alum and chromic sulfate to give salts of the luteo type.

Improved methods for preparing luteo salts, based on the reactions of anhydrous diamines with anhydrous chromic salts, have been described.

Results of attempts to prepare tri-trimethylenediamine chromic salts were inconclusive.

It has been shown that ammonation under pressure of chloropentammino chromic salts depends on their solubility in liquid ammonia, the rate of reaction increasing in the order $Cl^- < Br^- < NO_3^-$, which is the order of increasing solubility in liquid ammonia. Hexammino chromic nitrate may be easily prepared by the sodamide-catalyzed ammonation of chloropentammino chromic nitrate at atmospheric pressure.

URBANA, ILL. RECEIVED OCTOBER 16, 1942

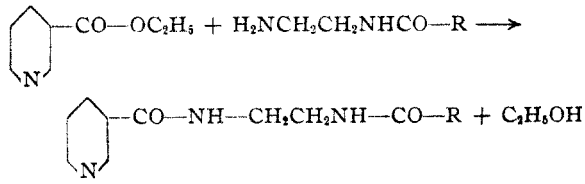
[CONTRIBUTION FROM THE FOOD AND DRUG LABORATORY, FLORIDA DEPARTMENT OF AGRICULTURE]

Derivatives of Pyridine Acids. I. N-(2-Acylaminoethyl)-nicotinamides

BY ERNEST M. HODNETT AND VINCENT E. STEWART

Compounds containing the nicotinic acid group exhibit a variety of physiological properties. Those in which the nicotinic acid is contained in an amide linkage are of most recent interest. In order to further this study it was considered desirable to combine this group with the ethylenic linkage, which is also characteristic of some compounds possessing medicinal properties.

Monoacylethylenediamines were prepared by the method of Hill and Aspinall.[1,2] These were treated with ethyl nicotinate[3] by heating in equimolecular proportions for several hours at about 100°. The reaction proceeded as follows



Upon cooling to room temperature the reaction mixture crystallized, and the N-(2-acylaminoethyl)-nicotinamide was purified by recrystallization. The products were characterized by analysis and by the preparation of hydrochlorides and picrates.

Acetylethylenediamine, propionylethylenediamine, butyrylethylenediamine, valerylethylenediamine and caproylethylenediamine were treated with ethyl nicotinate to yield the corresponding substituted nicotinamide.

Hydrolysis of N-(2-acetylaminoethyl)-nicotinamide by refluxing with dilute hydrochloric acid or phosphoric acid yielded the expected products: nicotinic acid (hydrochloride), ethylenediamine (hydrochloride), and acetic acid. Nicotinic acid was identified by mixed melting point determination with an authentic sample, ethylenediamine by the analysis of chloride in the hydrochloride, and acetic acid by determination of the Duclaux constant.

(1) Hill and Aspinall, THIS JOURNAL, **61**, 822 (1939).
(2) Aspinall, *ibid.*, **62**, 852 (1941).
(3) McElvain and Adams, *ibid.*, **45**, 2738 (1923).

Experimental

N-(2-Acetylaminoethyl)-nicotinamide.—One-half mole (75.5 g.) of ethyl nicotinate and one-half mole (51.0 g.) of acetylethylenediamine were heated at 100° for fifteen hours. The reaction mixture began to crystallize after four hours of heating. The crude product was recrystallized from a mixture of alcohol (1 vol.) and benzene (3 vols.). The weight of dry product after one recrystallization was 60.8 g. (58.7%). The sample taken for analysis of nitrogen by the Kjeldahl method was recrystallized four times in the above manner; m. p. 170–171° (cor.).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: N, 20.3. Found: N, 20.3.

The higher homologs were prepared and purified in a similar manner. N-(2-Acylaminoethyl)-nicotinamides which have been investigated are very soluble in water, alcohol and chloroform. The lower members are moderately soluble in hot benzene and insoluble in carbon tetrachloride and ether, while the higher members are very soluble in hot benzene, soluble in hot carbon tetrachloride, and soluble in ether. The hydrochlorides are soluble in water and are recrystallizable from a mixture of alcohol and ether. The picrates are also soluble in water and are recrystallizable from alcohol.

The compounds were digested with difficulty in preparation for analysis of nitrogen by the Kjeldahl method. The analysis was more nearly in accordance with the theoretical content when both copper sulfate and selenium were used as catalysts and the digestion was started over a low flame and gradually increased during about thirty hours.

Pharmacology

The pharmacology of the compounds which have been synthesized was studied by Dr. C. C.

TABLE I

Reacting ethylene-diamine	Resulting nicotinamide	Recrystallizing solvent mixture: Alcohol (vol.)	Benzene (vol.)	Yield, %	M. p., °C. (cor.)	Nitrogen, %: Calcd.	Found
Acetyl-	N-(2-Acetylaminoethyl)-	1	3	59	170–171	20.3	20.3
Propionyl-	N-(2-Propionylaminoethyl)-	1	3	68	126–127	19.0	19.2
Butyryl-	N-(2-Butyrylaminoethyl)-	1	9	63	157–159	17.9	17.8
Valeryl-	N-(2-Valerylaminoethyl)-	1	20	58	141–142	16.9	16.8
Caproyl-	N-(2-Caproylaminoethyl)-	0	1	47	124–125	16.0	16.0

Pfeiffer of the research laboratories of Parke, Davis and Co., Detroit, Michigan. The authors acknowledge this valuable assistance of Parke, Davis and Co.

All of these nicotinamides are convulsant stimulants. Compared with coramine (N,N-diethylnicotinamide), to which they bear some structural resemblance, they are less toxic but lack potency. The mouse LD-50's are given in Table II. The toxicity increases with the lengthening of the carbon chain of the acyl group but the potency of coramine is not attained.

TABLE II

Empirical formula of nicotinamide	LD-50's of nicotinamide (g./kg.)[a]	Picrate M. p., °C. (cor.)	Hydrochloride M. p., °C. (cor.)	% Cl Calcd.	Found
$C_{10}H_{14}N_2O_2$	4.0	178–180	222–226	14.5	14.5
$C_{11}H_{16}N_2O_2$	4.0	177–179	177–180	13.8	13.7
$C_{12}H_{18}N_2O_2$	3.5	163–166	186–189	13.1	13.1
$C_{13}H_{20}N_2O_2$	1.5	170–172	182–186	12.4	12.1
$C_{14}H_{22}N_2O_2$	1.0	168–170	174–177	11.8	11.7

[a] Coramine (N,N-diethylnicotinamide), 250 mg./kg.

The acetyl derivative and the propionyl derivative are not analgesic in subcutaneous doses as high as 600 mg./kg., which is the effective oral dosage of aspirin. The acetyl derivative and the caproyl derivative are inactive as analeptics against barbiturate depression at a dosage level of 150 mg./kg., whereas coramine shortens the sleeping time by thirty minutes. The lack of analeptic power is also evident by the short convulsant time before death occurs. On the contrary, the prelethal period of convulsions is prolonged when coramine is administered.

Summary

A synthesis of N-(2-acylaminoethyl)-nicotinamides has been developed and properties of members of the lower aliphatic series have been investigated.

The compounds are convulsant stimulants. They are less toxic than coramine but lack potency.

TALLAHASSEE, FLA. RECEIVED OCTOBER 13, 1942

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND OF PHYSIOLOGICAL CHEMISTRY, THE OHIO STATE UNIVERSITY]

Application of the Mercaptalation Assay to Synthetic Starch[1]

BY M. L. WOLFROM, C. S. SMITH AND A. E. BROWN

The role of the Cori ester in carbohydrate metabolism has been made clear by the reversible, enzymic transformation: glycogen + free phosphate ⇄ Cori ester. Using a phosphorylase preparation isolated from heart and liver tissue, Cori[2] and others[3] have succeeded in preparing a polysaccharide similar to glycogen. In the vegetable world, Hanes[4] has demonstrated that a phosphorylase, capable of converting starch to the Cori ester and of resynthesizing the latter to a polysaccharide resembling starch by reversal of the enzymic action, is present in pea and potato extracts. It is therefore definitely established that phosphorylases acting *in vitro* on the Cori ester, which has been shown to be α-*d*-glucopyranose 1-phosphate,[5] are able to synthesize polysaccharides resembling, or identical with, the natural products.

Since the discovery of synthetic starch there have been attempts to correlate this material with natural starch. Hanes[4] showed that syn-

(1) Presented before the Division of Sugar Chemistry and Technology at the 103rd meeting of the American Chemical Society, Memphis, Tennessee, April 23, 1942.

(2) Gerty T. Cori, C. F. Cori and G. Schmidt, *J. Biol. Chem.*, **129**, 629 (1939).

(3) A. Schäffner and H. Specht, *Naturwissenschaften*, **26**, 494 (1938); W. Kiessling, *Biochem. Z.*, **302**, 50 (1939); P. Ostern, D. Herbert and E. Holmes, *Biochem. J.*, **33**, 1858 (1939).

(4) C. S. Hanes, (a) *Proc. Roy. Soc.* (London), **B128**, 421 (1940); (b) **B129**, 174 (1940).

(5) (a) M. L. Wolfrom and D. E. Pletcher, THIS JOURNAL, **63**, 1050 (1941); (b) M. L. Wolfrom, C. S. Smith, D. E. Pletcher and A. E. Brown, *ibid.*, **64**, 23 (1942).