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SYNTHESIS OF NOVEL SUCCINIMIDES: SPIRO-, AND N-MANNICH BASE DERIVATIVES WITH POTENTIAL ANTICONVULSANT ACTIVITY

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ABSTRACT

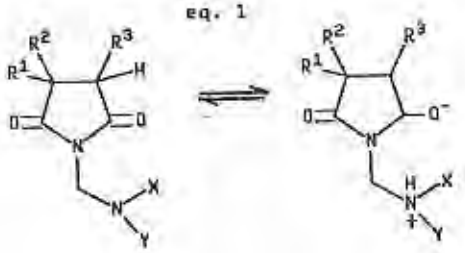
Several substituted N-aminomethylsuccinimides (I) and 1`-alkyl, or aralkyl Spiro [indolin-2-one-3,3`-pyrrolidine-2`,5`-diones] (III, XVI) were prepared. The pK_a values and the anti-MMS activity of some selected members are reported. Compound XVI showed matching protection mode when compared with ethosuximide.

INTRODUCTION

The beneficial anticonvulsant properties of succinimide derivatives has promoted many workers to perform different structural modifications in order to achieve better CNS availability[1]. One prominent approach was the introduction of N-Mannich base residues into the succinimide structure[2]. Spirosuccinimides have also been elaborated by other authors[3,4] as means of potentiating the anticonvulsant activity.

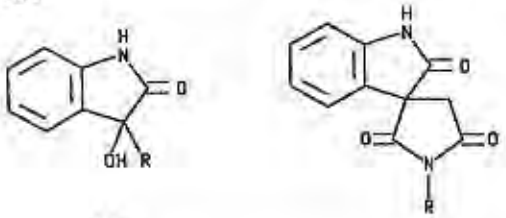
The objective of the present work has been focussed primarily on the synthesis of certain N-Mannich base analogues (I) for the purpose of suppressing the dissociation of the parent succinimide at physiologic pH due to possible formation of zwitterion structures (eq. 1). This might potentiate the liposolubility characteristics for successful passage across the blood-brain barriers.

eq. 1



Ia Ib

Moreover, certain isatin derivatives (II) were reported to exhibit anticonvulsant activity[5,6]. This has promoted us to design some novel hybrid spirostructures (III) comprising an isatin moiety on one hand and a succinimde residue on the other.



II III

EXPERIMENTAL

All melting points were recorded in open glass capillaries on a Griffin melting piont apparatus and are uncorrected. The IR spectra were performed, for Nujol mulls, on Beckman 4210 spectrophotometer. The ^{1}H-NMR spectra were scanned on Varian

EM-390 spectrometer using TMS as internal standard. The pK_a measurements were determined on Orion specific ion-meter 407 A/L and pH-electrode 91-02. Micrioanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Ethosuximide was obtained from Park-Davis Medical, England.

Starting Materials:

Ethyl 2,3-dicyano-3, 3-disubstituted propanoates (VIa-e), ethyl cycloalkylidenecyanoacetates (VIIa, b) and ethyl substituted-1-cyano-1-cycloalkylcyanoacetates (VIIIa, b) were prepared according to reported procedures[4,7-9].

Substituted succinic acids (IXa-g):

They were synthesized according to reported methods[4,10,11]. The 2-(1-carboxy-1-cyclohexyl) butyric acid (IXg) was recrystallized from benzene, yield 63%, m.p. 151-153°C. Anal. for $C_{11}H_{18}O_4$ calcd.; C: 61.7, H: 8.5, found; C: 61.8, H: 8.5.

Substituted succinic anhydrides (Xa-g):

These were prepared according to published methods[4,10,12]. The 4`-ethyl Spiro [cyclohexyl-3`-furan-2`,5`-dione] (Xg) was recrystallized from benzene, yeild 80%, m.p. 75-77°C. Anal. for $C_{11}H_{16}O_3$ calcd.; C: 67.4, H: 8.2, found; C: 67.5, H: 8.0.

Substituted succinimides (XIa-g):

They were prepared according to previously reported methods[13,14]. The 4`-ethyl Spiro [cyclohexyl-3`-pyrrolidine-2`,5`-dione] (XIg) was recrystallized from methanol, yield 75%, m.p. 70-72°C. Anal. for $C_{11}H_{17}NO_2$ calcd.; C: 67.7, H: 8.8, N: 7.2, found; C: 67.8, H: 8.9, N: 7.0.

Substituted N-aminomethylsuccinimides (Ia-n):

General Procedure: A Mixture of a cooled appropriate amine (0.05 mol) and 36% formalin solution (5 ml, 0.067 mol) was kept at 4°C for 15 min. This was then added immediately, to a stirred solution of the selected substituted succinimide (XI) (0.05 mol) in ethanol (5 ml). Stirring was continued for 5 hr at room temperature and the reaction mixture was then diluted with an aqual volume of water and the product was extracted with ether (4x5 ml). The combined extracts were dried over anhyd. Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was either recrystallized, or the proper salt was prepared and recrystallized from the appropriate solvent(s) (Table 1). IR cm^{-1}: 1775-1690 (cyclic imide). ^{1}H-NMR for compound If ($CDCl_3$) δ: 1.8 (m, 14H, cyclopentyl + $CH_2CH_2CH_2$ in piperidine), 3.0 (m, 6H, N-CH_2-N + CH_2-N-CH_2 in piperidine), 3.5 (m, 2H, C-2 in succinimide) and 9.3 ppm (m, 1H, $^+$NH).

Ethyl (3-cyanoindolin-2-on-3-yl) cyanoacetate (XIII):

It was prepared according to reported procedure[7]. The compound was recrystallized from ethanol/water, yield 70%, m.p. 256-258°C. Anal. for $C_{14}H_{11}N_3O_3$ cacld.; C; 62.5, H:4.0, N: 15.6, found; C: 62.7, H: 4.0, N: 15.4.

(3-Carboxyindolin-2-on-3-yl) acetic acid (XIV):

It was prepared according to reported method[7]. The product was recrystallized from benzene/n-hexane, yield 72%, m.p. 220-222°C. Anal. for $C_{11}H_9NO_5$ calcd.; C: 56.2, H: 3.9, N: 6.0, found ; C: 56.0, H: 4.0, N: 6.0.

Spiro [indolin-2-one-3,3`-furan-2`,5`-dione] (XV):

It was prepared as reported for analogous compounds[9,12]. The compound was recrystallized from ethanol, yield 64%, m.p. above 310°C. Anal. for $C_{11}H_7NO_4$ calcd.; C: 60.9, H: 3.3, N: 6.5, found; C: 60.9, H: 3.0, N: 6.6.

1`-Phenylamino Spiro[indolin-2-one-3,3`-pyrrolidine-2`,5`-dione] (XVI):

Phenylhydrazine (11.5 g, 0.1 mol) was added dropwise to solution of compound XV (21.7 g, 0.1 mol) in glacial acetic acid (15 ml). The reaction mixture was refluxed for 6 hr, the product was extracted with chloroform (4x5 ml). The combined extracts were dried over anhyd. Na_2SO_4, the solvent was then removed under reduced pressure and the residue was recrystallized from the proper solvents (Table 2). IR cm^{-1}: 3300 (NH), 1750 (cyclic imide) and 1620 (C=C aromatic). ^{1}H-NMR (CF_3COOH) δ: 2.3 (s, 2H, C-2` in pyrrolidine) and 7.1-7.7 ppm (m, 9H, Ar-H).

1`-Substituted Spiro [indolin-2-one-3,3`-pyrrolidine-2`,5`-dione] (IIIa-d):

Compound XV (13.0 g, 0.06 mol) was treated with an appropriate amine (0.1 mol) while cooling. The mixture was then heated in an oil bath at 160°C for 90 min. After cooling to room temperature the residue was treated with dil. HCl (1%) and scratched with a glass rod. The solid obtained was recrystallized from the proper solvent(s) (Table 2). IR cm^{-1}: 3290-3365 (NH), 1690-1750 (C=O imide) and 1610-1625 (C=C aromatic).

pK_a Measurements:

This was processed by applying a potentiometric technique using two newly synthesized compounds (Ii, XVI) together with ethosuximide for comparison. The utilized method[15] is based on measurement of hydronium-ion concentration of a solution containing 1 mmol of the tested compound and 0.5 mmol NaOH. The results are illustrated in Table 3.

Evaluation of Anticonvulsant Activity:

Compound Ii and XVI were tested for their possible anticonvulsant activity using maximal metrazole induced seizures (MMS) assay[16]. Anticonvulsant activity was determined by recording the ratio of the number of mice which displayed induced protection, that has been elicited by the tested compounds, to the total number of mice used. Protection, in this respect, could be defined as failure to observe a single episode of colonic spasms of at least 5 sec duration during a period of 30 min following administration of metrazole[17]. For comparison purposes, ethosuximide[18] was chosen as a standard anticonvulsant agent.

All compounds were dissolved in propylene glycol. Metrazole was administered subcutaneously (200 mg/kg), whereas all other compounds were given intraperitoneally (0.0014 mol/kg). Albine male Swiss-Webster mice, weighing 25-40 g were selected. Food and water were given ad libitum. The animals were subdivided into groups, each of five mice. The control group were receiving only propylene glycol. The results for MMS assay are shown in Table 3.

RESULTS AND DISCUSSION

The synthetic routes followed for preparation of the target compounds are depicted in Scheme 1 and 2. Condensation of ketonic compounds (IVa-e) with ethyl cyanoacetate (V) and potassium cyanide in acidic medium afforded the corresponding dicyano derivatives (VIa-e). Subsquent hydrolysis of (VIa-e) gave the expected dicarboxy ana-

logues (IXa-e)[7]. On the other hand, condensation of cycloalkanones (IVc, d) with ethyl cyanoacetate (V) in the presence of piperidine[8], gave the respective alkylidenecynoacetates (VIIa, b) which were treated with potassium cyanide followed by addition of alkyl iodide to yield the expected derivatives (VIIIa, b)[4,9]. Hydrolysis of VIIIa, b and dehydration of the dicarboxy analogues (IXa-g) afforded the anhydrides (Xa-g)[8,9]. The reaction of X with dry ammonia gas gave the corresponding succinimides (XIa-g)[13]. The N-Mannich base derivatives (Ia-n) (Scheme 1, Table 1) were prepared through an analogous procedure described by Magarian *et. al.*[19].

Furthermore, the condensation of isatin (XII) with ethyl cyanoacetate (V) provided ethyl (3-cyanoindolin-2-on-3-yl) cyanoacetate (XIII)[7]. Hydrolysis of the latter yielded (3-carboxyindolin-2-on-3-yl) acetic acid (XIV)[7]. Dehydration of XIV afforded the Spiro [indolin-2-one-3, 3`-furan-2`, 5`-dione] (XV)[9,12] which upon reaction with phenylhydrazine gave the 1`-phenylamino Spiro [indolin-2-one-3,3`-pyrrolidine-2`,5`-dione] (XVI)[20]. Aminolysis of XV, using different amines produced the required 1`-substituted Spiro [indolin-2-one-3,3`-pyrrolidine-2`,5`-diones] (IIIa-d)[4]. The newly synthesized compounds were substantiated by microanalysis. The IR and ^{1}H-NMR spectra were consistent with the assigned structures.

The introduction of N-phenylamino grouping (XVI) or N-Mannich base resdiue (Ii) into the succinimide skeleton appeared to have a positive effect in suppressing the ionization when compared with ethosuximide (Table 3). This might be of benifit when considering transportation across the blood-brain barriers. The MMS assays (Table 3) revealed reliable, and in one case matching, protection modes for compound XVI when compared with ethosuximide.

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Table 1: Substituted N-aminomethylsuccinimides (Ia-n).

Comp. No.	$R^1;R^2$	R^3	X;Y	Yield (%)	M.P.(°C) (Cryst. Solv.)[a]	Molecular Formula	Analyses (%) Calculated / Found C	H	N	Cl	Br
Ia	$CH_3;CH_3$	H	$(CH_2)_4$[b]	34	168-170 (M/Et)	$C_{11}H_{19}ClN_2O_2$[c]	53.5 53.4	7.8 7.9	11.3 11.5	14.4 14.2	
Ib	$CH_3;CH_3$	H	$C_2H_5;C_2H_5$	36	209-211 (M/Et)	$C_{11}H_{21}ClN_2O_2$[c]	53.1 53.0	8.5 8.6	11.3 11.0	14.2 14.3	
Ic	$CH_3;C_2H_5$	H	$(CH_2)_4$[b]	40	216-218 (E/Et)	$C_{12}H_{21}ClN_2O_2$[c]	55.3 55.1	8.1 8.0	10.7 10.5		
Id	$CH_3;C_2H_5$	H	$(CH_2)_5$[d]	32	188-190 (M/Et)	$C_{13}H_{23}ClN_2O_2$[c]	56.8 56.5	8.4 8.7	10.2 10.0	12.9 13.0	
Ie	$CH_3;C_2H_5$	H	$(CH_2)_4O$[e]	35	175-177 (E/Et)	$C_{12}H_{21}ClN_2O_3$[c]	52.1 52.2	7.6 7.8	10.1 10.0	12.8 13.0	
If	$(CH_2)_4$[f]	H	$(CH_2)_5$[d]	42	228-230 (M/Et)	$C_{14}H_{23}ClN_2O_2$[c]	58.6 58.5	8.1 8.0	9.8 9.9	12.4 12.5	
Ig	$(CH_2)_4$[f]	H	$C_2H_5;C_2H_5$	35	208-210 (E/Et)	$C_{13}H_{23}ClN_2O_2$[c]	56.8 56.7	8.4 8.2	10.2 10.0	12.9 13.0	
Ih	$(CH_2)_5$[g]	H	$(CH_2)_4$[b]	32	180-182 (E/Et)	$C_{14}H_{23}ClN_2O_2$[c]	58.6 58.8	8.1 8.2	9.8 9.9	12.4 12.5	
Ii	$(CH_2)_5$[g]	H	$(CH_2)_5$[d]	32	190-192 (M/Et)	$C_{15}H_{25}ClN_2O_2$[c]	59.9 60.0	8.4 8.5	9.3 9.1	11.8 11.6	
Ij	$CH_3;p\text{-}BrC_6H_4$	H	$(CH_2)_4$[b]	42	242-244 (E)	$C_{22}H_{22}BrN_5O_9$[h]	45.5 45.2	3.8 4.0	12.1 12.3		13.8 13.9
Ik	$CH_3;p\text{-}BrC_6H_4$	H	$(CH_2)_5$[d]	38	243-245 (E)	$C_{23}H_{24}BrN_5O_9$[h]	46.5 46.5	4.1 4.2	11.8 11.9		13.4 13.6
Il	$(CH_2)_4$[f]	C_2H_5	$(CH_2)_4$[b]	26	268-270 (E)	$C_{21}H_{27}N_5O_9$[h]	51.1 51.3	5.5 5.7	14.2 14.3		
Im	$(CH_2)_4$[f]	C_2H_5	$(CH_2)_5$[d]	43	103-105 (I)	$C_{16}H_{26}N_2O_2$	69.1 69.2	9.4 9.1	10.1 10.4		
In	$(CH_2)_5$[g]	C_2H_5	$(CH_2)_5$[d]	34	148-150 (M/Et)	$C_{17}H_{29}ClN_2O_2$[c]	62.1 62.3	8.9 9.0	8.5 8.8		

[a] M/Et = Methanol/Ether; E/Et = Ethanol/Ether; E = Ethanol; C = Chloroform; I = Isopropanol.

[b] Pyrrolidino residue. [c] Hydrochloride. [d] Piperidino residue.

[e] Morpholino residue. [f] Cyclopentyl residue. [g] Cyclohexyl residue. [h] Picrate.

Table 2: 1'-Substituted Spiro [indolin-2-one-3,3'-pyrrolidine-2',5'-diones] (XVI) and (IIIa-d).

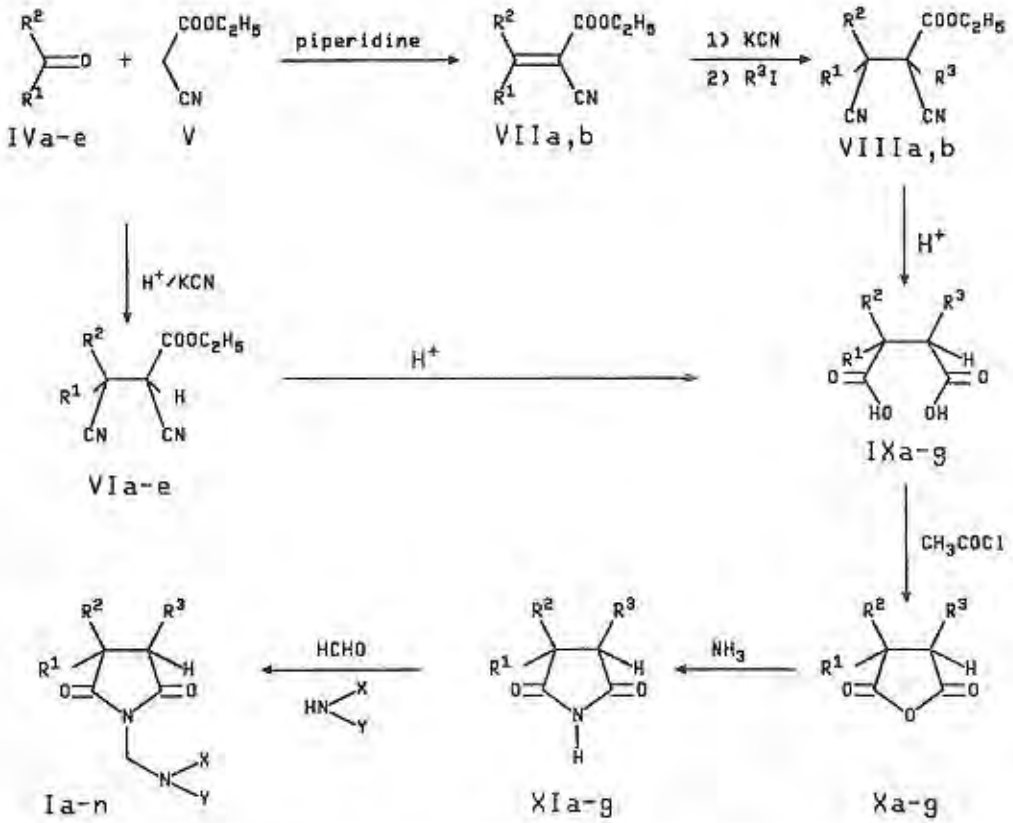
Comp. No.	R	Yield (%)	M.P.(°C) (Cryst. Solv.)[B]	Molecular Formula	Analyses (%) Calcd./Found C	H	N
XVI	NHC_6H_5	55	120-122 (E/W)	$C_{17}H_{13}N_3O_3$			13.7 13.7
IIIa	$CH_2C_6H_5$	42	213-215 (M)	$C_{18}H_{14}N_2O_3$	70.6 70.3	4.6 4.4	9.2 9.0
IIIb	$CH(CH_3)_2$	40	100-102 (I)	$C_{14}H_{14}N_2O_3$			10.9 10.9
IIIc	n-C_4H_9	36	78-80 (E/W)	$C_{15}H_{16}N_2O_3$	66.2 66.3	5.9 6.0	10.3 10.1
IIId	cyclo(C_6H_{11})	48	115-117 (M)	$C_{17}H_{18}N_2O_3$	68.5 68.2	6.1 5.9	9.4 9.0

[B] E/W = Ethanol/Water; M = Methanol; I = Isopropanol.

Table 3: pK_a Values and anticonvulsant activity of the tested compounds using MMS assay in relevance to ethosuximide.

Comp. No.	pK_a	Dose (mg/kg)	Number of animals (protected/total)[a]
Ii	9.5	371.0	4/5
XVI	8.5	429.0	5/5
Ethosuximide	8.2	200.0	5/5
Propylene glycol	---	0.1-0.5 (ml)	0/5 0/5

[a] Results were recorded after 30 min of metrazole administration.



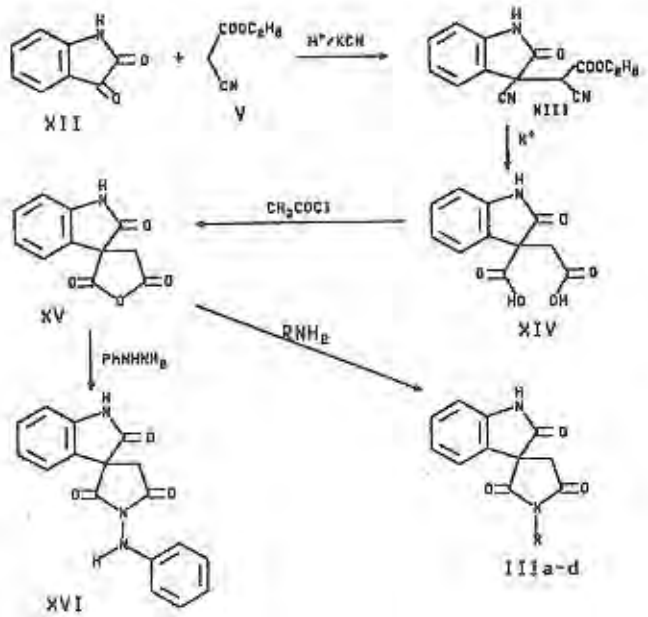
R^1,R^2 = CH_3,CH_3; CH_3,C_2H_5; $(CH_2)_4$ cycl.; $(CH_2)_5$cycl. or CH_3,p-BrC_6H_4

R^3 = C_2H_5 (VIIIa,b)

R^3 = H or C_2H_5 (IXa-g,.....)

X, Y = $(CH_2)_4$cycl.; C_2H_5,C_2H_5; $(CH_2)_5$cycl. or $(CH_2)_4O$cycl.

Scheme 1



Scheme 2

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تشييد ساكسينيميدات جديدة : مشتقات سبايرو ' قواعد "مانيخ" كمضادات للتشنجات

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قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة الاسكندرية

تم فى هذا البحث تشييد العديد من مركبات ١-الكيل - ، أو أر الكيل سبايرو (اندولين-٢-أون-٣ ، ٣-بيروليدين-٢ ، ٥-داى أون) وكذلك مركبات ن-أمينوميثيل ساكسينيميدات.

وقد تم إثبات التركيب البنائى للمركبات الجديدة المحضرة عن طريق إجراء التحاليل الدقيقة للعناصر المكونة وعن طريق دراسة أطياف الاشعة تحت الحمراء والرنين النووى المغناطيسى.

هذا وقد تم قياس ثبات تأين بعض الساكسينيميدات المشيدة بالمقارنة مع عقار ايثوساكسيميد ، وبالاضافة الى ذلك فقد تم تقييم نفس هذه المركبات أقربازينيا. وقد دلت النتائج على إنخفاض درجة تأين هذه المركبات مما قد يساعد على سهولة نفاذها من الجدار الدهنى الفاصل بين الدم والمخ ، أما بالنسبة للنتائج الأقربازينية فقد ثبت أن المركبات المختبرة لها فعالية واضحة فى منع التشنجات وأن المركب XVI يضاهى نفس فعالية عقار ايثوساكسيميد المستخدم اكلينيكيا.

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