SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 5-AMINOPYRAZOLES

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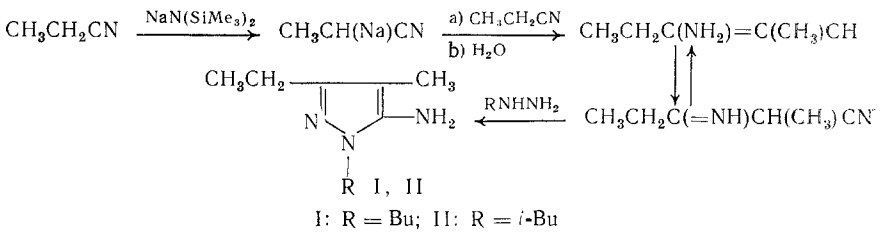
Compounds which contain the pyrazole ring exhibit a variety of biological activities (analgesic, antiinflammatory, etc.). The 5-aminopyrazoles are also potentially biologically active substances which are readily obtained by the cyclization of dimers of nitriles derived from aliphatic carboxylic acids with substituted hydrazines [1]. A study of the literature on these compounds indicates that until the present work, there was no convenient method for the preparation of dimeric nitriles.

It is known that under the action of a base, an aliphatic nitrile containing a mobile α-hydrogen atom will undergo dimerization with formation of a tautomeric mixture of enaminonitriles and iminonitriles. Alkali metals [7, 11], Grignard reagents [2, 3, 5, 8], and salts of dialkyl phosphates and alkali metals [4, 7] have been used as dimerizing agents. The main drawback of these methods is the relatively low yields obtained.

In the present communication, we propose a method of preparing dimeric nitriles with a possible yield of 90-95%. It consists of treating the nitrile with sodium bis(trimethylsilyl)-amide at a low temperature (—60°C), and subsequent condensation of the sodium derivative obtained with a second mole of the nitrile, followed by hydrolysis:



I, II

I: R = Bu; II: R = *i*-Bu

The nitrile dimers are then used for the synthesis of 5-aminopyrazoles. Pharmacological studies showed 1-butyl- and 1-isobutyl-4-methyl-5-aminopyrazoles (I and II) to possess significant anticonvulsant activity.

EXPERIMENTAL CHEMISTRY

Sodium bis(trimethylsilyl)amide was obtained from hexamethyldisilazane and sodium metal [6].

Propionitrile Dimer. To a solution of 54 g (0.25 moles) of sodium bis(trimethylsilyl)-amide in 100 ml of absolute ether, cooled to —50 to —70°C, was added dropwise with vigorous mixing, 16 g (0.29 moles) of propionitrile in 20 ml of absolute ether. Mixing was continued at the same temperature for another hour, a further 16 g (0.29 moles) of propionitrile in 20 ml of absolute ether added, and the temperature gradually allowed to rise to room temperature over a period of about 1 hour. The salt obtained was decomposed with water, the ether layer separated, and the aqueous layer extracted with ether (4 × 40 ml). The ether extracts were combined and dried over $MgSO_4$. The ether was evaporated and the residue fractionally distilled to give 29.2 g (91%) of the dimer, bp 109°C (3 mm of mercury) [8].

The same method was used to prepare: acetonitrile dimer, yield 63%, mp 66°C [10], butyronitrile dimer, yield 89%, bp 147-148°C (10 mm of mercury) [9], valeronitrile dimer yield, 89%, bp 157-158°C (10 mm of mercury) [11].

1-Isobutyl-3-ethyl-4-methyl-5-aminopyrazole (II). To a boiling mixture of 20 g (0.23 moles) of isobutylhydrazine and 24.6 g (0.23 moles) of dipropionitrile in 40 ml of isopropyl

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TABLE 1. Preventive Anticonvulsant Effect of Compounds on Mice Injected with Lethal Doses of Strychnine

Compound	Dose, mg/kg	Number of animals	No. of animals destroyed, %
Control	—	20	100
I	250	10	0
II	200	10	80
Diphenine	200	12	50
Hexamidine	250	10	90

Note. Diphenine (250 mg/kg) caused marked loss of motor function and a number of the animals were destroyed by the diphenine before injection of strychnine; diphenine was therefore used at a dosage of 200 mg/kg.

alcohol was added 11 ml (0.23 moles) of concentrated HCl. The mixture was refluxed in a water bath for 20 min, a further 25 ml of concentrated HCl added and refluxing continued for 1.5 h. The isopropyl alcohol was evaporated and the residue made alkaline, first with 40% KOH, then with solid alkali. The crystalline material was separated, dried, and recrystallized from hexane to give 20 g (70%) of product with mp 66-67°C. Found, %: C 66.21, H 10.76. $C_{10}H_{19}N_3$. Calculated, %: C 66.29, H 10.57.

1-Butyl-3-ethyl-4-methyl-5-aminopyrazole (I). The same method was used to prepare 1-butyl-3-ethyl-4-methyl-5-aminopyrazole (I), yield 58.3%, mp 117°C. Found, %: C 66.46, H 10.57. $C_{10}H_{19}N_3$. Calculated, %: C 66.29, H 10.52. IR spectra show that both compounds absorb strongly at 3400 cm^{-1} (NH_2).

EXPERIMENTAL PHARMACOLOGY

The physiological action of the compounds was studied on male nonpedigree white mice. The compounds were injected intraperitoneally 30 min before the intravenous injection of a lethal dose of strychnine. For comparison known anticonvulsant agents were used — diphenine and hexamidine (see Table 1).

Examination of the specific preventive action of the compounds on models of lethal strychnine poisoning of animals showed that compound II, in doses which did not destroy motor functions, exhibited weak anticonvulsant effect.

In contrast, compound I showed considerably greater antagonism to the action of strychnine. A preliminary injection of this compound completely prevented the onset of convulsions caused by administration of a lethal dose of strychnine. Furthermore, all the animals survived.

Diphenine and hexamidine had less effect on strychnine convulsions.

Derivatives of 5-aminopyrazole have been prepared and have been shown to have a more selective action against strychnine convulsions than known drugs of this type; this suggests new lines of approach in the search for anticonvulsants.

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