Synthesis of 3-[*p*-(1'-Pyrazolyl)]phenylsydnones

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The synthesis of some hitherto unknown sydnones, *i.e.*, derivatives of 3-phenylsydnone with a pyrazolyl moiety in the *p*-position of the phenyl nucleus, has been described. The structures for all of the sydnones have been confirmed by elemental analysis, and ir and nmr spectral studies.

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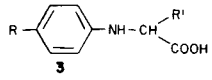
Sydnones have been studied extensively because of their biological properties and yet there is hardly any one which has pharmacological activity high enough for practical purposes. A number of 3-tolylsydnones have been tested on normal intact animals and are reported to have CNS depression action (1). A similar study has been made with 3-tolylsydnones to see the effect of an additional group like -CH_3, -Br, -Cl, and -NO_2 on the CNS depression action. It has been reported that it is only the group in the phenyl ring of 3 tolylsydnones which is responsible for the enhanced CNS depression action (2).

The above results prompted us to introduce a heteroaromatic moiety in the 3-phenylsydnone in order to study the variation in the pharmacological as well as chemical properties. The pyrazole ring is one of the heterocycles which has received much attention, because of its diverse properties. Certain alkylpyrazoles have shown quite significant bacteriostatic, bactericidal and fungicidal action. Wright, *et al.*, have studied the antidiabetic activity of 3,5-dimethylpyrazole and found them to possess hypoglycemic activity as great as 100 times that of tolbutamide (3). Several alkyl and arylpyrazoles possess sharply pronounced CNS depression action (4). With this in view an attempt has been made to introduce a pyrazolyl moiety into the *p*-position of the phenyl nucleus in 3-phenylsydnone.

For the synthesis of such compounds, two alternative routes are possible: (i) on a preformed *p*-aminophenylpyrazole nucleus, the sydnone ring can be built up; and (ii) on a preformed *p*-aminophenylsydnone, a pyrazole ring can be built. In view of the sensitivity of the sydnone ring to alkali as well as acid, it was decided to use the first of these methods, *viz.*, building the sydnone ring on an appropriate phenylpyrazole.

Table I



3

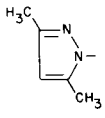
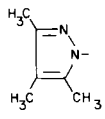
R	R'	M.p. °C	Formula	Calcd. Found	C%	H%
	H	174-175	$C_{11}H_{11}N_3O_2$	Calcd.	58.13	4.85
				Found	58.10	4.78
	CH_3	171-172	$C_{12}H_{13}N_3O_2$	Calcd.	62.34	5.63
				Found	62.21	5.60
	C_6H_5	169-170	$C_{17}H_{15}N_3O_2$	Calcd.	69.61	5.19
				Found	69.58	5.13
	H	201-202	$C_{13}H_{15}N_3O_2$	Calcd.	63.66	6.12
				Found	63.53	6.20
	CH_3	205-206	$C_{14}H_{17}N_3O_2$	Calcd.	64.86	6.56
				Found	64.74	6.54
	C_6H_5	200-201	$C_{18}H_{19}N_3O_2$	Calcd.	71.03	5.92
				Found	70.93	5.89
	H	205-206	$C_{14}H_{17}N_3O_2$	Calcd.	64.86	6.56
				Found	64.82	6.55
	CH_3	216-217	$C_{15}H_{19}N_3O_2$	Calcd.	65.89	6.96
				Found	65.80	6.89
	C_6H_5	186-187	$C_{20}H_{21}N_3O_2$	Calcd.	71.64	6.27
				Found	71.58	6.24

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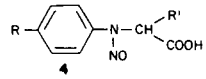
Table II



4

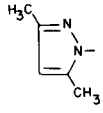
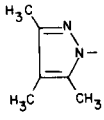
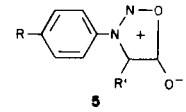
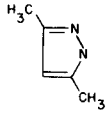
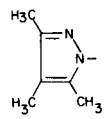
R	R′	M.p. °C	Formula	Calcd. Found	C%	H%
	H	143-144	$C_{11}H_{10}N_4O_3$		53.67	4.07
					53.42	3.99
	CH_3	131-132	$C_{12}H_{12}N_4O_3$		55.39	4.62
					55.12	4.60
	C_6H_5	128-129	$C_{17}H_{14}N_4O_3$		63.34	4.35
					63.28	4.15
	H	166-167	$C_{13}H_{14}N_4O_3$		56.93	5.11
					56.89	5.07
	CH_3	132-133	$C_{14}H_{16}N_4O_3$		58.33	5.56
					58.24	5.48
	C_6H_5	115-116	$C_{19}H_{18}N_4O_3$		65.13	5.14
					65.02	4.98
	H	163-164	$C_{14}H_{16}N_4O_3$		58.32	5.55
					58.30	5.54
	CH_3	136-137	$C_{15}H_{18}N_4O_3$		59.60	5.96
					59.48	5.89
	C_6H_5	153-154	$C_{20}H_{20}N_4O_3$		65.57	5.46
					65.45	5.38

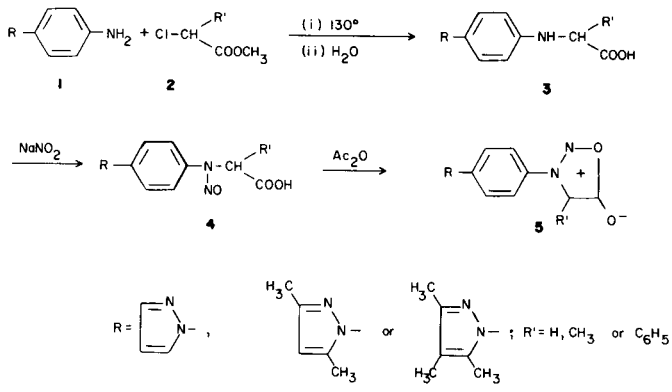
Table III



5

R	R′	M.p. °C	Yield %	Formula	Calcd. Found	C%	H%	Nmr ppm δ Sydnone 4-H	Nmr ppm δ Pyrazole 4-H
	H	188-189	62	$C_{11}H_8N_4O_2$		57.90	3.51	6.7 (s)	6.5 (t)
						57.81	3.60		
	CH_3	163-164	61	$C_{12}H_{10}N_4O_2$		59.51	4.13	—	6.6 (t)
						59.62	4.10		
	C_6H_5	169-170	60	$C_{17}H_{12}N_4O_2$		67.10	3.95	—	6.4 (t)
						67.24	3.90		
	H	139-140	75	$C_{13}H_{12}N_4O_2$		60.94	4.68	6.85 (s)	6.1 (s)
						61.01	4.56		
	CH_3	161-162	65	$C_{14}H_{14}N_4O_2$		63.10	5.30	—	6.05 (s)
						62.98	5.18		
	C_6H_5	171-172	63	$C_{19}H_{16}N_4O_2$		68.47	5.10	—	6.05 (s)
						68.37	4.98		
	H	189-190	76	$C_{14}H_{14}N_4O_2$		62.20	5.18	6.8 (s)	—
						62.24	5.16		
	CH_3	195-196	68	$C_{15}H_{16}N_4O_2$		63.39	6.77	—	—
						63.46	6.69		
	C_6H_5	159-160	70	$C_{19}H_{18}N_4O_2$		69.36	6.55	—	—
						69.42	6.48		

Scheme



1-*p*-Aminophenylpyrazoles **1** were prepared by reduction of *p*-nitrophenylpyrazoles with tin and hydrochloric acid, which in turn were prepared following the literature methods (5,6). The amine was condensed with appropriately substituted α-halogeno acetic esters **2** in the presence of hydrated sodium acetate, and the glycyl ester thus obtained was hydrolysed with sodium hydroxide solution. The *N*-[*p*-(1′-pyrazolyl)]phenylglycines **3** were nitrosated by suspending in water or dilute hydrochloric acid as the case may be. The *N*-nitrosoglycines **4** were cyclised with acetic anhydride to give the corresponding sydnones **5**, according to the Scheme.

All the sydnones exhibit a strong ir band in the range of 1725-1760 cm^{-1} due to sydnone carbonyl stretching. The C-H stretchings of the sydnone and pyrazole appear in the range of 3100-3200 cm^{-1}. Since these could not be distinguished in the ir spectra, the structures for the sydnones and their derivatives were confirmed by the nmr spectra. The data for the nmr signals of sydnone 4-proton and pyrazole 4-proton are given in Table III. The methyl groups in the case of 3-[*p*-(3′,5′-dimethyl-1′-pyrazolyl)]-phenylsydnone and 3-[*p*-(3′,4′,5′-trimethyl-1′-pyrazolyl)]-phenylsydnone show signals at δ 2.45-2.00.

EXPERIMENTAL

All melting points reported herein are uncorrected. Ir spectra of sydnones (as potassium bromide discs) were run on Beckman spectrophotometer. Nmr spectra were determined at 60 MHz on a Varian A-60 nmr spectrophotometer with TMS as an internal reference.

Glycines (**3**).

A mixture of appropriately substituted 1-*p*-aminophenylpyrazoles (0.1 mole), ethyl α-chloroacetate or methyl α-chloropropionate or methyl α-chlorophenylacetate (0.1 mole), sodium acetate (0.15 mole) and ethanol 25 ml. were heated in an oil-bath at 130° for 25 hours. The reaction mixture was cooled poured into water and extracted with ether and the ether was evaporated. The oil was further hydrolysed with 10% aqueous sodium hydroxide solution (0.15 mole), then extracted with ether to remove the unreacted amine and the aqueous layer was cooled and neutralised with hydrochloric acid to give the desired glycines. All of the glycines were crystallised from aqueous ethanol and are listed in Table I (yields are in the range of 70-75%).

N-Nitrosoglycines (**4**).

To a well stirred mixture of glycines (R′ = H) (0.05 mole) in water (100 ml.) at 0-5°, a solution of sodium nitrite (0.06 mole) in water (14 ml.) was added dropwise during 30 minutes. The mixture was allowed to stand overnight, filtered and neutralised with hydrochloric acid. The precipitated nitrosoglycines were filtered, washed thoroughly with cold water and dried in air.

The remaining glycines (R′ = CH_3 and C_6H_5) were nitrosated in 25% hydrochloric acid (100 ml.) at 0-5°. The stirring was continued for 3 hours. The solid was filtered and washed with cold water and dried in air. All the nitrosoglycines were crystallised from aqueous ethanol and are listed in Table II (yields are in the range of 75-80%).

Sydnones (**5**).

All the *N*-nitrosoglycines were heated with acetic anhydride (1:5 by weight) on a water-bath for 3 hours. The reaction mixture was poured on crushed ice to get the corresponding sydnones. All the sydnones were crystallised from ethanol. The results are set out in Table III.

Acknowledgement.

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REFERENCES AND NOTES

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