SYNTHESIS OF TRICYCLIC ARYLSPIRO COMPOUNDS AS POTENTIAL ANTILEUKEMIC AND ANTICONVULSANT AGENTS

Magid A. Abou-Gharbia* and Peter H. Doukas

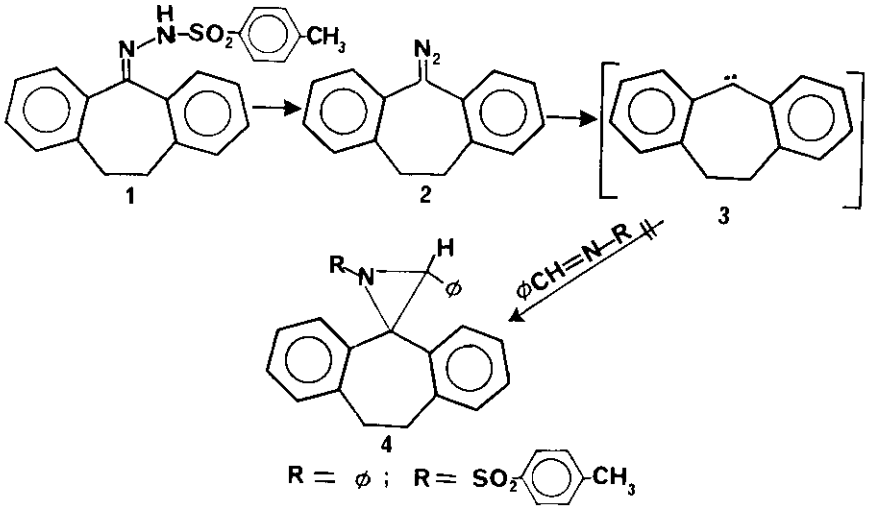
Department of Medicinal Chemistry, School of Pharmacy, Temple University
3307 North Broad Street, Philadelphia, Pennsylvania 19140, USA

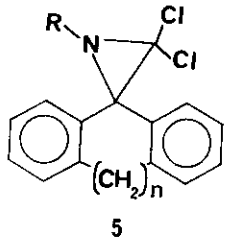
Abstract - Spiroaziridines, carboxanilides and spirosuccinimides were prepared as part of a study concerned with the relationships between chemical structure and biological activity.

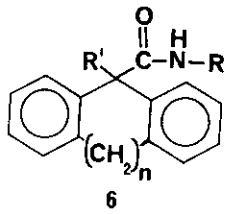
Several recently reported spirofluorenes[1,2] have been found to exhibit antileukemic activity in a general screening program[3]. This has encouraged us to extend our work and prepare some modified spiro-analogs so as to explore the relationship between structural changes and biological activity. The similarity in structure of these compounds to known anticonvulsants has also prompted us to explore the structure-activity relationships in this area. The synthesis of several prototypical structures is herein reported.

The reaction of 11-dihydro-5H-dibenzo (a,d) cyclohepten-5-one with p-toluenesulfonylhydrazine afforded the tosylhydrazone (1) in 76% yield[4]. The diazo compound (2)was prepared in 75% yield by the treatment of (1) with sodium methoxide in pyridine at 60°C. Attempts to prepare spiroaziridines (4) via reaction of the carbene (3), generated by the thermolysis of (2), with imines were unsuccessful. Spirodichloroaziridines (5a-e), however, were easily prepared via the reaction of dichlorocarbene[5] with the corresponding imine[6], in yields of 65-88%. Hydrolysis of the spirodichloroaziridines was achieved by boiling the appropriate compounds in excess water for 20 minutes, affording the corresponding carboxanilides (6a-e) in almost quantitative yield (Table 1). Recrystallization of (6d) from absolute ethanol afforded ethoxycarboxanilide (6e) in 91% yield as a result of nucleophilic displacement of chlorine with ethanol.

Spirosuccinimides (8a-c) were prepared in 72-85% yield via the reaction of spiroimide (7) with formaldehyde and secondary amines (Table 1). As part of the structure activity study it was of interest to prepare reduced analogs of the spirosuccinimides (spiropyrrolidines 9). Hence, compound (8a) was reflexed with lithium aluminum hydride in dry ether for 2 hours. This reduction afforded a mixture of three compounds[7], one of which was separated by fractional crystallization from petroleum ether (b.p. 30-60°): ether (1:1). This compound (50% yield), with a m.p. of 80-82°C had the following spectral characteristics: IR (KBr): absence of carbonyl; NMR ($CDCl_3$): δ 2.15-2.40 (t, 2H), 2.45 (s, 3H), 2.85 (s, 2H), 2.85-3.1 (t, 2H), 7.15-7.75 (m, 8H); m/e: 235 (M^+) . The compound was shown to be the spiropyrrolidine (10) on the basis of spectral and analytical data derived from unambiguously synthesized (10). Compound (10) was prepared (62% yield) by alkylating (7) with methyl iodide, in the presence of sodium methoxide in methanol, and subsequent reduction of the N-methyl derivative with lithium aluminum hydride. Formation of (10) from (8a) can be rationalized by nucleophilic hydride attack on the central carbon of the $-N-CH_2-N-$bond, in addition to reduction of the







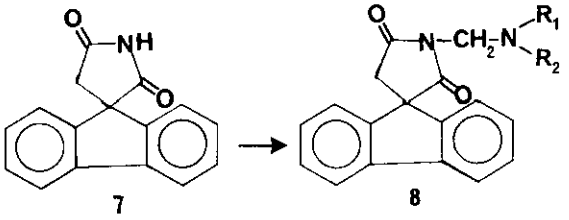
a. n = 0 , R = H , R′ = Cl

b. n = 0 , R=p-$CH_3C_6H_4$, R′ = Cl

c. n = 0 , R= α-Naphthyl, R′ = Cl

d. n = 2 , R=p-$CH_3C_6H_4$, R′ = Cl

e. n = 2 , R=p-$CH_3C_6H_4$, R′ = OC_2H_5



a. R_1=R_2=CH_2-C_6H_5

b. R_1=R_2=CH_2-CH_3

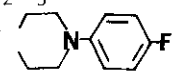
c. R_1, R_2 = 

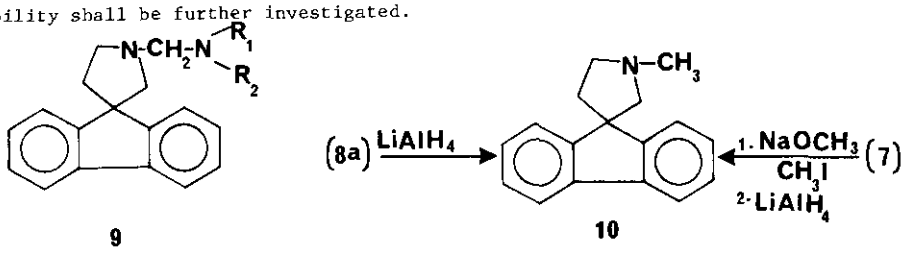
Table 1* - Physical and Spectral Properties of Selected Azaspiranes

Cpd. No.	Yield %	mp, °C	Spectral Data
5b[8]	88	135-136	IR (KBr) 1645 Cm^{-1} (-N), 745 (C-Cl); ^{1}HNMR ($CDCl_3$) δ2.28 (s, 3H), 6.85-7.85 (m, 12H); m/e 352 (M^+).
5c	65	109-110	IR (KBr) 1650 cm^{-1} (-N), 750 (C-Cl); ^{1}HNMR ($CDCl_3$) δ7.25-7.95 (m, 15H).
5d	78	135-137	IR (KBr) 1630 cm^{-1} (-N), 745 (C-Cl); ^{1}HNMR ($CDCl_3$) δ2.25 (s,3H), 3.25 (s, 4H) 6.60-8.00 (m, 12H); m/e 380 (M^+)
6c	92	186-187	IR (KBr) 3300 cm^{-1} (-NH), 1680 (-CON); ^{1}HNMR ($CDCl_3$) δ7.20-8.15 (m, 16H).
6d	95	125-127	IR (KBr) 3290 cm^{-1} (-NH), 1665 (-CON); ^{1}HNMR ($CDCl_3$) δ2.25 (s, 3H), 3.25 (s, 4H), 6.85-7.75 (m, 13H).
6e	91	177-179	IR (KBr) 3300 cm^{-1} (NH) 1650 (-CON); ^{1}HNMR ($CDCl_3$) δ1.00-1.30 (t, 3H), 2.25 (s, 3H), 3.20 (s, 4H), 3.35-3.80 (q, 2H), 6.90-7.60 (m, 13H); m/e 371 (M^+).
8a	85	101-103	IR (KBr) 1750, 1700 Cm-1 (-CONCO-); ^{1}HNMR ($CDCl_3$) δ 3.20 (s, 2H), 3.85 (s, 4H), 4.75 (s, 2H), 7.10-7.85 (m, 18H).
8b	72	87-89	IR (KBr) 1760, 1700 cm^{-1} (-CONCO-); ^{1}HNMR ($CDCl_3$) δ 1.00-1.30 (t, 6H), 2.50-2.85 (q, 4H), 3.25 (s, 2H), 4.65 (s, 2H), 7.20-7.80 (m, 8H).
8c	79	169-172	IR (KBr) 1745, 1700 cm^{-1} (-CONCO-); ^{1}HNMR ($CDCl_3$) δ2.55-3.00 (m, 4H), 3.10-3.30 (m, 4H), 3.35 (s, 2H), 4.75 (s, 2H), 6.85-7.00 (m, 4H), 7.30-7.80 (m, 8H).

*All compounds had correct mass spectral and elemental analyses.

two carbonyl groups.

The apparently facile nucleophilic displacement of the dibenzylamino function is suggestive of a possible mode of action on the biological level, namely the alkylation of tissue via a similar mechanism involving a nucleophile derived from the biological milieau. This possibility shall be further investigated.



9 10

This work was supported by an American Cancer Society Institutional Grant (No. 584-095-14).

References and Notes

1. M. Abou-Gharbia, and M. M. Joullié . J. Pharm. Sci., 1977, 66, 1654.

2. M. Abou-Gharbia, T. T. Su, and M. M. Joullié, J. Pharm. Sci., 1978, 67, 953.

3. Antileukemic activity was determined by the National Cancer Institute, NIH, Bethesda, Maryland 20014, USA.

4. I. Moritani, S. Murahashi, K. Yoshinga, and H. Ashitaka, Bull. Chem. Soc. (Japan), 1967, 40, 1506.

5. A. G. Cook, and E. K. Fields, J. Org. Chem., 1962, 27, 3686.

6. Several imines were prepared via the condensation of the tricyclic arylketones with N-Arylamines, using boron trifluoride or zinc chloride as catalyst; eg: dibezosuberenylidene-p-toluidine was prepared in 60% yield; m.p. 156-157°C; IR (KBr) 1600 (C=N); ^{1}HNMR ($CDCl_3$) δ 2.25 (s, 3H), 3.25 (s, 4H), 6.5-8.1 (m, 12H).

7. Attempts to separate and purify the other two components were unsuccessful, however the IR spectrum of the mixture indicated the presence of either a partially reduced or unreduced starting material.

8. Compounds 5(a & b) were previously reported (Ref. 1); their antileukemic and anticonvulsant properties are currently under investigation.

Received, 23rd December, 1978