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CHEMISTRY

On the Anti-Tubercular Properties of Some Derivatives of Benzoxazine-1,3

by

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In 1951, T. Urbański and S. Ślopek published a paper [1] on the anti-tubercular properties of a number of nitroparaffin derivatives, and particularly of derivatives of 5-nitro-tetrahydro-1,3-oxazine [2]-[7].

One of the compounds — 5-nitro-5-ethyltetrahydro-1,3-oxazine hydrochloride (designated as *T* 41) — showed an action similar to that of streptomycin against experimental TB in mice. However, a toxic action was observed upon prologned administration of the product. The toxic action may be produced by the presence of a nitro-group, and this led us to look for less toxic derivatives of 1,3-oxazine and to subject them to examination as anti-tubercular agents.

Thus, a number of derivatives of 4,4,6-trimethyl-tetrahydro-1,3-oxazine were recently prepared by T. Urbański and B. Chylińska [8]. (A number of compounds belonging to this group were originally obtained by M. Kohn [9]).

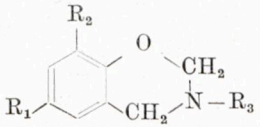
As shown by S. Ślopek, some of these compounds possess a moderate, although unquestionably bacteriostatic, action *in vitro* against *Mycobacteria*.

Continuing further this line of research, the authors of the present paper prepared a number of derivatives of benzoxazine-1,3, which form a group of compounds known since 1900 [10]-[13] and which have recently been examined by a number of authors, particularly Burke and his coworkes [14]-[18], from the point of view of the reactions leading to phenol-formaldehyde resins.

The following are the benzoxazine-1,3 derivatives prepared by the authors of the present paper (Table I).

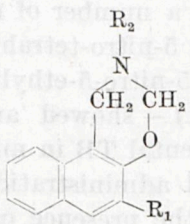
Products (1) and (2) have been described by Burke. The rest are new to the literature. The derivatives of naphtoxazine are shown in

TABLE I



No.	Name	R_1	R_2	R_3	Free bases m. p. °C.	Hydrochloride m. p. °C	Analysis				References
							Calculated		Found		
							% N	% Cl	% N	% Cl	
1	*T* 339	–Br	–	$-C_6H_{11}$	92–93	240–243					[6]
2	*T* 346	$-CH_3$	–	$-CH_2C_6H_5$	79–80	110–112					[6]
3	*T* 340	–Br	–	$-CH_2C_6H_5$	85–87	182–184	4.1	10.4	4.2	10.1	
4	*T* 348	–Br	–	$-C_2H_5$	–	171–172	5.0	16.6	5.2	17.0	
5	*T* 375	$-CH_3$	–	$-C_6H_{11}$	30–32	210–212	6.1	12.7	6.4	12.3	
6	*T* 379	–	$-OCH_3$	$-C_6H_{11}$	54–56	150–153	5.6	12.5	5.8	12.3	

TABLE II



No.	Name	R_1	R_2	Free bases m. p. °C	Hydrochloride	Analysis		References
						Calculated	Found	
						% N	% N	
1	*T* 356	H	$-CH_3$	67–68	190–193			[6]
2	*T* 378	H	$-C_6H_4COOH$	215	–			[6]
3	*T* 380	–COOMe	$-CH_2C_6H_5$	106–107	–	4.0	4.3	

TABLE III

Name	Bacteriostatic concentration			Lethal dose DL_{50} per os
	Myc. 297	*Smegm.*	H_{37} Rv	
T 339	3.9	7.8	7.8	3 g./kg.
T 346	31	31	31	–
T 356	7.8	15.5	15.5	–
T 340	3.9	7.8	3.9	3 g./kg.
T 348	62	31	15.5	–

Table II. Compounds (1) and (2) have also been described by Burke. Table III gives the bacteriostatic concentrations of some of the compounds *in vitro* against saprophytic *Mycobacteria*, which have been determined by one of us (S. Ślopek).

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