7
2k	3.26 (J = 6.0)	3.59 (J = 6.0)	7.47 and 7.57 (2H and 1H, both m, H-3,5 and H-4 corr.); 7.95 (2H, d, J = 7.6, H-2,6)	6.49 (1H, dd, J = 8.2 and J = 1.6, H-6); 6.61 (1H, d, J = 1.7, H-2); 6.65 (1H, d, J = 8.0, H-4); 7.06 (1H, t, J = 8.0, H-5)	3-Cl	4.27
2l	3.28 (J = 5.7)	3.65 (J = 5.7)	7.45 and 7.54 (2H and 1H, both m, H-3,5 and H-4 corr.); 7.94 (2H, dd, J = 7.6 and J = 1.3, H-2,6)	6.78 (1H, dd, 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, J = 7.8, H-2,6)	6.74 (1H, dd, 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, dd, 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 corr.); 7.95 (2H, d, J = 7.2, H-2,6)	6.60, 6.75 and 6.93 (1H, 1H and 2H corr., all m, H-6,4 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, dd, J = 7.1, H-2,6)	6.62 and 7.12 (1H each, m, H-4 and H-5); 6.71 (1H, dd, J = 7.9 and J = 1.1, H-6); 7.23 (1H, dd, 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, dd, J = 7.4, H-2,6)	6.45 and 7.07 (1H each, both m, H-4 and H-5); 6.58 (1H, dd, 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 corr., 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

* Spectrum obtained by subtracting the spectrum of the starting 4-nitroaniline from the spectrum of its mixture with the product **2j**

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

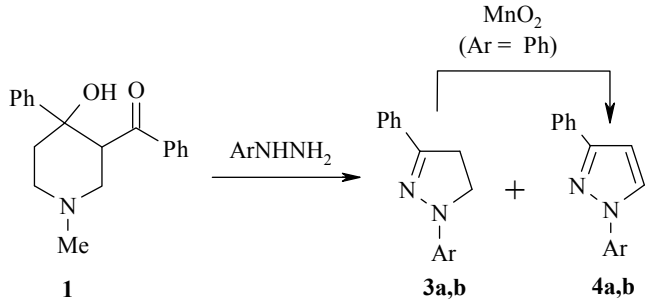
Com-pound	*m/z* (I_{real} %)*
2a	225 [M] (27), 120 (5), 118 (5), 105 (100), 93 (6), 91 (6), 77 (47), 65 (10), 52 (15)
2b	239 [M] (28), 238 (25), 120 (100), 118 (20), 105 (31), 91 (26), 77 (63), 65 (14), 51 (20)
2c	253 [M] (100), 238 (14), 148 (13), 134 (85), 119 (15), 118 (21), 105 (48), 91 (15), 77 (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	259 [M] (34)*[2], 140 (100)*[2], 132 (15), 127 (17)*[2], 111 (8), 105 (39), 77 (56), 65 (8), 51 (16)
2g	303 [M] (40)*[2], 184 (100)*[2], 171 (9)*[2], 155 (6)*[2], 118 (12), 105 (58), 91 (19), 77 (87), 51 (21)
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 strongest ion peaks given.
*[2] Ions containing the ^{35}Cl and ^{79}Br isotopes.
*[3] As the hydrazone.



spectrum of compound **2q** but in the case of the 1,2-bis(2-benzoylethylamino)benzene (**2t**) the molecular ion initially loses a molecule of phenyl vinyl ketone and the odd electron (pseudomolecular) ion formed of 2-amino-substituted **2s** eliminates a phenacyl radical to give ion F_1.

When changing from arylamines to arylhydrazines a more complex chain of consecutive reactions of piperidol **1** takes place. In fact, the ^{1}H NMR and mass spectrometric analysis of the reaction mixture showed that for phenylhydrazine the final products of the reaction discussed are the 1,3-diphenyl-substituted 4,5-dihydropyrazole **3a** and pyrazole **4a**.



1 **3a,b** **4a,b**

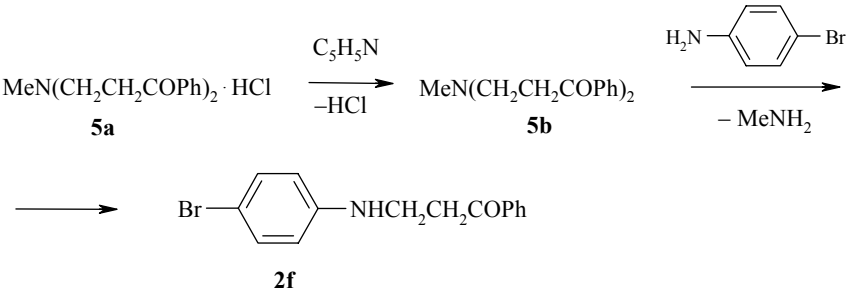
3,4 a Ar = Ph, **b** Ar = $C_6H_3(NO_2)_2$-2,4

Both substances have similar chromatographic mobility and are separated chromatographically only as a mixture with overall yield 55% (in the ratio 1 : 2 according to the ^{1}H NMR data). Oxidation of this mixture with manganese dioxide gave a high yield of the individual pyrazole **4a**. The use of the 2,4-dinitrophenyl derivative in place of phenylhydrazine led, as expected, to complete dehydrogenation of the intermediate dihydropyrazole **3b** *in status nascendi*.

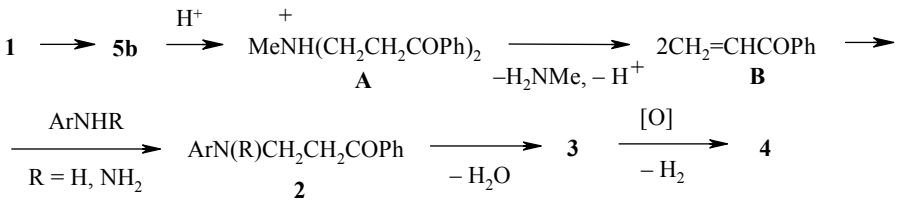
Starting from the basis that the 3-benzoyl-substituted γ-piperidol **1** undergoes a retroaldol reaction in the first stage of conversion to the 3-aminopropanones **2** we have studied the reaction of 4-bromoaniline with the Mannich base **5b**. The reaction was carried out in the presence of an equivalent amount of pyridine for conversion of the Mannich salt **5a** to the free base **5b**. As a result the expected aminopropanone **2f** was formed in 60% yield.

TABLE 4. Peak Intensities for the Characteristic Ions in the Mass Spectra of Compounds **2a-i, k-q,t**

Com-pound	W_M	F_1	F_2	F_3	F_4	F_5	F_6	$\sum_M + F_i$, %
2a	11.0	37.6	2.0	—	1.8	—	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



On the basis of the results obtained before [1] and in this work the results can be rationalized by the following scheme of successive reactions for piperidol **1** in the presence of arylamines and arylhydrazines:



The Mannich base **5b** formed as a result of the retroaldol cleavage gives the intermediate cation **A** after protonation and, in turn, this decomposes to methylamine and the phenyl vinyl ketone **B**. The latter then takes part in a Michael reaction with arylamines to give the new bases **2** which are usually hard to synthesize by direct condensation using the Michael method. In the case of R = NH_2 the amino ketones readily undergo heterocyclization and convert to the dihydropyrazoles **3**.

According to the predictive PASS program [6] the 3-(N-arylamino ketones **2a-c,e,g,k,n,o,q** may possess a 66 to 78% probability of antileishmanial activity. Compounds **2e,n,o** may show vasodilator activity on heart vessels (probability 60-71%). The amino ketones **2c,d,g,h,p,r,u** and the hydrazone of amino ketone **2q** should be tested for antiviral (Herpes virus) activity, a probability of possessing such activity is 61-67%.

The trifluorophenyl-substituted amino ketone **2m** is promising for testing as a tyrosine phosphatase inhibitor (74% probability) and the N-(2-fluorophenyl)amino ketone **2p** as an interferon (59%) and GABA receptor (61%) agonist. There is also a high probability for the bioactivity of amino ketone **2r** as interferon (70%) and interleukin (90%) antagonist.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker WP-400 spectrometer using $CDCl_3$ with TMS as internal standard and mass spectra on a Finnigan MAT Incos 50 instrument (70 eV). IR spectra were recorded on an IR-75 instrument for KBr tablets. TLC was carried out on Silufol UV-254 plates and spots were revealed using iodine vapour. The characteristics of the compounds synthesized are given in Tables 1-4.

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 refluxed for 3-5 h in a Dean and Stark apparatus. The solvent was evaporated to half volume and cooled. The precipitated crystals were separated and recrystallized from the corresponding solvent. The oily products **2q,r,u** were separated by column chromatography on silica gel eluting with a mixture of hexane and chloroform (5 : 1). Compound **2q** was also characterized as the hydrazone in 36% yield as light-yellow crystals by refluxing a methanol solution of the amino ketone (2.8 g, 10 mmol) with

hydrazine hydrate (2 ml). Mp 86-88ºC. 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, d, NH_2); 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 has been reported in [7], mp 111-112ºC.

Compounds 2s,t,u and also the diacetate of compound **2s** have been prepared before [1].

B. Pyridine (0.16 g, 2 mmol), 4-bromoaniline (0.71 g, 4.1 mmol), and TsOH (10 mg) were added to a suspension of the Mannich salt **5a** (0.66 g, 2 mmol) in toluene (30 ml). The mixture was refluxed for 3 h, solvent evaporated off, and the residue was recrystallized from ether to give the aminopropanone **2f** (0.36 g, 60%).

1,3-Diphenyl-4,5-dihydropyrazole (3a) and 1,3-Diphenylpyrazole (4a). A mixture of the 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 refluxed for 5 h. Solvent was distilled off and the residue was separated on a silica gel chromatography column with hexane as eluent to give the mixture of compounds **3a** and **4a** (0.5 g, 55%) (in the ratio 1 : 2 according to the ^1H NMR spectrum and mass spectrometry). ^1H NMR spectrum of dihydropyrazole **3a** (obtained by subtracting the spectrum of pyrazole **4a** from its mixture with **3a**), δ, ppm (*J*, Hz): 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, N–C_6H_5 fragment); 7.1 (2H, d, $J = 8.0$, H-2,6 N–C_6H_5 fragment); 7.25-7.80 (7H, m, $H_{arom.}$).

Oxidation of the Mixture of 3a and 4a. MnO_2 (0.7 g, 8 mmol) was added to a solution of a mixture of compounds **3a** and **4a** (0.1 g, 0.4 mmol) in toluene (30 ml) and the suspension obtained was refluxed for 3 h. The solid phase was filtered and washed on the filter with hot toluene (10 ml). The combined filtrates were evaporated to one quarter initial volume and cooled to give the 1,3-diphenylpyrazole **4a** (80 mg, 80%) as grayish-white crystals with mp 82ºC (mp 84-85ºC [8]).

1-(2,4-Dinitrophenyl)-3-phenylpyrazole (4b) was prepared similarly to the mixture of **3a** and **4a** from the piperidol **1** (0.6 g, 2 mmol) and 2,4-dinitrophenylhydrazine (0.8 g, 4 mmol). The reaction mixture was separated by column chromatography on silica gel to give compound **4b** (0.45 g, 60%) as yellowish crystals with mp 159-160ºC (mp 162-163ºC [9]).

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