Synthesis of 3-Carboethoxy-4,11-dihydro-11-alkyl/phenyl-4-oxopyrimido[1,2-*b*][1,2,4]benzothiadiazine 6,6-Dioxides. A Novel Heterocyclic Ring System [1]

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The synthesis of some novel 3-carboethoxy-4,11-dihydro-11-alkyl/phenyl-4-oxopyrimido[1,2-*b*][1,2,4]benzothiadiazine 6,6-dioxides (**IVa-c**) from 3-amino-4-alkyl/phenyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**Ia-c**) and diethyl ethoxymethylenemalonate (**II**) is described. The compounds have been screened for their antibacterial activity.

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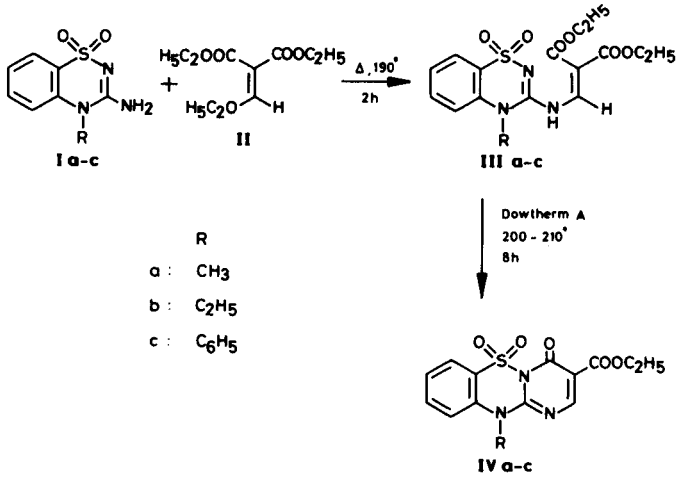
The development of chlorothiazide [2], hydrochlorothiazide and diazoxide [3], clinically well accepted drugs, led to the chemistry of 1,2,4-benzothiadiazine 1,1-dioxide as a novel class of heterocycles. The clinical success of diazoxide and others led to a spate of research which yielded compounds possessing CNS depressant [4], antiinflammatory [5] and antimicrobial [6] activities. In view of the wide spectrum of biological activity exhibited by 1,2,4-benzothiadiazine 1,1-dioxides, efforts have been made to incorporate this moiety in various systems [7,8] such as pyridones, pyrrolones and isoindolones but the title ring system has not been previously reported.

Diethyl ethoxymethylenemalonate (EMME:II) as a synthon [9] has attracted considerable interest on account of its versatility as a reagent in the development of various heterocyclic systems. The reaction of EMME with amines such as aromatic amines [10], 2-aminopyridines [11] and 6-aminopyrimidines [12] has been widely used for the synthesis of their respective quinolines, 1,8-naphthyridines and pyridopyrimidines of potential biological activity including antitumor, antibacterial and anticonvulsive agents.

In continuation of our efforts toward the synthesis of novel heterocyclic systems of biological interest, we report herein a facile synthesis of 3-carboethoxy-4,11-dihydro-11-alkyl/phenyl-4-oxopyrimido[1,2-*b*][1,2,4]benzothiadiazine 6,6-dioxides **IVa-c**, an entirely new class of heterocyclic system by condensing 3-amino-4-alkyl/phenyl-4*H*-1,2,4-benzothiadiazine-1,1-dioxides **Ia-c** and **II** under thermal conditions to obtain diethyl *N*-(4-substituted-4*H*-1,2,4-benzothiadiazine 1,1-dioxide-3-yl)aminomethylenemalonates **IIIa-c** followed by their cyclization to furnish **IVa-c** employing dowtherm A in 70-75% yields (Scheme I). The intermediates **Ia-c** [13] are obtained by the reaction of 3-chloro-4-substituted-4*H*-1,2,4-benzothiadiazine 1,1-dioxides with ammonia.

The characterization of **IIIa-c** is based on pmr spectroscopy. The pmr spectrum of **III** revealed two doublets

Scheme I



at δ 8.8 and δ 10.8. Upon deuterium oxide addition, the signal at δ 8.8 collapsed to a singlet while the signal at δ 10.8 disappeared. The pmr spectrum of **IV** did not reveal any exchangeable proton and exhibited only a downfield multiplet in the region δ 7.2-7.6 and a singlet at δ 8.7 due to phenyl and vinylic protons respectively. The structures of **IIIa-c** and **IVa-c** have been further confirmed by ir and mass spectra.

The compounds **IVa-c** synthesized were evaluated for antibacterial activity according to literature method [14] against nalidixic acid as standard. Compounds **IVa, IVb** and **IVc** showed moderate antibacterial activity (220 cm^2, 235 cm^2 and 220 cm^2 respectively) whereas nalidixic acid exhibited 656 cm^2.

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and were uncorrected. Infrared spectra were recorded on a Perkin Elmer 221 spectrometer. The pmr spectra were recorded on JEOL FT FX-90Q spectrometer using TMS as an internal stand-

Table 1

No.	Products R	Yield (%)	mp °C	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (KBr) (cm^{-1})			M^+ (m/e)
3a	CH_3	90	170	$C_{16}H_{19}N_3O_6S$	50.39 50.25	5.02 5.00	11.02 11.10	3150, 1680,	2990, 1370,	1730, 1090	381
3b	C_2H_5	92	212	$C_{17}H_{21}N_3O_6S$	51.63 51.55	5.35 5.46	10.63 10.70	3160, 1680,	2980, 1375,	1725, 1080	395
3c	C_6H_5	92	205	$C_{21}H_{21}N_3O_6S$	56.88 56.82	4.77 4.80	9.48 9.52	3155, 1680,	2985, 1370,	1725, 1090	443
4a	CH_3	70	195	$C_{14}H_{13}N_3O_5S$	50.14 50.21	3.91 3.98	12.53 12.60	2960, 1350,	1730, 1180	1670,	335
4b	C_2H_5	75	245	$C_{15}H_{15}N_3O_5S$	51.57 51.60	4.33 4.31	12.03 12.11	2970, 1350,	1720, 1180	1665,	349
4c	C_6H_5	75	230	$C_{19}H_{15}N_3O_5S$	57.43 57.50	3.80 3.78	10.57 10.60	2965, 1340,	1730, 1170	1670,	397

ard. Mass spectra were recorded on VG micromass 70-70H mass spectrometer.

Typical Reaction Procedure.

Diethyl *N*-(4*H*-Methyl-1,2,4-benzothiadiazine 1,1-Dioxide-3-yl)-aminomethylenemalonate (**IIIa**).

A mixture of 3-amino-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (2.11 g, 0.01 mole) and diethyl ethoxymethylenemalonate (2.16 g, 0.01 mole) was heated at 170-180° for 2 hours. The residue obtained after cooling was treated with *n*-hexane and chloroform to give **IIIa**. It was filtered and recrystallised from ethanol; ^{1}H nmr: δ 10.80 (d, NH, 1), 8.80 (d, NH-CH, 1), 3.73 (s, NCH_3, 3), 4.21 (d of q, CH_2, 4) and 1.42 (d of t, CH_2CH_3, 6).

3-Carboethoxy-4,11-methyl-4-oxopyrimido[1,2-*b*][1,2,4]benzothiadiazine 6,6-Dioxide (**IVa**).

A solution of **IIIa** (3.81 g, 0.01 mole) in dowtherm A (20 ml) was heated to 200° for 8 hours. Dowtherm A was removed by washing with *n*-hexane. The residue obtained was purified by recrystallisation from a mixture of chloroform:*n*-hexane (1:1); ^{1}H nmr: δ 8.70 (s, C-2H, 1), 4.40 (q, CH_2, 2), 3.71 (s, N-CH_3, 3) and 1.45 (t, CH_2CH_3, 3).

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REFERENCES AND NOTES

[1] RRL(H) Communication No. 2248.

[2] F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

[3] A. A. Rubin, F. E. Roth and M. M. Winbury, *Nature*, **192**, 176 (1961).

[4] S. C. Bell, U. S. Patent 3,449,337 (1969); *Chem. Abstr.*, **71**, 81442 (1969).

[5] L. Raffa, M. Dibella, P. Farrari, A. Monzari, M. G. Andrisano and G. Baggio, *Farmaco. Ed. Sci.*, **34**, 199 (1979).

[6] M. Dibella, A. Monzari, M. G. Andrisano, U. Fabio and G. P. Quaglio, *Farmaco. Ed. Sci.*, **34**, 189 (1979).

[7] S. C. Bell, Peter H. L. Wei and S. J. Childress, *J. Org. Chem.*, **29**, 3206 (1964).

[8] P. H. L. Wei, S. C. Bell and S. J. Childress, *J. Heterocyclic Chem.*, **3**, 1 (1966).

[9] W. P. William and J. K. Thomas, in "Advances in Heterocyclic Chemistry", Vol **11**, A. R. Katritzky and A. J. Boulton, eds, Academic Prsss, New York, 1970, p 139.

[10] H. Koga, A. Itoh, S. Murayama, S. Suzue and T. Irikura, *J. Med. Chem.*, **23**, 1358 (1980).

[11] G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

[12] B. H. Rizkalla and A. D. Broom, *J. Org. Chem.*, **37**, 3980 (1972).

[13] A. V. N. Reddy, A. Kamal and P. B. Sattur, *Synthesis*, 864 (1986).

[14] F. O'Brien and R. K. S. Wood, *Nature*, **242**, 532 (1973).