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New substituted 2-(pyrazol-1-yl) *o*-, *m*-, *p*-methylacetanilides with potential local anaesthetic and antiarrhythmic action. Part I

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Abstract

Fifteen substituted 2-(pyrazol-1-yl)acetanilides were synthesized by N-alkylation of pyrazole and some of its derivatives with several 2-iodoacetanilides. The new compounds exhibited local anaesthetic and antiarrhythmic actions. The new compounds have been characterized by elemental chemical analysis, UV–Vis, IR, ^{1}H, ^{13}C NMR spectra and pharmacology research.

Keywords: Pyrazolyl-acetanilides; Local anesthetics; Antiarrhythmics

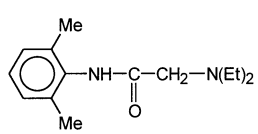
1. Introduction

The first amides used as local anesthetics were discovered during the investigations made in the acetanilide series for getting antipyretics. In 1946, Löfgren [1] investigated 30 new substituted acetanilides and found out that a local anesthetic should contain both a lipophylic aromatic structure and a hydrophylic one having a tertiary amino-group, such as lidocaine, the drug used even nowadays (Scheme 1).

For better activity, the two parts should contain not only ester, ether, amino and carbonyl groups, but mainly amides.

In the aminoacetanilides synthesis, Löfgren used the acylation reaction of the aromatic amines with chloroacetyl chloride in the presence of sodium acetate; the acetanilides obtained were treated with cyclic or acyclic secondary amines [1–3]. Later on, primary amines were also used for getting aminoacetanilides [4]. Some other compounds having lidocaine-like molecular structure were also tested for the local anesthetic action [5,6]. 2-Aminoacetanilides were found to have antiarrhythmic properties besides their anesthetic ones [7–9]. Several researchers insisted on changing the amino group with heterocyclic amines [10] or on replacing them with ether groups [8–11].

To obtain a good local anesthetic is still a very topical issue. The present paper therefore reports the synthesis and characterization of some new compounds analogous to lidocaine, where the amino-group is replaced by less basic pyrazole derivatives and the benzene ring is substituted by a methyl radical in the *ortho*, *meta* and *para* positions.



Lidocaine

Scheme 1.

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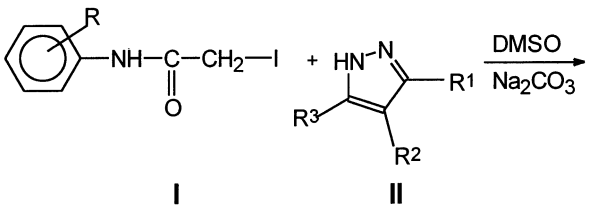

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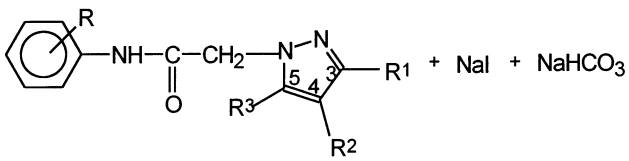


III

where: R = 2-Me, 3-Me, 4-Me

R^1	R^2	R^3
H	H	H
Me	H	Me
Me	I	Me
Me	NO_2	Me
Ph	H	Me

Scheme 2.

2. Chemistry

Both lidocaine and its analogous compounds are known to be obtained by reaction of some chloroacetanilides with amines [1,12]. We have chosen another synthesis route since the 2-chloroacetanilides we got obtained by the Löfgren [1] and Büchi [13] methods did not react with pyrazole or its derivatives. Therefore, all 2-chloroacetanilides initially prepared by us have been transformed into the more reactive iodoacetanilides, by reaction with sodium iodide in anhydrous acetone [14].

Treatment of pyrazole and its derivatives **II** with substituted 2-iodoacetanilides **I** in DMSO and in the presence of sodium carbonate gave 15 new compounds, substituted 2-(pyrazol-1-yl)acetanilides **III** according to the reaction (Scheme 2, Table 1):

The new synthesized compounds were characterized by elemental analyses (C, H, N), determinations of molecular weights by mass spectrometry, purity determinations, UV–Vis, IR, ^{1}H and ^{13}C NMR spectra.

3. Experimental

All the compounds used in the present paper: 2-chloroacetanilides, 2-iodoacetanilides and the substituted pyrazoles were prepared according to literature [12–17].

Carbon, hydrogen and nitrogen analyses were carried out by microcombustion.

Thin layer chromatography (TLC) was carried out on silica gel E. Merck plates, in a one-dimensional technique; for the development solution of 7.5:1:2:1 petroleum ether–ethyl ether–methylene chloride–ethyl acetate was used. The visualization was made with a UV lamp, $\lambda = 254$ nm.

Molecular weight was obtained with a GC–MS 8000 MD 800 Fission's spectrometer at 70 eV with source temperature 200°C, carrier gas He at 2 ml/min.

The melting points were determined with a Boetius apparatus and are not corrected.

Electronic spectra within 200–800 nm range were obtained with Unicam UV–Vis spectrometer in ethanol solution. The concentration was 10^{-4} M.

Table 1
Analytical data and some properties

No.	Comp.				Molecular mass	C (%)		H (%)		N (%)		I (%)	
	R	R^1	R^2	R^3		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
1	2′-Me	H	H	H	215.26	66.96	67.10	6.09	6.50	19.52	19.88	-	
2	2′-Me	Me	H	Me	243.31	69.11	69.52	7.04	7.33	17.27	17.54		
3	2′-Me	Me	I	Me	369.21	45.54	45.84	4.37	4.68	11.38	11.40	34.37	34.68
4	2′-Me	Me	NO_2	Me	288.31	58.33	58.71	5.59	5.89	19.43	19.61		
5	2′-Me	Ph	H	Me	305.38	74.73	75.09	6.27	6.52	13.76	13.90		
6	3′-Me	H	H	H	215.26	66.96	67.30	6.09	6.42	19.52	19.80		
7	3′-Me	Me	H	Me	243.31	69.11	69.43	7.04	7.28	17.27	17.60		
8	3′-Me	Me	I	Me	369.21	45.54	45.91	4.37	4.58	11.38	11.41	34.37	34.78
9	3′-Me	Me	NO_2	Me	288.31	58.33	58.81	5.59	5.79	19.43	19.63		
10	3′-Me	Ph	H	Me	305.38	74.73	75.08	6.27	6.59	13.76	14.09		
11	4′-Me	H	H	H	215.26	66.96	67.25	6.09	6.41	19.52	19.72		
12	4′-Me	Me	H	Me	243.31	69.11	69.40	7.04	7.29	17.27	17.58		
13	4′-Me	Me	I	Me	369.21	45.54	45.83	4.37	4.67	11.38	11.39	34.37	34.79
14	4′-Me	Me	NO_2	Me	288.31	58.33	58.67	5.59	5.84	19.43	19.71		
15	4′-Me	Ph	H	Me	305.38	74.73	75.04	6.27	6.58	13.76	14.08		

Table 2
Some properties of the prepared compounds **III**

No.	Comp.				Formula [a]	Molecular mass		M.p. (°C)	Yield (%)	R_F
	R	R^1	R^2	R^3		Calc.	Exp. (SM)			
1	2′-Me	H	H	H	$C_{12}H_{13}N_3O$	215.26	215	144–146	54.5	0.11
2	2′-Me	Me	H	Me	$C_{14}H_{17}N_3O$	243.31	243	151–152	36.2	0.17
3	2′-Me	Me	I	Me	$C_{14}H_{16}N_3OI$	369.21	369	193–194	53	0.27
4	2′-Me	Me	NO_2	Me	$C_{14}H_{16}N_4O_3$	288.31	288	217–218	46.35	0.19
5	2′-Me	Ph	H	Me	$C_{19}H_{19}N_3O$	305.38	305	135–137	56.8	0.31
6	3′-Me	H	H	H	$C_{12}H_{13}N_3O$	215.26	215	80–82	46.5	0.11
7	3′-Me	Me	H	Me	$C_{14}H_{17}N_3O$	243.31	243	136–138	79.5	0.13
8	3′-Me	Me	I	Me	$C_{14}H_{16}N_3OI$	369.21	369	155–156	54.5	0.19
9	3′-Me	Me	NO_2	Me	$C_{14}H_{16}N_4O_3$	288.31	288	189–191	38.5	0.13
10	3′-Me	Ph	H	Me	$C_{19}H_{19}N_3O$	305.38	305	145–147	23.4	0.24
11	4′-Me	H	H	H	$C_{12}H_{13}N_3O$	215.26	215	161–163	40.1	0.13
12	4′-Me	Me	H	Me	$C_{14}H_{17}N_3O$	243.31	243	145–147	52.5	0.20
13	4′-Me	Me	I	Me	$C_{14}H_{16}N_3OI$	369.21	369	212–214	65.6	0.23
14	4′-Me	Me	NO_2	Me	$C_{14}H_{16}N_4O_3$	288.31	288	246–248	43.9	0.14
15	4′-Me	Ph	H	Me	$C_{19}H_{19}N_3O$	305.38	305	180–182	20.2	0.33

[a] Analytical results for C, H, I, N were within $\pm 0.4\%$ of calculated values.

IR spectra were recorded in the 4000–400 cm^{-1} range using a BIO-RAD FTS-135 spectrometer and KBr pellets.

NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR), respectively, in $CDCl_3$ or DMSO-d_6 in 5 mm NOREL-57 PP grade sample tubes. The chemical shifts were referred to TMS as internal standard.

The 15 new compounds were synthesized according to the following example. Several changes of the reaction conditions were made as a function of the substituents nature in the heterocycle.

3.1. 2-(Pyrazol-1-yl) 2′-methylacetanilide

A total of 2 g (7.3 mmols) 2′-methyl-2-iodoacetanilide and 0.5 g (7.3 mmols) pyrazole were dissolved in 4 ml of DMSO to which an equimolecular amount of sodium carbonate was then added. The mixture was heated at 60°C for 5 h. The resulting solution was treated with 10% Na_2CO_3 solution. The solid raw product was recrystallized from ethanol.

4. Pharmacology

4.1. Acute toxicity (LD_{50})

White mice weighting 20 ± 2 g each were used in batches of six; the new compounds were administered in doses ranging between 250 and 750 mg/kg of body weight, per os. The graphic method [18] was used.

*I*nfiltration local anesthetic action was determined by Bianchi's method [19]. The mice were injected subcutaneously 1 cm from the tails bases with 1% lidocaine hydrochloride and 1% suspension of the compounds to be tested at a dose corresponding to 1/10 of LD_{50}. The time of enduring pain without the reflex movement of the tail was registered. The mean enduring time versus the effect of lidocaine considered to be equal to 100 was expressed.

To test the surface local anesthetic action the corneal reflex of rabbits by mechanical stimulation before and after the application of the new compounds to be tested was used comparatively with lidocaine as a reference substance. The number of touches without of the rabbit blinking their eyes, was registered [18].

4.2. Antiarrhythmic action

A total of 13 batches, each of five white male mice weighting 20 ± 2 g were used as follows: to 10 batches were administered the studied compounds per os in an equal dose of 1/10 LD_{50}, and to two batches were given 50 mg/kg of body weight lidocaine hydrochloride and 75 mg/kg of body weight quinidine sulfate. The remaining batch was used as the control. Heart fibrillation, artificially created by chloroform atmosphere, appeared after 30 min. The latent time of the appearance of heart fibrillation was measured using Hackenberger's technique [20] for the new compounds were compared to lidocaine and quinidine sulfate.

5. Results and discussion

5.1. Chemical and spectral results

Some of the properties are given in Table 2. The purity of the new compounds and of the intermediary ones was checked through thin layer chromatography using silica gel G chromoplates (R_f given in Table 2).

The compounds electronic spectra recorded in ethanolic solution show the λ_{max} values exist in the characteristic ranges (222–246 nm and 254–280 nm) of the chromophores present in the molecule (benzene, pyrazole ring, carbonyl group), but with different bathochromic shifts for each compound. These bands are assigned to the $\pi-\pi^*$ transitions.

IR spectra recorded in the 4000–400 cm^{-1} range in KBr pellets reflect the molecular structure of the new compounds. The bands characteristic of the secondary amides [21] and also the bands characteristic of pyrazole [22] and benzene ring [21] can be visualized. The amide band I (very strong), due to the stretching frequency, ν_{CO} appears within the 1660–1690 cm^{-1} range as a function of each compound; the amide band II, due to the δ_{NH} and ν_{CN} coupling is present within the 1500–1570 cm^{-1} range and the bands due to the stretching of the pyrazole ring can be found within the 1500–1354 cm^{-1} range. The different positions of these bands could be explained by the influence of the substituents in the aromatic ring. The broad multiplet band (2759–3200 cm^{-1}) present in the IR spectrum of pyrazole and of substituted pyrazoles due to intermolecular hydrogen bonds characteristic of pyrazole [22] cannot be found in the IR spectrum of the new compounds.

^1H and ^{13}C NMR spectra recorded at 300 and at 75 MHz, respectively, in the $CDCl_3$ and DMSO-d_6 solution support the structure formulas assigned to these compounds, deduced from the equation of the synthesis reaction and from the data of the UV–Vis and IR spectra. Tables 3 and 4 give the chemical shifts, δ (ppm) and the coupling constants of representative compounds. Chemical shifts occur within the range characteristic of different kinds of protons in the molecules.

The positions of the protons and of the substituents in the ring can be found out using HETCOR and COSY. Our results of the increments of the chemical shifts in the ^{13}C NMR spectra for the compounds **5**, **10**, **15** are in agreement with the literature data [23] The tautomeric 3(5)-phenyl-methylpyrazole by reaction with 2-iodoacetanilides could lead to a mixture of two isomers but in fact only the formation of one isomer (**5**, **10**, **15**) was observed by ^1H NMR spectroscopy (Scheme 3). This can be plausibly explained by steric

Table 3
^1H resonance data for representative compounds, δ (ppm), J (Hz) [a]

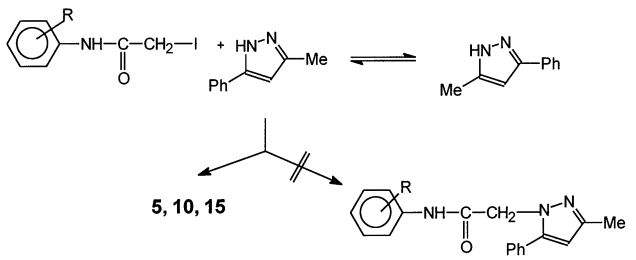
Comp.	R^1	R^2	R^3	R^1	R^3	CH_2	NH
	H-3	H-4	H-5	CH_3 (3)	CH_3 (5)		
1	7.72 d, 2.1	6.40 dd, 2.1, 2.3	7.55 d, 2.3			4.98 s	8.25 bs
2		5.92 s		2.16 s	2.27 s	4.78 s	8.28 bs
3				2.28 s	2.34 s	4.86 s	8.18 bs
4				241 s	2.57 s	5.13 s	9.72 bs
5		6.46 s		7.30–7.81 [b]	2.36 s	4.90 s	8.38 bs
10		6.46 s		7.32–7.81 [b]	2.34 s	4.87 s	8.50 bs
15		6.45 s		7.40–7.82 [b]	2.36 s	4.86 s	8.42 bs

[a] s = singlet; bs = broad singlet; d = doublet; dd = double doublet.
[b] Ph protons. Solvent: $CDCl_3$, DMSO-d_6.

Table 4
^{13}C resonance data for representative compounds, δ (ppm)

Comp.	R^1	R^2	R^3	R^1	R^3	CO	CH_2
	C-3	C-4	C-5	CH_3 (3)	CH_3 (5)		
1	141.72	107.09	131.50			165.17	55.66
2	149.98	106.46	140.91	13.43	10.99	165.55	52.51
3	151.87	64.39	142.52	14.06	12.03	164.79	53.61
4	144.91	131.60	142.38	13.43	11.47	164.33	52.29
5	152.39	103.77	141.54	128.61–132.55 [a]	11.14	165.13	52.75
10	152.33	103.90	141.65	128.19–132.88 [a]	11.28	165.25	52.85
15	152.31	103.83	141.57	125.35–132.80 [a]	11.23	165.06	52.74

[a] Ph carbon. Solvent: $CDCl_3$, DMSO-d_6.



Scheme 3.

Table 5
Acute toxicity (LD_{50}) in mice

Comp.	LD_{50}	
	Body weight per os (mg/kg)	Body weight (mmol/kg)
1	593 (425–604)	2.76
2	489 (415–530)	2.01
3	565 (420–600)	1.53
4	470 (414–518)	1.63
6	589 (466–615)	2.74
7	538 (485–620)	2.21
8	508 (461–584)	1.38
11	602 (543–631)	2.80
12	519 (484–563)	2.14
13	543 (470–600)	1.47
Lidocaine hydrochloride	292 [a]	1.01

[a] See Ref. [24].

Table 6
Infiltration local anesthetic action

Comp.	Mean response time (s) 4 tests ($\bar{x} \pm$ s.e.) [a]	Effect vs. lidocaine (7.75 = 100)
1	5.50 ± 0.41	70.97
2	3.25 ± 0.20	41.94
3	4.86 ± 0.22	62.71
4	2.50 ± 0.14	32.26
6	4.08 ± 0.38	52.65
7	4.50 ± 0.4	58.06
8	4.05 ± 0.43	52.26
11	5.13 ± 0.44	66.19
12	4.25 ± 0.28	54.84
13	3.15 ± 0.31	40.65
Lidocaine hydrochloride	7.75 ± 0.54	100

[a] $\bar{x} \pm$ e.s. = mean value $\pm$ standard error.

factors and resonance energy. A noncoplanar phenyl group in the 5-position would lose its resonance energy of conjugation to the pyrazole ring which would not be the case in the 3-position. The structures were ascertained by using the Overhauser effect (NOE). The irradiation of the resonance frequency of methylene group resulted in the enhancement of the 5-Me group signal. No equilibrium between the s-*cis* and s-*trans* possible conformations could be observed. It is worth mentioning the strong shielding of the 4-C atom bound to iodine in compounds **3**, **8** and **13** in the ^{13}C NMR spectra. To assign the chemical shifts of the methyl groups 2D experiments (COSY ^{13}C–H) were necessary.

5.2. Pharmacological results

The acute ;toxicity (LD_{50}) of the compounds ranges within 470–602 mg/kg body weight, per os. Compounds **1**, **6** and **11** are the least toxic (Table 5).

The anesthetic and antiarrhythmic actions were tested using 1/10 of the LD_{50} value of the compounds as a working dose [24].

The anesthetic action was tested using Bianchi's [19,25] experiment on mice (Table 6) and the corneal reflex test on rabbits (Table 7) using lidocaine as a reference substance.

At first, the animals responded to the mechanical stimuli after 1.60–2 s. When the compound solutions were injected in mouse tail, the mean response time ranged between 2.50 ± 0.14 and 5.50 ± 0.41 s.

Compared to lidocaine, the most active compounds were in the order **1**, **11**, **3**, **7**, **12**, **6** and **8** that showed an activity between 71 and 52% of the reference substance effect.

Structurally, the most active compounds were characterized by the presence of the methyl group in the *ortho* or *para* position on the benzene ring: compounds **1** and **11** had 71 and 66%, respectively of the lidocaine action. Compound **4** with a nitro group in position 4 of the pyrazole ring was the least active one, although its molecule had a methyl group in the *ortho* position of the benzene ring, similar to compound **1**.

Table 7 shows that the surface local anesthetic effect of the studied compounds appears 12–15 min following their contact with the cornea of the rabbit's eye. When compounds **1**, **7** and **11** were used the action appeared 9 min, after the treatment. The mean number of stimuli endured without blinking ranges within 2.00 ± 0.17 and 3.25 ± 0.23 when touching the cornea. The most active compounds were: **1**, **3**, **7**, **11** and **12** with a local anesthetic action between 40 and 32.10% of the effect of lidocaine tested under the same conditions (Table 7).

The influence of the studied compounds was determined on the experimental fibrillation induced in mice by an atmosphere of chloroform [20]. The reference substances were quinidine sulfate and lidocaine hydrochloride.

All tested compounds delayed the appearance of the toxic fibrillating effect of chloroform, with compounds **2**, **7**, **6** and **11** being the most active. The observed

Table 7
Surface local anesthetic action (corneal reflex test)

Comp.	No. of impulses generating the oculo-palpebral reflex											Effect of lidocaine	
	At starting time	3′	6′	9′	12′	15′	18′	21′	24′	27′	30′	Mean ($\bar{x} \pm$ s.e.) [a]	8.10 = 100	*P*
1	1.5	2.2	2.3	3	3	5	6	4	3	2	2	3.25 ± 0.23	40.12	<0.01
2	2	2	2	2	2	3	4	3	2	2	2	2.40 ± 0.19	29.63	<0.1
3	2.2	2	2	2	3	4	5	3	2	2	2	2.70 ± 0.20	33.33	<0.01
4	2	2	2	2	3	3	2	2	2	2	2	2.20 ± 0.17	27.16	<0.2
6	2	2	2	2	3	3	4	3	2	2	2	2.50 ± 0.20	30.86	<0.1
7	1.8	2.2	2	3	4	5	3	2	2	2	2	2.72 ± 0.22	33.58	<0.1
8	2	2	2	2	3	4	4	2	2	2	2	2.50 ± 0.21	30.86	<0.1
11	2	2	2	3	5	4	3	3	2	2	2	2.70 ± 0.21	33.33	<0.01
12	2	2	2	2	2	3	4	4	3	2	2	2.30 ± 0.19	28.40	<0.01
13	2	2	2	2	2	3	3	2	2	2	2	2.20 ± 0.17	27.16	<0.1
L	2	2	7	10	14	14	12	9	8	3	2	8.10 ± 0.54	100	

[a] $\bar{x} \pm$ e.s. = mean value ± standard error.

Table 8
The action of 2-(pyrazol-1-yl)acetanilides, lidocaine and quinidine on the experimental fibrillation in mice

Comp.	Dose body weight per os (mg/kg)	Time of fibrillation appearance (s) ($\bar{x} \pm$ s.e.) [a]	Activity of substances with the standard taken as 100	
			Lidocaine	Quinidine
Control mice		5.20 ± 0.46		
1	60	14.00 ± 1.20	65.76	20.92
2	50	17.40 ± 1.50	91.07	28.98
3	55	14.60 ± 1.20	70.22	22.34
4	50	10.90 ± 0.89	42.68	13.58
6	60	16.20 ± 1.41	82.14	26.14
7	53	16.60 ± 1.40	85.09	27.07
8	50	12.60 ± 1.02	55.36	17.61
11	60	15.80 ± 1.40	79.15	25.18
12	52	15.00 ± 1.28	73.21	23.30
13	55	13.50 ± 1.22	62.05	19.74
Lidocaine hydrochloride	50	18.60 ± 1.64	100	31.82
Quinidine sulfate	75	47.40 ± 3.90	314.29	100

[a] $\bar{x} \pm$ e.s = mean value ± standard error.

delays ranged from 13 to 29% of that produced by quinidine, but ranged from 42 to 91% of that produced by lidocaine (Table 8).

6. Conclusions

We have obtained 15 substituted 2-(pyrazol-1-yl)acetanilides and characterized them by several methods (both chemical and spectral).

The studied compounds exhibited infiltration and surface local anesthetic actions, and an antifibrillating action, but their potency was lower than that of lidocaine and quinidine respectively. Anyhow, taking into account their lower toxicity versus lidocaine, the new compounds may deserve further consideration as potential antiarrhythmic agents.

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