Pakistan J. Sci. Ind. Res., Vol. 31, No. 4, April 1988

SYNTHESIS OF SUBSTITUTED PYRROLO [3,2-b] [I,4] THIAZINE 1,1-DIOXIDES

D. L. Wang, Said M. Bayomi* and J. W. Sowell

Departments of Pharmaceutical Chemistry, College of Pharmacy, University of South Carolina, U.S.A.

(Received March 12, 1987; revised March 30, 1988)

Primary amines were reacted with acetyl methyl carbinol to give the corresponding α-alkylamino-ketones (I) which were condensed with sulphonyldiacetonitrile to give the corresponding 1-substituted 2-amino-3-cyanomethylsulphonyl-4,5-dimethylpyrroles (II). The substituted 2-aminopyrroles (II) were condensed with trienthylorthoformate followed by base treatment to yield the 5-substituted 2-cyano-6,7-dimethylpyrrolo [3,2-b] [I, 4] thiazine-l, 1-dioxides (IV). Alkylation of obtained compounds (IV) was accomplished by forming sodium salts with sodium hydride in THF, followed by the addition of ethyl iodide to yield the targeting compounds (V).

Key words: Condensed, Alkylation, Targeting compound.

INTRODUCTION

A variety of 1,4-benzothiazine and thiazine-l,1-dioxide derivatives have been prepared and evaluated for biological activity [1-5]. The research work undertaken in this paper describes a facile route for the synthesis of a new system of substituted pyrrole [3,2-b] [I, 4]-thiazine-l, 1-dioxides (V). This fused heterocyclic system could potentially be of value as a medicinal agent or serve as precursor to pharmaceutically active drug.

Recently, the synthesis of a variety of 1,4,5-trialkyl-2-amino-3-(alkyl or aryl)-sulphonylpyrroles (II) was reported [6]. As an extension of that technology, commercially available primary amines were reacted with acetyl methyl carbinol (acetoin) and the intermediate α-alkylaminoketones (II), were converted into the corresponding formimidate derivaties (III) with triethylorthoformate. The intermediate formimidate (III) underwent cyclization in the presence of a base catalyst to give 5-substituted-2-cyano-6, 7-dimethylpyrrolo-[3,2-b] [1,4] thiazine-1, 1-dioxides (IV) in excellent yields (Table 1).

The ir spectra of the cyclized compounds show the N-H stretching absorption at 330 to 3200 cm^{-1}. The nitrile exhibited a strong absorptions peak in the region from 2200 to 2195 cm^{-1} [8]. Sulphonyl absorbs in the region of 1320 to 1300 and 1100 to 1075 cm^{-1}. The nmr spectra using d_6-DMSO as a solvent are what is expected (see experiment). Alkylation of (IV) was accomplished by forming the sodium salts with sodium hydride in tetrahydrofuran, followed with ethyl iodide to give 5-substituted-4-ethyl-2cyano-6, 7-dimethyl-1, 1,4-dihydropyrrolo [3,2-b] [1,4] thiazine-1, 1-dioxides (V).

All attempts to hydrolyze the nitrile group to the corresponding carboxylic acid (VI) were unsuccessful [9,10].

In the current pharmacological work, only the compound (IVf) was found to possess slight skeletal muscle relaxant activity.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus, and are uncorrected. The nmr spectra were determined on a Varian EM360A spectrometer using methylsilane as internal reference. Infrared spectra were determind on a Beckman Acculab 4 spectrophotometer.

N_1-Benzyl-2-amino-3-cyanomethylsulphonyl-4,5-dimethylpyrrole (IIa). The procedure given for the preparation of (IIa) is a general route for the synthesis of (IIb-f). A 200 ml round bottom flask, equipped with a Dean Stark trap, reflux condenser, drying tube, and magnetic stirrer, was charged with acetoin (5.2 g, of an 85% aqueous solution, 0.05 mole), benzyl amine (5.4 g, 0.05 mole), and 50 ml of benzene. The mixture was refluxed until evolution of water occurred (1-2 hr). After cooling, sulphonyldiacetonitrile (7.2 g, 0.05 mole) was added, and the mixture was then refluxed for 2 hr. The organic solvent was removed in vacuo and the residue was diluted with 75 ml of methanol and stirred in an ice-bath. The solid formed was collected by filtration, air dried, and recrystallized from methanol. IR (KBr): 3420, 3340 (NH_2), 2240 (CN), 1305 and 1180 (SO_2 cm^{-1}; nmr ($CDCl_3$) ζ: 2.00 (s, 3H, C_4-CH_3), 2.10 (s, 3H, C_5-CH_3), 3.90 (s, 2H, -CH_2CN), 4.6 (broad s, 2H, NH_2), 4.85 (s, 2H, benzylic protons), 6.90-7.40 (m, 5H, aromatic protons) ppm.

*Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt

Compound (IIb) had ir (KBr): 3445, 3395 (NH_2), 2250 (CN), 1300 and 1110 (SO_2) nmr ($CDCl_3$) z: 0.90-200 (broad s, 10H, aliphatic cyclohexyl protons), 2.05 (s, 6H, C_4 and C_5-CH_3), 2.20-2.40 (broad m, 1H, -CH- of cyclohexyl adjacent to N_1), 3.90 (s, 2H, -CH_2CN), 4.80 (broad s, 2H,-NH_2) ppm.

Compound (IIc) had ir (KBr) : 3480 and 3380 (NH_2) 2250 (CN), 1300 and 1110 (SO_2) cm^{-1}. nmr ($CDCl_3$) ζ:0.95 (t, 3H, -CH_2)$_3$-CH_3), 1.20-1.80 (m, 4H, -CH_2-CH_2-CH_2-CH_3), 2.05 (s, 3H, C_4-CH_3), 2.10 (s. 3H, C_5-CH_3) 3.55 (t, 2H,-CH_2-CH_2-CH_2-CH_3), 3.90 (s, 2H, -CH_2-CN), 4.80 (broad s, 2H, -NH_2) ppm.

Compound (IId) had ir (KBr): 3460 and 3370 (NH_2) 2250 (CN), 1300 and 1110 (SO_2) cm^{-1}. nmr ($CDCl_3$) ζ: 1.95 (s, 3H, C_4-CH_3), 2.05 (s, 3H, C_5-CH_3), 2.85 (t, 2H, benzylic protons), 3.80 (t, 2H, -CH_2-CH_2-Ph), 3.85 (s, 2H, -CH_2CN), 4.15 (broad s, 2H, NH_2), 6.90-7.40 (m, 5H, aromatic protons) ppm.

Compound (IIe) had ir (KBr): 3445 and 3280 (NH_2) 2255 (CN), 1320 and 1115 (SO_2) cm^{-1}. nmr ($CDCL_3$) ζ: 2.00 (s, 3H, C_4-CH3), 2.10 (s, 3H, C_5-CH_3), 3.90 (s, -2H, -CH_2-CN), 4.7 (broad s, 2H, NH_2), 4.9 (s, 2H, CH_2-pyridine), 7.20-8.65 (m, 4H, aromatic protons).

Compound (IIf) had ir (KBr) : 3420 and 3270 (NH_2) -2250 (CN), 1310 and 1015 (SO_2) cm^{-1}. nmr ($CDCl_3$) ζ: 1.60-1.90 (m, 2H, -CH_2-CH_2-morpholine), 2.00 (s, 6H, C_4 and C_5-CH_3), 2.10-2.50 (m, 6H, -CH_2-CH_2-CH_2-morpholine, and -CH_2-adjacent to nitrogen morpholine), 3.50-3.80 (m, 6H, -CH_2-CH_2-CH_2- adjacent to oxygen of morpholine), 3.80 (s, 2H, -CH_2CN), 5.70-6.3 (broad s, 2H, NH_2) ppm.

5-Benzyl-2-cyano-6,7-dimethylpyrrolo [3,2-b] [1,4] thiazine-1, 1-dioxide (IVa). The procedure given for the synthesis of (IVa) was utilized for the synthesis of (IVb-f). A mixture of 1-benzyl-2-amino-3-cyanomethylsulphonyl-4, 5-dimethylpyrrole (IIa) 7.6 g, 0.025 mole) [6] and triethylorthoformate (4.5 g, 0.03 mole) was heated in an oil-bath at 140-155° for 3.5 hr with stirring. The solid obtained after cooling was stirred with 20 ml of propanol in ice-bath for 15 min. The crude product was collected by filtration, washed with cold isopropanol, air dried and recrystallized from methanol. ir (KBr): 3240 (NH), 2200 (CN), 1310 & 1085 (SO_2) cm^{-1}. nmr (d_6-DMSO) ζ: 1.95 (s, 3H, C_7-CH_3), 2.15 (s, 3H, C_6-CH_3), 5.20 (s, 2H' benzylic protons) 6.70-7.40 (m, 5H, aromatics), 7.90 (s, 1H, vinyl proton), 12.40 (broad s, 1H, NH);

Compound (IVb) had ir (KBr): 3220 (NH_2), 2205 (CN), 1320 and 1125 (SO_2) cm^{-1}; nmr (D_6-DMSO) ζ: 1.20-2.00 (broad m, 10H, cyclohexyl protons), 2.00 (s, 3H, C_7-CH_3), 2.20 (s, 3H, $C_6$6CH_3°, 3.90-4.30 (broad m, 1H, -CH-of cyclohexyl adjacent to N_5), 7.90 (s, 1H, vinyl proton), 11.75 (broad s, 1H, NH) ppm.

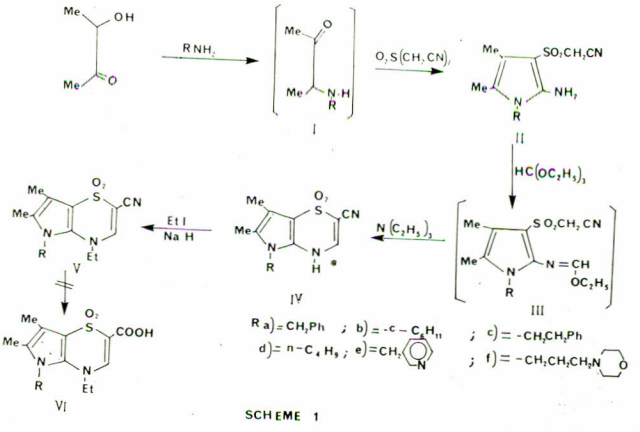
This compound (IVc) had ir (KBr): 3240 (NH), 2200 (CN), 1310 and 1085 (SO_2) cm^{-1}; nmr (d_6-DMSO): 0.90 (t, 3H, -(CH_2)$_3$-CH_3), 1.10-1.70 (m, 4H, -CH_2 -CH_2-CH_2 -CH_3), 2.10 (s, 3H, C_6-CH_3), 2.16 (s, 3H, C_7-CH_3), 3.70-4.10 (t, 2H, -CH_2-(CH_2)$_2$-CH_3) 7.90 (s, 1H, vinyl proton) 12.20 (broad s, 1H, NH)ppm.

This compound (IVd) had ir (KBr) : 3250 (NH), 2215 (CN), 1315 and 1090 (SO_2) cm^{-1}; nmr (d_6-DMSO) ζ:1.95 (s, 3H, C_7-CH_3), 2.05 (s, 3H, C_6-CH_3), 4.10 (t, 2H -CH_2-CH_2-Ph), 7.90 (s, 1H, vinyl proton), 12.20 broad s, 1H, NH)ppm.

This compound (IVe) had ir (KBr) : 3230 (NH), 2200 (CN), 1310 and 1090 (SO_2) cm^{-1}; nmr (d_6-DMSO ζ: 2.00 (s, 3H, C_7-CH_3), 2.10 (s, 3H, C_6-CH_3), 5.30 (s, 2H, -CH_2-pyridine), 7.25 (m, 2H aromatic protons), 7.90 (s, 1H, vinyl proton), 8.2al-8.50 (m, 2H, aromatic pyridyl), 10.80-11.20 (broad s, 1H, NH)ppm.

This compound (IVf) had ir (KBr): 3160 (NH), 2190 (CN), 1310 and 1090 (SO_2) cm^{-1} ; nmr (DMSO d_6) //: 1.95-2.40 (m, 2H, -CH_2 -CH_2 -CH_2-morpholine), 2.10 (s, 3H, C_7-CH_3), 2.20 (s, 3H, C_6-CH_3), 3.00-5.50 (broad m, 13H, -CH_2-CH_2-CH_2 morpholine and NH protons), 7.90 (s, 1H, vinyl proton), 12.40 (broad s, 1H, NH)ppm.

5-Benzyl-2-cyano-6, 7-dimethyl-4-ethylpyrrolo [3,2-b] [1,4]-thiazine-1, 1-dioxide (Va). This procedure given for (Va) is used for the synthesis of (Vb-d) To a suspensionof 5-benzyl-2-cyano-6,7-dimethylpyrrolo 3,2-b 1,4 thiazine-1, 1-dioxide (IVa) 5.2 g, 0.017 mole) in 50 ml of tetrahydrofuran, sodium hydride (a 50% mineral oil dispersion, 0.9 g, 0.018 mole) was added with stirring and cooling in ice-bath. After 20 min., ethyl iodide (15 ml.) was added and the mixture was refluxed for 5 days. The solvent was removed in vacuo and the residue was diluted with 50 ml of water and the insoluble product was collected, air dried



SCHEME 1

Table 1. Physical and analytical data of the synthesized compounds

Comp. No.	Yield %	M.P. (°C)	Molecular formula		Analysis (%) C	H	N
II a	78	101-102	$C_{12}H_{17}N_3O_2S$	Calcd.	59.38	5.65	13.85
				Found:	59.31	5.68	13.81
b	68	117-118	$C_{14}H_{21}N_3O_2S$	"	56.92	7.17	14.23
				"	51.00	7.13	14.25
c	65	78-80	$C_{12}H_{19}N_3O_2S$	"	53.50	7.11	15.60
				"	53.56	7.10	15.55
d	75	134-136	$C_{16}H_{19}N_3O2S$	"	60.54	6.03	13.24
				"	60.46	6.10	13.45
e	66	145-147	$C_{14}H_{16}N_4O_2S$	"	55.24	5.30	18.41
				"	55.34	5.55	18.27
f	73	142-144	$C_{15}H_{24}N_4O_3S$	"	52.92	7.11	16.46
				"	53.00	7.30	16.51
IV a	93	312-14	$C_{16}H_{15}N_3O_2S$	"	61.32	4.82	13.41
				"	61.18	4.90	13.27
b	95	304-6	$C_{15}H_{19}N_3O_2S$	"	58.99	6.27	13.76
				"	59.07	6.39	13.64
c	71	291-3	$C_{13}H_{17}N_3O_2S$	"	55.89	6.13	15.05
				"	55.78	6.03	15.89
d	99	290-3	$C_{17}H_{17}N_3O_2S$	"	62.36	5.23	12.84
				"	62.60	5.30	12.60
e	95	313-16	$C_{15}Hl4N_4O_2S$	"	57.30	4.44	17.83
				"	57.10	4.32	17.40
f	90	314-17	$C_{16}H_{22}N_4O_3S$	"	49.66	5.99	9.16
				"	49.30	6.00	8.87
V a	92	245-47	$C_{18}H_{19}N_3O_2S$	"	63.32	5.61	12.31
				"	63.01	5.29	12.00
b	97	191-193	$C_{17}H_{23}N_3O_2S$	"	61.31	6.95	6.98
				"	61.10	6.63	12.56
c	69	140-2	$C_{15}H_{21}N_3O_2S$	"	58.60	6.88	13.67
				"	58.41	6.61	13.41
d	90	197-199	$C_{19}H_{21}N_3O_2S$	"	64.20	5.96	11.82
				"	64.10	5.69	11.69

and recrystallized from absolute ethanol. This compound had ir (KBr): 2200 (CN), 1330 and 1100 (SO_2) cm^{-1}; nmr (d_6-DMSO) ζ: 1.20 (t, 3H, -N-CH_2-CH_3), 2.10 (s, 3H, C_7-CH_3), 2.20 (s, 3H? C_6-CH_3), 3.80-4.10 (q, 2H, -N-$C\underline{H}_2$-CH_3), 5.35 (s, 2H, benzylic proton), 6.80-7.40 (m 5H, aromatic protons), 8.00 (s, 1H, vinyl proton)ppm.

Similarly, compounds (Vb-d) were synthesized (see Table 1).

REFERENCES

1. J. Krapcho, A. Szabo and J. Williams, J. Med. Chem. **6**, 214 (1963).
2. S. O. Wintrop and R. Gaudry, US Pat. 2, 989, 528 (1961); Chem. Abstr., **56**, 4777d (1963).
3. J. Krapcho and C. F. Turk, J. Med. Chem., **16**, 776 (1973).
4. F. Duro, P. Condorelli, Farmaco Ed. Sci., **27** (8), 656 (1972); Chem. Abstr., **77**, 114331d (1972).
5. Raj Nandan Prasad, J. Med., Chem., **12**, 290 (1969).
6. R. J. Mattson, L. C. Wang, and J.W. Sowell, J. Heterocy. Chem., **17**, 1793 (1980).
7. R.H. Wolfe (Academic Press, New York, 1970) pp. 178-222.
8. R.M. Silverstein and G.C. Bassler, (John Wiley and Sons, Inc., New York, 1967),2nd ed, Chap 3.
9. R. Adams and A.F. Thal, Org. Synth., Coll **1**, 270 (1941).
10. F.L. Tames and W.H. Bryan, J. Org. Chem, **23**, 1225 (1958).