Revue Roumaine de Chimie, **2008**, *53*(4), 267–271

NEW PYRAZOLE DERIVATIVES WITH POTENTIAL LOCAL ANESTHETIC ACTIVITY

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Received June 21, 2007

2-Pyrazolyl acetanilides **5a-f** were synthesized by *N*-alkylation of pyrazoles **4a-c** with 2-iodoacetanilides **3a-d**. The new compounds, derived from the pyrazole, were characterized by elemental analysis, UV-Vis, IR, NMR and MS spectra.

INTRODUCTION

Local anesthetics are drugs that produce reversible loss of sensation in a specific area of the body. There are two major classes, defined by the nature of the carbonyl-containing linkage group: esters and amides.[1-3] There are important practical differences between these two classes of local anesthetic agents. Esters are relatively unstable in solution and are rapidly hydrolyzed in the body. In contrast, amide local anesthetics are relatively stable in solution, are slowly metabolized by hepatic amidases and hypersensitivity reactions are extremely rare. In current clinical practice esters have largely been superseded by the amides.

Among the local anesthetic, lidocaine, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, is a drug widely used.

Löfgren[4] discovered that the lidocaine and another substituted acetanilides possessing local anesthetic activity should contain a lipophylic aromatic structure, an intermediate chain and a hydrophylic one having a tertiary amino group.

Recently[5,6] we reported the synthesis and characterization of some new substituted 2-(pyrazol-1-yl)-acetanilides where benzene ring is substituted by alkyl radicals. Some of these compounds were tested and exhibited infiltration, surface local anesthetic and anti-arrhythmic actions. Herein we report the synthesis and characterization of novel pyrazolyl-acetanilides **5a-f** containing halogen atoms grafted on the benzene ring.

The new compounds **5** were obtained in order to investigate the influence of fluorine and bromine atoms on the anesthetic activity and to compare with those of previously reported alkylated pyrazolyl-acetanilides.

RESULTS AND DISCUSSION

Due to the low basicity and nucleofilicity of pyrazole, the alkylation of 1(*H*)-pyrazole derivatives at the nitrogen atom was performed with halogenated compounds with high reactivity and in the presence of a base such as alkaline hydroxides, carbonates.

Thus, the reaction between 2-chloroacetanilides **2** and pyrazoles **4** was performed in DMF in the presence of sodium carbonate and gave low yields (under 10%) and impure *N*-alkylated pyrazoles **5**. In order to increase the yield, the 2-chloroacetanilides **2** were replaced with the corresponding iodo derivatives **3**. The substitution of the chlorine atom with iodine was achieved by treating
2-chloroacetanilides **2** with sodium iodide in

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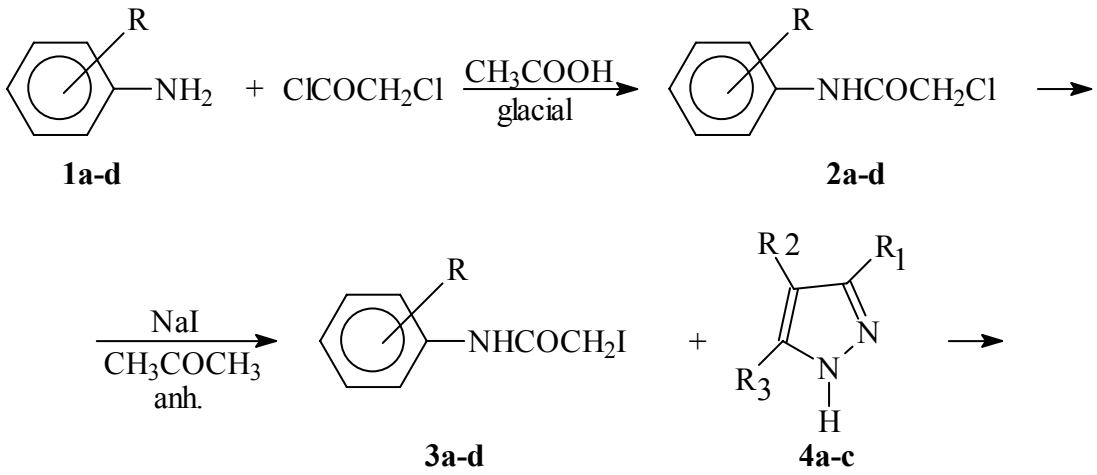
acetone at reflux.[7] The advantage of using sodium iodide instead of other iodides is its high solubility in acetone.

Compounds **5a-f** were synthesized by treatment of substituted 2-iodoacetanilides **3a-d** with pyrazole **4a** and its derivatives **4b,c** in DMF and in presence of sodium carbonate according to the reaction (Scheme 1).

Starting from iodoacetanilide **3b** and 3(5)-methyl-5(3)-phenylpyrazole **4c**, compound 2-[3-Phenyl-5-methyl-pyrazol-1-yl)]-2'-methyl-4'-bromoacetanilide **5d** was isolated as a single regioisomer. The positions of the methyl and phenyl groups in compound **5d** were determined on the basis of chemical shifts in ^{1}H and ^{13}C-NMR spectra, by NOE experiments and by comparison with ^{13}C-NMR data for similar compounds. The irradiation of the methylenic group resulted in the enhancement of the signal of the 5-methyl group.

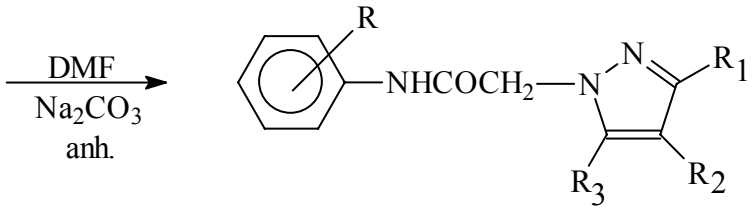
Some properties for the new compounds are given in Table 1.



1a-d **2a-d** **3a-d** **4a-c**

3a: R = 4'-Br; **3b**: R = 2'-Me-4'-Br; **3c**: R = 2'-F; **3d**: R = 4'-F

4a: $R_1 = R_2 = R_3$=H; **4b**:, $R_1 = R_3$ = Me R_2 = H; **4c**: R_1 or R_3 = Me or C_6H_5 R_2 = H



5a-f

5a: R = 4'-Br, $R_1 = R_2 = R_3$=H; **5b**: R = 4'-Br, $R_1 = R_3$ = Me R_2 = H;
5c: 2'-Me-4'-Br, $R_1 = R_3$ = Me R_2 = H; **5d**: 2'-Me-4'-Br, R_1 = Me, R_2 = H, $R_3 = C_6H_5$;
5e: R = 2'-F, $R_1 = R_3$ = Me R_2 = H; **5f**: R = 4'-F, $R_1 = R_3$ = Me, R_2 = H

Scheme 1

Table 1

Analytical and physical data for compounds **5a-f**

No.	Molecular formula	Molecular mass		Base peak	M.p.	Yield	R_f
		Calc.	Exp. (MS)	m/e 100%	(^{0}C)	(%)	
5a	$C_{11}H_{10}BrN_3O$	280.13	279, 281	81	193-195	46	0.06
5b	$C_{13}H_{14}BrN_3O$	308.18	307, 309	109	175-176	36	0.62
5c	$C_{14}H_{16}BrN_3O$	322.21	321, 323	109	167-170	37	0.24
5d	$C_{19}H_{18}BrN_3O$	384.28	383, 385	171	147-149	43	0.57
5e	$C_{13}H_{14}FN_3O$	247.25	247	109	133-134	36	0.16
5f	$C_{13}H_{14}FN_3O$	247.25	247	109	162-163	38	0.08

The new synthesized compounds were characterized by elemental analyses, UV-Vis, IR, NMR and MS spectra. The purity of the new compounds was checked through TLC (R_f are given in Table 1).

Electronic spectra. The electronic spectra of the compounds recorded in ethanolic solution show the λ_{max} values exist in the characteristic ranges 228-252 and 264-288 nm of the chromophores present in the molecule. These bands are assigned to the π-π* transitions.[8]

IR spectra. The IR spectra of the compounds recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the bands characteristic of the secondary amides. The strong band due to the ν_{NH} appears within the 3157-3277 cm^{-1} range. The very strong amide band I, ν_{CO} appears within the 1668-1693 cm^{-1} range. The very strong amide band II, due to the δ_{NH} + ν_{CN} coupling is present within the 1526-1554 cm^{-1} range. Also the bands due to the stretching of the pyrazole ring **5a-f** can be found within the 1366-1487 cm^{-1} range. The broad multiplet band[8] (2759-3200 cm^{-1}) present in the IR spectrum of pyrazoles **4a-c** due to the intermolecular hydrogen bonds cannot be found in the spectrum of the new compounds **5a-f**.

^{1}H-NMR and ^{13}C-NMR spectra. The NMR spectra of amides **5** were recorded in $CDCl_3$ at room temperature. In the H-NMR spectra of pyrazoles **5** the most deshielded proton was assigned to the NH group that appears as a broad singlet in the range 8.45-8.74 ppm. Deuteration of the amidic protons occurs easily in the presence of D_2O in the NMR vial. Thus, H-NMR spectra, carried out at different time intervals, show a decrease in the signal corresponding to the NH proton. The strong deshielded for methylenic groups (δ = 4.75-4.94 ppm) could be explained that they are grafted to a nitrogen atom and a carbonyl group. The H-4 proton appears as a double doublet in the spectrum of **5a** and as a sharp singlet in the spectra of the others pyrazoles **5b-f.** The multiplicity of H-3 in pyrazole **5a** is a result of its coupling with H-3 (^3J = 1.7 Hz) and H-5 (^3J = 2.3 Hz). The high values of chemical shifts for H-3 (δ = 7.72 ppm) and H-5 (δ = 7.54 ppm) in comparison with H-4 (δ = 6.40 ppm) are due to their position in the respect with the two nitrogen atoms from the pyrazole ring.

In the H-NMR spectrum of fluoropyrazole **5f** the presence of the coupling between fluorine and hidrogen atoms from the benzene ring is observed. The coupling constants between fluorine and hydrogen in the compound **5f** were found to be $^3J_{H/F}$ = 8.9 Hz and $^4J_{H/F}$ = 4.8 Hz, respectively. A similar long range coupling H/F (^3J) was identified in the H-NMR spectrum of fluoroderivative **5e** but only in the case of H-3' because the three others protons from the benzene ring appeared as multiplets.

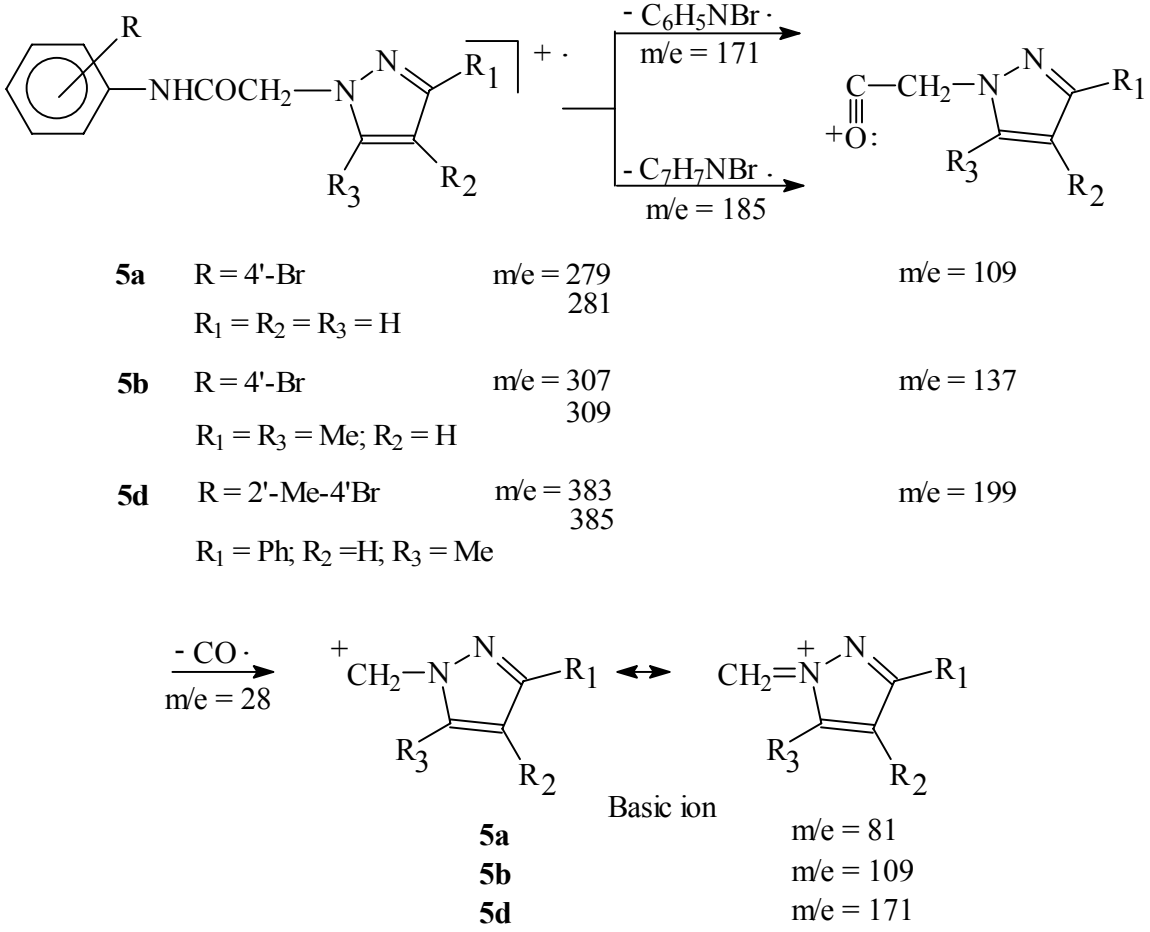
The ^{13}C-NMR spectra of pyrazoles **5a-f** show all the expected signals. The chemical shifts of compounds **5** were established by bidimensional experiments H/C, as well as by comparison with data reported for similar structures.[9-14] The carbon atoms in the α postion (C-3, C-5; δ = 131.5-152.2 ppm) in respect with the nitrogen atoms of the pyrazole ring are strongly deshielded when compared to the carbon in β position (C-4, δ = 103.9-106.8 ppm).

The chemical shifts for the carbon atoms of benzene ring in the fluoroderivatives **5e,f** were deduced on the basis of magnitude of coupling constants between fluorine and carbon atoms. Thus, in the case of compound **5e** the values of C/F constants are $^1J_{C/F}$ = 244.4 Hz, $^2J_{C/F}$ = 19.0 and 10.3 Hz, $^3J_{C/F}$ = 7.5 and 3.5 Hz, $^4J_{C/F}$ = 2.3 Hz. The signals for carbon atoms of the benzene ring in compound **5f** have the coupling constants: $^1J_{C/F}$ = 243.9 Hz (C4'), $^2J_{C/F}$ = 22.5 (C-3', C-5'), $^3J_{C/F}$ = 7.9 (C-2', C-6') and $^4J_{C/F}$ = 2.8 Hz (C-1').

The influence of halogens on the values on chemical shifts are significant in the case of geminal carbon (C-Hal). Thus, the chemical shifts for C-4' in bromopyrazoles **5a-d** are in the range 117.3-117.5. In the fluoropyrazoles **5e,f** the carbon bearing fluorine is strongly deshielded the corresponding δ values are 153.2 ppm for C-2' in compound **5e** and 160.5 ppm for C-4' in compound **5f**.

The chemical shifts of the amide carbonyl groups are very close and their values are in the range 165.2-165.7 ppm.

MS spectra. Table 1 gives the m/e values of the basic ion in the mass spectra of the new compounds. Fragmentation processes (Scheme 2) for the representative compounds can support the structure formulas assigned to the new compounds.



Scheme 2

EXPERIMENTAL

All the compounds used in the present paper: 2-chloroacetanilides, 2-iodoacetanilides, and the substituted pyrazoles were prepared according to literature.[7,15,16] All melting points were recorded with a Boetius apparatus and are uncorrected. Electronic spectra within 400-4000 nm range were obtained with VSU-2P Zeiss-Jena Spectrophotometer, using MgO as a standard. IR spectra (KBr, pellets) were measured on a BIO-RAD FTS-135 Spectrometer. NMR spectra were recorded on a Varian Gemini 300 Spectrometer operating at 300 MHz (^{1}H-NMR) and 75 MHz (^{13}C-NMR) respectively, in $CDCl_3$ or DMSO-d_6. The chemical shifts were referred to tetramethylsilane (TMS) as the internal standard GS-MS were recorded on a Varian Saturn 2000 GS/MS/MS.

General procedure for synthesis of pyrazoles 5

5 Mmol 2-iodoacetanilide derivative **3** and 5 mmol of pyrazole **4** were dissolved in 3 mL of DMF to which an equimolecular amount of sodium carbonate was then added. The reaction mixture was heated at 60 ^{0}C for 5 hours and then was treated with 10% sodium carbonate solution. The precipitate was filtered by suction and the product was recrystallized from ethanol.

***2-(Pyrazol-1-yl)-4'-bromoacetanilide* (5a)**

Anal. Calcd. for $C_{11}H_{10}BrN_3O$: C 47.17, H 3.60, Br 28.52, N 15.00. Found: C 47.38, H 3.97, Br 28.91, N 15.21.

^{1}H-NMR ($CDCl_3$, δ, ppm): 4.94 (s, 2H, CH_2); 6.40 (dd, 1H, *J* = 2.3, 1.7 Hz, H-4); 7.35 (d, 2H, *J* = 9.0 Hz, H-3', H-5'); 7.41 (d, 2H, *J* = 9.0 Hz, H-2', H-6'); 7.54 (d, 1H, *J* = 2.3 Hz, H-5); 7.72 (d, 1H, *J* = 1.7, H-3); 8.62 (bs, 1H, NH).

^{13}C-NMR ($CDCl_3$, δ, ppm): 55.3 (CH_2); 106.8 (C-4); 117.3 (C-4'); 121.4 (C-2', C-6'); 131.5 (C-5); 131.8 (C-3', C-5'); 136.0 (C-1'); 141.6 (C-3); 164.9 (CO).

***2-(3,5-Dimethyl-pyrazol-1-yl)-4'-bromoacetanilide* (5b)**

Anal. Calcd. for $C_{13}H_{14}BrN_3O$: C 50.67, H 4.58, Br 25.93, N 13.63. Found: C 50.01, H 4.88, Br 26.19, N 13.91.

^{1}H-NMR($CDCl_3$, δ, ppm): 2.27 (s, 3H, 3-Me); 2.28 (s, 3H, 5-Me); 4.75 (s, 2H, CH_2); 5.92 (s, 1H, H-4); 7.34 (d, 2H, *J* = 9.0 Hz, H-3', H-5'); 7.40 (d, 2H, *J* = 9.0 Hz, H-2', H-6'); 8.63 (bs, 1H, NH).

^{13}C-NMR ($CDCl_3$, δ, ppm): 11.0 (5-Me); 13.4 (3-Me); 52.2 (CH_2); 106.4 (C-4); 117.2 (C-4'); 121.4 (C-2', C-6'); 131.9 (C-3', C-5'); 136.2 (C-1'); 141.0 (C-5); 149.9 (C-3); 165.5 (CO).

***2-(3,5-Dimethyl-pyrazol-1-yl)-2'-methyl-4'-bromoacetanilide* (5c)**

Anal. Calcd. for $C_{14}H_{16}BrN_3O$: C 52.19, H 5.01, Br 24.80, N 13.04. Found: C 52.40, H 5.27, Br 25.19, N 13.29.

^{1}H-NMR ($CDCl_3$, δ, ppm): 2.06 (s, 3H, 2'-Me); 2.06 (s, 3H, 3-Me); 2.27 (s, 3H, 5-Me); 4.77 (s, 2H, CH_2); 5.93 (s, 1H, H-4); 7.29 (d, 1H, *J* = 2.2 Hz, H-3'); 7.32 (dd, 1H, *J* = 8.5, 2.2 Hz, H-5'); 7.95 (d, 1H, *J* = 8.5, H-6'); 8.50 (bs, 1H, NH).

^{13}C-NMR ($CDCl_3$, δ, ppm): 10.9 (5-Me); 13.3 (3-Me); 17.1 (2'-Me); 52.1 (CH_2); 106.4 (C-4); 117.3 (C-4'); 122.5 (C-6'); 129.5 (C-5'); 129.7 (C-2'); 132.9 (C-3'); 134.6 (C-1'); 140.5 (C-5); 149.9 (C-3); 165.4 (CO).

***2-[3-Phenyl-5-methyl-pyrazol-1-yl)]-2'-methyl-4'-bromoacetanilide* (5d)**

Anal. Calcd. for $C_{19}H_{18}BrN_3O$: C 59.38, H 4.72, N, 10.93. Found C 59.77, H 4.86, N, 11.12.

^{1}H-NMR ($CDCl_3$, δ, ppm): 1.89 (s, 3H, 2'-Me); 2.30 (s, 3H, 5-Me); 4.82 (s, 2H, CH_2); 6.40 (s, 1H, H-4); 7.14 (d, 1H, *J* = 2.4 Hz, H-3'); 7.22 (dd, 1H, *J* = 8.7, 2.4 Hz, H-5'); 7.28 (m, 1H, H-4"); 7.35 (m, 2H, H-3", H-5"); 7.73 (m, 2H, H-2", H-6"); 7.95 (d, 1H, *J* = 8.7, H-6');8.45 (bs, 1H, NH);

^{13}C-NMR ($CDCl_3$, δ, ppm): 11.3 (Me-5); 17.3 (Me-2'); 52.7 (CH_2); 103.9 (C-4); 117.5 (C-4'); 122.7 (C-6'); 125.4 (C-2", C-6"); 128.3 (C-4"); 128.7 (C-3", C-5"); 129.7 (C-2'); 129,8 (C-5'); 132.5 (C-1"); 133.0 (C-3'); 134.6 (C-1'); 141.7 (C-5); 152.2 (C-3); 165.2 (CO).

***2-(3,5-Dimethyl-pyrazol-1-yl)-2'-fluoroacetanilide* (5e)**

Anal. Calcd. for $C_{13}H_{14}FN_3O$: N 16.99. Found: N 17.22.

^{1}H-NMR ($CDCl_3$, δ, ppm): 2.27 (s, 3H, 3-Me); 2.29 (s, 3H, 5-Me); 4.79 (s, 2H, CH_2); 5.93 (s, 1H, H-4); 7.02-7.15 (m, 3H, H-3'); 7.00-7.12 (m, 3H, H-4', H-5', H-6'); 8.74 (bs, 1H, NH);

^{13}C-NMR ($CDCl_3$, δ, ppm): 10.8 (Me-5); 13.2 (Me-3); 52.3 (CH_2); 106.4 (C-4); 114.7 (d, *J* = 19.0 Hz, C-3'); 121.6 (d, *J* = 2.3 Hz, C-5'); 124.3 (d, *J* = 3.5 Hz, C-6'); 124.6 (d, *J* = 7.6 Hz, C-4'); 126.7 (d, C *J* = 10.3 Hz, C-1'); 140.7 (C-5); 150.1 (C-3); 153.5 (d, *J* = 2.3 Hz, C-2'); 165.7 (CO).

***2-(3,5-Dimethyl-pyrazol-1-yl)-4'-fluoroacetanilide* (5f)**

Anal. Calcd. for $C_{13}H_{14}FN_3O$: N 16.99. Found: N 17.28.

^{1}H-NMR ($CDCl_3$, δ, ppm): 2.27 (s, 3H, 3-Me); 2.28 (s, 3H, 5-Me); 4.76 (s, 2H, CH_2); 5.91 (s, 1H, H-4); 6.96 (t, 2H, *J* = 8.9 Hz, H-2', H-6') 7.39 (dd, 2H, *J* = 8.9, 4.8 Hz, H-3', H-5'); 8.72 (bs, 1H, NH).

^{13}C-NMR ($CDCl_3$, δ, ppm): 10.9 (5-Me); 13.2 (3-Me); 52.2 (CH_2); 106.3 (C-4); 115.4 (d, *J* = 22.5 Hz, C-3', C-5'); 121.7 (d, *J* = 7.9 Hz, C-2', C-6'); 133.2 (d, *J* = 2.8 Hz, C-1'); 140.9 (C-5); 149.8 (C-3); 160.5 (d, *J* = 7.9 Hz, C-4'); 165.5 (CO).

CONCLUSIONS

Six new pyrazolyl-acetanilides **5** with fluorine and bromine atoms grafted on the benzene ring were obtained by *N*-alkylation of pyrazoles **4a-c** with the 2-iodoacetanilides **3a-d**. The structure of the new compounds was assigned by elemental analysis, MS, IR and NMR spectroscopy. The anesthetic and anti-arrhythmic activity of the new pyrazolys-acetanilides **5** is currently under investigation and will be published elsewhere.

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