hydroxide solution. Only two fractions were encountered and these were identified by their peak eluant volumes as azelaic acid, 50.1 mole %, and sebacic acid, 49.9 mole %.

Application of the above described procedures to the dicarboxylic acids obtained from the heat-treated sample showed the mixture to be 48.8 mole percent azelaic and 51.2 mole percent sebacic acid.

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NEW ORLEANS 19, LA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazolopyrimidines: Their Synthesis and Structure[1]

LEONARD E. BRADY[2] AND ROBERT M. HERBST

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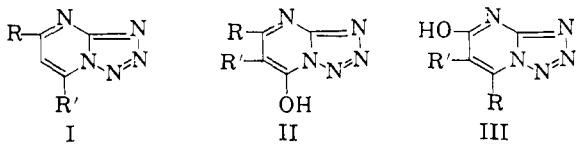
The reaction of 5-aminotetrazole with β-keto esters yields condensation products originally formulated as tetrazolo[*a*]-pyrimidines. The structure of this ring system has been substantiated through an alternative synthesis involving diazotization of 2-hydrazinopyrimidines and cyclization of the intermediate azidopyrimidines. Orientation of the substituents is supported by a study of the acylation of 5-aminotetrazole.

The formation of tetrazolopyrimidines by condensation of β-diketones and β-keto esters with 5-aminotetrazole was first described by Bülow.[3] The condensation with β-diketones in ethanol solution catalyzed with piperidine gave products assigned the structure I. With acetoacetic ester in glacial acetic acid a compound (IIa) was said to form; the possibility of formation of compounds of structure III was not considered. More recently Nachod and Steck[4] repeated Bülow's preparation of Ia for use in spectrographic studies without questioning the structure assignment. The arbitrary assignment of structures by Bülow made reinvestigation of this group of compounds desirable. Alternative methods of synthesis were devised with the object of demonstrating (1) the presence of the bicyclic system and (2) the orientation of the substituents according to II rather than III. The structural relationship of these compounds both to the purines and to bicyclic systems related to pentamethylenetetrazole made an extension of examples of this type of system attractive.



I II III

Ia. R = CH_3; R′ = CH_3
Ib. R = CH_3; R′ = C_6H_5
IIa. R = CH_3; R′ = H
IIb. R = C_6H_5; R′ = H
IIc. R = CH_3; R′ = CH_3
IId. R = CH_3; R′ = C_2H_5
IIe. R = CH_3; R′ = *n*-C_3H_7
IIf. R = CH_3; R′ = *iso*-C_3H_7
IIg. R = CH_3; R′ = *n*-C_4H_9
IIh. R—R′ = —$(CH_2)_4$—

The condensation of β-keto esters with 5-aminotetrazole was reinvestigated to determine the effect of solvents and catalysts on the reaction.It quickly became apparent that condensations in glacial acetic acid as recommended by Bülow[3] were not satisfactory. The product (IIa) obtained with acetoacetic ester was contaminated with large amounts of 5-acetamidotetrazole with which the product formed a molecular complex. The product described by Bülow as IIb, but for which no analysis was given, obtained with benzoylacetic ester under similar conditions proved to be 5-acetamidotetrazole. Using ethanol as solvent and piperidine as catalyst, as recommended for the condensation of β-diketones with 5-aminotetrazole,[3] greatly improved yields of tetrazolopyrimidines were obtained from β-keto esters. The condensation product (IIb) with benzoylacetic ester was actually obtained under these conditions. Similar condensations with a variety of alkylated acetoacetic esters gave the products IIc–IIh.

To establish the presence of a pyrimidine ring system in the products the procedure of Finnegan, Henry, and Lieber[5] for the synthesis of substituted 5-aminotetrazoles was adapted. These authors had shown that a variety of *S*-methyl thiuronium salts could be converted into 5-aminotetrazole derivatives by interaction successively with hydrazine to form aminoguanidines[6] and nitrous acid to form guanyl azides. The latter cyclized readily to form the tetrazoles. Considering 2-methylmercaptopyrimidines (IV) as cyclic *S*-

(1) Based on the doctoral thesis submitted to Michigan State University by Leonard E. Brady. Presented before the Division of Medicinal Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 7–12, 1958.

(2) Present address: Abbott Laboratories, North Chicago, Ill.

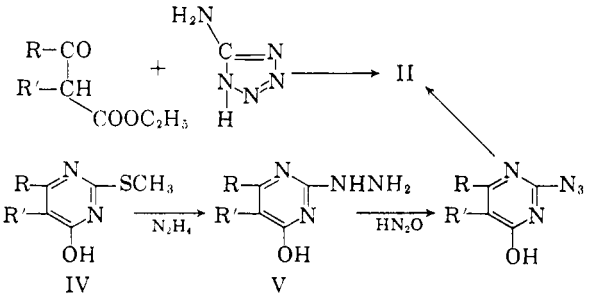
(3) C. Bülow, *Ber.*, **42**, 4429 (1909).

(4) F. C. Nachod and E. A. Steck, *J. Am. Chem. Soc.*, **70**, 2819 (1948).

(5) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(6) G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).

methyl thiuronium salts, it was found possible to convert them into 2-hydrazinopyrimidines (V) by interaction with hydrazine. Treatment of the hydrazinopyrimidines with nitrous acid completed the formation of the tetrazolopyrimidines (II) identical in all respects with the correspondingly substituted products obtained from alkylated acetoacetic esters and 5-aminotetrazole.



IV V

R and R′ defined as for II

The presence of the pyrimidine ring was also substantiated when 2-amino-4-methyl-6-hydroxypyrimidine was isolated as the result of attempts to reduce IIa in glacial acetic acid with hydrogen in the presence of platinum oxide. Neither hydrogenolysis of the tetrazole ring nor hydrogenation were observed in a similar attempt to reduce IIa in aqueous ethanol containing potassium hydroxide.

It remained to determine whether the orientation of the substituents in the tetrazolopyrimidines was in accord with II or III. Compounds of structure II would be expected if the initial reaction between β-keto esters and 5-aminotetrazole was azomethine formation. On the other hand, if the first step involved acylation of 5-aminotetrazole by the esters, compounds of structure III would be likely to result. With this in mind conditions for the acylation of 5-aminotetrazole were studied. Prolonged heating with an excess of carboxylic acid caused acylation of 5-aminotetrazole. The same products were obtained by interaction with the corresponding acyl chlorides or anhydrides. Direct interaction of 5-aminotetrazole with esters of carboxylic acids failed to cause acylation; starting materials could be recovered completely. On the other hand, interaction of 5-aminotetrazole with esters in glacial acetic acid solution gave modest yields (20–25%) of the acylaminotetrazole. Apparently acylation with esters is catalyzed in acetic acid solution. An attempt to induce acylation of 5-aminotetrazole with esters in ethanol solution in presence of piperidine was not successful.

Since piperidine failed to catalyze interaction of simple esters with 5-aminotetrazole in ethanol solution, whereas under similar conditions azomethine formation with simple carbonyl compounds has been shown to take place readily,[7,8] it seems likely that the initial step in the condensation of β-keto esters with 5-aminotetrazole involves azomethine formation. Subsequent elimination of the elements of ethanol from the azomethine would give tetrazolopyrimidines of structure II. Although structure III cannot be excluded unequivocally on the basis of available evidence, the formation of compounds of structure II seems more probable.

The tetrazolopyrimidines prepared from 5-aminotetrazole and β-keto esters are listed in Table I. With the exception of IIf all of these compounds were also prepared from the appropriate 2-methylmercaptopyrimidines. In addition 5,7-dimethyltetrazolo [*a*]pyrimidine (Ia) was prepared both from acetylacetone and 5-amino-tetrazole and from 2-methylmercapto-4,6-dimethylpyrimidine.

The requisite 2-methylmercaptopyrimidines (Table II) were prepared by interaction of S-methyl thiuronium iodide and appropriate β-keto esters in aqueous alcoholic solution in presence of potassium hydroxide.[9] 2-Hydrazinopyrimidines (Table III) were prepared by interaction in alcoholic solution of 2-methylmercaptopyrimidines and either anhydrous or 85% hydrazine hydrate. Benzal derivatives of the hydrazinopyrimidines are described in Table IV. The 2-hydrazinopyrimidines were converted into azido compounds or tetrazolopyrimidines by interaction with sodium nitrite in dilute, aqueous acid solution.

Screening of the compounds in Table I in the Parke, Davis Laboratories indicated no marked inhibitory action on growth in microbiological systems. When administered to mice intraperitoneally, IIa and IIh were lethal at dosage levels of 5 mg. per kg. The other compounds were slightly less toxic; IIb was tolerated up to 150 mg. per kg. No pronounced central nervous effects were observed below the lethal dose.[10] The compounds failed to show anticancer activity when screened by the Cancer Chemotherapy National Service Center.

EXPERIMENTAL[11]

5-Hydroxytetrazolo[a]pyrimidines were prepared by three methods: (A) the condensation of β-keto esters with 5-aminotetrazole in glacial acetic acid[3]; (B) the condensation of β-keto esters and 5-aminotetrazole in ethanolic solution in the presence of piperidine; (C) the diazotization of 2-hydrazino-6-hydroxypyrimidines.

(A) A mixture of 42.5 g. (0.5 mole) of anhydrous 5-aminotetrazole[12] and 78 g. (0.6 mole) of ethyl acetoacetate in 250 ml. of glacial acetic acid was heated under reflux for 48 hr. The solid which precipitated on cooling could be separated by repeated fractional crystallization from water into IIa

(7) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 923 (1954).

(8) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 926 (1954).

(9) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(10) The cooperation of Dr. Graham M. Chen of the Parke, Davis Laboratories is gratefully acknowledged.

(11) Microanalyses on all compounds were done by Micro-Tech Laboratories, Skokie, Ill. All melting points were taken in open capillaries and are not corrected.

(12) R. M. Herbst and J. A. Garrison, *J. Org. Chem.*, **18**, 941 (1953).

TABLE I

5-HYDROXY TETRAZOLO[*a*]PYRIMIDINES

Cpd. No.	R	R′	Method	Yield, %	M.P.	Formula	Analyses: Calculated C	H	N	Found C	H	N
IIa	CH_3	H	A	17	247–248 dec.	$C_5H_5N_5O$	39.7	3.3	46.4	39.8	3.6	46.6
			B	40	247–248							
			C	52	247–248							
IIb	C_6H_5	H	B	21	224–225 dec.	$C_{10}H_7N_5O$	56.3	3.3	32.8	56.6	3.6	33.1
			C	71	224–225 dec.							
			A	0								
IIc	CH_3	CH_3	B	49	226 dec.	$C_6H_7N_5O$	43.6	4.3	42.4	43.9	4.5	42.3
			C	56	226 dec.							
IId	CH_3	C_2H_5	B	46	182–183	$C_7H_9N_5O$	46.9	5.1	39.1	46.8	5.1	39.0
			C	40	182–183							
IIe	CH_3	*n*-C_3H_7	B	52	145–146	$C_8H_{11}N_5O$	49.7	5.7	36.2	49.8	5.8	36.3
			C	60	145–146							
IIf	CH_3	*i*-C_3H_7	B	16	182–183	$C_8H_{11}N_5O$	49.7	5.7	36.2	49.7	5.6	36.2
IIg	CH_3	*n*-C_4H_9	B	30	151–152	$C_9H_{13}N_5O$	52.2	6.3	33.8	52.1	6.3	34.1
			C	63	151–152							
IIh	—$(CH_2)_4$—		B	26	199–200 dec.	$C_8H_9N_5O$	50.2	4.7	36.6	50.0	5.0	36.6
			C	31	199–200 dec.							

TABLE II

2-METHYLMERCAPTO-6-HYDROXYPYRIMIDINES

Cpd. No.	R	R′	Yield, %	M.P.	Formula	Analyses: Calculated C	H	N	S	Found C	H	N	S
IVa	CH_3	H	50	219	Ref. 9								
IVb	C_6H_5	H	14	238	Ref. 9								
IVc	CH_3	CH_3	19	216–217	$C_7H_{10}N_2OS$	49.4	5.9	16.5	18.8	49.4	5.9	16.5	17.0
IVd	CH_3	C_2H_5	16	201–202	Ref. 9								
IVe	CH_3	*n*-C_3H_7	6	181–182	$C_9H_{14}N_2OS$	54.5	7.1	14.1	16.2	54.5	7.2	13.9	16.0
IVg	CH_3	*n*-C_4H_9	9	159–160	$C_{10}H_{16}N_2OS$	56.6	7.6	13.2	15.1	56.6	7.6	13.4	15.1
IVh	—$(CH_2)_4$—		27	218–219	$C_9H_{12}N_2OS$	55.1	6.2	14.3	16.3	54.9	6.4	14.3	16.2

and a substance whose elemental analysis approximated that of a complex of two molecules of 5-acetamidotetrazole and one molecule of IIa; the complex melted at 238° with decomposition.

Anal. Calcd. for $(C_5H_5N_5O)(C_3H_5N_5O)_2$: C, 32.6; H, 3.7; N, 51.8. Found: C, 33.6; H, 3.7; N, 52.0.

The IIa prepared in this manner is described in Table I.

Interaction of ethyl benzoylacetate and 5-aminotetrazole in glacial acetic acid[3] gave a product, m.p. 267–268° with decomposition, identical in all respects with 5-acetamidotetrazole.

(B) The preparation of IIa will serve as an example. A solution of 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole, 19.5 g. (0.15 mole) of ethyl acetoacetate and 1 ml. of piperidine in 100 ml. of absolute ethanol was heated under reflux for 48 hr. The reaction mixture was evaporated to dryness on a steam bath and the residue recrystallized twice from hot water. Yields, melting points, and analytical data for compounds prepared by this method are given in Table I.

In the preparation of IIb from ethyl benzoylacetate and 5-aminotetrazole in the presence of piperidine, the piperidine salt of the product separated on cooling the reaction mixture. The piperidine salt crystallized from water, apparently as a hydrate, m.p. 119° (air dried) followed by resolidification and remelting at 144°; after drying at 100°, m.p. 144°.

Anal. Calcd. for $C_{15}H_{18}N_6O$: C, 60.4; H, 6.1; N, 28.2. Found: C, 60.3; H, 6.3; N, 28.2.

IIb was obtained by acidifying a hot aqueous solution of the piperidine salt with concentrated hydrochloric acid.

All the tetrazolopyrimidines in Table I can be crystallized from hot water or from aqueous ethanol.

(C) The preparation of IIa is typical of the series. To a solution of 5 ml. of concentrated hydrochloric acid in 30 ml. of water was added 4.0 g. of 2-hydrazino-4-methyl-6-hydroxypyrimidine (IVa). While stirring and cooling in an ice bath a saturated aqueous solution of sodium nitrite was added dropwise until the first excess was shown by the starch–potassium iodide end point. Stirring and cooling were continued for 15 min. when solid sodium carbonate was added until the mixture reached *p*H 8. At this point the material that had separated during the diazotization redissolved. The mixture was allowed to come to room temperature when it was acidified (*p*H 5) with hydrochloric acid. The solid which precipitated was recrystallized from hot water. IIa prepared in this way was shown to be identical with that prepared by Methods A and B by melting point and mixture melting point determinations and by comparison of infrared absorption spectra.

2-Methylmercaptopyrimidines were synthesized from S-methylisothiuronium iodide and the appropriate β-keto esters in aqueous ethanolic solution in the presence of potassium hydroxide.[9] The compounds prepared in this way are described in Table II.

2-Hydrazinopyrimidines were prepared by interaction of the 2-methylmercaptopyrimidines in ethanol solution with anhydrous hydrazine (Method A) or 85% hydrazine hydrate (Method B). 2-Hydrazino-4,5-dimethyl-6-hydroxypyrimidine (Vc) was prepared by both methods and will serve as an example. (A) A solution of 4.1 g. of 2-methylmercapto-4,5-dimethyl-6-hydroxypyrimidine and 8.2 g. of anhydrous hydrazine in 150 ml. of absolute ethanol was heated under reflux for 28 hr. The mixture was evaporated to dryness

TABLE III

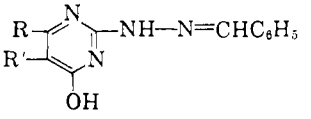
2-HYDRAZINO-6-HYDROXYPYRIMIDINES

Cpd. No.	R	R′	Method	Yield, %	M.P.	Formula	Analyses Calculated C	H	N	Found C	H	N
Va	CH_3	H	B	43	230–231 dec.	$C_5H_6N_4O$	42.8	5.8	40.0	43.1	5.7	39.8
Vb	C_6H_5	H	A	35	219–220 dec.	$C_{10}H_{10}N_4O$	59.4	5.0	27.7	59.6	5.0	27.7
Vc	CH_3	CH_3	A	19	333 dec.	$C_6H_{10}N_4O$	46.7	6.5	36.3	46.5	6.6	36.3
			B	41	333 dec.							
Vd	CH_3	C_2H_5	A	18	232[a]	$C_7H_{12}N_4O$	50.0	7.2	33.3	50.2	7.3	33.5
Ve	CH_3	n-C_3H_7	B	68	215–216[b]	$C_8H_{14}N_4O$	52.7	7.7	30.8	52.8	7.8	30.8
Vg	CH_3	n-C_4H_9	B	16	201–202	$C_9H_{16}N_4O$	55.1	8.2	28.6	55.3	8.4	28.8
Vh	—$(CH_2)_4$—		B	41	324 dec.	$C_8H_{12}N_4O$	53.3	6.7	31.1	53.2	6.8	31.4

[a] Resolidified and remelted at 320° with decomposition on continued heating. [b] Resolidified and remelted at 323° with decomposition on continued heating.

TABLE IV

2-BENZALHYDRAZINO-6-HYDROXYPYRIMIDINES



R	R′	Yield, %	M.P.	Formula	Analyses Calculated C	H	N	Found C	H	N
CH_3	H	44	228–229	$C_{12}H_{12}N_4O$	63.1	5.3	24.6	62.9	5.4	23.6
C_6H_5	H	56	261–262	$C_{17}H_{14}N_4O$	70.3	4.9	19.3	70.5	4.7	19.3
CH_3	CH_3	32	241–242	$C_{13}H_{14}N_4O$	64.4	5.8	23.1	64.2	5.9	23.0
CH_3	C_2H_5	17	228–229	$C_{14}H_{16}N_4O$	65.6	6.3	21.9	65.8	6.3	21.7
CH_3	n-C_3H_7	34	199–200	[a]	64.5	6.9	20.1	64.0	6.8	20.0
CH_3	n-C_4H_9	27	192–193	$C_{16}H_{20}N_4O$	67.6	7.1	19.7	67.4	7.2	19.6

[a] Calculated for the hemihydrate: $C_{15}H_{18}N_4O \cdot {}^1/_2H_2O$.

and the residue recrystallized from ethanol. (B) A solution of 4.3 g. of 2-methylmercapto-4,5-dimethyl-6-hydroxypyrimidine in 75 ml. of ethanol was stirred under reflux on a steam bath with 12.6 g. of 85% hydrazine hydrate. The evolution of methylmercaptan ceased after 60 hr. after which the solution was chilled and the solid that separated recrystallized from ethanol. The product was identical with the material prepared by Method A. In Table III are given yields, melting points and analytical data for compounds prepared in both ways.

2-Benzalhydrazinopyrimidines. A solution of 1.1 g. of benzaldehyde in 5 ml. of ethanol and 0.6 g. of glacial acetic acid was treated with water until faintly cloudy. To this mixture 0.7 g. of 2-hydrazino-4-methyl-6-hydroxypyrimidine was added. The mixture was heated in a beaker on a steam bath until evaporated to dryness and the residue recrystallized from absolute ethanol. Other benzal derivatives were prepared in a similar manner. Table IV gives melting points, yields and analytical data for the benzal derivatives.

5,7-Dimethyltetrazolo[a]pyrimidine (Ia) was prepared from acetylacetone and 5-aminotetrazole in ethanol with piperidine as catalyst,[3] yield 49%, m.p. 151–152° after crystallization from water.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.7; N, 47.0. Found: C, 48.3; H, 4.6; N, 46.9.

The aqueous mother liquors from recrystallization of Ia deposited a second product on thorough chilling. The product crystallized from water as long, fine needles, m.p. 139–140°.

Anal. Found: C, 57.1; H, 5.5; N, 30.1.

The analysis corresponds with values calculated for a product formed by combination of one molecule of 5-aminotetrazole and two of acetylacetone with elimination of three molecules of water. It was not investigated further.

An alternate method of preparation involved interaction of 85% hydrazine hydrate and 2-methylmercapto-4,6-dimethylpyrimidine[13] in ethanol as described for the hydroxy analogs to form 2-hydrazino-4,6-dimethylpyrimidine, m.p. 165°, after crystallization from ethanol.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 52.5; H, 7.3; N, 40.6. Found: C, 52.0; H, 7.2; N, 40.8.

The *benzal* derivative was crystallized from ethanol, m.p. 160°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.0; H, 6.2; N, 24.8. Found: C, 68.8; H, 6.2; N, 24.9.

Treatment of 2-hydrazino-4,6-dimethylpyrimidine with sodium nitrite in aqueous, acid solution as described for the hydrazinohydroxypyrimidines gave Ia, m.p. 151–152° after crystallization from ethanol. Mixture melting point determination and comparison of infrared spectra showed the product to be identical with the material prepared by Bülow's method.

Hydrogenolysis of 5-hydroxy-7-methyltetrazolo[a]pyrimidine. A solution of 3 g. of IIa in 150 ml. of glacial acetic acid was shaken with 175 mg. of platinum oxide at 65° for 24 hr. under 49 p.s.i. hydrogen pressure. After removal of the catalyst the solvent was evaporated and the residue recrystallized from water, m.p. 297° with decomposition. The product was identical with 2-amino-4-methyl-6-hydroxypyrimidine prepared by the method of Jaeger.[14]

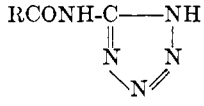
An attempt to hydrogenate IIa in 50% ethanol in the presence of 1.5 molar equivalents of potassium hydroxide with platinum oxide at room temperature and 49 p.s.i.

(13) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).

(14) J. Jaeger, *Ann.*, **262**, 365 (1891).

TABLE V

5-ACYLAMINOTETRAZOLES



R	M.P.[a]	Method	Yield, %	Formula	Analyses Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
CH_3	268–269	A	36	$C_3H_5N_5O$	28.4	4.0	55.1	28.5	4.1	55.2
	Ref. 15	B	90							
C_2H_5	265	A	27	$C_4H_7N_5O$	34.0	5.0	49.6	34.0	5.2	49.4
	265	B	27							
n-C_3H_7	250	A	39	$C_5H_9N_5O$	38.7	5.8	45.1	38.7	5.8	45.2
	250	B	36							
$(C_2H_5)_2CH$	237–238	A	8							
	237–238	B	77	Ref. 16						
C_6H_5	280	B	54	Ref. 17						

[a] All melting points with decomposition.

hydrogen pressure was not successful. Only IIa was recovered from the reaction mixture.

Acylation of 5-aminotetrazole. (A) A mixture of 7.4 g. of anhydrous 5-aminotetrazole and 150 ml. of glacial acetic acid was boiled under reflux for 48 hr. After evaporation of the solvent the residue was recrystallized twice from water, yield 4 g. (36%) of 5-acetamidotetrazole, m.p. 268–269° with decomposition.[15] Similar preparations were done with propionic, *n*-butyric and diethylacetic acid. Yields, melting points and analytical data are given in Table V.

(B) Comparable acyl derivatives were obtained by warming anhydrous 5-aminotetrazole with acetic anhydride,[15] propionic anhydride, *n*-butyryl chloride, diethylacetyl chloride,[16] and benzoyl chloride.[17] Data for the products are included in Table V.

(C) A mixture of 15.8 g. (0.11 mole) of ethyl diethylacetate and 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole in 250 ml. of glacial acetic acid was boiled under reflux for 24 hr. The crystalline product that separated on cooling was recrystallized from water, yield 4.1 g., m.p. 238°, identical in all respects with 5-diethylacetamidotetrazole obtained in Methods A and B.

(D) Attempts to prepare the acyl derivatives by warming 5-aminotetrazole with ethyl acetate, ethyl propionate, ethyl *n*-butyrate, or ethyl benzoate alone or in ethanol or 1,4-dioxane solution in the presence of piperidine were unsuccessful. In each case 5-aminotetrazole was recovered completely.

EAST LANSING, MICH

(15) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895).

(16) R. Stollé and O. Roser, *J. prakt. Chem.*, **136**, 314 (1933).

(17) R. Stollé and F. Henke-Stark, *J. prakt. Chem.*, **124**, 261 (1930).

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of 1-Isobornyl-5-alkyl Tetrazoles[1]

CARLETON W. ROBERTS[2] AND MILTON L. MASKALERIS[3]

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The reaction of nitriles with 1,1-disubstituted olefins in the presence of an acid catalyst to form *N*-substituted amides (Ritter Reaction) has been utilized to prepare a series of *N*-isobornylalkanamides from camphene and acetonitrile, propionitrile, *n*-butyronitrile, and *n*-valeronitrile. These amides have been converted by the von Braun procedure to the corresponding 1-isobornyl-5-alkyl tetrazoles. The first member in the series, 1-isobornyl-5-methyl tetrazole, possesses stimulatory activity toward rats at dosages of 10 mg./kg.

Gross and Featherstone[4] have studied the ultraviolet spectra of several series of pentamethylenetetrazoles and 1,5-disubstituted tetrazoles. The several series of compounds showed a surprising range of physiological activity, from strong sedatives to strong analeptics. On the basis of an admittedly empirical correlation, the authors conclude, "that without exception, substances possessing a potent and stimulatory action showed little or no absorption in the ultraviolet." Typical of the compounds studied in the 1,5-disubstituted

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(2) Present address: Polymer Research Laboratory, The Dow Chemical Co., Midland, Mich.

(3) Present address: The Pennsylvania State University, University Park, Pa.

(4) F. W. Schueler, S. C. Wang, R. M. Featherstone, and E. G. Gross, *J. Pharmacol. Exptl. Therap.*, **97**, 266 (1949).