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THE SYNTHESIS OF ALKYLATED PENTAMETHYLENETETRAZOLE DERIVATIVES

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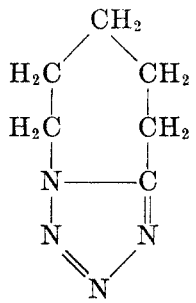
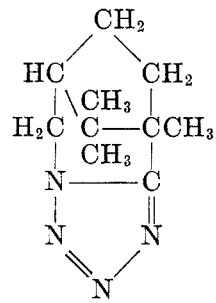
Certain tetrazole derivatives have attained notable success as medicinal agents. Perhaps the best known member of this group is Metrazol (1), pentamethylenetetrazole (I), which has found application as an analeptic agent because of its stimulatory action on the central nervous system. Several other tetrazoles, likewise bicyclic structures which can be formed from cyclohexanone derivatives, have received favorable comment in the pharmacologic literature as analeptic agents. Notable among these are the "camphor tetrazole" (II) and the tetrazoles derived from α-thujone and mixtures of α- and β-thujone (2, 3). More recently several methyl substituted pentamethylenetetrazoles (III) have been described (4, 5, 6, 7) and a number of other bicyclic tetrazoles have been studied in which the tetrazole ring is fused to either a larger (8) or a smaller (9, 10) ring system than the seven membered heterocycle of pentamethylenetetrazole.



(I)



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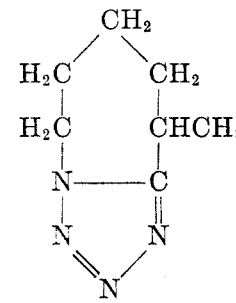

(III)

In view of the interest attaching to pentamethylenetetrazole, it seemed desirable to initiate a systematic investigation of derivatives both of the fused bicyclic type and of the monocyclic type and to attempt to correlate the changes in structure with changes in pharmacologic action. The tetrazole ring system (IVa and b) is an unusual cyclic structure in that the possibility of position isomerism is limited by the presence of only two replaceable hydrogen atoms. The tautomeric shift of the hydrogen attached to nitrogen permits the existence of three monosubstituted isomers and two series of disubstituted derivatives. Examples of all types are known. The addition of fused ring systems usually in

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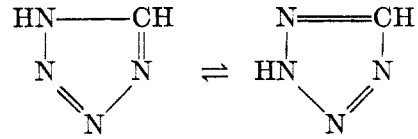
the 1,5 positions greatly increases the number of isomeric substitution products that may be prepared.

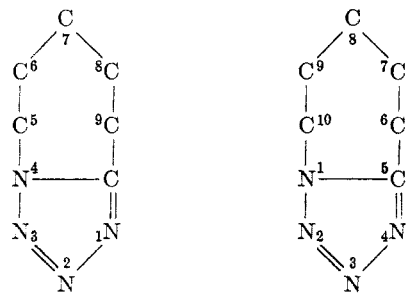


IVa IVb

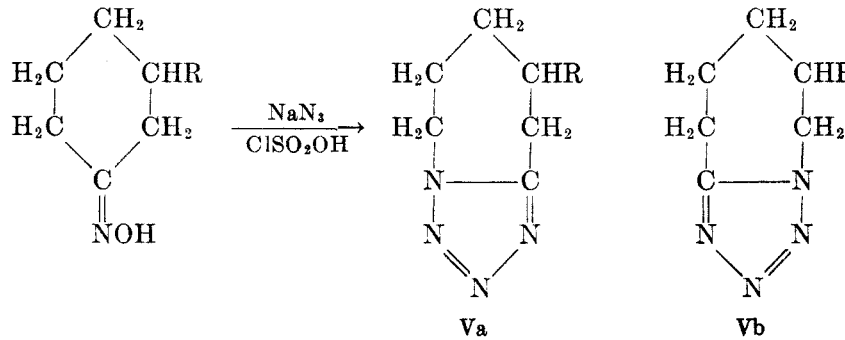
The present report is concerned only with the preparation of mono- and polyalkylpentamethylenetetrazole derivatives. These can be prepared readily by methods essentially similar to those applied to the synthesis of pentamethylenetetrazole itself. The method chosen involves treatment of the oxime of a suitably substituted cyclohexanone with sodium azide and chlorosulfonic acid in an inert organic solvent (4). During the reaction a carbon-carbon bond adjacent to the carboximino group is ruptured to permit introduction of the nitrogen and formation of the seven-membered heterocyclic entity. Either the 1,2- or the 1,6-bond of the cyclohexanone oxime will be broken. Except in the case of symmetrically substituted oximes, isomeric compounds of structures Va and b will result in varying proportions, depending on the extent to which the reaction involves the 1,6- or the 1,2-bond, respectively.[4]

No attempt has been made to establish the form represented by the compounds described in Table II; however, it is probable that each compound represents a single molecular species of structure Va or b in view of the sharpness of the melting points, which did not change on crystallization from different solvents and which were always easily reproducible in different preparations. For purposes of uniformity it has been assumed that the 1,6-bond is broken and structures have been assigned arbitrarily so that the position of methyl groups is always indicated by the lowest number. Only a single alkylpentamethylenetetrazole can be formed from the 4-alkylcyclohexanone oximes and from 3,5-

[4] Although the pentamethylenetetrazole structure is classified as 6,7,8,9-tetrahydro-5-azepotetrazole (VIa) in Chemical Abstracts, we would prefer to consider the new compounds as alkylpentamethylenetetrazole derivatives numbered as in (VIb). The accepted numbering of the tetrazole ring is retained in VIb and the names bear a more obvious relationship to that commonly used for the parent bicyclic system.



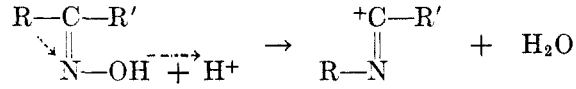
VIa VIb



dimethylcyclohexanone oxime. The product formed from 2-methylcyclohexanone oxime probably has the structure corresponding to a 10-methylpentamethylene-tetrazole (analogous to Vb) since Ungnade and McLaren (11) have shown that the Beckmann rearrangement product of this oxime is almost exclusively the cyclic amide formed by breaking the 1,2-bond of the cyclohexanone ring.

In their initial phases the reactions leading to tetrazole formation appear to be closely akin to the Beckmann rearrangement. Since the two processes take place under similar conditions, it is probable that an intermediate is formed at some stage which may be converted either into an amide by the addition of water or some group which may eventually be replaced by a hydroxyl group, or to a tetrazole by the additon of hydrazoic acid. Newman and Gildenhorn (12) have recently discussed the mechanism of the Schmidt reaction for the conversion of acids to amines by interaction with hydrazoic acid, and Smith (13) has suggested a mechanism for another aspect of the same reaction, the conversion of ketones to amides by interaction with hydrazoic acid. These reactions bear a close relationship to the Curtius and the Beckmann rearrangements, respectively, and similarity in the mechanism of these reactions has been implied by both authors. Smith has postulated the formation of an imino carbonium ion, $R—N{=}C^{+}—R$, as an intermediate in the Schmidt reaction with ketones, an intermediate also postulated by Waters (14) for the Beckmann rearrangement. In the mechanism suggested by Waters an intermediate of the type, $R_2{=}C{=}N^{+}$, is considered to result from the dissociation of a ketoxime ester and then rearrange to the imino carbonium ion form. Unless it is assumed that the charge on the nitrogen in the Waters intermediate retains its configuration, difficulty is experienced in accounting for the different rearrangement products of geometrically isomeric ketoximes. We would suggest that the intermediate formed by dissociation of the oxime according to Waters is not essential, and that the imino carbonium ion proposed by Smith is formed directly from the oxime or ketoxime ester. The reaction may be visualized as involving the addition of a proton to the hydroxyl oxygen of the oxime followed by elimination of water, or the proton may serve simply as an attractive force drawing the hydroxyl group away from the nitrogen as an ion and eventually uniting with it to form water. In either case it would not be unreasonable to assume that the alkyl (or aryl) group in *trans* position with respect to the hydroxyl group is pulled closer to the nitrogen as the hydroxyl group is drawn away, the rearrangement being completed by the simultaneous formation

of the imino carbonium ion and the elimination of the hydroxyl ion. In this way the effect of the configuration of the isomeric oximes on the rearrangement products may be explained without the assumption of ionic intermediates with a configurationally stable charge. A mechanism of this type has recently been discussed by Pearson and Ball (29) who indicate, however, the formation of the



sulfuric acid ester of the oxime as an intermediate. Although there are numerous reports of the rearrangement of oxime esters in the literature, it is conceivable that the reaction may take place without ester formation in the presence of such a strong proton donor as sulfuric acid.

As has already been pointed out by Smith, the imino carbonium ion may serve equally well as an intermediate for amide formation in either the Schmidt reaction or the Beckmann rearrangement, as well as for tetrazole formation. The latter process would be completed by addition of hydrazoic acid to the carbonium ion followed by cyclization and elimination of a proton.

As indicated in Table II a variety of pentamethylenetetrazole derivatives having alkyl groups variously substituted on the pentamethylene ring has been prepared from suitably substituted cyclohexanone oximes. Alkyl substitution caused very marked changes in the solubility of the homologs as compared with the parent structure. Pentamethylenetetrazole is extremely soluble in water, aqueous solutions containing 70% by weight of the tetrazole being easily prepared. The introduction of a single methyl group into the pentamethylene ring caused the solubility to decrease to barely 5% for the most soluble isomer. Introduction of a second methyl group caused almost complete disappearance of water solubility at room temperature. Similarly, water solubility disappeared almost completely upon substitution of a single alkyl group of three or more carbon atoms on the pentamethylene ring. Excepting the three isomeric monomethylpentamethylenetetrazoles, the water solubility of all the compounds listed in Table II is less than 1% by weight at room temperature and in most instances the compounds are insoluble in water for all practical purposes.

The results of investigations of the pharmacologic actions of the alkylpentamethylenetetrazoles listed in Table II have been reported in detail by Gross and Featherstone (15). Their results indicated that the compounds were generally stimulants of the central nervous system although interesting exceptions were noted. Contrary to the conclusion expressed by Issekutz and co-workers (5) based on investigations with tetramethylenetetrazole derivatives, the activity of pentamethylenetetrazoles was not increased by polysubstitution with alkyl groups. The substitution of a single methyl group on the pentamethylene ring increased the central nervous stimulating action and the effect was enhanced by moving the substituent away from the linkage common to both members of the fused ring system, 8-methylpentamethylenetetrazole exhibiting the highest potency. Introduction of a second alkyl group caused a profound drop in activity to levels much lower than that of the unalkylated system. Of particular interest were

the results of modification of the methyl group in position 8 by replacing its hydrogens with methyl and ethyl groups. The stimulatory potency increased markedly as the group in position 8 became successively isopropyl and *tert*-butyl. On the other hand, when the group was modified to become *sec*-butyl or *tert*-amyl, a profound loss of activity resulted. Further modification of the group as in 8-cyclohexylpentamethylenetetrazole resulted in a compound having mildly sedative action.

During the course of these investigations it was observed that pentamethylenetetrazole would form a crystalline quaternary salt with both methyl benzenesulfonate and methyl iodide. In this connection it might be emphasized that the pentamethylenetetrazoles fail to form salts with either acids or bases, that their water solutions are generally neutral in reaction toward litmus and that they fail to exhibit most of the characteristic reactions of nitrogen bases. Nevertheless, an exothermic reaction was observed to take place between methyl benzenesulfonate and pentamethylenetetrazoles, resulting in the formation of a quaternary salt. Which of the four nitrogen atoms is involved in quaternary salt formation has not been determined. The quaternary salts are very soluble in water. Several compounds of this type are described in Table III.

Although the analeptic activity of pentamethylenetetrazole disappeared upon quaternary salt formation, it seemed worthwhile to attempt to solubilize one of the most active alkylpentamethylenetetrazole derivatives in this manner. The quaternary salt of 8-*tert*-butylpentamethylenetetrazole with methyl benzenesulfonate was prepared and was found to retain some stimulatory action (15), but water-solubility was acquired at too great a sacrifice in activity to make the compound useful.

EXPERIMENTAL[5]

Cyclohexanones: Except for the three isomeric methylcyclohexanones which were available from commercial sources, the alkylcyclohexanones were prepared by the catalytic hydrogenation of the corresponding di- or tri-alkylcyclohexenones or by the oxidation of the appropriate alkylcyclohexanols. The dialkylcyclohexenones were prepared by the Knoevenagel technique (16) from ethyl acetoacetate and aliphatic aldehydes as modified by Horning, Denekas, and Field (17). Catalytic hydrogenations were carried out essentially as suggested by Henze, Wilson, and Townley (18). The oxidation of the cyclohexanols[6] followed the procedure outlined for the preparation of menthone from menthol (19). 3,5,5-Trimethylcyclohexanone was prepared both by catalytic hydrogenation of isophorone and by oxidation of trimethylcyclohexanol. The properties of the various cyclohexanones are given in Table I.

Cyclohexanone oximes. The cyclohexanones were converted into their oximes by treatment with an aqueous solution of hydroxylamine. The liquid oximes were purified by distillation, usually under reduced pressure, while the solid oximes were purified by crystallization from aqueous (75–80%) methanol except in the case of 4-*tert*-butylcyclohexanone oxime where propylene dichloride was a more effective solvent for crystallization. The properties of the oximes are summarized in Table I.

Pentamethylenetetrazoles. The cyclohexanone oximes were converted into tetrazoles by procedures essentially analogous to those recorded in the patent literature (4). As a typical

[5] Microanalyses on all compounds were carried out by Mr. William Saschek.

[6] We are indebted to the Dow Chemical Company for the preparation of generous samples of 4-isopropylcyclohexanol, 4-*sec*-butylcyclohexanol, and 4-*tert*-butylcyclohexanol.

TABLE I

ALKYL SUBSTITUTED CYCLOHEXANONES AND THEIR OXIMES

ALKYLCYCLOHEXANONE	YIELD, %	B.P., °C./MM.	REF.	OXIMES						
				YIELD, %	B.P., °C./MM.	M.P., °C.	MOLECULAR FORMULA	N		REF.
								Calc'd	Found	
2-Methyl	—	—	(20)	53	117–118/22	—	$C_7H_{13}NO$	—	—	(20)
3-Methyl	—	—	(21)	60	121–122/25 108/12	—	$C_7H_{13}NO$	—	—	(21)
4-Methyl	—	—	(22)	81	115/20 120/26	—	$C_7H_{13}NO$	—	—	(22)
4-Isopropyl	91	212.5–213	(23)	92	117/6	—	$C_9H_{17}NO$	9.0	9.0	
4-*tert*-Butyl	84	83–84.5/6	(24)	85	—	137.5–138.5	$C_{10}H_{19}NO$	8.4	8.3	
4-*tert*-Amyl	61	109–111/11	[b]	92[a]	—	98–99	$C_{11}H_{21}NO$	7.6	8.0	
4-Cyclohexyl	94	125–127/6	(25)	96	—	103.5–104.5	$C_{12}H_{21}NO$	7.2	7.8	
3,5-Dimethyl	89	181–182	(16)	87	—	63–64	$C_8H_{15}NO$	—	—	(16)
3-Methyl-5-ethyl	86	200–201.5	(18)	73	127–128/11	—	$C_9H_{17}NO$	9.0	9.0	
3-Methyl-5-*n*-propyl	83	217.5–219	[c]	68	139–140/11	—	$C_{10}H_{19}NO$	8.3	8.2	
3-Methyl-5-isopropyl	73	216–217	(16)	90	134–136/11	—	$C_{10}H_{19}NO$	8.3	8.1	
3-Methyl-6-isopropyl	85	204–207	(26)	83	—	79–80	$C_{10}H_{19}NO$	—	—	(26)
3,5,5-Trimethyl	85	187–188	(16, 27)	92	—	79–81	$C_9H_{17}NO$	—	—	(16, 28)

[a] Allowing for recovered ketone.

[b] Calc'd for $C_{11}H_{20}O$: C, 78.5; H, 12.0. Found: C, 78.5; H, 12.1.

[c] Calc'd for $C_{10}H_{18}O$: C, 77.9; H, 11.8. Found: C, 78.0; H, 11.6.

example the preparation of 8-isopropylpentamethylenetetrazole may be described. Powdered sodium azide (58.5 g.) was suspended in 1 l. of ethylene dichloride in a 5-l. three-necked flask equipped with an efficient mechanical stirrer, a dropping-funnel with the tip immersed in the liquid reaction mixture,[7] an exit tube, and a long-stemmed alcohol thermometer with the bulb immersed in the reaction mixture. The apparatus was set up in an efficient hood. To the vigorously stirred suspension 478 g. of chlorosulfonic acid was added through the dropping-funnel at such a rate that the temperature of the reaction mixture did not rise above 35°. After complete addition of the chlorosulfonic acid a solution of 70 g. of 4-isopropylcyclohexanone oxime in 500 cc. of ethylene dichloride was added drop-wise with continuous, vigorous stirring at such a rate that the temperature of the reaction mixture remained between 35–45°. Occasionally, external cooling was required. Upon complete addition of the oxime, stirring was continued until the reaction mixture had cooled to room temperature, when water was added slowly, with vigorous stirring and external cooling, in sufficient quantity to decompose the excess chlorosulfonic acid. The aqueous acid layer was then separated from the ethylene dichloride solution, the acid neutralized with aqueous sodium hydroxide, and the neutral solution extracted with four 300-cc. portions of ethylene dichloride. The extracts were combined with the ethylene dichloride solution, dried over sodium sulfate, and the solvent removed by distillation. The residue was boiled with 300 cc. of 10% aqueous hydrochloric acid for three hours and the product was extracted from the acid mixture with several portions of ethylene dichloride. After washing the combined extracts with water and drying over sodium sulfate, the solvent was removed by distillation and the residue was fractionated under reduced pressure; b.p. 159–160° at 6 mm. On standing the distillate crystallized, after which the product could be purified by recrystallization from ether-petroleum ether, from which it separated as fine needles, m.p. 48–49°.

In other cases the crude tetrazoles frequently crystallized readily so that distillation under reduced pressure could be omitted, since satisfactory purification could be achieved more easily by crystallization. In some instances it was also possible to omit the treatment with hydrochloric acid. This step was designed to hydrolyze the cyclic amides formed as by-products through Beckmann rearrangement of the oximes and could be omitted when the quantity of by-product was very small or did not interfere with the crystallization of the tetrazole.

The alkylpentamethylenetetrazoles were generally moderately or easily soluble in solvents such as ethyl ether, methyl or isopropyl alcohol, benzene and the chlorinated hydrocarbons such as ethylene or propylene dichloride. They were practically insoluble in water or petroleum ether except in the case of the isomeric monomethylpentamethylenetetrazoles which showed moderate water-solubility. The properties and analyses of the tetrazoles prepared by the above procedure are recorded in Table II.

Quaternary salts. The quaternary salts of the pentamethylenetetrazoles were formed by heating an equimolar mixture of the tetrazole and methyl benzenesulfonate on a boiling-water bath until the exothermic reaction was complete. In a typical preparation a mixture of 69 g. (0.5 mole) of pentamethylenetetrazole and 86 g. (0.5 mole) of methyl benzenesulfonate was heated on a boiling-water bath. A homogeneous solution resulted; the temperature rose gradually to about 90° when an exothermic reaction set in causing a rapid further rise to about 170°. Heating was continued for about a half-hour while the mass cooled to the bath temperature. On standing for several days at room temperature the thick, gummy product crystallized; then purification was easily effected by recrystallization from ethylene dichloride, from which the product separated as glistening plates, m.p. 145–146°.

The quaternary salt of 8-*tert*-butylpentamethylenetetrazole was prepared in the same way, while the methiodide of pentamethylenetetrazole was prepared by prolonged boiling of a solution of the tetrazole in absolute isopropyl alcohol with an excess of methyl iodide.

The quaternary salts are very soluble in water. The benzenesulfonates exhibit moderate

[7] Unconfirmed reports that serious explosions had resulted when concentrated sulfuric acid and similar reagents were dropped through vapors containing hydrazoic acid made this precautionary technique seem desirable. We have not attempted to confirm the observations.

TABLE II

ALKYL SUBSTITUTED PENTAMETHYLENETETRAZOLES

ALKYLPENTAMETHYLENETETRAZOLE[a]	YIELD, %	M.P., °C.	CRYSTALS	SOLVENT	MOLECULAR FORMULA	ANALYSIS					
						Calc'd			Found		
						C	H	N	C	H	N
10-Methyl (5)	61	31–32 b.p. 185–186/15	Ref. (4, 6)	—	$C_7H_{12}N_4$	55.2	7.9	36.8	55.0	7.5	36.7
7-Methyl (8)	63	53–54	Ref. (7)	Ether-pet. ether	$C_7H_{12}N_4$	55.2	7.9	36.8	55.1	7.6	36.8
8-Methyl (7)	57	43–44	Ref. (4)	Ether-pet. ether	$C_7H_{12}N_4$	55.2	7.9	36.8	55.3	8.1	36.7
8-Isopropyl (7)	67	48–49	Small needles	Ether-pet. ether	$C_9H_{16}N_4$	60.0	8.9	31.1	60.2	8.6	31.2
8-*sec*-Butyl (7)	50	70–71	Prisms	Heptane-propyl-enedichloride	$C_{10}H_{18}N_4$	61.9	9.3	28.9	62.0	9.1	29.3
8-*tert*-Butyl (7)	68	132.5–133	Needles	Isopropyl alcohol	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.5	9.1	28.9
8-*tert*-Amyl (7)	57	73–74	Needles	Methanol	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.6	9.7	26.9
8-Cyclohexyl (7)	51	92–93	Leaflets	Heptane	$C_{12}H_{20}N_4$	65.5	9.1	25.5	65.6	9.3	25.3
7,9-Dimethyl (6,8)	58	156	Leaflets	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.8	8.4	33.4
7-Methyl-9-ethyl (8,6)	32	88.5–89.5	Small needles	Isopropyl alcohol	$C_9H_{16}N_4$	60.0	8.9	31.1	59.6	8.8	31.4
7-Methyl-9-*n*-propyl (8,6)	37	64.5–65.5	Prisms	Isopropyl alcohol	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.9	9.2	29.0
7-Methyl-9-isopropyl (8,6)	50	135	Small needles	Ether-pet. ether	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.7	9.0	29.0
7-Methyl-10-isopropyl (8,5)	27	49–49.5	Prisms	Ether-pet. ether	$C_{10}H_{18}N_4$	61.9	9.3	28.9	62.0	9.4	29.0
7,9,9-Trimethyl (8,6,6)	72	115–117	Needles	Water	$C_9H_{16}N_4$	60.0	8.9	31.1	60.2	8.9	30.9

[a] The numbers in parentheses indicate the corresponding positions of the respective groups as substituents on the 6,7,8,9-tetrahydro-5-azepotetrazole nucleus.

TABLE III

QUATERNARY SALTS OF PENTAMETHYLENETETRAZOLES

COMPOUND	YIELD, %	M.P., °C.	CRYSTALS	SOLVENT	ANALYSIS N		
					FORMULA	Calc'd	Found
Pentamethylenetetrazole methyl benzenesulfonate	63	145–146	Glistening plates	Ethylene dichloride	$C_{13}H_{18}N_4O_3S$	18.1	18.3
Pentamethylenetetrazole methiodide	40	175–180	Needles	Abs. isopropyl alcohol	$C_7H_3IN_4$	20.0	20.0
8-*tert*-Butylpentamethylenetetrazole methyl benzenesulfonate	71	171.5–172.5	Needles	Propylene dichloride	$C_{17}H_{26}N_4O_3S$	15.3	15.1

solubility in cold methanol and cold isopropyl alcohol, while both the iodide and the benzenesulfonates are rather easily soluble in hot ethylene or propylene dichloride but only sparingly soluble in the cold solvents. The methiodide is rather easily soluble in hot absolute isopropyl alcohol but difficultly soluble in the cold solvent. The properties and analyses of the quaternary salts are summarized in Table III.

SUMMARY

1. The preparation and properties of a series of alkyl substituted pentamethylenetetrazole derivatives have been described.

2. The formation of quaternary salts of pentamethylenetetrazoles with methyl iodide and methyl benzenesulfonate has been observed and their preparation described.

3. Relationships between the structure and pharmacologic properties of the alkylpentamethylenetetrazoles are discussed.

4. The relationship between the mechanism of tetrazole formation from cyclohexanone oximes and the Beckmann rearrangement is discussed and intermediates are suggested for the reactions which will account for the simultaneous occurrence of both reactions.

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