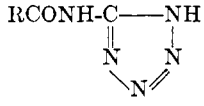
TABLE V

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]

Received December 15, 1958

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

(1) From a thesis submitted to the Graduate School, Purdue University, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, August 1956.

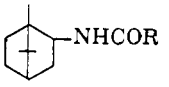
(2) Present address: Polymer Research Laboratory, The Dow Chemical Co., Midland, Mich.

(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).

TABLE I

N-ISOBORNYL-*n*-ALKANAMIDES

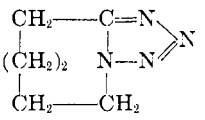


Group, R	M.P.	Yield, %	Percentage Composition					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3-	141.0–141.5[a,b]	48	—	—	—	—	—	—
C_2H_5-	115.0–116.0[c]	58	—	—	—	—	—	—
n-C_3H_7-	89.0–90.5[d]	47	75.28	75.30	11.28	11.18	6.27	6.38
n-C_4H_9	107.5–108.5	71	75.90	75.94	11.47	11.30	5.90	5.87

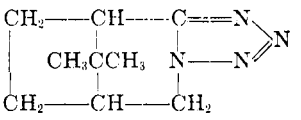
[a] M. O. Foster, *J. Chem. Soc.*, **73**, 395 (1898), reported m.p. 143°; M. O. Foster and J. Hart-Smith, *J. Chem. Soc.*, **77**, 1157 (1900), reported m.p. 144°; reference 6 reported m.p. 142–143°. [b] P. F. Frankland and F. Barrow, *J. Chem. Soc.*, **95**, 2025 (1909), reported m.p. 145.5°. [c] Reference *b* reported m.p. 117°. [d] Reference *b* reported m.p. 97°

tetrazole series were 1-cycohexyl-5-methyl tetrazole and 1-methyl-5-cyclohexyl tetrazole; both of these compounds were analeptics and showed no absorption in the ultraviolet. Other older and, in one instance, commercially interesting disubstituted tetrazoles are those possessing the pentamethylene structure [Metrazole, Cardiazole (I)], the "camphor tetrazole" (II), and compounds derived from the thujones.[5]

A consideration of the structure of the "camphor tetrazole" led to the conception of incorporating other types of bicyclic systems with the tetrazole nucleus. This paper reports the synthesis of four bicyclic substituted tetrazoles where the bicyclic moiety is attached to the 1-position of the tetrazole ring, and the 5-position of the tetrazole ring is reserved for alkyl substituents.



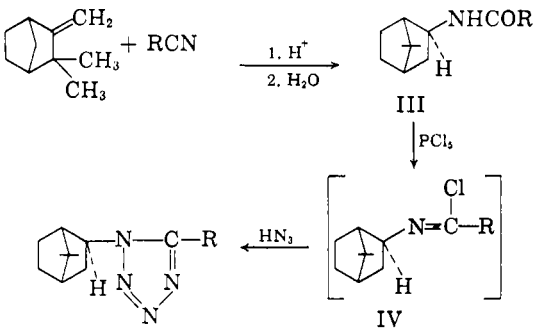
I



II

Ritter and co-workers[6] have described several examples of the reaction in which a nitrile reacts with an olefin or alcohol in the presence of an acid catalyst to give *N*-substituted amides. In the earliest reference, Ritter describes the reaction of acetonitrile with camphene to give *N*-isobornylacetamide (III) in excellent yield. Utilizing essentially a comparable procedure we have prepared a series of *N*-isobornyl alkanamides[7,10] from camphene and acetonitrile, propionitrile, *n*-butyronitrile, and *n*-valeronitrile.

The *N*-isobornyl alkanamides (Table I) were treated with phosphorus pentachloride in benzene to give the corresponding imino chlorides (IV); these intermediates were not isolated but, rather, were treated *in situ* with a benzene solution of hydrogen azide.[11–13] From the reaction mixtures were isolated the 1-isobornyl-5-alkyl tetrazoles (V) (Table II).



III IV

Spectra. The infrared spectra of the 1-isobornyl-5-alkyl tetrazoles showed absorption maxima in the 9.00 to 10.00μ region; the particular peaks were at 9.15, 9.30, 9.60, 9.70 and 9.9μ. These compare with the tetrazole ring peaks assigned[14] previously

(5) E. K. Harvill, C. W. Roberts, R. M. Herbst, *J. Org. Chem.*, **15**, 58 (1950).

(6) J. J. Ritter and co-workers, *J. Am. Chem. Soc.*, **70**, 4045 (1948); **71**, 4128 (1949); **73**, 4076 (1951); **74**, 763 (1952).

(7) Stein[8] and, subsequently, Luskin[9] reported that contrary to Ritter, the reaction of camphene with hydrogen cyanide gives 3-formamidoisocamphane. Higher alkyl nitriles do not appear to give the originally reported[6] rearrangement of the camphene to the isobornyl structures.

(8) G. A. Stein, M. Stelzinger, H. Arnold, D. Reinhold, W. Gaines, and K. Pfister, III, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

(9) L. S. Luskin, A. J. McFaull, and G. E. Gantert, *J. Org. Chem.*, **21**, 1430 (1956).

(10) That the isobornyl moiety of the compounds described in this paper is correct is based on a comparison of the infrared spectra of *N*-isobornylacetamide (this paper) with the spectra of 2-formylisocamphane, *N*-formyl-*d*-bornylamine and *dl*-*N*-formylisobornylamine kindly supplied by Dr. G. A. Stein. Similar comparisons were made with spectra for formamidoisocamphane, isocyanatoisocamphane, and isobornyl isocyanate kindly supplied by Dr. L. S. Luskin. The authors wish to express their appreciation for the copies of these spectra.

(11) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

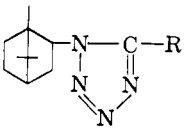
(12) E. K. Harvill, R. M. Herbst, E. C. Schreiner and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(13) R. M. Herbst, C. W. Roberts, H. T. F. Givens, and E. K. Harvill, *J. Org. Chem.*, **17**, 262 (1952).

(14) E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

TABLE II

1-ISOBORNYL-5-ALKYL TETRAZOLES



Group, R	M.P.	Yield, %	Percentage Composition					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3-	81.5–83.5	29	65.42	65.52	9.15	9.58	25.43	25.61
C_2H_5-	93.5–95.0	22	66.63	66.51	9.46	9.28	23.91	24.03
n-C_3H_7-	75.5–76.0	52	67.70	67.33	9.74	9.56	22.56	22.65
n-C_4H_9	63.5–65.0	62	68.66	68.64	9.99	9.75	21.35	21.41

at 9.40 to 10.10μ for 5-substituted tetrazoles, 9.14 to 9.20μ and 10.08 to 10.30μ for 1,5-disubstituted tetrazoles[15] where the substituents were methyl and chlorophenyl. In a recent report[16] several 5-dialkylaminoalkyl tetrazoles were reported to have associated peaks at 9.08μ.

No absorption was evidenced by the tetrazoles reported in this present paper in the ultraviolet region.

Pharmacological testing. Preliminary pharmacological testing was carried out by the authors. Interperitoneal injections of solutions of the 1-isobornyl-5-methyl tetrazole in sesame oil in rats at 10 mg./kg. of rat showed stimulation after 10 min.; these convulsive reactions lasted nearly 2 hr. In Amytal-sedated rats, a total dosage of 26 mg./kg. of rat of 1-isobornyl-5-methyl tetrazole was necessary to achieve the same order of convulsive reaction. The 1-isobornyl-5-ethyl tetrazole and the 5-alkyl tetrazoles containing larger alkyl groups appeared to effect sedation or to possess the opposite effect to that displayed by the first member of the series. The amides, *N*-isobornyl-acetamide (NSC 3681), *N*-isobornyl-*n*-butyramide (NSC 3680), and *N*-isobornyl-*n*-valeramide (NSC 3683) were tested against Sarcoma-180 and Ca-755.[17] *N*-Isobornylacetamide showed an acute toxicity at 150 mg./kg. in Swiss mice. The tetrazoles showed no activity when screened as analgesics, hypotensive agents, tranquilizers or diuretics.[18]

EXPERIMENTAL[19]

Typical experimental details are given for one series of preparations from the camphene to the tetrazole.

N-Isobornyl-n-valeramide. In a 500-ml., three necked flask equipped with a Claisen adapter, thermometer, dropping funnel, and a stirrer was placed 150 ml. (2.63 moles) of glacial acetic acid and 56 ml. (1.05 moles) of concentrated sulfuric acid. After cooling the mixture to 15°, 27.3 g. (0.33 mole) of *n*-valeronitrile was added during 20 min. maintaining the temperature below 20°. A solution of 40.8 g. (0.30 mole) of camphene in 35 ml. of glacial acetic acid was added dropwise during 30 min. at a temperature below 30°. After mixing was complete, the reaction mixture was warmed to 45° for 4 hr. and to 80° for 3 hr. The mixture was cooled to 30° and poured into a fourfold volume of cracked ice and water. Sufficient 6*N* sodium hydroxide was added to bring the *p*H to 5.0. The collected solid was washed twice with distilled water and air dried. The product, 69.2 g. (97.3%) was dissolved in 330 ml. of acetone, decolorized by refluxing with 10 g. of Norite, and filtered. The chilled filtrate was filtered to obtain the first crop of product. By careful concentration of the mother liquors, four subsequent crops were obtained; a total of 50.5 g. of pure product was isolated, m.p. 107–108.5° (71.7%). The data for the other *N*-isobornylalkanamides are in Table I.

1-Isobornyl-5-n-butyl tetrazole. In a 500-ml., round bottomed, three necked flask equipped with a dry port, thermometer, reflux condenser (protected with a Drierite tube) and stirrer was placed 22.3 g. (0.1 mole) of *N*-isobornyl-*n*-valeramide and 300 ml. of anhydrous benzene. Maintaining the temperature below 40°, 20.9° (0.1 mole) of phosphorus pentachloride was added portionwise through the dry port. As addition proceeded the amide appeared to react and dissolve; when the phosphorus pentachloride was all added the mixture was stirred for 30 min. at 40° to insnre complete reaction. The Drierite tube exit was connected to a source of vacuum and sufficient vacuum was applied to remove the hydrogen chloride evolved from the reaction. The reaction mixture was then cooled to 20° and a solution of hydrogen azide (8.6 g., 0.2 mole; 5.56 g. hydrogen azide/100 ml. benzene) in benzene was added dropwise from a funnel replacing the dry port. Stirring was continued for 1 hr. at 25° and for 3 hr. at reflux (the condenser outlet was attached to an open T-tube to a vacuum source to prevent escape of hydrogen azide or hydrogen chloride to the hood or room) for 30 min. The cooled reaction mixture was treated with an aqueous solution of sodium hydroxide to *p*H 7. The benzene layer was separated and the aqueous layer extracted with two 25 ml. portions of benzene. The benzene

(15) C. W. Roberts, G. F. Fanta, and J. D. Martin, *J. Org. Chem.*, 24, 654 (1959).

(16) P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.*, 23, 1599 (1958).

(17) Acknowledgment is gratefully made to the Cancer Screening Program, National Institutes of Health for the screening data on these compounds.

(18) Acknowledgment is gratefully made to the Lederle Laboratories, Pearl River, N. Y., for these preliminary data.

(19) All melting points are corrected (capillary). Microanalyses by Dr. C. T. Yeh and Mrs. D. W. Margerum, Purdue University. Infrared spectra by Mrs. B. Pollister using sodium chloride prisms on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra by Mr. E. Choplinski using a Cary spectrophotometer.

extracts were combined, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to about 50 ml. and chilled; the semisolid residue was treated with 75 ml. of petroleum ether (b.p. 95–110°), rechilled and filtered to give 18.7 g. of crude product. After three recrystallizations from petroleum ether (b.p. 95–110°) there was obtained 16.1 g. (61.5%) of 1-isobornyl-5-*n*-butyl tetrazole, m.p. 63.5–65°. The data for the tetrazoles are in Table II.

WEST LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Effect of Associated Salts and Amines on Polymerization of Butadiene by Amylsodium[1]

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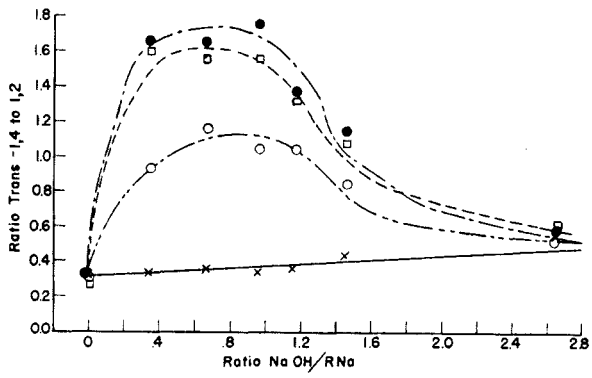
Received November 10, 1958

Triethyl amine and sodium hydroxide caused amylsodium to polymerize butadiene in a 1,4- rather than the usual 1,2-manner. The combination resembles in some aspects the alfin group of reagents but is less satisfactory with respect to the yield, size of polymer and freedom from gel of the polybutadiene. The conditions under which this combination operates are described.

Prior work has demonstrated that the association of sodium isopropoxide and sodium chloride with allylsodium caused the predominant polymerization of butadiene to change from a 1,2- to a 1,4-process. Similar effects were achieved with other straight chain alkenyl- or benzyl-sodium reagents. These combinations are known generally as alfin catalysts.[2] The organosodium components have unsaturation in the chain or the ring. No such change has been found, hitherto, when the organic moiety is saturated.[2a,3] The present paper reports that the association of triethyl amine and sodium hydroxide—sodium chloride happened to be present also—with amylsodium caused a similar alteration in the polymerization of butadiene. Alone, amylsodium polymerized butadiene largely in a 1,2-manner, the ratio of *trans*-1,4- to -1,2- structures being 0.3 or 0.4 (only 23–28% *trans*-1,4-), but with appropriate amounts of triethyl amine and sodium hydroxide the ratio became as high as 1.75 ,that is, 64% *trans*-1,4-structure, only a little less than the 75% achieved with a good alfin reagent which in turn is as much as in free radical polymerization.

Around 200 experiments (not all reported in this paper) were made in demonstrating this effect. Amylsodium was made from amyl chloride and sodium. Water was added in varying amounts to different preparations so that different ratios of sodium hydroxide to amylsodium were obtained. Then a specific quantity (usually 10 ml.) of each reagent was added to 30 ml. of butadiene in 200 ml. of solvent, said solvent being cyclohexane, triethyl amine, or mixtures of these two liquids. By this means a wide coverage of conditions was assured although the experiments by no means encompassed all possible variations. Adequate controls and tests with other components were made.

The principal results are shown in six graphs. In the first the highest proportion of 1,4-polymerization was realized when the ratio of sodium hydroxide to amylsodium was around 0.8 and the amine was approximately one half by volume of the total solvent. The bottom curve on the graph shows a control series where no amine was present; the proportion of 1,4-structure increased only a



10-ml. catalyst suspension 30-ml. butadiene One-hour polymerization		Solvent: Cyclohexane, ml.	Solvent: $(C_2H_5)_3N$, ml.
	×	200	0
	○	150	50
	●	100	100
	□	50	150

Fig. 1. Infrared ratio as a function of amine concentration and oxide ratio

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) (a) A. A. Morton, E. E. Magat, and R. L. Letsinger, *J. Am. Chem. Soc.*, 69 950 (1947); (b) A. A. Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950); (c) A. A. Morton, F. H. Bolton, F. W. Collins, and E. F. Cluff, *Ind. Eng. Chem.*, **44**, 2876 (1952); (d) A. A. Morton, I. Nelidow, and E. Schoenberg, *Proc. Third Rubber Tech. Conf.*, 108 (1954); (e) A. A. Morton, *Advances In Catalysis*, IX 745 (1957), Academic Press, Inc. New York.

(3) British Patent **782970**, Sept. 18, 1957, issued to Polymer Corp. Ltd., of Canada, describes the use of amylsodium with sodium isopropoxide and sodium chloride as a reagent which can cause a high proportion of 1,4- polymerization. However, their amylsodium was prepared in xylene, which would react at once to give xylylsodium.