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The Dialkylaminoalkylation of Some 5-Monosubstituted Tetrazoles

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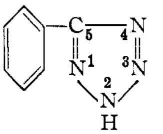
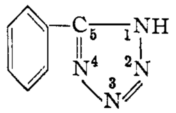
A number of 5-aryltetrazoles have been alkylated with various dialkylaminoalkyl chlorides. The ultraviolet spectra of the hydrochlorides and methiodides are reported.

It was shown in an earlier paper[1] that 5-phenyltetrazole could be alkylated with methyl iodide in the presence of aqueous sodium hydroxide. Although there are two tautomeric forms of 5-phenyltetrazole having a hydrogen on a nitrogen, in the methylation of this compound the resultant compound is predominantly the 2-substituted isomer.





Recently Henry[2] has shown that by the use of selective solvents both isomers can be isolated in a ratio of approximately four parts of the 2-substituted tetrazole to one part of the 1-substituted tetrazole.

An examination[1] of the ultraviolet spectra of 5-phenyltetrazole and of the isomeric methyl-5-phenyltetrazoles showed that each gave nearly the same maximum.

A number of 5-substituted tetrazoles were accordingly alkylated by various dialkylaminoalkyl halides using aqueous sodium hydroxide diluted with acetone. As in the methylation of 5-phenyltetrazole, only one isomer was isolated in each alkylation; no attempt was made to obtain the other isomer.

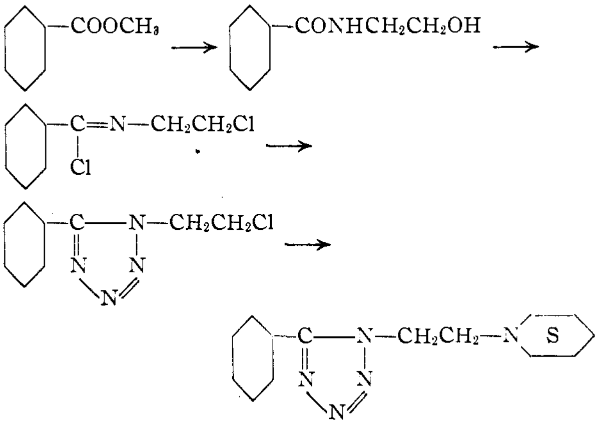
In one case the 1-isomer was prepared by an unequivocal synthesis. A mixed melting point determination with the isomer obtained by direct alkylation exhibited a 25° depression.

1-[2-(1-Piperidyl)-ethyl]-5-phenyltetrazole was prepared, following the method of von Braun,[3] by converting methyl benzoate to 2-benzamidoethanol, chlorinating with thionyl chloride to give N-2-chloroethylbenzimidyl chloride treating with hydrazoic acid to form 1-(2-chloroethyl)-5-phenyltetrazole and finally amination with piperidine, as shown in the chart.

An examination of the ultraviolet spectra of both the hydrochlorides and methiodides of the basic disubstituted tetrazoles indicated that the curves within each of the two series were nearly coincident. Just as the ultraviolet spectrum of 1-methyl-5-phenyltetrazole did not materially differ from that of the isomeric 2-methyl-5-phenyltetrazole, so the spectrum of 1-[2-(1-piperidyl)-ethyl]-5-phenyltetrazole did not differ from that of its corresponding 2-isomer.

It has been assumed that the isomer obtained in each alkylation is the 2-isomer.

The 5-aryltetrazoles were prepared by converting the appropriate nitriles to their iminoethers which were in turn treated with hydrazine and then nitrous acid, in the manner first described by Pinner.[4]



Although benzotriazole which carries an active hydrogen atom on a nitrogen condensed readily with formalin and piperidine,[5] the Mannich reaction failed when applied to 5-phenyltetrazole. This might have been anticipated in view of the acidic nature of the hydrogen on tetrazole. As noted by Benson,[6] the 5-substituted tetrazoles are about as strongly acidic as the simple carboxylic acids, which do not yield an isolable product in this reaction.

The methiodides were found to have little or no curarimimetic or ganglionic blocking activity; the hydrochlorides little or no analgetic, local anesthetic or antispasmodic effects.

Experimental[7,8]

5-Phenyltetrazole,[3] 5-(4-nitrophenyl)-tetrazole,[9] 5-cyclohexyltetrazole,[1] 2-benzamidoethanol,[10] 5-(2-thienyl)-tetrazole,[1] 5-(3-thienyl)-tetrazole[1] and piperonylonitrile[11] were prepared as described in the literature.

5-Piperonylotetrazole.—Piperonylonitrile[11] (49 g., 0.33 mole) was converted to the methyl imino ester, yield 65 g. (90%), m.p. 162–163°.

Treatment with hydrazine and nitrous acid in the regular manner gave the tetrazole, 20 g. (35%), m.p. 253–255° (dec.).

Anal. Calcd. for $C_8H_6N_4O_2$: C, 50.52; H, 3.18; N, 29.47. Found: C, 50.81; H, 3.33; N, 28.95.

2-(2-Dimethylaminoethyl)-5-phenyltetrazole.—All of the alkylations were essentially the same and this is a typical example.

5-Phenyltetrazole (7.3 g., 0.05 mole) and dimethylamino-

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[1] B. Elpern and F. C. Nachod, THIS JOURNAL, **72**, 3379 (1950).

[2] R. A. Henry, *ibid.*, **73**, 4470 (1951).

[3] J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

[4] A. Pinner, *ibid.*, **27**, 984 (1894).

[5] G. B. Bachman and L. V. Heisey, THIS JOURNAL, **68**, 2496 (1946).

[6] F. Benson, *Chem. Revs.*, **41**, 1 (1947).

[7] All melting points are corrected. Microanalyses were performed by Mr. M. E. Auerbach and staff.

[8] Ultraviolet spectra were obtained by Dr. F. C. Nachod and staff.

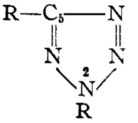
[9] A. Pinner, *Ann.*, **298**, 1 (1897).

[10] A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).

[11] E. Marcus, *Ber.*, **24**, 3650 (1891).

TABLE I

2,5-DISUBSTITUTED-TETRAZOLE HYDROCHLORIDES



R_2	R_5	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Absorption max. λ, mμ	Absorption max. ε × 10³
$(CH_3)_2NCH_2CH_2CH_2$–	Phenyl-	$C_{12}H_{18}ClN_5$	165.7–167.1	[a]		13.25	13.00	239	16.6[b]
$OC_4H_8NCH_2CH_2$–	Phenyl-	$C_{13}H_{18}ClN_5O$	212.6–214	23.69	23.69	11.99	12.21	240	16.7
$C_5H_{10}NCH_2CH_2$–[c]	Phenyl-	$C_{14}H_{20}ClN_5$	219–221.5	23.84	23.78	12.01	12.00	240	16.7
$(C_2H_5)_2NCH_2CH_2$–	Phenyl-	$C_{13}H_{20}ClN_5$	126.2–127.5	24.85	25.04	12.58	12.61	240	16.8
$(CH_3)_2NCH_2CH_2$–	Phenyl-	$C_{11}H_{16}ClN_5$	213.4–215	27.61	27.85	[d]		240	16.2
$(CH_3)_2NCH_2CH_2$–	Cyclohexyl-	$C_{11}H_{22}ClN_5$	190–191.5	26.96	26.97	13.65	13.36	[e]	
$(CH_3)_2NCH_2CH_2$–	2-Thienyl-	$C_9H_{14}ClN_5S$	210.8–211.8	[f]		[f]		256	6.9[h]
$(CH_3)_2NCH_2CH_2$–	3-Thienyl-	$C_9H_{14}ClN_5S$	219.5–221	[g]		[g]		245	12.4
$(CH_3)_2NCH_2CH_2$–	4-Nitrophenyl-	$C_{11}H_{15}ClN_6O_2$	224–225	[i]		11.87	11.72	...	..
$(CH_3)_2NCH_2CH_2$–	Piperonyl-	$C_{12}H_{16}ClN_5O_2$	229–230.8	[j]		11.91	11.75	215	22.6[k]
$(C_4H_9)_2NCH_2CH_2$–	Piperonyl-	$C_{18}H_{28}ClN_5O_2$	112.2–113.6	[l]		9.29	9.22	...	..

[a] *Anal.* Calcd.: C, 53.86; H, 6.77. Found: C, 53.97; H, 6.73. [b] Abs. max. 275, ε, 1000. [c] Abs. max. 232, ε 10400. [d] *Anal.* Calcd.: C, 52.06; H, 6.36. Found: C, 52.33; H, 6.15. [e] Only end absorption. [f] *Anal.* Calcd.: C, 41.61; H, 5.43; S, 12.34. Found: C, 41.64; H, 5.24; S, 12.13. [g] *Anal.* Calcd.: C, 41.61; H, 5.43; S, 12.34. Found: C, 41.74; H, 5.40; S, 12.44. [h] Abs. max. 271, ε 7300. [i] *Anal.* Calcd.: C, 44.22; H, 5.06. Found: C, 44.80; H, 5.48. [j] *Anal.* Calcd.: C, 48.40; H, 5.42. Found: C, 48.35; H, 5.55. [k] Abs. max. 263, ε 8500; abs. max. 298, ε 6500; resembles the spectrum of piperonal. [l] *Anal.* Calcd.: C, 56.61; H, 7.39. Found: C, 56.61; H, 7.12.

TABLE II

2,5-DISUBSTITUTED-TETRAZOLE METHIODIDES

R_2	R_5	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Iodine, % Calcd.	Iodine, % Found	Absorption max. λ, mu	Absorption max. ε × 10³
$(CH_3)_2NCH_2CH_2CH_2$–	Phenyl-	$C_{13}H_{20}IN_5$	198.4–199.8	[a]		34.00	33.94	...	..
$OC_4H_8NCH_2CH_2$–	Phenyl-	$C_{14}H_{20}IN_5O$	221.2–221.6	17.46	17.59	31.63	31.62	221	21.3
$C_5H_{10}NCH_2CH_2$–	Phenyl-	$C_{15}H_{22}IN_5$	170–173	17.55	17.62	31.79	31.60	220	21.2
$(C_2H_5)_2NCH_2CH_2$–	Phenyl-	$C_{14}H_{22}IN_5$	132–133.5	[b]		32.78	32.42	223	23.4
$(CH_3)_2NCH_2CH_2$–	Phenyl-	$C_{12}H_{18}IN_5$	234.5–240	19.50	19.21	35.33	35.20	223	23.4
$(CH_3)_2NCH_2CH_2$–	Cyclohexyl-	$C_{12}H_{24}IN_5$	206.2–207	[c]		34.74	34.62	220	16.4
$(CH_3)_2NCH_2CH_2$–	2-Thienyl-	$C_{10}H_{16}IN_5S$	238–240	19.18	19.24	34.75	34.45	219	16.6[d]
$(CH_3)_2NCH_2CH_2$–	3-Thienyl-	$C_{10}H_{16}IN_5S$	234–235	[e]		34.75	34.97	[f]	
$(CH_3)_2NCH_2CH_2$–	4-Nitrophenyl-	$C_{12}H_{17}IN_6O_2$	234–235	20.79	20.42	[g]		...	..
$(CH_3)_2NCH_2CH_2$–	Piperonyl-	$C_{13}H_{18}IN_5O_2$	232 dec.	[h]		31.48	31.24	218	38.1[i]

[a] *Anal.* Calcd.: C, 41.83; H, 5.40. Found: C, 41.79; H, 5.58. [b] *Anal.* Calcd.: C, 43.42; H, 5.73. Found: C, 43.51; H, 5.75. [c] *Anal.* Calcd.: C, 39.45; H, 6.62. Found: C, 39.28; H, 6.47. [d] Abs. max. 256, ε 11.6; abs. max. 271, ε 12.8. [e] *Anal.* Calcd.: C, 32.88; H, 4.42. Found: C, 32.88; H, 4.12. [f] Inflection point, 245; ε 12.3. [g] *Anal.* Calcd.: C, 35.66; H, 4.24. Found: C, 35.75; H, 4.54. [h] *Anal.* Calcd.: C, 38.73; H, 4.50. Found: C, 38.64; H, 4.61. [i] Abs. max. 261, ε 9900; abs. max. 300, ε 7600; resembles the spectrum of piperonal.

ethyl chloride hydrochloride (7.2 g., 0.05 mole) were suspended in acetone (80 ml.). Sodium hydroxide (8.4 g., 0.21 mole) in water (7.5 ml.) was added all at once and the mixture stirred and refluxed for 1 hour. Water (50 ml.) was added and the mixture extracted with benzene. The solvent was removed from the benzene extract and the residual oil divided into two parts, one of which was converted into the hydrochloride and the other into the methiodide.

1-(2-Chloroethyl)-5-phenyltetrazole.—2-Benzamidoethanol[10] (16.6 g., 0.1 mole) was suspended in thionyl chloride (47.6 g., 0.4 mole) and maintained below 40° until solution was effected. After warming gently on a water-bath 3 hours the excess thionyl chloride was removed *in vacuo*. The residual N-2-chloroethylbenzimidyl chloride was dissolved in dry benzene (150 ml.), a 4% solution of hydrazoic acid in benzene (100 ml.) added all at once and the mixture warmed at 75° until the moderate evolution of hydrogen chloride stopped. The solvent was removed *in vacuo*, and water (150 ml.) was added to the orange residue. After heating on a steam-bath for 30 minutes, this oil was extracted with benzene and dried azeotropically. The oily residue foamed so excessively, distillation was not attempted and the oil was used directly in the amination.

1-[2-(1-Piperidylethyl)]-5-phenyltetrazole Hydrochloride.—1-(2-Chloroethyl-5-phenyltetrazole (2.1 g.), piperidine (15 ml.) and benzene (100 ml.) were refluxed 3.5 hours. After concentrating the reaction mixture to dryness *in vacuo*, the residue was extracted with dilute hydrochloric acid. The acidic extract was treated with charcoal and then made strongly alkaline. The oil that formed was extracted with benzene, dried azeotropically and then treated with alcoholic hydrogen chloride. The white gum which came down was triturated with isopropyl alcohol and there was obtained 0.7 g. (24%) of white crystals, m.p. 213.5–215.5°.

Anal. Calcd. for $C_{14}H_{20}ClN_5$: C, 57.23; H, 6.86; Cl, 12.07. Found: C, 57.37; H, 6.67; Cl, 12.10.

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