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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED (3,3-DIMETHYL-1,2,3,4- TETRAHYDROISOQUINOLYLIDENE-1)ACETANILIDES AND MALONANILIDES

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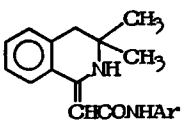
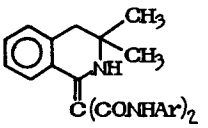
Substituted amides of the isoquinoline series include compounds with high levels of antiarrhythmic and antiaggregant activities [4].

We report here the synthesis of new compounds of this class, i.e. substituted (3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1)acetanilides (I) and malonanilides (II), with the aim of identifying the relationship between their structures and antiarrhythmic and antiaggregant properties.



Ia-m

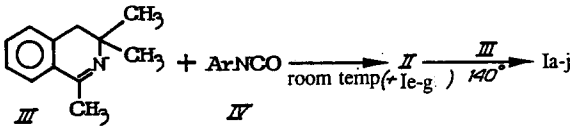


IIa-i

see Tables 1 and 2

The selection of the method used for the synthesis of acetanilides was based on consideration of a number of limitations associated with known method for their preparation. Thus, the Ritter reaction can only be used to prepare compounds in which the amide nitrogen has an alkyl substituent or an aromatic ring which is either unsubstituted or is substituted with alkyl groups [3]. The Bishler–Napiral'skii reaction is not suitable for preparing compounds with a heme substituent in position 3 because of low yields.

In looking for an efficient method for preparing compounds I, we studied the reaction between 1,3,3-trimethyl-3,4-dihydroisoquinoline (III) and isocyanates (IV). When carried out at room temperature with a molar ratio of initial reagents of 1:1, this reaction was found to produce, instead of the expected monocarbamoylated compounds (I), dicarbamoylated compounds (II) in the case of *n*-substituted (IV) reagents and mixtures of compounds with triple and other levels of carbamoylation in the case of *o*-substituted (IV) reagents.



Previous studies have demonstrated that malonanilide IIa unexpectedly melts at temperatures of greater than 140°C, with release of a phenylisocyanate molecule, so the melt contains reactive phenylisocyanate [2]. This property of compound IIa opened a pathway to preparing monocarbamoylated derivatives. In fact, heating equivalent quantities of IIa and III in *o*-xylene produced only monoanilide Ia, at high yield. The same result was obtained upon reacting equivalent quantities of phenylisocyanate and III in boiling *o*-xylene. The first of these methods enabled us to synthesize compounds Ia-j. Compounds Ik-m were prepared using the Ritter reaction [6].

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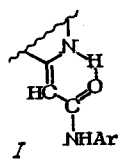
TABLE 1. Physicochemical Properties of Compounds Ia-i

Compound	Ar	Yield, %	Melting temperature, °C	PMR spectrum, δ, ppm, SSCC, Hz*						IR spectrum**, cm^{-1}
				3—CH_3 s, 6H	4—H s, 2H	CH = s, 1H	aromatic H, m	NH br., s, 1H	other H	
a	C_6H_5	72	199—201	1,12	2,75	5,15	6,8—7,7 (9H)	9,60	—	3459, 3270 br. 1661, 1622
b	$C_6H_4NO_2$-*n*	67	184 with degradation	1,27	2,80	5,14	6,8—8,5 (8H)	9,63	—	3442, 3290 br. 1646
c	C_6H_4Cl-*n*	68	172—5	1,25	2,79	5,12	6,7—7,7 (8H)	9,59	—	3449, 3295 br. 1640
d	C_6H_4Br-*n*	78	185—6	1,17	2,70	5,08	7,0—7,6 (8H)	9,54	—	3448, 3295 br. 1638
e	$C_6H_3Cl_2$-2,4	69	155—6	1,29	2,84	5,19	7,1—7,8 (6H) 8,44 d, J = 9 (1H)	9,68	—	3435, 3300 br. 1643
f	$C_6H_4NO_2$-*o*	53	137—8	1,25	2,72	5,08	6,7—7,6 (6H) 7,96 d, J = 8 (1H) 8,62 d, J = 8 (1H)	9,89	9.49 br., s (1H, NHCO)	3388 br. 3295 br. 1648
g	C_6H_4Cl-*o*	67	143—4	1,28	2,83	5,16	6,8—7,7 (7H) 8,37d, J = 8 (1H)	9,63	—	3420, 3290 br. 1640
h	$C_6H_4CH_3$-*n*	79	190—1	1,14	2,69	5,09	6,9—7,7 (8H)	9,55	2.20 s (3H, 2=CH_3)	3430, 3250 br. 1635
i	2-Thienyl	62	205—6	1,22	2,77	5,07	6,4—7,7 (7H)	9,43	—	3444, 3290 br. 1632
j	$CH_2C_6H_3(OCH_3)$-3,4	36	120—2	1,24	2,79	5,04	6,8—7,7 (7H)	9,59	3.86 s (6H, $2OCH_3$) 4.44 d J = 6 (2H, CH_2), 5.49 br. s (1H, NHCO)	3455, 3280 br. 1626
k	$C_6H_3(CH_3)_2$-2,4	83	163—4	1,20	2,64	5,05	6,8—7,7 (7H)	9,61	2.10 s (6H, $2CH_3$)	3440, 3290 br. 1635
l	$C_6H_2(CH_3)_3$-2,4 6	85	179—81	1,20	2,74	5,05	6,9—7,6 (6H)	9,60	2.22 s (9H, $3CH_3$)	3430, 3290 br. 1632
m	$C_6H_4CH_3$-*o*	78	166—9	1,17	2,67	5,19	6,8—7,8 (8H)	9,67	2.19 s (3H, CH_3)	3430, 3280 br. 1665, 1627

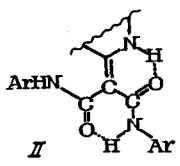
*Taken in $CDCl_3$.

**Taken in 0.01 M $CHCl_3$ solutions.

The IR spectra of dilute solutions of Ia-*l* contained bands from the associated amide carbonyl groups (1640-1620 cm^{-1}), along with those from the free amide group N—H and the hydrogen-bonded amide group (3450-3420 and 3300-3250 cm^{-1} respectively). The PMR spectra contained only one signal, from the vinyl proton (about 5.1 ppm). These data correspond to an enamine structure in the Z configuration, stabilized by intramolecular hydrogen bonds. Widening of the singlet signals at 9.5 ppm was due to the amine proton. Signals from amide protons presumably overlapped with those from aromatic protons and were only seen with compound If, because of the formation of intramolecular hydrogen bonds with the *o*-nitro group (this is supported by the reduced value of ν_{NH}) in compound Ij (Table 1).



I



II

Compounds IIa-i were prepared by interaction of one equivalent of compound III with two equivalents of the appropriate IV in boiling benzene (Table 2). The PMR spectra of malonanilides IIa-i contained widened singlets in the regions 10.1-10.8 and 11.1-11.4 ppm, corresponding to amide and amine group protons involved in intramolecular hydrogen bonding of the type shown in Scheme 3. In the IR spectra, bands at 1670 cm^{-1} were associated with the free carbonyl group, and bands at 1640-1620 cm^{-1} with the bound carbonyl group. A number of bands was seen in the region of the valent vibrations of the N—H bond, associated with free and bound NH-groups.

CHEMICAL METHODS

IR spectra were taken on UR-20 and Specord M80 spectrometers; PMR spectra were recorded using an RYa-2310 (60 MHz) with HMDS as the internal standard. Melting temperatures were determined by a capillary method using a PTP

TABLE 2. Physicochemical Properties of Compounds IIa-i

Compound	Ar	Yield, %	Melting temperature, °C	PMR spectrum**, δ, ppm, Hz					IR spectrum***, cm^{-1}
				3-CH_3 s (6H)	4-H s (2H)	aromatic H, m	NHCO br., s	NH, br., s	
a	C_6H_5	92	140	1,20	2,78	7,0—7,8 (14H)	10,55	11,32	3453, 3300 br. 1670, 1620
b	$C_6H_4NO_2$-*n*	98	198	1,30	3,02	6,6—8,5 (12H)	10,67	11,43	3400 br., 3280 br. 1628, 1615
c	C_6H_4Cl-*n*	77	182	1,07	2,62	7,1—7,6 (12H)	10,58	11,07	3390, 3310 br. 3170 br., 1648, 3275 br.
d	C_6H_4Br-*n*	92	185	1,19	2,93	6,8—7,6 (12H)	10,06	11,24	3387, 3311 br. 3273 br., 3150 br., 1647
e	C_6H_4Cl-*o*	51	118	1,24	2,86	6,8—7,6 (12H)	10,86	11,14	3408, 3312 br. 1644
f	2-Thienyl	73	170	1,05	2,51	6,3—7,4 (10H)	8,21 10,85	11,18	3280 br., 3150 br. 1671
g	3-Thienyl	78	166	1,18	2,65	7,1—7,4 (3H) 7,8—9,0 (9H)	10,65	11,40	3440, 3290 br. 1648
h ****	$CH_2C_6H_3(OCH_3)_2$-3,4	67	144	1,17	2,74	6,4—7,7 (10H)	5,28 8,46	11,12	3457, 3350 br. 1636
i *****	$C_6H_4CH_3$-*n*	72	168	1,23	2,80	6,7—7,7 (12H)	10,37	11,36	3308, 3212 br. 1636

*All substances melted with degradation around the temperature at which melting started.

**Spectra of IIb and II d were taken in DMSO-D_6; others were taken in $CDCl_3$.

***Spectra of IId, IIf, and IIg were taken in 0.01 M $CHCl_3$; others were taken in Vaseline.

****The PMR spectrum also contained the following signals: 3.68 s (3H, OCH_3), 3.80 s (6H, $2OCH_3$), 3.84 s (3H, OCH_3), 4.11 widened d, J = 6 Hz (2H, NCH_2), 443 widened d, J = 6 Hz (2H, NCH_2).

*****The PMR spectrum also contained the signal: 2.28 s (6H, $2CH_3$).

apparatus. Product purity was checked and reactions followed using TLC analysis on Silufol-254 plates, treated before use with NH_3 vapors; the eluent was a mixture of hexane and ether (1:1), and the developing reagent was a benzene solution of chloranil. The results of elemental analysis agreed with calculated values.

Malonamides II used for synthesis of compounds Ie and If were not characterized as they were used in reactions without being extracted.

(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1)acetanilides (Ia-j). Mixtures of 0.005 mole of compound III and 0.005 mole of the appropriate anilide II were heated at 140°C in 10 ml of *o*-xylene (a-d) or without solvent (g, i, j) for 2 h, and were then cooled. Product was precipitated by addition of 70 ml of pentane and collected by filtration; when reactions were carried out without solvent, product was directly crystallized from ethyl acetate (j), methanol (b), ethanol (d, f, i), or propan-2-ol (others).

(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1)malonanilides (IIa-i). The appropriate isocyanate (0.03 mole), dissolved in 15 ml of benzene, was added with mixing to a solution of 0.015 mole of III in 15 ml of benzene, boiled for 1 h under reflux and kept overnight at room temperature (without allowing entry of moisture). The resulting crystals were collected by filtration and washed with hexane.

PHARMACOLOGICAL METHODS

The biological activities of the compounds were evaluated in terms of acute toxicity, antiarrhythmic activity and antiaggregant activity in relation to platelets.

Acute i.v. toxicity was measured using white mice of both sexes, weighing 16-20 g [1].

Antiarrhythmic activity was studied in a model of arrhythmia induced by i.v. dosage of white mice with calcium chloride at a dose of 280 mg/kg [3].

Antiaggregant activity was determined by the Born photometric method [5] using dog plasma platelets, and expressed as the percent reduction in optical density. Platelet aggregation was induced with ADP at a concentration of 0.05 mg per ml of plasma. All compounds were tested at the same concentration, i.e. 0.2 mg per ml of plasma.

TABLE 3. Acute Toxicity, Antiaggregant and Antiarrhythmic Activities of the Hydrochlorides of Some Compounds I and II

Compound	Acute toxicity, LD_{50}, mg/kg	Inhibition of platelet aggregation, %	Antiarrhythmic activity	
			ED_{50}, mg/kg	Antiarrhythmic index (LD_{50}/ED_{50})
Ia	Insoluble	8,3	—	—
Ic	100 (78,8—127,0)	18,3	Inactive	—
Id	228,1 (148,3—350,8)	35,4	72,1 (42,1—123,6)	3,2
Ie	125,0 (103,9—150,5)	31,6	Inactive	—
Ih	Insoluble	8,3	»	—
Ii	20,9 (13,2—33,0)	33,3	»	—
Ik	90 (84,9—95,4)	27,1	0,6 (0,5—0,8)	150
Il	80 (74,1—86,4)	22,1	18,7 (14,9—23,4)	4,3
Im	89,7 (77,5—103,8)	8,3	Inactive	—
IIc	189,0	None	11,6	16,3
IIe	67,0	15,0	23	3,0
IIi	50,0	93	10,1	5,0

Screening of the hydrochlorides of compounds Ia, Ic-e, Ih, Ii, and Ik-m showed that all inhibited platelet aggregation. Compounds Ie, Ik, and Il also had antiarrhythmic activity (Table 3).

The percent inhibition of platelet aggregation increased with increasing lipophilicity of the substituents in the aromatic rings at the amide nitrogen. There was a linear relationship between these parameters, expressed by:

$$T = 0{,}27\pi + 1{,}07 \; (r = 0.76;\ s = 0.157;\ n = 8),$$

where T is the percent inhibition of platelet aggregation and π is the lipophilic constant of the substituent [7].

Toxicity varied from 228 mg/kg for the least toxic compound, Id, with an *n*-bromophenyl substituent at the amide nitrogen, to 21 mg/kg in the most toxic compound, Ii, with a 2-thienyl group. The relationship between toxicity and lipophilicity of the substituent at the amide nitrogen was described by:

$$(1/C_{LD_{50}}) = 1{,}28\pi^2 - 2.31\pi + 1.43$$
$$(R = 0.81,\ F = 6.94,\ n = 7),$$

where C_{LD50} is the mean toxic dose in mole/kg.

The minimum on the parabola occurred at π = 0.90 and $1/C_{LD50}$ = 0.39 (C_{LD50} = 0.41 mole/kg), which corresponded well with the least toxic compound, Id. This same compound had the greatest effect in inhibiting platelet aggregation and, additionally, had antiarrhythmic properties.

Compounds Ik and Il, which were structurally close and had similar levels of activity in inhibition of platelet aggregation, had a significant difference (31-fold) in terms of antiarrhythmic activity, which may be of interest for further studies.

Compounds IIa, IIe, and IIi, whose molecules contained two carbamoyl groups, differed from the corresponding compounds Ia, Ig, and Ih in having antiarrhythmic activity. Compounds IIc and IIe had lower antiaggregatory activity, though this was considerably greater with compound IIi as compared with compound Ii (see Table 3).

These data demonstrate the potential value of studying acid anilides of the isoquinoline series for new compounds with antiaggregant and antiarrhythmic activities.

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