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THE SYNTHESIS OF 1,5-DISUBSTITUTED TETRAZOLES

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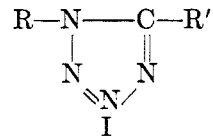
In a previous communication the synthesis of various alkylated pentamethylenetetrazoles was described (1). The activity of pentamethylenetetrazole (Metrazol) as an analeptic and respiratory stimulant was enhanced by the substitution of alkyl groups in the pentamethylene ring (2). In continuing our studies of the effect of structure on the pharmacologic activity in the tetrazole series it became of interest to determine whether similar relationships existed in a series of simple 1,5-disubstituted tetrazoles (I). Although a number of such structures in which one of the substituents on the tetrazole ring is an aromatic group are known (3), only a single example, 1,5-dimethyltetrazole, in which both substituents are aliphatic in character has been described.



I

Initially the scope of this investigation was limited to a group of compounds in which R and R′ were groups such as methyl, ethyl, butyl, isobutyl, cyclohexyl, and phenyl. A series of tetrazoles exhibiting systematic variations of the foregoing substituents in both positions was prepared so that the pharmacologic effects of lengthened and branched chains in the aliphatic series, of cycloaliphatic, and of aromatic groups could be correlated. As the work progressed the results of pharmacologic tests indicated the desirability of synthesizing a number of other structures to elaborate more completely the trends.

Several methods for the synthesis of 1,5-disubstituted tetrazoles have been described (3). Schmidt (4) has described an apparently simple method for the conversion of ketones into tetrazoles by interaction with hydrazoic acid in the presence of sulfuric acid. The process appears to be an elaboration of the Schmidt reaction (5) for the conversion of ketones to amides and is said to take place when the ketone reacts with two moles of hydrazoic acid. According to Schmidt (6) hydrazoic acid will decompose in the presence of concentrated sulfuric acid with liberation of nitrogen and formation of an imine radical. Through interaction of the ketone with this radical an oxime is assumed to form and undergo rearrangement to the amide under the influence of sulfuric acid (7). Tetrazole

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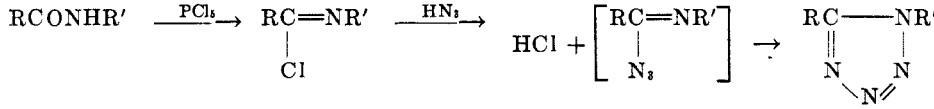
formation is explained by the interaction of a second mole of hydrazoic acid with the oxime or some intermediate during the rearrangement. In support of these suggestions the formation of 1,5-dimethyltetrazole by interaction of the benzenesulfonic ester of acetoxime and sodium azide (8), and the failure of amides to yield tetrazoles under the conditions of the Schmidt reaction have been cited. The formation of a compound said to be 1-benzyl-5-methyltetrazole by interaction of the toluenesulfonate of methyl benzyl ketoxime and sodium azide has also been described (8). Smith (9) has recently subjected that aspect of the Schmidt reaction involving the interaction of ketones and hydrazoic acid to a critical study and has developed a more acceptable interpretation of the mechanism involved in both amide and tetrazole formation.

In attempts to apply Schmidt's procedure to the synthesis of symmetrically substituted 1,5-dialkyltetrazoles it was not possible to confirm his results completely. Under the conditions set forth by this author we obtained 1,5-dimethyltetrazole in 12% yield from acetone, N-methylacetamide being the major product of the reaction. Schmidt (4) reported an 80% yield of the tetrazole in this case. Similarly, from diethyl ketone, N-ethylpropionamide was formed in 88% yield, together with correspondingly small amounts of the tetrazole, while diisobutyl ketone under similar conditions gave 46% of N-isobutylisovaleramide and 24% of 1,5-diisobutyltetrazole. Although the conditions of the reactions were subjected to considerable variation, in our hands the procedure failed to lead to a tetrazole as the major product in any instance.

Lack of success in duplicating Schmidt's claims prompted the investigation of procedures for the preparation of 1,5-disubstituted tetrazoles from N-substituted amides. Forster (10) had demonstrated the possibility of synthesizing 1-hydroxy-5-phenyltetrazole by interaction of benzhydroximidyl chloride and sodium azide. At about the same time Schroeter (11) succeeded in converting the imide chloride of benzanilide into 1,5-diphenyltetrazole by warming the chloride with sodium azide suspended in amyl ether. von Braun and Rudolph (12) improved the procedure by treating the imide chlorides with hydrazoic acid in benzene or chloroform solution. Most imide chlorides, R'C(Cl)=NR, excepting those derived from N-aryl aromatic amides in which both R and R' are aryl groups, are rather unstable substances which undergo thermal decomposition quite readily. For instance, imide chlorides in which R' is aromatic and R is aliphatic decompose readily on warming with the formation of an alkyl chloride and an aromatic nitrile (13). Since the use of hydrazoic acid solutions permitted the reaction with the imide chlorides to take place at room temperature or only slightly above, von Braun and Rudolph were able to increase the scope of the



procedure to include many imide chlorides which had not been susceptible to reaction at the higher temperatures required when sodium azide was employed.

The foregoing sequence of reactions was applied by von Braun and Rudolph

only to imide chlorides in which R′ was aromatic and R was either aliphatic or aromatic. The restriction to imide chlorides derived from anilides appeared to be based on earlier work by von Braun and his co-workers (14, 16) in which it was shown that the chlorides of aliphatic amides of the type $RCH_2C(Cl)=NR'$, where R was either hydrogen or an aliphatic group and R′ was either aliphatic or aromatic, were characterized by such great reactivity that they could not be isolated. Such imide chlorides readily formed amidine-like condensation products apparently due to a primary shift of hydrogen from the *alpha*-carbon to nitrogen followed by a reaction between the tautomeric forms with elimination of hydrogen chloride (15).

$$RCH_2C(Cl)=NR' \rightleftarrows RCH=C(Cl)NHR'$$

$$\begin{matrix} RCH_2C(Cl)=NR' \\ + \\ RCH=C(Cl)NHR' \end{matrix} \rightarrow \begin{matrix} RCH_2C=NR' \\ | \\ RCH=C(Cl)NR' \end{matrix} + HCl$$

The same authors also indicated that imide chlorides of the type $R_2CHC(Cl)=NR'$, where R and R′ are both aliphatic, are likewise unstable, but that the complete replacement of the hydrogen on the *alpha*-carbon by alkyl groups would lead to stable products.

Although von Braun attributed a rather high degree of instability to most imide chlorides, this conclusion was based on attempts to isolate these compounds. Our experience with a variety of purely aliphatic, as well as mixed aliphatic-aromatic N-substituted amides, indicates that all of these compounds can easily be converted into derivatives that behave like imide chlorides by interaction with phosphorus pentachloride in an inert solvent, provided the reaction mixtures are kept near or only slightly above room temperature. Although von Braun and his coworkers frequently employed inert solvents or diluents, their reactions were always carried out with a large excess (2–3 moles) of phosphorus pentachloride. Our experience has indicated that the addition of an equimolar quantity of phosphorus pentachloride to a benzene solution or suspension of the substituted amide sufficed for complete conversion of the latter to the corresponding imide chloride. The resulting benzene solution of the imide chloride upon treatment with a solution of hydrazoic acid in the same solvent gave evidence of further reaction by the elimination of hydrogen chloride. It was generally found desirable to heat the reaction mixture slowly to boiling after complete addition of the hydrazoic acid, and to maintain this temperature for some time in order to obtain the maximum yield of tetrazole. Throughout this period hydrogen chloride evolution continued at a gradually decreasing rate. These observations suggest the possibility of the initial formation of an imide azide which slowly cyclizes to the tetrazole, although we have not attempted to isolate such intermediates. The presence of hydrogen chloride to the extent that it was soluble in the benzene solution and of phosphorus oxychloride, formed by interaction of the amides with the pentachloride, did not appear to interfere with the reaction

of the imide chlorides and hydrazoic acid. In several experiments in which the benzene solution of the imide chloride was concentrated to remove hydrogen chloride and at least part of the oxychloride, no improvement in the yield of tetrazole was noted. In fact, with the more heat-sensitive imide chlorides the best results were obtained when all procedures that involved warming prior to treatment with hydrazoic acid were avoided insofar as possible.

In Table II are recorded the code numbers, names, and other pertinent data for all the 1,5-disubstituted tetrazoles prepared during the course of this work. All the products were colorless, crystalline solids, insoluble in cold water excepting those having relatively small aliphatic substituent groups. Both 1,5-dimethyl and 1-isobutyl-5-methyltetrazole were quite soluble in cold water, 10% solutions in water being used for testing purposes. When one of the substituents was a cyclic group and the other a methyl group, the compounds usually exhibited a slight solubility in cold water and a sufficiently increased solubility in hot water to permit satisfactory recrystallization. Most of the compounds were readily soluble in organic solvents such as benzene, toluene, ether, ethanol, ethyl acetate, and acetone, especially on warming, but they were practically insoluble in petroleum ether. Only 1,5-diphenyltetrazole failed to exhibit moderate solubility in most of these solvents. All of the compounds were heat-stable and those of lower molecular weight could be distilled under reduced pressure. They failed to form salts with aqueous acids or bases and withstood treatment with hot 50% sulfuric acid or 40% sodium hydroxide solution.

The results of screening tests of the pharmacologic action of the compounds have been reported by Gross and Featherstone (17). They concluded that the optimal structural features for maximum stimulatory action were the presence of a saturated cyclic group or a comparably large aliphatic group in position 1 and a small group, preferably methyl, in the 5 position of the tetrazole ring. Potent stimulatory effects were exhibited by 1-cyclohexyl-5-methyl-, 1-cyclohexyl-5-ethyl-, 1-cyclopentyl-5-methyl-, and 1-isobutyl-5-methyl-tetrazole. The first two also exhibited marked respiratory stimulation and analeptic action, the methyl compound being effective at much lower dosage than the ethyl compound.

EXPERIMENTAL[5]

Amides. The N-substituted amides were prepared by treatment of the appropriate primary amines with suitable acid anhydrides or acid chlorides. When acid anhydrides were used, the amine was treated with an excess of the anhydride usually with the corresponding acid as solvent. When acid chlorides were used, these were added dropwise to a benzene solution of two moles of amine or one mole of amine together with one mole of pyridine. External cooling was applied when needed. After washing the benzene solution of the amide with water and drying over sodium sulfate, the solvent was removed by distillation and the residual amide was purified either by crystallization from the appropriate solvent or by distillation under reduced pressure. In Table I are listed the amides used or prepared

[5] Microanalyses were carried out on all compounds described in this communication by Mr. William Saschek.

as intermediates together with their physical constants, analyses, and other pertinent data in those instances where the products have not been previously described in the literature.

Tetrazoles from ketones. Caution: Hydrazoic acid vapors are highly toxic and all reactions involving its use should be carried out in a good hood. The use of heavy metals such as mercury in thermometers or seals should be avoided. Although the preparation of 1,5-diisobutyl-

TABLE I

N-SUBSTITUTED AMIDES $R_1NH—COR_2$

AMIDE	R_1	R_2	M.P. (B.P.), °C.[i]	REFERENCE
N-Methylacetamide	CH_3	CH_3	(206)	18
N-Isobutylacetamide	iso-C_4H_9	CH_3	(219.5–224)	19
Acetanilide	C_6H_5[j]	CH_3	114	20
Propionanilide	C_6H_5[j]	C_2H_5	103.5–104	21
Isobutyranilide	C_6H_5	iso-C_4H_9	109–110	22
Hexahydrobenzanilide	C_6H_5	cyclo-C_6H_{11}	131–132	23
Benzanilide	C_6H_5[j]	C_6H_5	160–161	24
N-Methylbenzamide	CH_3	C_6H_5	77	25
N-Ethylbenzamide	C_2H_5	C_6H_5	68.5	25
N-Isobutylbenzamide	iso-C_4H_9	C_6H_5	(180–181/ 11 mm.)	26
N-Cyclohexylbenzamide	cyclo-C_6H_{11}	C_6H_5	149.5	27, 28
N-Cyclohexylacetamide	cyclo-C_6H_{11}	CH_3	107–109	28
N-Cyclohexylpropionamide	cyclo-C_6H_{11}	C_2H_5	92	23
N-Cyclohexyl-*n*-butyramide	cyclo-C_6H_{11}	*n*-C_3H_7	66–67	[a]
N-Cyclohexylisobutyramide	cyclo-C_6H_{11}	iso-C_3H_7	119	[b]
N-Cyclohexyl-*n*-valeramide	cyclo-C_6H_{11}	*n*-$_4CH_9$	68	[c]
N-Cyclohexylisovaleramide	cyclo-C_6H_{11}	iso-C_4H_9	105.5–107	[d]
N-Cyclohexylhexahydrobenzamide	cyclo-C_6H_{11}	cyclo-C_6H_{11}	172–173	[e]
N-Methylhexahydrobenzamide	CH_3	cyclo-C_6H_{11}	115–116	[f]
N-Ethylhexahydrobenzamide	C_2H_5	cyclo-C_6H_{11}	94–95	14
N-Isobutylhexahydrobenzamide	iso-C_4H_9	cyclo-C_6H_{11}	127–128	[g]
N-Cyclopentylacetamide	cyclo-C_5H_9	CH_3	(146–149/ 22 mm.)	[h]
Acetyl-*p*-anisidine	*p*-$CH_3OC_6H_4$[j]	CH_3	127	29

[a] Crystallized from heptane. *Anal.* Calc'd for $C_{10}H_{19}NO$: N, 8.3. Found: N, 8.2. [b] Crystallized from heptane. *Anal.* Calc'd for $C_{10}H_{19}$:NO: N, 8.3. Found: N, 8.2. [c] Crystallized from ether. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.8. [d] Crystallized from benzene. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.7. [e] Crystallized from 87% isopropyl alcohol. *Anal.* Calc'd for $C_{13}H_{23}NO$: N, 6.7. Found: N, 6.8. [f] Crystallized from aqueous methanol. *Anal.* Calc'd for $C_8H_{15}NO$: N, 9.9. Found: N, 10.1. [g] Crystallized from heptane. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.6. [h] *Anal.* Calc'd for $C_7H_{13}NO$: N, 11.0. Found: N, 10.9. [i] Boiling points are indicated by temperatures enclosed in parentheses. [j] Obtained from commercial sources.

tetrazole from diisobutyl ketone is not typical since it represents the only instance in which a moderate yield of tetrazole was obtained, it illustrates the procedure used in the less successful reactions with acetone and diethyl ketone. Powdered sodium azide (98 g., 1.5 moles) was placed in a 3-l. three-necked flask equipped with a stirrer, a dropping-funnel with outlet below the liquid level, an alcohol thermometer with bulb in the reaction mixture,

TABLE II

1,5-Disubstituted Tetrazoles $R_1N{-}CR_2$ (N, N, N)

TT-no.[c]	R_1	R_2	Yield, %	M.P., °C.	Crystals	Solvent	Molecular Formula	Analyses					
								Calc'd			Found		
								C	H	N	C	H	N
9 (4)	CH_3	CH_3	24[a]	73–74	Prisms, leaflets	Benzene-ether	$C_3H_6N_4$	36.8	6.1	57.2	37.0	5.9	57.1
020	C_4H_9(iso)	CH_3	46	45–45.5	Prisms	Heptane	$C_6H_{12}N_4$	51.4	8.6	40.0	51.8	8.4	39.7
10	C_4H_9(iso)	C_4H_9(iso)	24[b]	41–43.5	Needles	Ether-petroleum ether	$C_9H_{13}N_4$	59.3	9.9	30.8	59.5	9.9	30.4
21 (30)	C_6H_5	CH_3	39	97.5–99	Needles	Water	$C_8H_8N_4$	60.0	5.0	35.0	60.0	5.1	34.9
27	C_6H_5	C_2H_5	66	49	Prisms	Heptane-ethyl acetate	$C_9H_{10}N_4$	62.1	5.7	32.2	61.9	5.7	32.5
47	C_6H_5	C_4H_9(iso)	67	55–56	Long prisms	Benzene-petroleum ether	$C_{11}H_{14}N_4$	65.3	6.9	27.7	65.2	7.2	27.7
44	C_6H_5	C_6H_{11}(cyclo)	50	99.5–100.5	Prisms	Aqueous methanol	$C_{13}H_{16}N_4$	68.4	7.0	24.6	68.4	7.2	24.3
20 (11)	C_6H_5	C_6H_5	75	144–145	Prisms	Ethyl acetate	$C_{13}H_{10}N_4$	70.3	4.5	25.2	70.3	4.6	25.0
19 (12)	CH_3	C_6H_5	43	104–105	Needles	Water	$C_8H_8N_4$	60.0	5.0	35.0	60.0	5.1	34.9
49	C_2H_5	C_6H_5	30	70–71	Prisms	Ether	$C_9H_{10}N_4$	62.1	5.7	32.2	62.1	5.8	32.0
46	C_4H_9(iso)	C_6H_5	66	51–52	Needles	Benzene-petroleum ether	$C_{11}H_{14}N_4$	65.4	6.9	27.7	65.5	6.7	27.8
48	C_6H_{11}(cyclo)	C_6H_5	37	132–133	Leaflets	Methanol	$C_{13}H_{16}N_4$	68.4	7.0	24.6	68.4	7.2	24.4
79	C_6H_{11}(cyclo)	CH_3	51	124–124.5	Heavy needles	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.7	8.7	33.8
18	C_6H_{11}(cyclo)	C_2H_5	33	112–112.5	Needles	Water	$C_9H_{16}N_4$	60.0	8.9	31.1	59.9	8.6	31.1
067	C_6H_{11}(cyclo)	C_3H_7(*n*)	75	79–80	Needles	Heptane	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.8	9.3	28.9
071	C_6H_{11}(cyclo)	C_3H_7(iso)	61	85–86	Needles	Heptane	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.8	9.4	28.9
073	C_6H_{11}(cyclo)	C_4H_9(*n*)	25	43.5–45	Coarse prisms	Ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	62.8	9.3	27.1
17	C_6H_{11}(cyclo)	C_4H_9(iso)	27	78.5–79	Needles	Petroleum ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.4	9.5	26.9
5	C_6H_{11}(cyclo)	C_6H_{11}(cyclo)	45	179.5–180	Flat prisms	Isopropyl alcohol	$C_{13}H_{22}N_4$	66.7	9.4	23.9	66.4	9.4	23.9
24	CH_3	C_6H_{11}(cyclo)	26	97–98	Leaflets	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.9	8.7	33.7
14	C_2H_5	C_6H_{11}(cyclo)	52	84–86	Needles	Ethyl acetate-pet. ether	$C_9H_{16}N_4$	60.0	8.9	31.1	59.8	8.9	31.2
51	C_4H_9(iso)	C_6H_{11}(cyclo)	25	75–76	Needles	Petroleum ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.2	9.4	26.7
09	C_5H_9(cyclo)	CH_3	69	62–63	Needles	Toluene-heptane	$C_7H_{12}N_4$	55.3	8.0	36.6	55.5	7.9	36.8
0103	$C_6H_{11}CH_2$	CH_3	10	87–88	Needles	Heptane	$C_9H_{16}N_4$	60.0	8.9	31.1	60.1	8.8	31.3
69	*p*-$CH_3OC_6H_4$	CH_3	47	93–94	Needles	25% Isopropyl alcohol	$C_9H_{10}N_4O$	56.8	5.3	29.5	57.2	5.1	29.5
70	*p*-HOC_6H_4	CH_3	59	177–179	Needles	Water	$C_8H_8N_4O$	54.5	4.5	31.8	54.5	4.8	32.0

[a] Yield from acetone only 12%. [b] Prepared from diisobutyl ketone. [c] The compounds have been identified by these code numbers in the publications of Gross and Featherstone (17). Figures in parentheses are references in the present article.

and an outlet tube leading to a trap for the absorption of acidic vapors. The sodium azide was covered with 1200 ml. of ethylene dichloride, and with continuous stirring 882 g. of sulfuric acid was added dropwise at such a rate that the reaction mixture remained below 40°. Occasionally, external cooling with a cold-water bath was necessary. Addition of the acid required about 45 minutes, whereupon 71 g. (0.5 mole) of diisobutyl ketone dissolved in 200 ml. of ethylene dichloride was added at such a rate that the addition could be completed within an hour while the temperature could be kept below 45° with only occasional external cooling. Stirring was continued for two hours after complete addition of the ketone while the temperature dropped slowly to 30°, after which the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was then diluted with 500 ml. of water, with cooling, and the ethylene dichloride layer was separated. The aqueous layer was neutralized by the portionwise addition of sodium carbonate and the oily material which separated was taken up in ethylene dichloride. The saturated salt solution was decanted from the sodium sulfate that crystallized and was extracted once with ethylene dichloride. The combined ethylene dichloride solutions were dried over sodium sulfate, concentrated to a small volume, and the residual material was fractionated under reduced pressure. Thirty-six grams (46%) of N-isobutylisovaleramide distilled at 134–137° at 10 mm. followed by a small intermediate fraction and 22 g. (24%) of 1,5-diisobutyltetrazole was collected at 166–170° at 8 mm. The latter crystallized on cooling and could be recrystallized from ether-petroleum ether mixtures, separating as needles, m.p. 41-43°.

In addition to the procedure outlined, diisobutyl tetrazole could be prepared in slightly lower yield by the treatment of a benzene solution of diisobutyl ketone and hydrazoic acid with concentrated sulfuric acid. Other techniques such as treatment of an ethylene dichloride solution of the ketone with sodium azide and chlorosulfonic acid, treatment of the ketoxime dissolved in ethylene dichloride with sodium azide and either concentrated sulfuric acid or chlorosulfonic acid, and treatment of a benzene solution of the ketoxime and hydrazoic acid with concentrated sulfuric acid led to N-isobutylisovaleramide as the main product and such small amounts of the tetrazole that they could not readily be separated in pure form from the accompanying amide.

Tetrazoles from amides. The following description of the preparation of 1-cyclohexyl-5-methyltetrazole from N-cyclohexylacetamide is typical of the procedure employed for the synthesis of most of the products listed in Table II. N-Cyclohexylacetamide (100 g., 0.71 mole) was dissolved in 500 ml. of dry benzene in a 2-l. three-necked, round-bottom flask, fitted with a stirrer with a benzene seal, and a reflux condenser surmounted by a calcium-chloride tube. The third opening was connected to a 500-ml. Erlenmeyer flask containing 147 g. (0.71 mole) of phosphorus pentachloride. The benzene solution was stirred and cooled while the phosphorus pentachloride was added portionwise, accompanied by vigorous evolution of hydrogen chloride. When formation of the imide chloride was complete, as evidenced by the disappearance of the phosphorus pentachloride, the Erlenmeyer flask was replaced by a dropping-funnel through which 34 g. (0.79 mole) of hydrazoic acid in benzene solution[6] was added. After the initial vigorous reaction had subsided, the reaction mixture was allowed to stand at room temperature for an hour before it was gradually warmed to the boiling point on a water-bath and maintained at this temperature until hydrogen chloride evolution ceased (about three hours). The solvent was then removed under reduced pressure and the residue was treated with ice and water to decompose any phosphorus oxychloride present. After boiling the crude product under reflux for about an hour with water and cooling in an ice-bath, the 1-cyclohexyl-5-methyl tetrazole was filtered off and recrystallized twice from water, from which it separated as colorless needles, m.p. 124–124.5°; yield, 60 g. (51%).

[6] Solutions of hydrazoic acid in benzene were prepared by treatment of a sludge of sodium azide and water under benzene with concentrated sulfuric acid as suggested by von Braun (31).

SUMMARY

1. Reinvestigation of the Schmidt procedure for the preparation of tetrazoles from aliphatic ketones by interaction with hydrazoic acid in the presence of sulfuric acid failed to confirm the claims of that author. The major product of the reaction is a substituted amide accompanied by only small amounts of the anticipated tetrazoles.

2. It has been shown that the preparation of tetrazoles from N-substituted amides by conversion into the imide chloride and interaction of the latter with hydrazoic acid is not limited to anilides as intimated by von Braun and Rudolph, but may be applied successfully to a great variety of substituted amides including completely aliphatic types. The stability of the imide chlorides is such that they can be prepared successfully in benzene solution.

3. A group of twenty-six 1,5-disubstituted tetrazoles, of which twenty-two have not been previously described, many of them having only aliphatic or cycloaliphatic substituents at the 1 and 5 positions of the tetrazole ring, has been prepared from the appropriately substituted amides.

4. A number of N-substituted amides not previously described have been prepared to serve as intermediates for tetrazole syntheses.

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