Tetracyclic Tetrazoles

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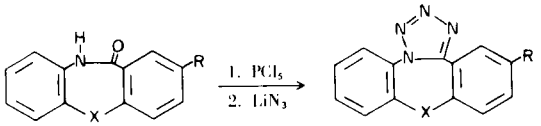
A tetrazole nucleus was fused to the basic tricyclic ring structure of some neuroleptic agents with a seven-membered central ring (1) in order to study the biological properties of the resultant compounds. Two of the compounds reported here, IIa,b (Table I), were found to exhibit mild analgesic activity (2).

When the lactams Ia-c (3-5) were reacted first with phosphorus pentachloride and then treated with sodium azide, an aqueous workup gave only starting material. However, when lithium azide (6) was used in this reaction sequence (Scheme I), the tetrazoles IIa-c were readily formed.

SCHEME I



I II

X = O, S, N-CH$_3$; R = H, Cl, F

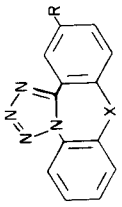
EXPERIMENTAL

The melting points in Table I were determined on a Hersberg apparatus and are uncorrected. All new compounds show satisfactory spectral properties, particularly in respect of their ir, nmr and mass spectra.

General Procedure for the Preparation of the Tetrazoles (IIa-c).

A suspension containing 10 mmoles of the required lactam and 2.28 g. (11 mmoles) of phosphorus pentachloride in 20 ml. of anhydrous toluene was heated at reflux (under nitrogen) for 4 hours. The solvent was removed from the resulting dark orange solution under reduced pressure. To insure the complete removal of hydrogen chloride and phosphorus oxychloride, 10 additional ml. of toluene was added and the solvent was again removed under reduced pressure. A solution of the residue dissolved in 20 ml. of DMF was added dropwise to a suspension containing 1.3 g. (20 mmoles) of sodium azide and 0.84 g. (20 mmoles) of lithium chloride in 50 ml. of DMF. The reaction mixture was heated at 100° for 18 hours, allowed to cool and then poured into 200 ml. of water. The bulky precipitate was removed by filtration, washed well with water and then air dried. The crude product was recrystallized from methanol.

Table I



Compound	X	R	Yield (%)	Molecular Formula	M.p., °C	Analysis Caled. C	H	N	Halogen	Found C	H	N	Halogen
IIa	O	H	80	$C_{13}H_8N_4O$	206-208	66.09	3.41	23.72	---	66.47	3.43	23.91	---
IIb	O	Cl	81	$C_{13}H_7ClN_4O$	209-210	57.60	2.60	20.70	13.06	57.53	2.70	20.50	13.20
IIc	O	F	87	$C_{13}H_7FN_4O$	185-186	61.42	2.78	22.04	7.47	61.72	2.84	22.27	7.76
IId	S	Cl	63	$C_{13}H_7ClN_4S$ (a)	246-248	54.40	2.46	19.50	12.30	54.46	2.60	19.33	12.43
IIe	N-CH$_3$	H	71	$C_{14}H_{11}N_5$	149-150	67.45	4.45	28.10	---	67.44	4.69	28.20	---

(a) Caled. S, 11.10. Found 11.11.

Acknowledgment.

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