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2-(2'-Arylamino)ethyl-1,3,4-oxadiazoles and Thiadiazoles.

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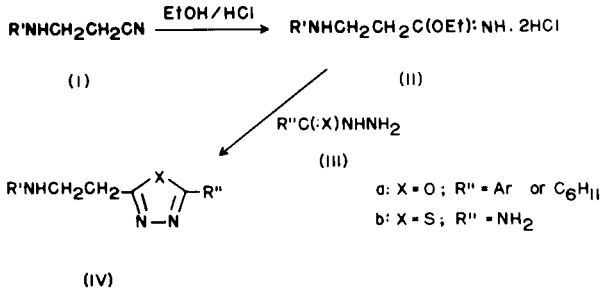
1-Arylamino-2-cyanoethanes (I, R' = Ar) (1,2) were converted to iminoether hydrochlorides (II) (3). Condensation of the latter with acylhydrazines (III), including thiosemicarbazide, under alkaline conditions, was unsuccessful, presumably because of the instability of the free bases. Under acidic conditions oxadiazoles (IVa) and thiadiazoles (IVb) were obtained, mostly in low yields.



For the cyanoethylation of aniline, base and diethylamine hydrochloride were more convenient to use than aniline hydrochloride and diethylamine (1). Compounds (II) were found to be dihydrochlorides, not monohydrochlorides (3). A slight modification of Bekhli's procedure (3) improved yields and raised melting points (at which decomposition occurred).

The preparation of oxadiazoles (IVa) was best carried out at *p*H 4-5; the analogous thiadiazoles (IVb) require less care in adjusting the *p*H of the reaction mixture. Formation of 1,2,4-triazoles does not appear to occur: aminoguanidine (4), formhydrazide and acethydrazide gave tars with II.

The syntheses may be extended to cyclohexyl derivatives, starting with (I, R' = cyclohexyl) (5).

Elemental analyses and physical properties distinguish the oxadiazoles and thiadiazoles listed in the Tables from 1,2,4-triazoles and possible acyclic intermediates.

The oxadiazole (IVa, R' = Ph, R" = 4-pyridyl) occurs in two forms melting at 106° and 116° respectively. Although the latter form was more stable, the transformation of the lower melting form was rather slow. The ultra-violet spectra of both forms in methanol were identical. The infra-red spectra were closely similar; the main differences were: the low melting form had a single band at 750 cm^{-1}, while the corresponding band of the higher melting form was split; the free NH band of the low melting form (3398-3400 cm^{-1}) was shifted to 3360-3368 cm^{-1} in the higher melting form.

EXPERIMENTAL

Melting points (uncorrected) and analytical data are listed in the Tables. The following examples illustrate the preparative methods.

Ethyl 2-Phenylaminopropaniminoate (II, R' = Ph) Dihydrochloride.

2-Phenylamino-1-cyanoethane (1) (0.1 mole) in a mixture of absolute ethanol (23 ml.) and dry chloroform (30 ml.), was treated with 2 equivalents of dry hydrogen chloride at or below -5°. After standing in a refrigerator overnight, the mixture was diluted with anhydrous ether and filtered. The white prisms were washed with ether and obtained in near-quantitative yield, m.p. 120-121° (dec.); Bekhli (3) reports 67% yield, m.p. 110° (dec.).

2-(2'-Phenylamino)ethyl-5-cyclohexyl-1,3,4-oxadiazole.

A mixture of (II, R' = Ph) dihydrochloride (0.025 mole) and the hydrazide of carboxycyclohexane (0.025 mole) in methanol (100 ml.) was brought to *p*H 4-5 by addition of a solution of potassium hydroxide (0.025 mole) in methanol (50 ml.). The mixture was boiled under reflux for 10 minutes and, after standing at room temperature for 30 minutes, adjusted to *p*H 7-8 with 5% aqueous sodium carbonate solution. The solution was evaporated to dryness in vacuum, and the residue extracted with benzene. Recrystallization of this extracted product from a mixture of benzene and light petroleum gave flat needles, 1.2 g. (18%), m.p. 111°.

2-(2'-Phenylaminoethyl)-5-amino-1,3,4-thiadiazole.

To a boiling solution of thiosemicarbazide (0.044 mole) in methanol (250 ml.) ethyl 2-phenylaminopropaniminoate dihydrochloride (0.04 mole) was added. After being boiled under reflux for 2 hours, a solution of potassium hydroxide (0.04 mole) in methanol (30 ml.) was added and refluxing continued for another hour. The solution was concentrated to 50 ml. on a water bath in vacuum and adjusted to *p*H 7-8 with 5% aqueous sodium carbonate solution. The white precipitate was filtered, washed with water and recrystallized from a mixture of methanol, ether and light petroleum to give white prisms, 2.15 g. (24%), m.p. 162°.

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TABLE I

N-Substituted 2-(2'-Arylamino)ethyl-1,3,4-oxadiazoles (IVa)

R'	R''	Yield %	m.p. °C	Recrystallization	Analysis
Ph-	Ph-	24-35	121	prisms from benzene	Found: C, 72.97; H, 5.82; N, 15.85. $C_{16}H_{15}N_3O$ requires: C, 72.43; H, 5.70; N, 15.84%.
Ph-	Cyclohexyl	18	111	flat needles from benzene/light petroleum	Found: C, 71.15; H, 7.76; N, 15.24. $C_{16}H_{21}N_3O$ requires: C, 70.79; H, 7.80; N, 15.48%.
Ph-	4-pyridyl	9	106	needles from benzene/light petroleum	Found: C, 67.74; H, 5.25; N, 20.98. $C_{15}H_{14}N_4O$ requires: C, 67.66; H, 5.30; N, 21.04%.
m-ClC_6H_4-	Ph-	8	138	needles from benzene/light petroleum	Found: C, 64.27; H, 4.78; N, 14.09. $C_{16}H_{14}ClN_3O$ requires: C, 64.09; H, 4.71; N, 14.02%.
p-ClC_6H_4-	Ph-	60	104	needles from benzene/light petroleum	Found: C, 62.98; H, 5.73; N, 12.32; O, 9.21. $C_{16}H_{14}ClN_3O$ + C_2H_5OH (*i.e.* $C_{18}H_{20}ClN_3O_2$) requires: C, 62.53; H, 5.83; N, 12.15; O, 9.25%.
p-ClC_6H_4-	Cyclohexyl	71	104	needles from benzene/light petroleum	Found: C, 61.58; H, 7.34; N, 11.49; O, 9.66. $C_{16}H_{20}ClN_3O$ + C_2H_5OH (*i.e.* $C_{18}H_{26}ClN_3O_2$) requires: C, 61.45; H, 7.45; N, 11.94; O, 9.09%.
p-$MeOC_6H_4$-	Ph-	4	128	needles from benzene/light petroleum	Found: C, 69.19; H, 5.83; N, 13.96. $C_{17}H_{17}N_3O_2$ requires: C, 69.11; H, 5.81; N, 14.23%.
p-$EtOC_6H_4$-	Ph-	45	111	rods from benzene/light petroleum	Found: C, 70.16; H, 6.34; N, 13.20. $C_{18}H_{19}N_3O_2$ requires: C, 69.86; H, 6.19; N, 13.58%.
cyclohexyl	Ph-	9	66	needles from ether/light petroleum	Found: C, 70.87; H, 7.93; N, 15.40. $C_{16}H_{21}N_3O$ requires: C, 70.79; H, 7.80; N, 15.48%.
cyclohexyl	4-pyridyl	12-19	76	needles from ether/light petroleum	Found: C, 66.12; H, 7.41; N, 20.46. $C_{15}H_{20}N_4O$ requires: C, 66.15; H, 7.41; N, 20.57%.

TABLE II

2-(2'-Arylamino)ethyl-5-amino-1,3,4-thiadiazoles (IVb)

R'	Yield %	m.p. °C	Recrystallization	Analysis
Ph-	24	162	prisms from methanol/ether/light petroleum	Found: C, 54.76; H, 5.69; N, 25.08. $C_{10}H_{12}N_4S$ requires: C, 54.51; H, 5.49; N, 25.44%.
m-ClC_6H_4-	5	167	plates from chloroform	Found: C, 47.11; H, 4.49; N, 21.66; S, 12.51. $C_{10}H_{11}ClN_4S$ requires: C, 47.14; H, 4.35; N, 22.00; S, 12.59%.
p-ClC_6H_4-	38	158	plates from methanol/ether	Found: C, 47.57; H, 4.47; N, 21.76; S, 12.42. $C_{10}H_{11}ClN_4S$ requires: C, 47.14; H, 4.36; N, 22.00; S, 12.59%.
p-$EtOC_6H_4$-	24	200	needles or plates from methanol	Found: C, 54.85; H, 6.32; N, 21.01; S, 11.24. $C_{12}H_{16}N_4OS$ requires: C, 54.51; H, 6.10; N, 21.19; S, 12.13%.

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