New Pyrazole Derivatives as Lidocaine Analogue

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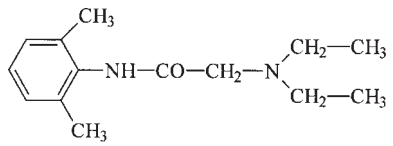
*The alkylation of pyrazoles **4a-d** with 2',4'-dimethyl-2-iodoacetanilide **3** gave 2-(pyrazol-1-yl)-2',4'-acetanilides **5a-d**. The reaction of 3(5)-phenyl-5(3)-methylpyrazole with **3** gave a single regioisomer **5e**. The structure of new compounds **5** was assigned by elemental analysis and NMR spectroscopy. The anesthetic and antiarrhythmic activity of compounds **5b** and **6a**,**b** were tested and compared to the lidocaine hydrochloride and quinidine sulfate, respectively.*

Keywords: anesthetic activity, pyrazoles derivatives, alkylation, NMR spectroscopy

Local anesthetic agents can be defined as drugs which are used clinically to produce reversible loss of sensation in a circumscribed area of the body. There are two classes of local anaesthetic drugs defined by the nature of the carbonyl-containing linkage group: esters and amides. There are important practical differences between these two groups of local anaesthetic agents. Esters are relatively unstable in solution and are rapidly hydrolysed in the body. In contrast, amide local anesthetics are relatively stable in solution, are slowly metabolised by hepatic amidaes and hypersensitivity reactions are extremely rare. In current clinical practice esters have largely been superseded by the amides.

In 1946 Löfgren [1] discovered that the substituted acetanilides possessing local anesthetic activity should contain a lipophylic aromatic structure, an intermediate chain and a hydrophylic one having a tertiary amino group, such as lidocaine, a drug currently used. New compounds having lidocaine as structure were investigated for their local anesthetic action and some of them also presented anti-arrhythmic properties [1-5]. Recently, it was reported the anesthetic activity of substituted acetanilides in which the diethylamino group from lidocaine has been replaced by a pyrazole ring [6,7].

Herein we report the synthesis and pharmacological activity of new 2-(pyrazol-1-yl)-2',4'-dimethylacetanilides **5**, analogues to lidocaine where the amino group was replaced by less basic pyrazole derivatives.



Lidocaine

Experimental part

The compounds used in the present paper 2',4'-dimethylphenyl-2-chloroacetanilide, 2',4'-dimethyl-2-iodoacetanilide and the substituted pyrazoles were prepared according to literature[8-11]. TLC was made on silicagel Merck plates; for the development, petroleum ether: ethyl ether: methylene chloride: ethyl acetate = 7.5:1:2:1 were used; the visualization was made with an UV lamp. Elemental analysis were carried out by microcombustion. NMR spectra were recorded on a Varian Gemini 300 BB spectrometer operating at 300 MHz for proton and 75 MHz for carbon. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. The chemical shifts were expressed in δ ppm.

General procedure for synthesis of pyrazole derivative 5

2 g (7 mmol) 2',4'-dimethyl-2-iodoacetanilide **3** and 7 mmols pyrazole derivative **4** were dissolved in 4 mL DMSO and an equimolecualar amount of sodium carbonate added. The reaction mixture was heated at 60ºC for 5 h and then was treated with 10% sodium carbonate solution. The precipitate was filtered by suction and the amides 5 were recrystallized from ethanol.

2-(Pyrazol-1-yl)-2',4'-dimethylacetanilide (**5a**). The product was recrystallized from ethanol and white crystals with mp 178-9 °C were obtained; yield 78 %, *Anal.* Calcd. for $C_{13}H_{15}N_3O$: C 68.10, H 6.59, N 18.33; Found: C 68.36, H 6.74, N 18.51. R_f = 0.16.

2-(3,5-Dimethylpyrazol-1-yl)-2',4'-dimethylacetanilide (5b). The product was recrystallized from ethanol and white crystals with mp 158-9 °C were obtained; yield 38 %, *Anal.* Calcd. for $C_{15}H_{19}N_3O$: C 70.01, H 7.44, N 16.33; Found: C 70.39, H 7.64, N 16.66. R_f = 0.17.

2-(4-Iodo-3,5-dimethylpyrazol-1-yl)-2',4'-dimethylacetanilide (**5c**) The product was recrystallized from ethanol and white crystals with mp 186-7 °C were obtained; yield 45 %, *Anal.* Calcd. for $C_{15}H_{18}IN_3O$: N 10.96; Found: N 11.21. R_f = 0.27.

2-(3,5-Dimethyl-4-nitro-pyrazol-1-yl)-2',4'-dimethylacetanilide (5d) The product was recrystallized from ethanol and white crystals with mp 215-7 °C were obtained; yield 63 %, *Anal.* Calcd. for $C_{15}H_{18}N_4O_3$: C 59.59, H 6.00, N 18.53; Found: C 60.33, H 6.25, N 18.63. R_f = 0.11.

2-(3-Phenyl-5-methylpyrazol-1-yl)-2',4'-dimethylacetanilide (**5e**) The product was recrystallized from ethanol and white crystals with mp 147-8°C were obtained; yield 78 %, *Anal.* Calcd. for $C_{20}H_{21}N_3O$: C 75.21, H 6.63, N 13.16; Found: C 75.44, H 7.03, N 13.33. R_f = 0.31.

Results and discussion

Initially, the intention was to alkylate pyrazoles **4** with 2',4'-dimethyl-2-chloroacetanilide **2**. The latter were prepared by acylation of 2,4-dimethylaniline with

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Table 1

SELECTED H-NMR DATA FOR COMPOUNDS **5a-e** ($CDCl_3$, δ ppm, J Hz)

Compound	H-3	H-4	H-5	3-Me	5-Me	CH_2	NH
5a	7.70; d 2.0	6.39; dd 2.4; 2.0	6.39; d 2.4	-	-	4.97; s	8.12; bs
5b	-	5.92; s	-	2.27; s	2.27; s	4.78; s	8.14; bs
5c	-	-	-	2.27; s	2.28; s	4.85; s	8.04; bs
5d[a]	-	-	-	2.24; s	2.40; s	5.10; s	9.66; bs
5e	-	5.92; s	-	3-Ph	2.37; s	4.90; s	8.23; bs

[a] DMSO-d_6; s = singlet; d = doublet; bs = broad singlet;

Table 2

SELECTED C-NMR DATA FOR COMPOUNDS **5a-e** ($CDCl_3$, δ ppm)

Compound	C-3	C-4	C-5	3-Me	5-Me	CO	CH_2
5a	141.6	106.9	131.3	-	-	165.1	55.5
5b	150.0	106.5	140.9	13.5	11.1	165.6	52.5
5c	151.8	64.3	142.4	14.0	12.0	164.7	53.5
5d[a]	144.9	131.5	142.4	13.8	11.5	164.2	52.2
5e	152.5	103.9	141.6	-	11.2	165.2	52.9

[a] DMSO-d_6

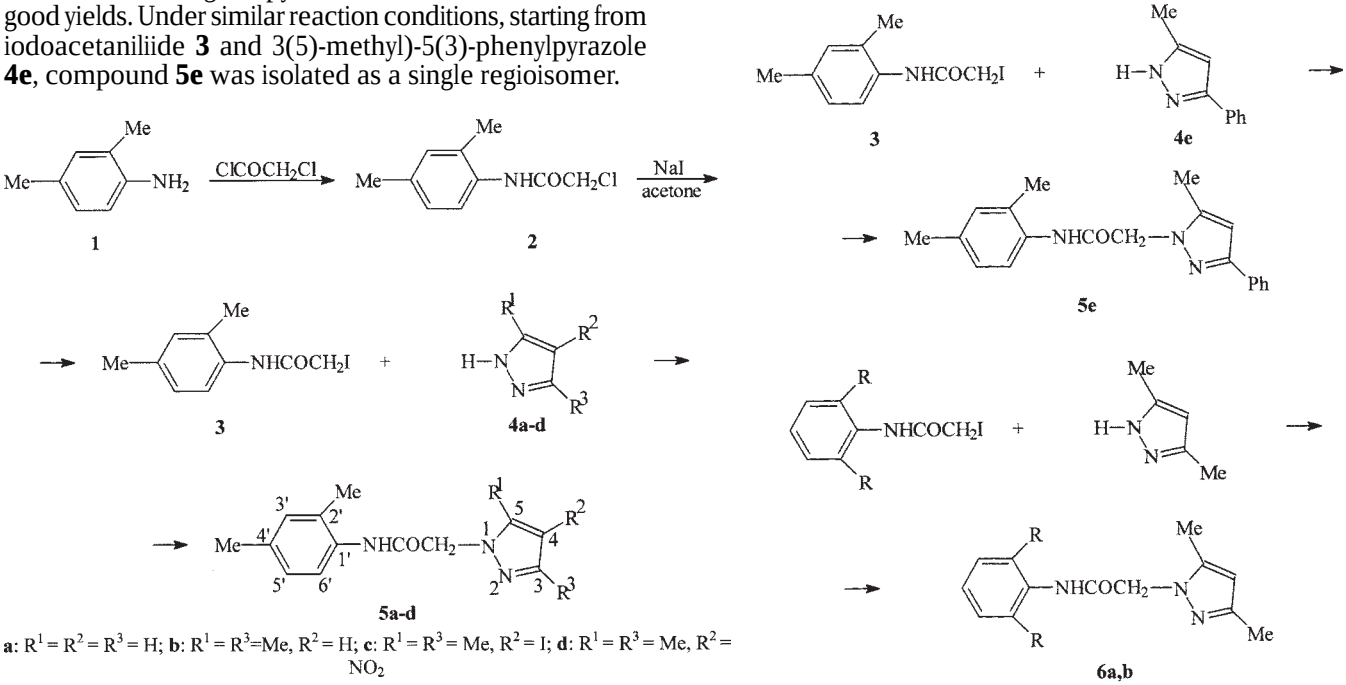
chloroacetyl chloride in the presence of anhydrous sodium acetate added to neutralize the resulting hydrochloric acid (scheme 1).

The *N*-alkylation of pyrazoles **4** with 2',4'-dimethyl-2-chloroacetaniliide gave no results due to the low reactivity of **2**, as well as the low reactivity of pyrazoles. In order to obtain the formation of *N*-substituted pyrazoles **5**, in the alkylation reaction of **4**, chloroacetanilide **2** has been replaced by the more reactive 2',4'-dimethyl-2-iodoacetanilide **3**. The transformation of the *N*-aryl-2-chloroacetanilide **2** into iodo derivative **3** was easily performed with sodium iodide in acetone, under reflux.

The *N*-alkylation of pyrazoles **4a-d** with iodoacetanilide **3**, in DMSO and in the presence of sodium carbonate, in acetone, at 60°C gave pyrazoles **5a-d** with moderate to good yields. Under similar reaction conditions, starting from iodoacetaniliide **3** and 3(5)-methyl)-5(3)-phenylpyrazole **4e**, compound **5e** was isolated as a single regioisomer.

The structure of the new compounds was assigned by elemental analysis and NMR spectroscopy (table 1 and table 2). The NMR spectra were recorded in $CDCl_3$ for compounds **5a-c,e** and in DMSO-d_6 for compound **5d**. In the H-NMR spectra the most deshielded proton appears as a broad singlet and was assigned to the NH groups. When the spectra were recorded in DMSO-D_6, the NH group was deshielded with 1.4-1.6 ppm more in respect with those recorded in $CDCl_3$ due to the formation of a hydrogen bond with the dimethyl sulfoxide.

The positions of the methyl and phenyl groups in compound **5e** 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



a: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = R^3 = Me$, $R^2 = H$; **c**: $R^1 = R^3 = Me$, $R^2 = I$; **d**: $R^1 = R^3 = Me$, $R^2 = NO_2$

6a: R = Et; **6b**: R = Me

Scheme 1

Table 3
THE ANTI-ARRHYTHMIC ACTION OF COMPOUNDS **5a, 6a, b** AND STANDARDS

Compound	Doze (mg/kg body weight)	Time of fibrillation (s)	Activity *vs.* lidocaine hydrochloride	Activity *vs.* quinidine sulfate
Control mice	-	5.20±0.46	8.60	-
5b	65	13.0±1.1	58.30%	18.55%
6a	48	15.5±1.6	76.92%	24.47%
6b	30	11.5±0.9	49.38%	15.71%
Lidocaine hydrochloride	50	18.6±1.6	100%	31.82%
Quinidine sulfate	75	47.4±3.7	314.29%	100%

[12]. The irradiation of the methylenic group resulted in the enhancement of the signal of the 5-methyl group.

The ^{13}C-NMR spectra of pyrazoles **5a-e** show all the expected signals. In table 2 the influence of the substituents (Me, Ph, I, NO_2) on the values of the chemical shifts on the carbon atoms (C-3, C-4, C-5) from the pyrazole ring is shown. Thus, in the case of 4-iodopyrrole derivative **5c** a strong negative increment ($\Delta\delta$ = 42.2 ppm) was observed at C-4 due to the effect of iodine, whereas the presence of the nitro group in the same position resulted in a deshielding of 25.0 ppm at C-4.

In comparison with unsubstituted pyrrole **5a**, the introduction of two methyl groups at the 3 and 5 positions resulted in a strong deshielding of the carbon atoms on which they are grafted (aprox. 3-11 ppm). The examination of the ^{13}C-NMR spectra of the compounds **5a,b** indicated that the chemical shifts of C-4 in both compounds are very close.

Pharmacological activity

Compounds **5b** and **6a,b** were tested for acute toxicity, anaesthetic and anti-arrhythmic activity on mice using 1/10 of the value of LD_{50} as a working dose. The compounds 6a,b were obtained by a similar procedure described for pyrazole derivatives 5.

The acute toxicities LD_{50} were found to be as follows: 650 mg/kg body weight per os for compound **5b,** 535 mg/kg body weight per os for compound **6a,** 485 mg/kg body weight per os for compound **6b,** and 292 mg/kg body weight per os for the lidocaine hydrochloride. The compound **5b** has a lower toxicity than the amides **6a,b** and all posses a lower toxicity with respect to lidocaine (292 mg/kg body weight per os) [13].

The infiltration local anesthetic action was determined by Bianchi's method [14, 15] using lidocaine hydrochloride as reference compound. When the compound solutions were injected in the mouse tail and the mean response time was in the range of 3.25-4.50 s and the effect *versus* lidocaine was between 42-58%. The most active compound was found to be **5b**, with 58% of the activity of the lidocaine action and the mean response time of 4.50±0.33 s.

The anti-arrhythmic action was determined by Hackenberg's technique [16]. The time of fibriliation appearence for compound **5b** and **6a,b** is shown in table 3.

Conclusions

Treatment of pyrazole and its derivatives **4** with 2',4'-dimethyl-2-iodoacetanilide **3** in DMSO in the presence of sodium carbonate gave substituted 2-(pyrazol-1-yl)-acetanilides **5a-e**.

The compounds **5b**, and **6a**,**b** were tested for acute toxicity, anaesthetic and anti-arrhythmic action. In comparison with lidocaine, all the compounds present a lower toxicity and a lower anesthetic activity and antiarrhythmic action.

Bibliography

1.LÖFGREN, L. Arkiv. Kemi. Mineral. Geol., 1949, A_{22}, p. 30; Chem. Abstr. 43, 1949, 1021f.; LÖFGREN, L., LUNDQVIST, B., Svensk Kem. Tid., 1946, 58, p. 206; Chem. Abstr. 43, 1949, 1022d.; LÖFGREN, L. WIDMARK, G., Svensk Kem. Tid., 1946, 58, p. 323; Chem. Abstr. 43, 1949, 1023d.; LÖFGREN, L., LUNDQVIST, B., Svensk Kem. Tid., 1946, 130, p. 729; Chem. Abstr. 45, 1951, P 8561e

2.GREWAL, M. S., GURDEV, S., Indian J. Physiol. Pharmacol. 1963, 7, p.245; Chem. Abstr., 61, 1964, 13759c

3.TENTHOREY, P. A., ADAMS, H. J., KRONBERG, J. H., TAKMAN, B. H., J. Med. Chem, **24**,1981, p. 1059

4.IOVU, M., MURGU, L., BURA, C., GHERGHI^{a}OR, M., Rev. Chim. (Bucure^{o}ti), **33**, 1982,, p. 601

5. IOVU, M., CRISTEA, A., IQLBAL, M., CIMPOAIE, D., HUBERT, R., Rev. Chim. (Bucure^{o}ti), **37**, 1986, nr. 10, p. 845

6.IOVU, M., ZĂLARU, C., DUMITRA^{a}CU, F., DRĂGHICI, C., CRISTEA, E. Il Farmaco, 55, 2000, p. 362

7.IOVU, M., ZĂLARU, C., DUMITRA^{a}CU, F., DRĂGHICI, C., CRISTEA, E. Il Farmaco, 58,2003, 301

8.GAIND, J. K. N., MIGLIANI, B. D., GUPTA, K. C., Indian J. Pharmacol. 1962, 24, p.254, Chem. Abstr. 58, 1963, 11321f

9.BÜCHI, J., LAUENER, G., RAGAZ, L., BÖNIGER, H., LIEBERHERR, R., Helv. Chim. Acta, 34, 1951, p. 278

10.CHUPP, J. P., OLIN, J. F., J. Org. Chem., 32,1967, p. 2297.

11.GEWALD, K., REHWALD, M., GRUNER, M. Liebigs Ann. Chem., 1993, p. 457

12.BEGTRUP, M., BOYER, G., CABILDO, P., CATIVIELA, C., CLARAMUNT, R. M., ELGUERO, J., GARCIA, J. I., TOIRON, C., VEDSØ, P., J. Magn. Reson. Chem., 31, 1993, p. 107

13.SMITH, E. R., DUCE, B. R., J. Pharmacol. Exp. Ther. 1971, 179, p.580

14.BIANCHI, C., Br. J. Pharmacol. 1956, 11, p. 104; Chem. Abstr. 50, 1956, 13374g.

15.CALIENDO, G., GRECO, G., GRIECO, P., MATTACE, R. G., MELI, L., NOVELLINO, E., PERISSUTTI, E., SANTAGADA, V., Eur. J. Med. Chem. 31, 1996, p. 91

16.HACKENBERGER, F., Pharmazie, 34, 1979, p. 491

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