

Synthesis and pesticidal activity of the substituted 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas

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3-(1-Aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas substituted on the phenyl were prepared by the reaction of the substituted 2-anilino-1-aza-1-cycloalkenes with methyl isocyanate. The structure of the title compounds was proved by i.r., u.v., and $^1\text{H-n.m.r.}$ spectra.

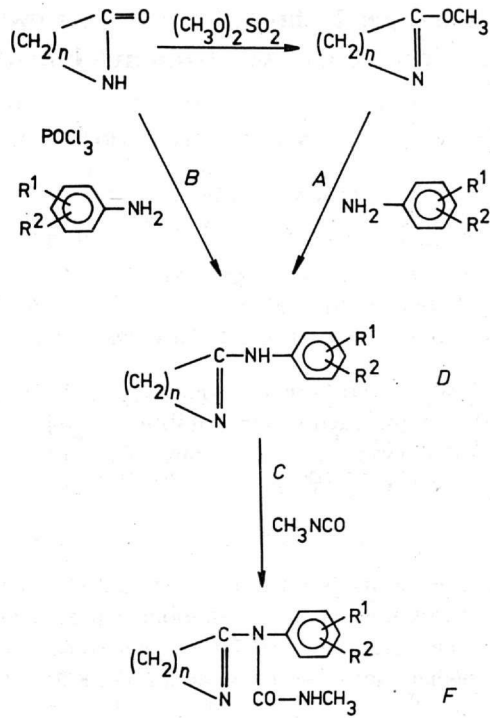
В работе описан синтез на фениле замещенных 3-(1-аза-1-циклоалкен-2-ил)-3-фенил-1-метилмочевин при помощи реакции замещенных 2-анилино-1-аза-1-циклоалкенов с метилизоцианатом. Структура полученных соединений была доказана при помощи ИК, УФ и ЯМР спектров.

Some derivatives of lactams with four- and five-membered rings as *N*-alkyl-2-phenylimino-1-aza-1-cycloalkenes, substituted on the phenyl, are known as acaricides [1].

Based on the fact that the $\text{—N}=\overset{\text{I}}{\text{C}}\text{—NH—}$ group, characteristic of substituted amidines, allowed to react with methyl isocyanate affords substituted ureas (Scheme 1) not described as yet, we synthesized a series of new 3-(1-aza-1-cyclohexen-2-yl)-3-phenyl-1-methylureas substituted on the phenyl and tested them for biological activity.

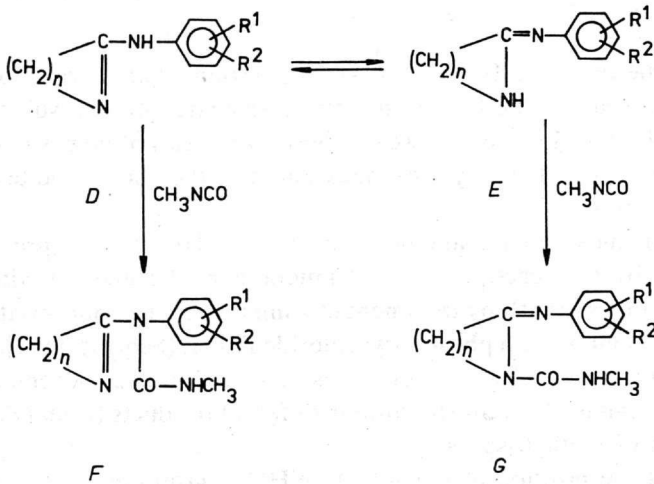
The starting substituted 2-anilino-1-aza-1-cycloalkenes were prepared by two methods: *A.* by the reaction of cyclic imidoethers (Scheme 1) with differently substituted anilines [2]; *B.* by treatment of a mixture of the appropriate lactam and the substituted aniline with phosphoryl chloride POCl_3 (Scheme 1) [1]. The starting substituted 2-anilino-1-aza-1-cycloalkenes can exist in two tautomeric forms (*D* and *E*), which can lead to two structurally different products (*F* and *G*; Scheme 2) after addition of methyl isocyanate.

To find out the position of the —CO—NHCH_3 group in the molecules of the final substances, the i.r., u.v., and $^1\text{H-n.m.r.}$ spectra of the compounds *I* and *XXVIII* were measured.



R¹, R², n — see Table 1.

Scheme 1



Scheme 2

Experimental

Infrared spectra were measured on a Specord 71 (Zeiss, Jena) spectrophotometer in chloroform and carbon tetrachloride. Cells of 0.1 cm thickness were used and the apparatus was calibrated with polystyrene foil. The wavenumbers were read with $\pm 0.5 \text{ cm}^{-1}$ accuracy.

Electronic spectra were measured on a Unicam SP 8000 spectrophotometer in the region of 300—700 nm; concentration of the compounds in dry methanol, ethanol, isopropyl alcohol, and *n*-heptane was 10^{-3} — 10^{-4} M.

$^1\text{H-n.m.r.}$ spectra were measured on a Tesla BS-477 spectrometer in deuterated chloroform at 60 MHz using TMS as internal standard.

Thin-layer chromatography on Al_2O_3 (0.3 mm thickness) was accomplished in the system benzene—acetone (95:5, v/v) and with the compounds VII—XV, XXXIII—XL in benzene—acetone (80:20, v/v).

2-Anilino-1-aza-1-cycloalkenes

Method A

A mixture of aniline (0.1 mole) and *O*-methylcaprolactim (0.1 mole) [3] was heated at 140—150°C for 3 h under the simultaneous distillation of methanol. After cooling the mixture to room temperature, a crude crystalline product was obtained and crystallized. The compounds I, II, IV, VII, XIII, XV, and XXII (Table 1) were prepared in this way.

Method B

To aniline (0.05 mole), phosphoryl chloride (0.06 mole) was added stepwise at 15—20°C under stirring and then benzene solution of lactam (0.05 mole) at 20—25°C. The reaction mixture was kept at the same temperature for 1 h. Then within 1 h the temperature of the reaction mixture was adjusted to 80—85°C which was maintained for 2—3 h (hydrogen chloride was liberated simultaneously). Then the reaction mixture was cooled to 20—25°C, water (400 ml) was added and after stirring the water layer was alkalinized by 45% solution of sodium hydroxide. The obtained precipitate was washed with water, dried, and purified by crystallization. The compounds III, V, VI, VIII—XII, XVI—XXI, XXIII—XXVII (Table 1) were prepared by the described method.

Substituted 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas

Into a flask provided with a stirrer and a cooler, the starting 2-anilino-1-aza-1-cycloalkene and methyl isocyanate (1.25 g; 0.022 mole) were added to benzene (50 ml) at 20—25°C; after the addition, the temperature increased by 4—5°C. After 1 h stirring the temperature of the reaction mixture increased to 50—60°C and stirring was continued for further 9 h at this temperature. Then the solvent was distilled off and the solid residue was crystallized. The compounds XXVIII—LIII (Table 2) were prepared by this method.

Table 1. Synthesized 2-anilino-1-aza-1-cycloalkenes

No.	<i>n</i>	R ¹	R ²	Formula	<i>M</i>	Calculated/found		Yield	M.p., °C	Ref.
						% N	% Cl (Br)			
I	5	H	H	C ₁₂ H ₁₆ N ₂	188.28	15.11		56.48	102—104	[4]
II	4	H	H	C ₁₁ H ₁₄ N ₂	174.25	14.88		60.5	102—104	[4]
						16.08			93—94	
III	3	H	H	C ₁₀ H ₁₂ N ₂	160.22	17.56		56.4	112—113	[4]
						17.48			Cyclohexane	
IV	5	H	2-Cl	C ₁₂ H ₁₅ ClN ₂	222.72	12.80	16.20	90.2	92—94	[4]
						12.58	15.92		<i>n</i> -Heptane	
V	4	H	2-Cl	C ₁₁ H ₁₃ ClN ₂	208.69	13.55	16.81	44.7	75—77	[4]
						13.42	16.99		Cyclohexane	
VI	3	H	3-Cl	C ₁₀ H ₁₁ ClN ₂	194.67	13.98	18.71	76.7	123—124	[4]
						14.39	18.21		Cyclohexane	
VII	5	H	4-Cl	C ₁₂ H ₁₅ ClN ₂	222.72	12.68	16.32	51.3	128—130	[4]
						12.58	15.92		<i>n</i> -Heptane	
VIII	4	H	4-Cl	C ₁₁ H ₁₃ ClN ₂	208.69	13.95	17.10	50.9	109—110	[4]
						13.42	16.99		Cyclohexane	
IX	3	H	4-Cl	C ₁₀ H ₁₁ ClN ₂	194.67	13.90	18.15	41.2	142—144	[4]
						14.39	18.21		Cyclohexane	
X	5	H	4-Br	C ₁₂ H ₁₅ BrN ₂	267.18	10.24	30.21	77.9	127—128	[4]
						10.49	29.91		<i>n</i> -Heptane	
XI	4	H	4-Br	C ₁₁ H ₁₃ BrN ₂	253.15	11.24	32.76	75.9	119—120	[4]
						11.07	31.57		Cyclohexane	
XII	3	H	4-Br	C ₁₀ H ₁₁ BrN ₂	239.02	11.50	33.21	75.3	140—142	[4]
						11.72	33.43		Cyclohexane	
XIII	5	H	4-OCH ₃	C ₁₃ H ₁₈ N ₂ O	218.30	12.23		36.7	83—85	[2]
						12.83	—		<i>n</i> -Heptane	
XIV	4	H	4-OCH ₃	C ₁₂ H ₁₆ N ₂ O	204.27	13.99		39.2	105—107	[2]
						13.71	—		Cyclohexane	

Table 1 (Continued)

No.	<i>n</i>	R ¹	R ²	Formula	<i>M</i>	Calculated/found		Yield %	M.p., °C	Ref.
						% N	% Cl (Br)		Solvent	
XV	3	H	4-OCH ₃	C ₁₁ H ₁₄ N ₂ O	190.25	14.08 14.73	—	59.6	104—106 Cyclohexane	
XVI	5	2-Cl	4-Cl	C ₁₂ H ₁₄ Cl ₂ N ₂	257.17	10.47 10.89	27.60 27.57	87.1	104—105 <i>n</i> -Heptane	
XVII	4	2-Cl	4-Cl	C ₁₁ H ₁₂ Cl ₂ N ₂	243.14	11.25 11.52	29.02 29.16	62.6	90—92 Sublimated	
XVIII	3	2-Cl	4-Cl	C ₁₀ H ₁₀ Cl ₂ N ₂	229.11	12.13 12.22	30.51 30.95	46.6	137—138 Cyclohexane	[1]
XIX	5	3-Cl	4-Cl	C ₁₂ H ₁₄ Cl ₂ N ₂	257.17	11.02 10.89	27.17 27.57	52.5	109—110 <i>n</i> -Heptane	
XX	4	3-Cl	4-Cl	C ₁₁ H ₁₂ Cl ₂ N ₂	243.13	11.33 11.52	29.20 29.16	78.9	100—102 Cyclohexane	
XXI	3	3-Cl	4-Cl	C ₁₀ H ₁₀ Cl ₂ N ₂	229.11	12.33 12.22	30.26 30.95	59.4	136—138 Cyclohexane	[1]
XXII	5	3-Cl	4-Cl	C ₁₃ H ₁₇ ClN ₂	236.75	11.69 11.83	14.83 14.93	39.8	110—113 <i>n</i> -Heptane	
XXIII	4	3-Cl	4-Cl	C ₁₂ H ₁₅ ClN ₂	222.72	12.69 12.58	15.52	28.8	109—111 Cyclohexane	
XXIV	3	3-Cl	4-CH ₃	C ₁₁ H ₁₃ ClN ₂	208.69	11.99 13.42	17.20 16.99	57.6	148—149 Cyclohexane	
XXV	5	2-Cl	5-CF ₃	C ₁₃ H ₁₄ ClF ₃ N ₂	290.72	9.74 9.64	—	75.2	113—115 <i>n</i> -Heptane	
XXVI	4	2-Cl	5-CF ₃	C ₁₂ H ₁₂ ClF ₃ N ₂	276.69	9.64 10.13	—	63.2	126—127 Sublimated	
XXVII	3	2-Cl	5-CF ₃	C ₁₁ H ₁₀ ClF ₃ N ₂	262.66	10.76 10.67	—	47.6	126—127 Cyclohexane	

Table 2

Synthesized 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas

No.	n	R ¹	R ²	Formula	M	Calculated/found		Yield	M.p., °C
						% N	% Cl (Br)		
XXVIII	5	H	H	C ₁₄ H ₁₉ N ₃ O	245.33	17.21	—	76.1	108—110
						17.13			<i>n</i> -Heptane
XXIX	3	H	H	C ₁₂ H ₁₅ N ₃ O	217.27	19.27	—	92.2	110—113
						19.34			Cyclohexane
XXX	5	H	2-Cl	C ₁₄ H ₁₈ ClN ₃ O	279.77	14.85	12.69	84.2	Glassy material
						15.02	12.67		
XXXI	4	H	2-Cl	C ₁₃ H ₁₆ ClN ₃ O	265.75	15.45	13.26	75.5	121—124
						15.81	13.34		Cyclohexane
XXXII	3	H	2-Cl	C ₁₂ H ₁₄ ClN ₃ O	251.71	16.66	14.16	69.7	85—88
						16.69	14.09		Cyclohexane
XXXIII	5	H	4-Cl	C ₁₄ H ₁₈ ClN ₃ O	279.77	14.69	12.70	80.7	95—97
						15.02	12.67		<i>n</i> -Heptane
XXXIV	4	H	4-Cl	C ₁₃ H ₁₆ ClN ₃ O	265.76	15.57	13.04	64.2	97—99
						15.81	13.34		Cyclohexane
XXXV	3	H	4-Cl	C ₁₂ H ₁₄ ClN ₃ O	251.71	16.65	14.22	75.7	126—128
						16.69	14.09		Cyclohexane
XXXVI	5	H	4-Br	C ₁₄ H ₁₈ BrN ₃ O	324.23	13.00	24.44	71.0	121—123
						12.96	24.65		<i>n</i> -Heptane
XXXVII	4	H	4-Br	C ₁₃ H ₁₆ BrN ₃ O	310.20	13.34	25.86	54.1	108—110
						13.55	25.76		Cyclohexane
XXXVIII	3	H	4-Br	C ₁₂ H ₁₄ BrN ₃ O	296.17	14.01	26.81	81.1	148—150
						14.19	26.98		Cyclohexane
XXXIX	5	H	4-OCH ₃	C ₁₅ H ₂₁ N ₃ O ₂	275.35	14.82	—	75.54	106—108
						15.26			<i>n</i> -Heptane
XL	4	H	4-OCH ₃	C ₁₄ H ₁₉ N ₃ O ₂	261.32	15.96	—	53.9	88—90
						16.08			Cyclohexane

Table 2 (Continued)

No.	<i>n</i>	R ¹	R ²	Formula	<i>M</i>	Calculated/found		Yield %	M.p., °C
						% N	% Cl (Br)		Solvent
<i>XLI</i>	3	H	4-OCH ₃	C ₁₃ H ₁₇ N ₃ O ₂	247.29	16.98	—	77.8	70—73
<i>XLII</i>	5	2-Cl	4-Cl	C ₁₄ H ₁₇ Cl ₂ N ₃ O	314.22	16.99	—	61.5	Cyclohexane
						13.37	22.57		76—79
<i>XLIII</i>	4	2-Cl	4-Cl	C ₁₃ H ₁₆ Cl ₂ N ₃ O	300.19	13.63	23.50	83.3	<i>n</i> -Heptane
						14.00	23.62		48—52
<i>XLIV</i>	3	2-Cl	4-Cl	C ₁₂ H ₁₃ Cl ₂ N ₃ O	286.16	14.31	24.65	90.6	Cyclohexane
						14.68	24.78		109—110
<i>XLV</i>	5	3-Cl	4-Cl	C ₁₃ H ₁₇ Cl ₂ N ₃ O	314.22	13.56	22.51	74.2	Cyclohexane
						13.37	22.57		103—105
<i>XLVI</i>	4	3-Cl	4-Cl	C ₁₃ H ₁₅ Cl ₂ N ₃ O	300.19	14.23	23.63	63.3	<i>n</i> -Heptane
						14.00	23.62		112—114
<i>XLVII</i>	3	3-Cl	4-Cl	C ₁₂ H ₁₃ Cl ₂ N ₃ O	286.16	14.64	24.68	97.6	Cyclohexane
						14.68	24.78		146—148
<i>XLVIII</i>	5	3-Cl	4-CH ₃	C ₁₅ H ₂₀ ClN ₃ O	293.80	13.85	12.09	78.5	Cyclohexane
						14.30	12.07		Glassy material
<i>XLIX</i>	4	3-Cl	4-CH ₃	C ₁₄ H ₁₈ ClN ₃ O	279.77	15.26	12.41	50.0	70—74
						15.02	12.67		Cyclohexane
<i>L</i>	3	3-Cl	4-CH ₃	C ₁₃ H ₁₆ ClN ₃ O	265.75	15.57	13.43	90.6	108—111
						15.81	13.34		Cyclohexane
<i>LI</i>	5	2-Cl	5-CF ₃	C ₁₅ H ₁₇ ClF ₃ N ₃ O	347.77	12.03	—	86.0	Glassy material
						12.08	—		68—72
<i>LII</i>	4	2-Cl	5-CF ₃	C ₁₄ H ₁₅ ClF ₃ N ₃ O	333.74	12.34	—	83.6	Cyclohexane
						12.59	—		77—79
<i>LIII</i>	3	2-Cl	5-CF ₃	C ₁₃ H ₁₃ ClF ₃ N ₃ O	319.72	12.86	—	93.5	Cyclohexane
						13.14	—		Cyclohexane

Results and discussion

The 2-anilino-1-aza-1-cycloalkenes afforded the appropriate 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas by the reaction with methyl isocyanate. Their purity was affirmed by elemental analysis and thin-layer chromatography. Their R_f values varied in dependence on the type of the lactam ring in the series $(\text{CH}_2)_3 < (\text{CH}_2)_4 < (\text{CH}_2)_5$. The R_f values of the prepared urea derivatives were higher than those of the 2-anilino-1-aza-1-cycloalkenes. To determine the structures of the synthesized substituted 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas, the spectral data of the compounds *I* and *XXVIII* and those of the model compound *N*-methyl-2-(phenylimino)-1-azacycloheptane [4] were taken into consideration. The spectral data were as follows:

Compound *I*: $\gamma(\text{C}=\text{N})$ 1637; $^1\text{H-n.m.r. (p.p.m.)}$ $(\text{CH}_2)_3$ 1.63 (m); (CH_2N) 3.08 (m); (CH_2-C) 2.5 (m); (C_6H_5) 7.05 (m); (NH) 4.75 (b).

Compound *XXVIII*: $\gamma(\text{CO})$ 1670; $\gamma(\text{C}=\text{N})$ 1628; $\gamma(\text{NH})$ bound 3148, 3033; $^1\text{H-n.m.r. (p.p.m.)}$ $(\text{CH}_2)_3$ 1.6 (m); (CH_2N) 4.03 (m); (CH_2-C) 2.53 (m); (C_6H_5) 7.00 (m); (NH) 10.33 (b); (CH_3) 2.86 (d).

All present groupings of atoms were characterized by $^1\text{H-n.m.r.}$ spectra except the position of the $-\text{CO}-\text{NHCH}_3$ group.

The group $>\text{C}=\text{N}-\text{O}$ ($\gamma(\text{C}=\text{N})$ 1614 cm^{-1}) in *N*-methyl-2-(phenylimino)-1-azacycloheptane was in conjugation with benzene ring. This was evident in the i.r. spectra from the shift of the band belonging to $\gamma(\text{C}=\text{N})$ to lower wavenumbers at simultaneous increase of intensity of the $\gamma(\text{C}=\text{C})$ vibration and its shift to lower wavenumbers.

This phenomenon was not observed in the i.r. spectra of the compound *I*. The electronic spectra of *N*-methyl-2-(phenylimino)-1-azacycloheptane and of the compound *I* were used to elucidate the question whether the $>\text{C}=\text{N}-$ bond in the compound *I* was or was not in conjugation with benzene ring. The u.v. spectra of the compound *I* measured in various solvents showed no shift of the band at λ 234 nm to higher wavenumbers at simultaneous increase of the integrated absorption in the region of 240–280 nm. On the other hand, the u.v. spectra of *N*-methyl-2-(phenylimino)-1-azacycloheptane (λ 234 nm \rightarrow λ 240.5 nm) proved the conjugation of the $>\text{C}=\text{N}-$ group with the phenyl residue. The solvents did not affect the position and intensity of the characteristic bands significantly.

From the presented data it follows that 2-anilino-1-aza-1-cycloalkenes appeared in the form *D* and the corresponding 3-(1-aza-1-cycloalken-2-yl)-3-phenyl-1-methylureas had the structure *F* (Scheme 2).

The tests for biological activity [5] showed that the prepared compounds had no significant herbicidal effects.

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