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Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecylamines. Synthesis and pharmacology

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Summary — The synthesis and biological activity of a series of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-8-amino derivatives are described. The activity of the compounds to antagonize the reserpine induced catatonia (anticataleptic) and their ability to reduce the oxotremorine induced tremor and salivation were determined in order to evaluate their potential as anti-Parkinson agents. Promising anticataleptic and mild to weak anticholinergic activities were observed for these compounds. The influence of substituents is discussed.

Résumé — La synthèse et l'activité biologique d'une série de dérivés pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undécyl-8-aminés sont décrites. *L'aptitude de ces composés à se comporter comme des antagonistes vis-à-vis de la catatonie induite par la réserpine (anticataleptique) ainsi que leur aptitude à réduire le tremblement et la salivation induites par l'oxtrémorine ont été évaluées dans le but de déterminer leur rôle éventuel comme anti-Parkinsoniens. Une action anti-cataleptique prometteuse et une activité anticholinergique moyenne à faible ont été observées. L'influence des substituants est discutée.*

polycyclic compounds / pentacyclo-undecylamines / anticataleptic activity / anticholinergic activity / anti-Parkinson activity / acute toxicity

Introduction

The synthesis and chemistry of novel polycyclic hydrocarbon 'cage' molecules have been the aim of many research groups over the past half century [1–3]. Their potential as biological active agents was realized with the discovery by Davis *et al* that 1-amino-adamantane 1, better known as amantadine, exhibits antiviral activity [4]. The biological activity profile of amantadine was further extended by the unexpected observation that amantadine can be beneficial to patients with Parkinson's disease [6]. The antiparkinsonian effects are further enchanced in combination therapy with levodopa [6]. The hydrophobicity of the hydrocarbon 'cage' of amantadine, although the amino group is protonated at physiological pH, enables it to cross the blood-brain barrier and to enter the central nervous system [6].

Considerable synthetic research has, since the introduction of amantadine, taken place in the field of polycyclic compounds [1–3, 7–10]. However, biological activity studies of novel polycyclic compounds have, to a large extend, been neglected. Compounds **2**, **3**, **4** and **5** for example were reported to possess antiviral properties [7–10]. The well known Cookson diketone **6** [11] formed the basis for numerous studies [1–3] into the chemistry of pentacycloundecyl compounds. We report the synthesis of the mono ketone **9** (scheme 1). Todate, the synthesis and biological evaluation of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecyl-8-amino derivatives have not been undertaken. We report here the synthesis of a series of 8 amino derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane and their anticataleptic and anticholinergic properties in order to test their potential as anti-Parkinson agents. The acute toxicity of these derivatives were also determined to establish their therapeutic indices.

Chemistry

The 8-amino derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.-0^{5,9}]undecane were prepared from the well-known Cookson diketone **6** [11]. We previously reported two routes (scheme 1) for the conversion of **6** to the mono

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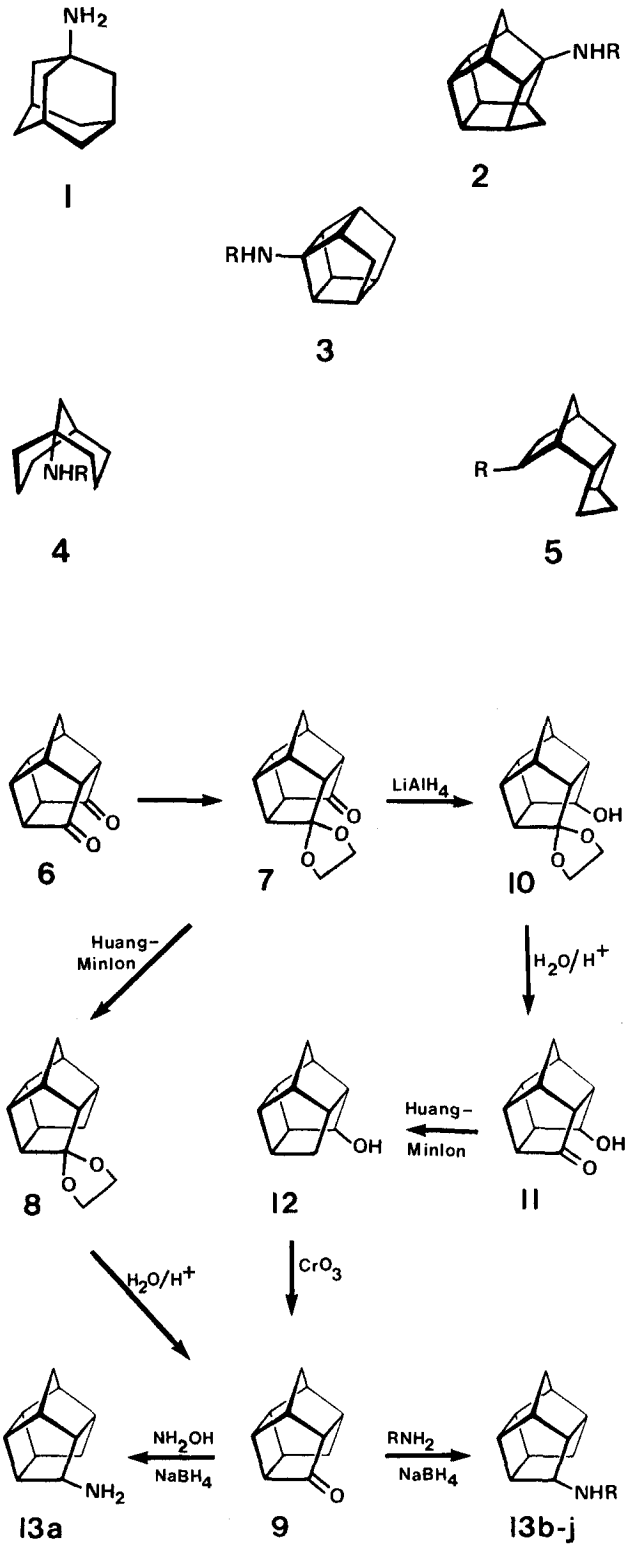

Scheme 1.

ketone **9** which proved to be a useful key intermediate for the synthesis of the amino compounds [12, 13]. The longer route *via* the ketol **11** was found to be more successful with respect to both yield and ease of reaction [12, 13].

The mono ketone **9** in a high yield (> 80%) could easily be converted by condensation with various primary alkylamines to the respective imines, which without purification afforded the desired secondary amines **13b–j** upon reduction with $NaBH_4$ (scheme 1, tables I and II). The primary amino derivative **13a** was prepared in 85% of yield, based on starting ketone **9**, by lithium aluminium hydride reduction of the oxime, which was obtained by condensation of the mono ketone **9** with hydroxyl amine (scheme 1, tables I and II). The ^{13}C NMR spectra of the newly synthesized pentacycloundecyl amines showed ^{13}C signals that correspond to the number of carbon atomes supporting the proposed structures.

Pharmacology

Three *in vivo* experiments were performed to study the potential of the pentacyclic amino compound **13** as an anti-parkinsonian agent. An Irwin dose-range study [14] in mice was performed to determine the acute toxicity of the test compounds. In the experiment for antagonism of the reserpine-induced catalepsy, the test compounds were evaluated for their action on the dopaminergic system [15, 16]. The reversal of reserpine induced catatonia by agents crossing the blood-brain barrier, was suggested to be a useful model in the search for anti-Parkinson agents [15]. Dopamine not being able to cross the blood-brain barrier, did not reverse the induced catatonia [15]. The ED_{50}-values for reversing the reserpine-induced catalepsy were estimated for the test compounds in order to rank their relative potencies. The anticholinergic activity of the compounds was evaluated in an anti-oxotremorine experiment for the reduction of induced tremor [17] and salivation. The results obtained appear in tables III and IV. Amantadine hydrochlorine was used as a control drug for both anticataleptic activity and anti-oxotremorine activity tests. Atropine sulphate was used as control in the anti-oxotremorine test.

Results and Discussion

The Irwin dose-range behavioural study indicated that the drug-induced behavioural changes are similar to those observed after administration of amantadine [18]. Signs of possible weak central nervous system stimulation were generally observed and for some

Table I. Physical data of pentacyclo undecylamines (**13a–j**).

	Substituent (R)	*mp (°C)*	*Formula (M+)*	*Yield[a] (%)*	*Analysis*					
					Calculated			*Found*		
					C	*H*	*N*	*C*	*H*	*N*
13a	Hydrogen	250	$C_{11}H_{16}NCl$ (161)	85	66.81	8.16	7.09	67.21	7.83	6.83
13b	Methyl	270	$C_{12}H_{18}NCl$ (175)	91	68.07	8.57	6.61	68.40	8.57	6.61
13c	Ethyl	312	$C_{13}H_{20}NCl$ (189	84	69.16	8.93	6.20	69.01	8.93	6.21
13d	β-Hydroxyethyl	268	$C_{13}H_{20}NCl$ (205)	92	64.58	8.34	5.79	64.32	8.21	5.62
13e	Isopropyl	236	$C_{14}H_{22}NCl$ (203)	80	70.12	9.25	5.84	69.88	9.10	5.62
13f	Butyl	265	$C_{15}H_{24}NCl$ (217)	80	70.98	9.53	5.52	70.91	9.69	5.31
13g	Isobutyl	278	$C_{15}H_{24}NCl$ (217)	82	70.98	9.53	5.52	70.62	9.71	5.34
13h	Pentyl	223	$C_{16}H_{26}NCl$ (231)	87	83.06	10.89	6.05	82.88	10.98	5.89
13i	Benzyl	276	$C_{19}H_{21}N$ (251)	90	75.11	7.70	4.87	74.82	7.52	4.98
13j	Octyl	186	$C_{19}H_{31}N$ (273)	90	83.45	11.42	5.12	83.01	11.60	5.01

[a]Isolated yield based on starting ketone **9**.

Table II. ^{13}C NMR data of pentacyclo undecylamines (**13a–j**).

Compound	*PPM*
13a	57.5; 52.9; 50.6; 49.3; 47.6; 46.8; 46.2; 42.6; 40.8; 40.1; 34.2
13b	60.1; 47.0; 44.4; 42.0; 41.8; 41.0; 40.0; 35.1; 35.0; 34.2; 33.0; 29.2
13c	57.8; 46.9; 44.2; 42.7; 42.11; 41.9; 41.0; 39.8; 35.5; 35.2; 34.1; 29.4; 11.0
13d	59.2; 57.3; 50.6; 47.0; 44.4; 41.9 (2 x C); 41.0; 39.9; 35.3; 35.1; 34.3; 29.3
13e	55.4; 50.8; 46.6; 43.9; 42.5; 41.7; 41.0; 39.5; 36.1; 35.2; 34.0; 29.5; 18.8 (2 x C)
13f	58.0; 47.3; 46.8; 44.1; 41.9 (2 x C); 41.0; 39.7; 35.4; 35.1; 34.1; 29.3; 27.4; 20.0; 13.3
13g	58.0; 54.2; 46.5; 43.6; 41.5 (2 x C); 40.7; 39.3; 34.9; 34.8; 33.8; 29.0; 25.0; 20.4 (2 x C)
13h	58.0; 47.4; 46.7; 44.0; 41.8 (2 x C); 40.9; 39.6; 35.3; 35.0; 33.9; 29.2; 28.7; 25.0; 21.7; 13.5
13i	130.8; 130.0 (2 x C); 128.7; 128.6 (2 x C); 57.2; 50.8; 46.7; 43.9; 42.3; 41.7; 40.7; 39.6; 35.7; 34.9; 33.9; 29.4
13j	58.0; 47.5; 46,7; 44.0; 41.9; 41.8; 40.9; 39.6; 35.4; 35.0; 34.0; 31.3; 29.3; 28.7 (2 x C); 26.7; 25.4; 22.2; 13.6

compounds even convulsions were noted. A clear increase in the locomotor activity was noted and stereotype behaviour (stimulation of dopamine receptors) [19] included, amongst others, head flicking and uncontrolled licking. The onset of the behavioural changes occurred as early as 30 min post-dose and lasted as long as 5 h. The high hydrophobicity of these compounds could account for this biokinetic behaviour. Deaths only occurred during the first 24 h post-

Table III. Acute toxicity (LD_{50}), anticataleptic activity (ED_{50}) and therapeutic index of the pentacyclo undecylamines (**13a–j**).

Compound	*LD_{50} (mg/kg)*	*ED_{50} mg/kg (95% confidence limits)*	*Therapeutic index[a]*
13a	> 1 000	86.2 (56–139)	> 11.6
13b	390	26.2 (16– 44)	> 14.8
13c	825	31.8 (20– 49)	25.9
13d	> 1 000	31.8 (51–131)	> 12.2
13e	994	93.5 (58–150)	10.6
13f	315	34.4 (21– 54)	9.1
13g	770	182.6 (77–434)	4.2
13h	382	27.2 (17– 46)	13.8
13i	> 1 000	74.0 (42–132)	> 13.5
13j	> 1 000	54.8 (31– 97	> 18.2
Amantadine	1 000	17.3 (9– 34)	57.8

[a]Therapeutic index LD_{50}/ED_{50}

Table IV. Anti-oxotremorine activity of pentacyclo undecylamines (**13a–j**).

		Mean score ± SEM	
Compound	*Dose[a] (mg/kg)*	*Tremor*	*Salivation*
13a	30	2.4 ± 0.2	2.2 ± 0.4
13b	30	2.5 ± 0.2	1.1 ± 0.4
13c	30	2.5 ± 0.2	1.4 ± 0.2
13d	100	2.6 ± 0.2	2.2 ± 0.2
13e	100	2.3 ± 0.2	2.5 ± 0.3
13f	30	2.2 ± 0.2	2.0 ± 0.2
13g	100	2.7 ± 0.2	2.4 ± 0.2
13h	100	2.3 ± 0.2	2.3 ± 0.3
13i	30	2.3 ± 0.2	2.3 ± 0.2
13j	30	2.6 ± 0.3	2.7 ± 0.2
Vehicle	–	3.0 ± 0.1	2.8 ± 0.1
Amantadine	100	2.6 ± 0.2	1.5 ± 0.2
Artropine	3	1.1 ± 0.3	0.3 ± 0.2

[a]Dose which exhibited the highest activity

dose (table III). The highest toxicity was observed for the N-methyl **13b**, N-butyl **13f** and N-pentyl **13h** derivatives. It appears that substitution of the primary amino **13a** with an alkyl group of medium lenght *ie* C_5 has a marked negative influence on the acute toxicity. The branched isopropyl **13e** and isobutylamines **13g** as well as the more hydrophylic ethanolamine **13d** exhibited relatively low acute toxicity.

The anticataleptic activities of the amino compounds are expressed in terms of the ED_{50}-values and therapeutic indices (table III). The straight chain amines **13b**, **13c**, **13f** and **13h** where the carbon chain is less than 5 carbons are approximately equiactive (ED_{50}-values vary between 26 and 35 mg/kg) and compare favourably with that of amantadine (17.3 mg/kg). However, their higher acute toxicity results in considerably lower therapeutic indices (TI 26) when compared with amantidine (TI 57). The branched amines **13e** and **13g** as well as the more hydrophylic ethanolamine **13d** showed mild to weak anticataleptic activities. The most promising compound of this series in terms of therapeutic index is the ethyl substituted amine **13c**.

The anti-oxotremorine activities (table IV) indicate weak to mild anticholinergic activity for the amines reducing oxotremorine induced salivation and to a lesser extend reducing tremor.

This study has shown the potential therapeutic value of the this pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecyl series. Promising activity was generally accompanied by higher toxicity. These results demonstrated that pentacycloundecyl-8-amines of this type possess promising anticataleptic activity. The N-ethyl substituted amine **13c** appears to be the most promising compound of this series. However, the therapeutic indices of all the compounds are less favourable throughout than that of amantadine. The weak anticholinergic activity found for these compounds suggests that any potential antiparkinsonian activity is due to their positive influence on the central dopaminergic system.

Experimental protocols

Chemical synthesis

Melting points were determined on a Gallenkamp apparatus (design no 889339) and are uncorrected. A Pye Unicam 104 instrument was used for glc analysis (2% Carbowax on Celite. Mass spectra were recorded at 70 eV on an ARI MS 12 spectrometer, using direct insertion. Elemental analyses were performed on a Perkin Elmer model 240 analyser and data were within about 0.4% of the theoretical values. NMR spectra were recorded on the following Varain spectrometers: T60, EM-390, HA-100 and CFT-20 and on a Bruker WM-300 spectrometer using TMS as internal standard with $CDCl_3$ and D_2O as solvents. Infrared spectra were obtained with a Beckmann Acculab 4 spectrometer in carbon tetrachloride and KBr-disks. Compounds **7**, **8**, **9**, **10**, **11** and **12** were synthesized according to previously reported procedures [12].

*8-Alkylamino pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanes (**13b–j**), general procedure*

Pentacyclo[5.4.0.$0^{2,16}$.$0^{3,10}$.$0^{5,9}$]undecane-8-one **9** (6.2 mmol) was dissolved in absolute alcohol (8 ml) which contained the desired alkylamine (8.5 mmol). The solution was sealed in a glass tube and heated for 12 h at 100°C. The solution containing the resulting imine was then cooled in ice and a solution of $NaBH_4$ (50 mmol) in cold water (20 ml) was added slowly. The mixture was then stirred for 5 h at room temperature, diluted with water (50 ml) and extracted with ether. The ether solution was washed 3 times with water and then extracted with 5% hydrochloric acid. The latter hydrochloric acid solution was washed twice with ether, made alkaline with $NaHCO_3$ and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated under reduced pressure. The free base was isolated as a colourless to light yellow oil and was redissolved in dry ether. Ether saturated with hydrogen chloride was added to the ether solution containing the free base. The resultant precipitate was recrystallised from ethanol to yield colourless crystals. The physical data of the amino compounds prepared are shown in tables I and II.

*8-Amino pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (**13a**)*

To a solution of pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one **9** (13 mmol) in ethanol (50 ml) hydroxylamine hydrochloride (29 mmol) and a 30% sodium hydroxide solution (20 ml) was added. The mixture was heated under reflux for 5 h, cooled and neutralised by bubbling carbon dioxide through the solution. The resultant solution was extracted with dichloromethane. The dichloromethane was then washed with water, dried over sodium sulphate and concentrated under reduced pressure to yield the desired oxime. The oxime was without purification dissolved in dry tetrahydrofuran (30 ml) and added dropwise over a period of 10 min to a stirred suspension of lithium aluminium hydride (13.1 mmol) in dry tetrahydrofuran (20 ml). The reaction mixture was then decomposed with aqueous ammonium chloride, diluted with water (200 ml) and extracted

with ether. The ether extract was washed twice with water and then extracted with 5% hydrochloric acid. The latter hydrochloric acid solution was washed twice with ether, rendered alkaline with sodium carbonate and extracted with ether. The ether extract was dried over sodium sulphate.

To this ether solution, ether that had been saturated with hydrogen chloride was added. The precipitated product was collected by filtration. Recrystallisation from ethanol yielded colourless crystals of **13a**, of which the physical data are shown in tables I and II.

Pharmacology

Irwin dose-range study/acute toxicity in the mouse

Male CD-1 mice were deprived of food for 18 h prior to the experiment but water was available *ad libitum* except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups comprising four mice each. The test compounds were tested at 1 000, 464, 214 and 100 mg/kg; the dose vol remained constant at 10 ml/kg. The animals were observed daily for 7 d post-dose and any mortalities were noted. The LD_{50}-values were estimated using the method of Horn [20].

Anti-exotremorine test in mice

Male CD-1 mice were deprived of food for 18 h prior to the experiment but water was available *ad libitum* except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups of ten mice each. The compounds were tested at doses of 100, 30 on 10 mg/kg at a constant dose vol of 10 ml/kg. Thirty min after administration of the test compound, vehicle or reference standard, the mouse received an intra-peritoneal injection of oxotremorine (0.4 mg/kg). The intensity of salivation and tremor were scored for all mice on a 0–3 scale, at 10, 20 and 30 min post-oxotremorine. Only the concentrations of the test compounds exhibiting the most promising anti-oxotremorine activity appear in table IV.

Antagonism of reserpine-induced catalepsy in the mice

Male CD-1 were deprived of food for 18 h prior to the experiment but water was available *ad libitum* except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups of five mice each. Four h prior to administration of the test compounds or vehicle, each mouse received an intraperitoneal dose of reserpine (5 mg/kg). Forty-five min after the administration of the test compounds or vehicle, each mouse was placed with its forepaws on a 5 cm high cork, in order to assess the presence or absence of catalepsy. Mice which remained in this position for 5 min were considered cataleptic. The ED_{50} (*ie* the dose of the test compound causing a reduction of the catalepsy score to 50% of the control group) values were determined. Each test compound was tested at doses of 100, 30 and 10 mg/kg. A constant dose vol of 10 ml/kg was employed.

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