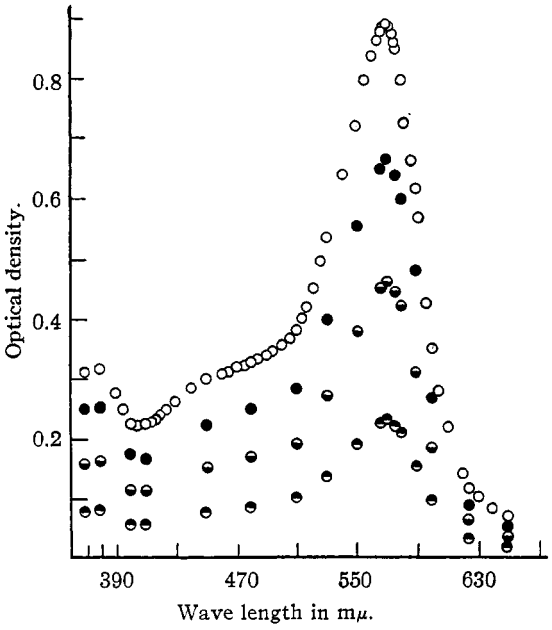


Fig. 9.—Absorption spectra (1-cm. tubes) of the colored products formed when glucose was treated according to Procedure II (using random-presulfonated α-naphthol): ○, 50γ; ●, 37.5γ; ◒, 25γ; and ◓, 12.5γ of glucose.

The test may be used along with the α-naphthol and orcinol tests[9,10,11] as an aid in distinguishing between various carbohydrates. This use was tried and proven successful with milk (lactose) and for glucose and galactose cerebrosides.

(9) Sørensen and Haugaard, *Compt. rend. trav. lab. Carlsberg*, **19**, No. 12, 1 (1933).

(10) Sørensen, *Biochem. Z.*, **269**, 271 (1934).

(11) Sørensen, *Compt. rend. trav. lab. Carlsberg. ser. chim.*, **21**, No. 8, 123 (1936).

The speed of the reactions is an important factor in identifying a monosaccharide.

Use for Quantitative Estimation.—As illustrated in Fig. 9, the reaction is additive and the most accurate estimation can be made at the absorption maximum. The carbohydrates in milk, cerebrosides and in blood filtrates give excellent results. As little as 10 γ of carbohydrate can be accurately estimated by this simple, rapid procedure. The orcinol reaction[9,10,11] has proven valuable for some of these purposes but the sulfonated α-naphthol reaction will be of further aid. It is necessary to use a standard for each determination because the size of the test-tubes used and the room temperature are important factors.

Interfering Substances.—It has been previously reported[12] that α-naphtholsulfuric acid gives color reactions with aldehydes. All four of the aldehydes tried in the present investigation gave an absorption maximum in the violet region and very little absorption above 540 mμ. Blood filtrates show an increased absorption at the shorter wave lengths but there seems to be no interference at the absorption maximum for hexoses.

Summary

The use of random-presulfonated α-naphthol (Procedure II) offers a more satisfactory method for a general carbohydrate test than the usual Molisch reaction. This new test can be used as an aid in identifying carbohydrate groups and offers a simple, rapid procedure for estimating small amounts of carbohydrates. A solution of sulfonates of α-naphthol does not darken on standing and is made up in water solution which is not possible for α-naphthol itself.

(12) Ekkert, *Pharm. Zentralh.*, **68**, 563 (1927).

BROOKINGS, SOUTH DAKOTA RECEIVED MARCH 4, 1949

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. IV. N-Trisubstituted Alkyl Pyridine Carboxamides as Antispasmodic Agents[1]

BY NATHAN SPERBER, DOMENICK PAPA AND ERWIN SCHWENK

In several recent publications, the pharmacological action associated with quaternary carbon compounds has been demonstrated. Trialkylacetamides[2] (R′ = $CONH_2$), trialkylethylamines[3] (R′ = CH_2NH_2), trialkylacetic acids[4] (R′ = COOH) and trialkylcarbinamines[5] (R′ = NH_2) of the general formula R_3C–R′ (I), wherein R_3 are alkyl groups of 3–5 carbon atoms and total 12–15 carbon atoms, have pronounced musculotropic, but rather feeble neurotropic, antispasmodic activity. In view of the known pharmacological and clinical action of pyridine carboxamides,[6] it appeared of interest to synthesize aryl and heterocyclic acid amides embodying the quaternary carbon moiety of I. This communication describes the synthesis and preliminary pharmacological data of a series of N-trisubstituted alkyl pyridine carboxamides[7,8] of the

(1) Presented in abstract before the Division of Medicinal Chemistry of the American Chemical Society at Atlantic City, September 20, 1949.

(2) Junkmann and Allardt, U. S. Patent 2,186,976, Jan. 16, 1940.

(3) Allardt and Junkmann, U. S. Patent 2,361,524, Oct. 31, 1944.

(4) Sperber, Papa and Schwenk, THIS JOURNAL, **70**, 3091 (1948).

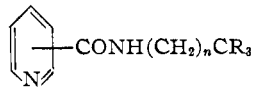
(5) Sperber and Fricano, *ibid.*, **71**, 3352 (1949).

(6) Nicotinamide (Niacinamide) and N,N-diethylnicotinamide (Coramine) are representative of clinically effective pyridine carboxamides.

(7) Billman and Rendall, THIS JOURNAL, **66**, 540 (1944), prepared a series of N-substituted pyridine carboxamides and amides of pyrazine monocarboxylic and pyrazine 2,3-dicarboxylic acids. They reported that "the benzylamide of nicotinic acid possessed pronounced antispasmodic activity."

(8) Badgett, Prevost, Ogg and Woodward, *ibid.*, **67**, 1136 (1945),

general formula II, wherein R_3 represents three alkyl groups or two alkyl groups and a phenyl group and n is 0 or 1.

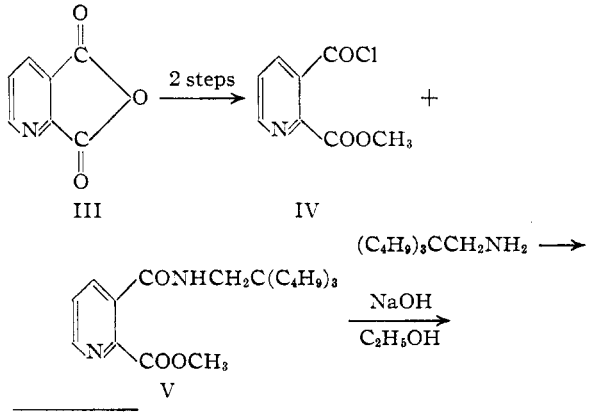


II

The amides II were synthesized by the following two methods: (a) reaction of picolinoyl, nicotinoyl or isonicotinoyl chloride hydrochlorides and the appropriately substituted amine in pyridine and (b) by the reaction of the esters of these acids and the amine in xylene. In general, the amides were obtained in good yield by the acid chloride procedure, the ester–amine reaction being used only in the case of the N-(2,2-dibutylhexyl)-picolinamide.

In the preliminary pharmacological examination of the amides, it became apparent that the insolubility of the compounds and the instability of the hydrochlorides would not permit an accurate evaluation of *in vitro* antispasmodic activity. In the case of N-(2,2-dibutylhexyl)-nicotinamide hydrochloride, which was studied in detail, hydrolysis to the amide occurred readily in hot water. The low basicity of this compound parallels that of nicotinamide and nicotinic acid which have been reported[9] to form unsatisfactory salts with methane-1,1-bis-(2-hydroxy-3-naphthoic acid) or 2-ethylhexylsulfuric acid. The basicity of the ring nitrogen is reduced by the presence of a carboxyl group in the β-position.

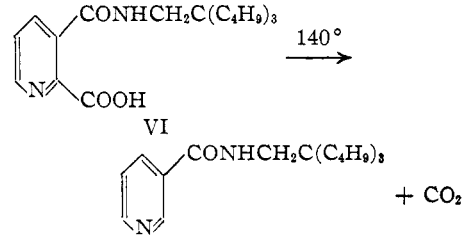
In view of the unfavorable solubility and stability of the hydrochlorides of the 3-pyridyl carboxamides, it appeared of interest to synthesize amides of formula II having a solubilizing group. On the basis of preliminary antispasmodic assay which indicated a high order of activity for N-(2,2-dibutylhexyl)-nicotinamide, N-(2,2-dibutylhexyl)-2-carboxynicotinamide (VI) was synthesized. The reactions for securing this compound are shown



III IV V

described a series of water insoluble N-alkyl nicotinamides for use in the fortification of cereals.

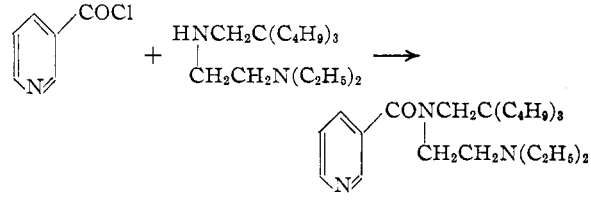
(9) Huber, Boehme and Laskowski, THIS JOURNAL, **68**, 187 (1946).



VI VII

When 2-carbomethoxynicotinoyl chloride (IV) reacted with 2,2-dibutylhexylamine in pyridine, V was obtained. The ester-amide (V) was hydrolyzed to the free acid (VI) and upon heating VI at 140° decarboxylation occurred to give N-(2,2-dibutylhexyl)-nicotinamide (VII). The latter was identical with VII synthesized from nicotinoyl chloride hydrochloride and 2,2-dibutylhexylamine, thus establishing the structures of V and VI.

Introduction of an N-substituted solubilizing group in VII was effected by the reaction of nicotinoyl chloride hydrochloride and N,N-diethyl-N'-(2,2-dibutylhexyl)-ethylenediamine in pyridine.



The disubstituted amide formed a soluble dihydrochloride which was suitable for testing.

N-(2,2-Dibutylhexyl)-1-methylnipecotamide (VIII) was prepared in order to evaluate pharmacologically the hydrogenated derivative of VII. When VII was reduced catalytically with hydrogen and Raney nickel catalyst in methanol at 175° and 200 atmospheres, VIII was obtained and not the expected product IX.[10]

Confirmation of the structure of VIII was established by reduction of VII in dioxane to IX and subsequent methylation of IX with formic acid and formaldehyde.[11] The product obtained by the latter procedure was identical to that obtained by the reduction of VII in methanol.

Pharmacology.—The antispasmodic activity of these compounds was determined on isolated rabbit intestinal muscle by measuring the relaxation produced by the test compound against barium chloride and Doryl induced spasms. A summary of the activity of compounds 1–7 is given in Table I. Compounds 8, 9 and 12 were completely inactive at concentrations of 1:500,000 while 10, 11 and 13 were effective at concentrations of 1:500,000 to 1:700,000. Introduction of

(10) The methylation of VII during reduction in methanol is not surprising, since it has been reported by Adkins, Kuick, Farlow and Wojcik, (THIS JOURNAL, **56**, 2425 (1934)) that the reduction product of ethyl nicotinate with Raney nickel and hydrogen in ethanol contained 20% ethyl N-ethylnipecotate.

(11) "Org. Syntheses," **25**, 89 (1945).

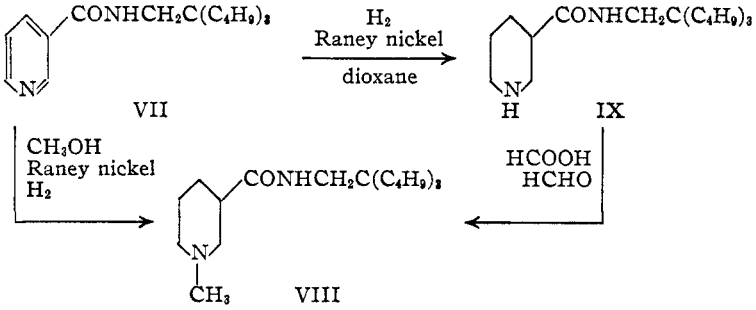
TABLE I

$RCONH(CH_2)_nC(R''')(R'')(R')$

	R	R'	R''	R'''	n	M. p., °C.	Yield, %	Formula	Nitrogen analyses, % Calcd.	Found	Maximum eff. diln. $BaCl_2$[a] × 10^5	Doryl[b] × 10^5
1	3-C_5H_4N	C_4H_9	C_4H_9	C_4H_9	1	104–104.5	70	$C_{20}H_{34}ON_2$	8.79	8.98	10.0	11.0
2	4-C_5H_4N	C_4H_9	C_4H_9	C_4H_9	1	91.5–92	71	$C_{20}H_{34}ON_2$	8.79	8.42	5.0	3.0
3	2-C_5H_4N	C_4H_9	C_4H_9	C_4H_9	1	[c]	74	$C_{20}H_{34}ON_2$	8.79	8.65	<5.0	<.50
4	3-C_5H_4N	C_4H_9	C_4H_9	C_4H_9	0	103–103.5	70	$C_{19}H_{32}ON_2$	C, 74.93	75.30	5.0	4.0
									H, 10.60	10.70		
5	3-C_5H_4N	C_4H_9	C_4H_9	C_6H_5	0	156.5–157	78	$C_{21}H_{28}ON_2$	8.64	8.81	<5.0	<5.0
6	3-C_5H_4N	C_4H_9	C_4H_9	C_6H_5	1	132.3–133	74	$C_{22}H_{30}ON_2$	8.28	8.27	9.0	18.0
									C, 78.04	78.23		
									H, 8.94	8.85		
7	3-C_5H_4N	C_2H_5	C_3H_7	C_3H_7	1	[d]	37	$C_{16}H_{26}ON_2$	10.68	10.31	2.0	2.0

[a] Papaverine activity 1 × 10^5. [b] Atropine activity, 1000 × 10^5. [c] B. p. 184–185° (0.5 mm.); $n^{22}D$ 1.4995, viscous, colorless liquid. [d] B. p. 200–202° (3 mm.); $n^{25}D$ 1.5200.

the carboxy group in 1 decreases the antispasmodic activity (compare compounds 1 and 12). Similarly, reduction of the pyridine ring results in a lowering of the antispasmodic potency.



Experimental

The arabic numbers in parentheses following the name of the compound are for reference to pharmacology.

The preparation of N-(2,2-dibutylhexyl)-nicotinamide will illustrate the general method for the synthesis of the N-trisubstituted alkyl pyridine carboxamides from the corresponding acid chloride hydrochloride and the amine.

In a one-liter, three-necked flask, fitted with a reflux condenser and two stoppers was placed 30.8 g. (0.25 mole) of dry nicotinic acid and 100 cc. of thionyl chloride. The mixture was refluxed for one hour and the excess thionyl chloride removed *in vacuo*. To the residue was added 100 cc. of dry benzene and the benzene and residual thionyl chloride removed *in vacuo* on the steam-bath. The flask was cooled in an ice-bath, fitted with a stirrer and dropping funnel and 200 cc. of pyridine added. To the stirred mixture, a solution of 53 g. (0.25 mole) of 2,2-dibutylhexylamine in 50 cc. of pyridine was added dropwise; the reaction mixture was heated for six hours on the steam-bath and then poured on a slurry of ice and water. The dark oil which crystallized was filtered and washed with cold, dilute ethanol. The crude amide was recrystallized twice from a mixture of ethanol–water. The hydrochloride, prepared in the usual manner, melted at 156.7–157.2° after recrystallization from a mixture of ethanol–ether.

Anal. Calcd. for $C_{20}H_{35}ON_2Cl$: Cl, 10.00. Found: Cl, 10.40.

When a sample of the hydrochloride was heated in water, hydrolysis occurred and the free base was recovered, m. p. and mixed m. p. with an authentic sample of VII, 103–103.5°.

The picrate was prepared in the usual manner and recrystallized from ethanol, m. p. 141.5–142.5°.

Anal. Calcd. for $C_{26}H_{37}O_8N_5$: N, 12.79. Found: N, 12.51.

N-(2,2-Dibutylhexyl)-picolinamide.[7,8]—A solution of 15.1 g. (0.10 mole) of ethyl picolinate and 23 g. (0.104 mole) of 2,2-dibutylhexylamine[8] in 50 cc. of xylene was refluxed for two days. The xylene was removed *in vacuo* and the residue fractionated.

Benzyl nicotinamide (8) was prepared by the reaction of nicotinoyl chloride hydrochloride with benzylamine in pyridine in 65% yield. The amide was recrystallized from xylene, m. p. 85–85.5°.[12]

Anal. Calcd. for $C_{13}H_{12}ON_2$: N, 13.20. Found: N, 13.08.

N-Tetradecylnicotinamide[8] (9) was prepared in 50% yield by the reaction of nicotinoyl chloride hydrochloride with tetradecylamine in pyridine, m. p. 81–82°.

N-(β-N',N'-Diethylaminoethyl)-N-(2,2-dibutylhexyl)-nicotinamide Dihydrochloride (10).—To nicotinoyl chloride hydrochloride (from 8 g. of nicotinic acid) in 30 cc. of pyridine, there was added a solution of 15.6 g. (0.05 mole) of N,N-diethyl-N'-(2,2-dibutylhexyl)-ethylenediamine[13] in 25 cc. of dry pyridine. The reaction mixture was heated with stirring on a steam-bath for four hours and the red suspension then poured on ice and water. The oil was extracted with ether, the ether extract washed with water and dried over sodium sulfate. After removing the ether, the residue distilled as a viscous, brown oil; yield 18 g. (80%), b. p. 212–214° (1 mm.). The dihydrochloride was prepared as usual and was recrystallized from alcohol–ether, m. p. 187–187.5°.

Anal. Calcd. for $C_{26}H_{49}ON_3Cl_2$: Cl, 14.46; N, 8.57. Found: Cl, 14.90; N, 8.28, 8.44.

N-(2,2-Dibutylhexyl)-2-carbomethoxynicotinamide (11).—A mixture of 19.2 g. (0.106 mole) of 2-carbomethoxynicotinic acid[14] and 75 cc. of thionyl chloride was refluxed for one hour and the excess thionyl chloride removed *in vacuo* with the aid of benzene. Seventy-five cc. of dry pyridine was added to the cooled mixture followed by a solution of 27.4 g. (0.129 mole) of 2,2-dibutylhexylamine in 25 cc. of pyridine. After the mixture had been heated and stirred for four hours on a steam-bath, it was poured on ice and the black oil which crystallized was filtered, washed with water and recrystallized from a mixture of benzene–petroleum ether; yield 25 g. (62.5%), m. p. 116–116.5°.

(12) Billman and Rendall (see ref. 7) prepared benzylnicotinamide in a yield of 93% by the reaction of nicotinic acid and benzylamine in xylene and obtained a product melting at 72–73°.

(13) Sperber and Papa, THIS JOURNAL, **71**, 886 (1949).

(14) Kirpal, *Monatsh.*, **20**, 767 (1900); **21**, 957 (1900).

Anal. Calcd. for $C_{22}H_{36}O_3N_2$: C, 70.16; H, 9.64; N, 7.45. Found: C, 70.66; H, 9.53; N, 7.18.

N-(2,2-Dibutylhexyl)-2-carboxynicotinamide (12).—A solution of 5.5 g. of N-(2,2-dibutylhexyl)-2-carbomethoxynicotinamide, 3 g. of sodium hydroxide, 40 cc. of ethanol and 10 cc. of water was allowed to stand for three hours at room temperature. The solution was poured into cold water and acidified with dilute hydrochloric acid. The tan, amorphous solid (5.2 g.) which separated was dried and recrystallized from a mixture of chloroform–petroleum ether from which it separated as a white crystalline solid; yield 2.8 g. (53%), m. p. 128–129°.

Anal. Calcd. for $C_{21}H_{34}O_3N_2$: N, 7.73. Found: N, 8.20.

Decarboxylation of N-(2,2-Dibutylhexyl)-2-carboxynicotinamide.—One gram of N-(2,2-dibutylhexyl)-2-carboxynicotinamide was heated for forty minutes at 140°. The residue was cooled and dissolved in a mixture of alcohol and water. The white precipitate which separated was filtered, washed with sodium carbonate solution, water and dried. The solid was recrystallized from a mixture of alcohol and water, m. p. 104–105, mixed m. p. with N-(2,2-dibutylhexyl)-nicotinamide (VII), 104–105°.

N-(2,2-Dibutylhexyl)-1-methylnipecotamide (VIII) (13).—A solution of 23.3 g. (0.063 mole) of N-(2,2-dibutylhexyl)-nicotinamide in 350 cc. of methanol was reduced with Raney nickel catalyst at an initial pressure of 1,500 lb. for ten hours at 170°. After removal of the catalyst and the solvent, a cloudy oil remained which was dissolved in ether, the ether solution dried and then distilled. The residue (23 g.) was a waxy, amorphous solid melting at 68–69°. The hydrochloride was prepared in the usual manner and melted at 168–169° after a recrystallization from alcohol–ether.

Anal. Calcd. for $C_{21}H_{43}ON_2Cl$: C, 67.24; H, 11.55; N, 7.47. Found: C, 66.68; H, 11.30; N, 7.52.

VIII formed a picrate after standing for three days, m. p. 129–130°. The methiodide, m. p. 231–232°, could not be recrystallized satisfactorily for analysis. The methylation of the piperidine nitrogen was indicated by the fact that no heat was evolved when VIII was treated with pyridine and acetic anhydride.

N-(2,2-Dibutylhexyl)-nipecotamide (IX).—A solution of 31.8 g. of N-(2,2-dibutylhexyl)-nicotinamide in 350 cc. of dioxane was reduced with Raney nickel catalyst at an initial pressure of 1,000 lb. at 165°. The catalyst and solvents were removed and the black, viscous residue distilled; yield 22 g., b. p. 212–214° (3.5 mm.), m. p. 70–72°. Attempts to recrystallize the product were unsuccessful. The following analysis was made on the liquid sample.

Anal. Calcd. for $C_{20}H_{40}ON_2$: C, 74.01; H, 12.43; N, 8.64. Found: C, 74.19; H, 12.57; N, 8.48.

A mixed melting point of VIII (m. p. 68–69°) and IX (m. p. 70–72°) was depressed (54–56°).

IX gave a gummy hydrochloride and picrate. When IX was treated with acetic anhydride and pyridine, considerable heat was evolved and an oily precipitate resulted when the solution was poured on ice.

N-(2,2-Dibutylhexyl)-1-methylnipecotamide (VIII) by the Methylation of IX.—To 15 g. (0.0463 mole) of IX was added with cooling 12.0 g. of 90% formic acid followed by 10.5 cc. of 37% formaldehyde solution.[10] The flask was heated on the steam-bath and carbon dioxide was evolved rapidly. After twelve hours, the viscous liquid was basified with sodium hydroxide pellets and the oily solid taken up in ether. The ether layer was washed with water, dried, the ether distilled and the oily residue fractionated; yield 14 g. (90%), b. p. 188–190° (1 mm.), colorless oil which crystallized slowly, m. p. 64–65°, mixed m. p. with a sample of VIII prepared by the reduction of VII in methanol (m. p. 68–68°) showed no depression (m. p. 65–66°).

Anal. Calcd. for $C_{21}H_{42}ON_2$: C, 74.47; H, 12.51; N, 8.28. Found: C, 74.50; H, 12.59; N, 8.23.

The methiodide of VIII (m. p. 228–229°), prepared from IX, did not depress the melting point of the methiodide (m. p. 231–232°) prepared by the reduction of VII in methanol (mixed m. p. 229–229.5°).

Acknowledgment.—The authors wish to express their appreciation to Mrs. Rosemarie Fricano for her assistance and to Dr. Richard Tislow and Mrs. Annette LaBelle for the pharmacological data reported herein.

Summary

A series of N-trisubstituted alkyl pyridine carboxamides has been prepared and tested for antispasmodic activity. N-(2,2-Dibutylhexyl)-nicotinamide was the most potent member of the series. The carboxy substituted and the N-methyl hydrogenated derivative of N-(2,2-dibutylhexyl)-nicotinamide have been synthesized.

BLOOMFIELD, NEW JERSEY RECEIVED OCTOBER 13, 1949

[CONTRIBUTION FROM THE INORGANIC CHEMISTRY BRANCH, CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

The Hydrazinolysis of Nitroguanidine and Alkylnitroguanidines[1]

BY RONALD A. HENRY, HENRY D. LEWIS AND G. B. L. SMITH

Phillips and Williams[2] first prepared nitroaminoguanidine, $NH_2NHC(NH)NHNO_2$, in low yield[3] by the hydrazinolysis of nitroguanidine in aqueous solutions. Attempts by these workers to isolate and identify the products of the side-reactions which were decreasing the yield were only partially successful; they showed that nitrous oxide was evolved in an amount corresponding to a loss of approximately one-half of the nitroguanidine.

A satisfactory prediction of the by-products in this reaction can be made, based upon previous studies by Davis and co-workers.[4] They have shown that monoalkylamines react with nitroguanidine in aqueous solution to give the corre-

(1) Part of the material presented in this paper was abstracted from the B.S. thesis of Henry D. Lewis, Polytechnic Institute of Brooklyn, June 1942.

(2) Phillips and Williams, THIS JOURNAL, **50**, 2465 (1928).

(3) Phillips and Williams stated that their yields were about 50%; repeated duplication of their work, together with more precise methods for the analysis of nitroaminoguanidine in the crude products, indicated that the yields were actually only 30–35%.

(4) Davis and Abrams, *Proc. Am. Acad. Arts and Sciences*, **61**, 437 (1926); Davis and Elderfield, THIS JOURNAL, **55**, 731 (1933); Davis and Luce, *ibid.*, **49**, 2303 (1927). The use of the Davis de-arrangement mechanism in this paper is schematic only and should not be taken to mean that this is the actual or sole mechanism involved.