SYNTHESIS OF SPIROIMIDES OF PHARMACOLOGIC INTEREST

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Abstract - Spiroimides of fluorene, indane and cyclopentane have been prepared as potential anticonvulsant agents. Certain azaspirane derivatives of fluorene are also reported.

Previous reports from this and other laboratories have presented the synthesis of spirosuccinimides with pharmacologic potential[1-4]. In the present paper we wish to report the synthesis of fluorene, indane and cyclopentane analogs within this series as part of a continuing study of the structural determinants for pharmacologic activity.

The Mannich bases of all the spiroimides were prepared in a manner analogous to that reported earlier[1, 2] (Scheme I). Briefly, 0.25 moles of the parent ketone 1 were condensed with 0.45 moles of ethyl cyanoacetate in benzene and acetic acid, with ammonium acetate as catalyst, and refluxed for 18 h under standard Knoevenagel conditions. The condensation product 2, once isolated and purified, was stirred at room temperature for 4 days in an aqueous ethanolic solution with 2.5 molar equivalents of KCN to yield the dicyano ester. The latter was hydrolyzed and decarboxylated, without prior purification, by refluxing in aqueous HCl/acetic acid for 2 days. Basification with 20% NaOH, heating with activated charcoal, filtration and re-acidification with 5.5M HCl afforded the corresponding diacid 3. Cyclization of the diacids to their corresponding anhydrides 4 was accomplished by refluxing in acetyl chloride for 3 h, removal of the solvent under reduced pressure, and recrystallization of the products from hot benzene. Ammonolysis of the cyclic anhydrides in benzene/ether (2.5:1.0) gave the corresponding amido acids which were cyclized in refluxing acetyl chloride, to yield the various parent spiroimides 5 which were recrystallized from hot ethanol/ether. The spiroimides were then reacted with formaldehyde and appropriate secondary amines to give the Mannich bases 6-10, 12, 14. The Mannich reactions were carried out as follows: three molar equivalents of amine

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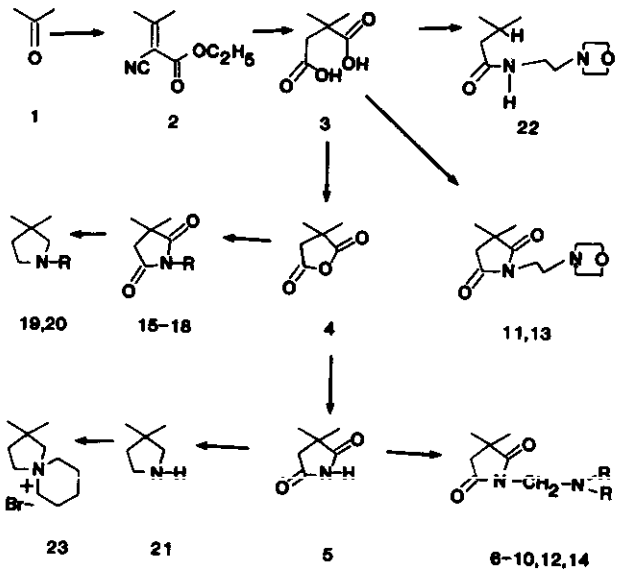
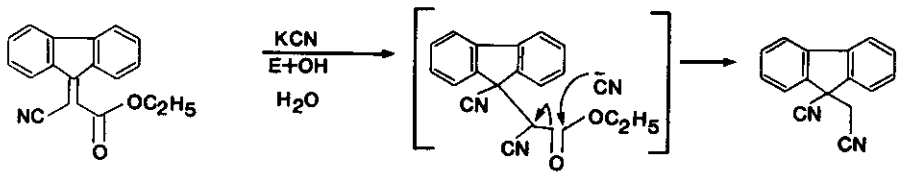
to one equivalent of imide were mixed thoroughly in a flask contained in an ice bath. To this was added 3 molar equivalents of aqueous formaldehyde with vigorous stirring. The solids thusly derived were recrystallized from hot benzene/petroleum ether (1:1).



Scheme I

During the solvent evaporation step for the isolation of the dicyanoester derived from fluorenylidine ethyl cyanoacetate and KCN, a large amount of solid had to be filtered in order to prevent "bumping" as the solvent volume was diminished. This white solid was shown to be the corresponding dicyano product 24 (Scheme II) as evidenced by NMR, mass spectral and elemental



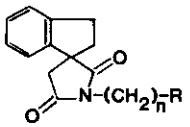
Scheme II

analysis (see table). Alteration of reaction conditions viz a viz ratio of reactants, sequence of addition, or application of heat did not alter the yield of the product (approximately 45%), although the use of heat (60°C) markedly accelerated the reaction rate. We postulate that the dicyano compound results from the liberation of ethyl cyanoformate derived from nucleophilic attack of ^{-}CN on the carbonyl of the dicyanoester. The dicyano derivative was hydrolyzed to the corresponding diacid by refluxing in acetic acid.

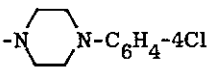
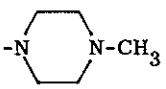
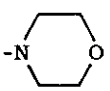
The N-(morpholino)-ethyl-spirosuccinimides, 11 and 13, were prepared by heating equimolar concentrations of the appropriate diacids and 2-N-aminoethylmorpholine for 2 h at 200°C followed by distillation and recrystallization from benzene/petroleum ether at 0°C. Attempts to prepare the analogous fluorenespirosuccinimide resulted in decarboxylation of the diacid and formation of 22, as shown by spectral and elemental analysis.

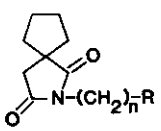
Alkyl Azaspirodiones, 15 and 16, derived from fluorenespirosuccinimide were prepared by alkylation of its sodium salt with methyl iodide and isopropyl bromide respectively. The arylazaspirodiones 17 and 18 were prepared by reacting the spiroanhydride with the appropriate amine[5] to form the corresponding amido acid which was then cyclized in refluxing acetyl chloride. Reduction of 15 and 16 with lithium aluminum hydride in ether afforded the corresponding azaspiranes 19 and 20. Reduction of flourenespiropyrrolidinedione with LAH in refluxing ether gave the corresponding azaspirane 21 in 72% yield. The dispiro compound 23 was prepared in 60% yield via reaction of 21 with 1,5-dibromopentane. Table 1 lists the melting points, yields and spectral data of the compounds prepared in this study. Several of the Mannich bases prepared above have demonstrated anticonvulsant activity in a standard pharmacologic assay using pentylenetetrazole as the convulsant agent. The bioassay of these agents shall be reported elsewhere.

Table 1. Physical and Spectral Properties of Spiroimides and Azaspiranes.[1]



Spiroindanylsuccinimides

Cpd #	n	R	mp°C	Yield	Spectral Data[2]
6	1		103	58%	2.1-3.0 (m,5H), 3.2 (s,2H), 7.1-7.5 (m,4H)
7	1		80-82	66%	1.1-1.8(brs, 6H), 2.0-3.5 (m,10H), 4.5(s,2H), 7.1-7.5 (m,4H)
8	1		185-187	91%	2.1-3.3(m,14H), 4.6(s, 2H), 6.7-7.5(m, 8H)
9	1	$-N(CH_2-C_6H_5)_2$	115-117	96%	2.3-3.26(m,6H), 3.8(s, 4H), 4.6(s,2H) 7.1-7.5 (m,14H)
10	1		113-114	67%	2.1-3.3(m,4H), 2.3(s,3H) 2.36-2.83 (m,8H) 3.0(s,2H), 4.53(s,2H) 7.1-7.5 (m,4H)
11	2		95-97	74%	2.0-2.8(m,8H), 2.8-3.4 (m,4H), 3.4-3.9(m,6H), 7.0-7.6 (m,4H)



Spirocyclopentylsuccinimides

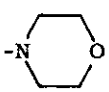
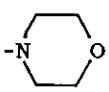
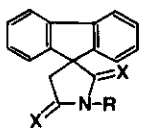
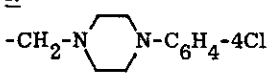
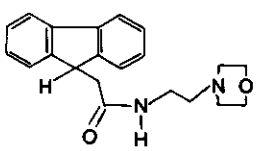
12	1		69-71	55%	1.5-2.0 (m,8H), 2.5-1.8 (m,6H), 3.5-3.9 (q,4H), 4.5 (s,2H)
13	2		63-65	80%	1.3-2.3 (m,8H), 2.3-2.7 (m,9H), 3.4-3.9(m,6H)

Table 1 - cont'd.

Spirofluorenes

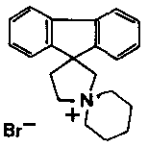


Cpd #	x	R	mp°C	Yield	Spectral Data
14	0		220-222	23%	2.7-3.5(m,10H), 4.7(s, 2H), 6.8-8.0 (m,12H)
15	0	$-CH_3$	187-190	75%	2.3(s,3H), 3.25 (s,2H), 7.2-7.45 (m,8H)
16	0	$-CH(CH_3)_2$	160-162	79%	1.0-1.2(d,6H), 2.2-2.75 (m,1H), 3.2(s,2H), 7.1-7.85(m,8H)
17	0	$-C_6H_4-2CH_3$	224-226	80%	2.3(s,3H), 3.3 (s,2H) 7.0-7.4 (m,11H)
18	0	$-C_6H_4-3CH_3$	175-177	74%	2.35 (s,3H), 3.35 (s,2H) 7.65 (m,11H)
19	H_2	$-CH_3$	80-82	69%	2.15-2.40 (t,2H), 2.45 (s,3H), 2.85 (s,2H), 2.85-3.1 (t,2H) 2.15-7.75 (m, 8H)
20	H_2	$-CH(CH_3)_2$	151-152	65%	0.85-1.15(d,6H), 2.2-2.35 (t,2H) 2.35-2.4(m,1H), 2.28(s,2H) 2.9(t,2H), 7.85 (m,8H)
21	H_2	-H	76-78	72%	2.1-2.35(t,2H), 2.35 (s,1H), 3.2(s,2H), 3.3-3.35(t,2H), 7.15-7.80(m,8H)
22			130-131	36%	2.1-2.8 (m,8H), 3.2-3.8 (m,6H) 4.5 (t,1H), 6.0 (brs,1H) 7.15-8.0 (m,8H)

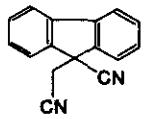
Analyses

	C	H	N
Calc'd.:	74.97	7.19	8.33
Found:	74.90	7.29	8.13

Table 1 - cont'd.

		mp°C	Yield	Spectral Data
23		292-294	60%	1.65-2.1(brs,6H),2.5-2.8(t,2H),3.9(s,2H), 4.1-4.65(m,6H),7.25-7.8(m,8H)

	C	H	N
Calc'd.:	68.20	6.53	3.78
Found:	68.06	6.40	4.08

		mp°C	Yield	Spectral Data
24		175-176	44%	3.3(s,2H), 7.2-8.1 (m,8H)

	C	H	N
Calc'd.:	83.45	4.38	12.17
Found:	83.19	4.32	11.94

1. All compounds had correct mass spectral and elemental analyses.

2. ^{1}HNMR Chemical shifts (ppm) in $CDCl_3$ with TMS internal standard.

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