continued for 7 hours. The boiling reaction mixture was filtered through a heated funnel into 1.5 liters of distilled water. The zinc sludge was extracted twice with 50 ml. of boiling 95% ethanol and the extract added to the filtrate. The white precipitate was collected, washed with water and dried in air. There was obtained 3.1 g. m.p. 232–233° dec., 86% yield. Recrystallization of 0.64 g. of the compound with 100 ml. ethanol (Norit A added) gave 0.37 g. of material melting at 232–234° dec.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 80.0; H, 5.37; N, 9.33. Found: C, 80.1; H, 5.50; N, 9.10.

2-Hydroxy-7-benzoylaminofluorene from 2-Amino-7-benzoylaminofluorene.—1.04 g. of 2-amino-7-benzoylaminofluorene (0.0035 mole), m.p. 230–232°, was dissolved in 150 ml. of boiling glacial acetic acid. Ten ml. of concentrated sulfuric acid and 40 ml. of distilled water was added and the suspension cooled in an ice-bath at 10°. The material was diazotized over a period of 0.25 hour by the dropwise addition of 0.25 g. (0.0036 mole) of sodium nitrite in 10 ml. of distilled water to the rapidly stirred suspension. The resulting dark-brown solution, which did not contain any excess nitrous acid as judged by a negative starch–iodide test, was added dropwise over a period of 1 hour to 500 ml. of a vigorously boiling and stirred solution of 0.2 *M* sulfuric acid. The resulting suspension was cooled to 15–20° in an ice-bath. The precipitate was collected and dried at reduced pressure over calcium chloride. The light tan material weighed 0.92 g. and melted at 242–247° dec.; 0.41 g. of the product was suspended in 50 ml. of 5% potassium hydroxide solution, Norit A was added and the suspension warmed on a water-bath to 75° for 5 minutes. The mixture was filtered, the filtrate cooled in an ice-bath and acidified with concentrated hydrochloric acid. The precipitate was collected and washed with water, and after drying at reduced pressure over calcium chloride there was obtained 0.10 g. of a gray material melting at 253–256° dec. Recrystallization of the compound from glacial acetic acid gave 0.05 g. which melted at 254–256° dec. The compound gave a positive spot test with diazotized sulfanilic acid indicating the presence of a hydroxyl group. A negative spot test was obtained with *p*-dimethylaminobenzaldehyde indicating the absence of a diazotizable amino group.[10]

Anal. Calcd. for $C_{20}H_{15}NO$: C, 79.7; H, 5.02; N, 4.65. Found: C, 79.4; H, 4.95; N, 4.62.

2-Hydroxy-7-benzoylaminofluorene from 2-Hydroxy-7-aminofluorene.[7]—2.0 g. (0.0086 mole) of the hydrochloride of 2-hydroxy-7-aminofluorene was dissolved with stirring in 40.0 ml. of pyridine and 1.0 ml. of benzoyl chloride (0.0087 mole) was added to the solution. The reaction mixture was boiled for 5 minutes under reflux and then cooled in an ice-bath; 100 ml. of distilled water was added which caused formation of a white precipitate. The ice-cold suspension was acidified with concentrated hydrochloric acid and allowed to stand overnight at 4°. The precipitate then was collected and washed with 130 ml. of boiling distilled water followed by 150 ml. of cold distilled water. After drying at reduced pressure over calcium chloride there was obtained 2.21 g. of a white, crystalline product, m.p. 254–256° dec., 86% yield. A mixture melting point with the authentic sample of 2-hydroxy-7-benzoylaminofluorene gave a melting point of 254–256° dec.

(10) J. H. Peters and H. R. Gutmann, THIS JOURNAL, **76**, 2267 (1954).

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Dehydration of Amino Amides of the Amidone Series

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It has been reported that when a stream of hydrogen chloride or hydrogen bromide is passed into

X	—N(A)(B)	Rd	Base	Method and % yield	M.p., °C.[a]	Neut. equiv. Calcd.	Neut. equiv. Found[b]	Halogen or oxalic acid, % Calcd.	Halogen or oxalic acid, % Found	N, % Calcd.	N, % Found	U.V. spectr. in *i*-C_3H_7OH, $\lambda_{max.}$ mμ	U.V. spectr. in *i*-C_3H_7OH, ε	Parasympathetolytic act. (atropine sulf. = 100) Rabbit ileum[c] molar P.R.	Parasympathetolytic act. (atropine sulf. = 100) Rabbit ileum[c] $f_{P.R.}$[e]	Mydriasis mice[d] molar P.R.	Mydriasis mice[d] $f_{P.R.}$
H	$-N(C_2H_5)_2$	$CONH_2$	Base $C_{14}H_{22}N_2O$	B 82	82	234.3	234.7	..	..	12.0	12.1	259.3	223	<0.5	..	<0.5	..
H	$-N(C_2H_5)_2$	CN	$C_2H_2O_4$ $C_{16}H_{22}N_2O_4$	A 85	171–173	306.4	307.1	29.4	29.7	9.1	9.0	257.5	221	.05	1.30	.4	1.10
H	$-N(C_2H_5)_2$	CN	$C_2H_2O_4$ $C_{16}H_{22}N_2O_4$	C 50	174	306.4	308.9	29.4	29.9	9.1	9.1	257.5	229	.05	1.40	< .5	..
H	$-NC_5H_{10}$	$CONH_2$	Base $C_{15}H_{23}N_2O$	B 80	99	246.4	245.9	..	..	11.4	11.4	259.3	219	< .5	..	.25	1.38
H	$-NC_5H_{10}$	CN	HCl $C_{15}H_{21}N_2Cl$	A 79	178	264.8	264.3	13.4	13.5	10.6	10.7	257.5	216	< .1	..	< .6	..
H	$-NC_5H_{10}$	CN	HCl $C_{15}H_{21}N_2Cl$	C 55	178	264.8	265.2	13.4	13.4	10.6	10.6	257.5	233	.07	1.17	< .5	..
C_6H_5	$-N(CH_3)_2$	$CONH_2$	Base $C_{13}H_{22}N_2O$	B 78	140	282.4	282.2	..	..	..	..	260.0	430	4.7	1.56	13.0	1.10
C_6H_5	$-N(CH_3)_2$	CN	$C_2H_2O_4$ $C_{24}H_{22}N_2O_4$	A 81	163	354.4	256.1	25.4	25.6	7.9	8.1	258.5	420	1.5	1.25	<1.0	..
C_6H_5	$-N(CH_3)_2$	CN	$C_2H_2O_4$ $C_{24}H_{22}N_2O_4$	C 25	163	354.4	353.9	25.4	25.9	7.9	7.9	258.5	490	0.9	1.32	<1.0	..
C_6H_5	$-NC_4H_8$	$CONH_2$	Base $C_{20}H_{24}N_2O$	B 83	146–147	308.4	311.5	..	..	..	..	260.0	423	59.7	1.27	27.0	1.19

X	—N<A/B>	Rd		Method and % yield	M.p., °C.[a]	Xent. equiv. Calcd.	Xent. equiv. Found[b]	Halogen or oxalic acid, % Calcd.	Halogen or oxalic acid, % Found	N, % Calcd.	N, % Found	U.V. spectr. in i-C3H7OH, λmax. mμ	U.V. spectr. in i-C3H7OH, λmax. ε	Parasympatholytic act. (atropine sulf. = 100) Rabbit ileum[c] molar P.R.	Parasympatholytic act. (atropine sulf. = 100) Rabbit ileum[c] fP.R.[f]	Mydriasis mice[d] molar P.R.	Mydriasis mice[d] fP.R.
C_6H_5	$-NC_4H_8$	CN	$C_{22}H_{24}N_2O_4$	A 83	200-201	380.4	380.6	23.7	23.4	7.4	7.6	258.5	420	2.60	1.20	....	....
C_6H_5	$-NC_4H_8$	CN	$C_{22}H_{24}N_2O_4$	C 49	201	380.4	383.8	23.7	23.6	7.4	7.5	258.5	461	2.75	1.19	....	....
C_6H_5	$-NC_5H_{10}$	$CONH_2$	$C_{21}H_{26}N_2O$	Base B 81	188	322.5	322.5	..	..	..	..	260.0	420	157	1.41	87.0	1.18
C_6H_5	$-NC_5H_{10}$	CN	$C_{22}H_{26}N_2O_1$	A 87	250	394.5	396.7	22.8	22.9	7.1	7.2	258.5	415	6.2	1.18	1.14	1.14
C_6H_5	$-NC_5H_{10}$	CN	$C_{22}H_{26}N_2O_1$	C 47	249	394.5	400.5	22.8	23.1	7.1	7.2	258.5	464	5.6	1.36	1.97	1.30
C_6H_5	$-NC_4H_8O$	$CONH_2$	$C_{20}H_{24}N_2O_2$	Base B 80	184	324.4	322.6	..	..	..	..	260.0	425	6.2	1.27	6.4	1.32
C_6H_5	$-NC_4H_8O$	CN	$C_{20}H_{22}N_2O$	Base A 78	81-83	306.4	309.5	..	..	9.1	9.0	258.5	415	0.13	1.25	<1.0	..
C_6H_5	$-NC_4H_8O$	CN	$C_{20}H_{22}N_2O$	Base C 52	81	306.4	312.3	..	..	9.1	9.2	258.5	435	.19	1.30	<1.0	..
$C_5H_{10}N-(CH_2)_2$	$-NC_5H_{10}$	$CONH_2$	$C_{23}H_{35}N_3O$	Base B 69	117 dec.	357.5	366.9	..	..	..	..	259.0	205	.10	1.41	<0.5	..
$C_5H_{10}N-(CH_2)_2$	$-NC_5H_{10}$	CN	$C_{23}H_{35}N_3Cl_2$	A 67	230-232	412.5	409.2	17.2	17.3	10.2	10.3	257.0	215	.15	1.40	<0.5	..
$C_2H_{10}N-(CH_2)_2$	$-NC_5H_{10}$	CN	2 HCl $C_{22}H_{35}N_3Cl_2$	C 65	230-232	412.5	418.4	17.2	16.8	10.2	10.0	257.0	198	.13	1.31	<0.5	..

[a] Koffler micro-apparatus. [b] Potentiometric perchloric acid titration. [c] Acetylcholine antagonism.[16] Molar potency ratios × 100 (atropine sulfate = 100). [d] Mydriatic activity in mice[16] (intraperitoneal). Molar potency ratios × 100 (atropine sulfate = 100). [e] $f_{P.R.}$: factor for computing fiducial limits of potency ratio (P = 0.95).

a nitrile of the amidone series at elevated temperatures, the iminohalide hydrohalide is formed,[1,2] which on subsequent heating is converted to a 2-iminopyrrolidine[7-11] or a 2-iminopiperidine hydrohalide.[1,2,5,7-9]

The imino-compounds are converted into 2-pyrrolidones by nitrous acid[7-10] or aqueous hydrogen bromide under pressure.[5] The formation of these 2-pyrrolidones by intramolecular reaction between *t*-amino and acid chloride groups was reported by Gardner, *et al.*,[3] and further explored by Clarke, *et al.*[4] When an amino acid of the amidone series is dissolved in cold thionyl chloride, interaction between the formed acid chloride group and the *t*-amino group starts around 60° and can be completed by further heating.[4]

With various dialkylamino groups, cyclization occurs with preferential elimination of a molecular equivalent of an alkaryl or the lower alkyl chloride[3-6]; with heterocyclic amino groups, an ω-chloroalkyl side-chain remains attached to the nitrogen atom of the newly formed heterocycle.[4]

A brief discussion of some possible mechanisms involved in these reactions has been published recently.[12]

In view of these facts, it was of interest to explore the behavior of aminoamides related to amidone[13-16] when treated with thionyl chloride under conditions appropriate to 2-pyrrolidone formation as described for the corresponding amino acids.[4]

Aminoamides of the amidone series, obtained by hydrolysis of the corresponding nitriles and dissolved in a sixfold molar excess of thionyl chloride, were refluxed for one to three hours. The basic reaction products were extracted from the alkalinized reaction mixture with ether, and purified.

The materials thus obtained were identical with the original nitriles.

No evidence of the expected intramolecular reaction between the amide and the *t*-amine group was obtained.

Experimental

Method A.—The substituted butyronitriles reported in the table have been synthesized by condensing the phenyl-

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(2) F. F. Blicke, U. S. Patent 2,513,270 (1950); *C. A.*, **45**, 5187 (1951).

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(6) D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *ibid.*, 500 (1949).

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(8) W. Wilson, *ibid.*, 2173 (1950).

(9) W. Wilson, *ibid.*, 3524 (1952).

(10) J. Cymerman and W. S. Gilbert, *ibid.*, 3529 (1952).

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(12) W. Wilson, *Chemistry and Industry*, 200 (1955).

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(15) W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, M. E. Speeter, L. C. Cheney and S. B. Binkley, *ibid.*, **19**, 794 (1954).

(16) P. Janssen, D. Zivkovic, P. Demoen, D. K. de Jongh and E. C. van Proosdij-Hartzema, *Arch. Intern. Pharmacodyn.*, **102**, 123 (1955).

acetonitrile with various *t*-aminoethyl chlorides, using sodium amide or lithium amide as described.[13-16]

Method B.—The basic amides were prepared by 90% sulfuric acid hydrolysis of the nitriles obtained by method A.[14,16]

Method C.—A mixture of 0.17 mole of the amidone-type amide and 1 mole of thionyl chloride was prepared in an ice-bath. No reaction occurred. This mixture was heated on a steam-bath for one to three hours, made strongly alkaline with sodium hydroxide and extracted with ether. The extracts were dried over potassium carbonate, and the ether removed by evaporation. The residual basic materials were purified by crystallization or fractionation *in vacuo* followed by salt formation as indicated in the table.

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Lithium Aluminum Hydride Reduction of Diethyl 2,6-Dimethyl-3,4-pyridinedicarboxylate

BY EDMUND C. KORNFELD

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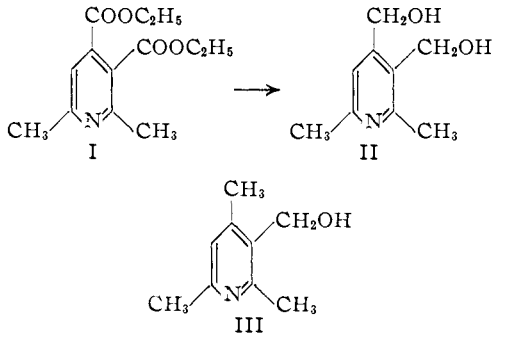
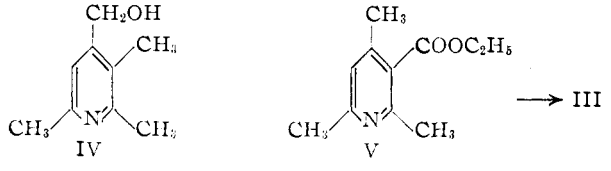
In a previous paper[1] it was shown that reduction of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate (I) with lithium aluminum hydride gave either the corresponding glycol (II) or a monohydric alcohol ($C_9H_{13}NO$) depending on the conditions used. The



latter product was formulated as III by analogy with the known reductive cleavage of pyridoxine to desoxypyridoxine,[2] and this alternative was favored in a review by Rudinger, Ferles and Protiva.[3] However, an unequivocal proof of structure was lacking. Subsequently Gaylord[4] suggested that the alternative formulation IV was preferred over III by analogy with the course of a number of other hydrogenolysis reactions effected by lithium aluminum hydride. In order to resolve this question we have now synthesized III by reduction of the ester V.[5]



The alcohol III so obtained, m.p. 87–88.5°, was not identical with the isomer, m.p. 127–128°, derived from I. Since the structure of III was established by its derivation from V, the monohydric alcohol obtained from I must be formulated as IV and not III. The 4-hydroxymethyl isomer IV was also obtained when the glycol II was subjected to catalytic hydrogenolysis in the presence of palladium catalyst. It is evident, therefore, that both chemical and catalytic reduction result in cleavage of the hydroxymethyl group in the 3-position, and the conclusion of Gaylord[4] appears to be correct.

(1) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).
(2) S. Harris, *ibid.*, **62**, 3203 (1940).
(3) J. Rudinger, M. Ferles and M. Protiva, *Chem. Listy*, **45**, 309 (1951).
(4) N. G. Gaylord, *Experientia*, **10**, 166 (1954).
(5) R. Michael, *Ann.*, **225**, 121 (1884); A. Hantzsch, *ibid.*, **215**, 42 (1882).

Experimental[6]

2,4,6-Trimethyl-3-hydroxymethylpyridine (III).—A solution of 1.6 g. of lithium aluminum hydride in 100 ml. of dry ether was stirred in an ice-bath, and to it was added dropwise during about 30 minutes a mixture of 8.0 g. of ethyl 2,4,6-trimethyl-3-pyridinecarboxylate and 100 ml. of ether. Stirring was continued for one-half hour at room temperature, after which the reaction mixture was treated cautiously with 3 ml. of water and 50 ml. of methanol. The suspension was saturated with carbon dioxide, filtered, and the solid was extracted twice with 50-ml. portions of hot methanol. The combined filtrates were evaporated to dryness, and the residue was taken up in chloroform. The chloroform solution was filtered, and the solvent was distilled. The residue was taken up in acetone, and the solution was filtered and then treated with dry hydrogen chloride. The salt which separated was filtered (2.1 g.) and recrystallized from a mixture of methanol and acetone, m.p. 168–170°.

Anal. Calcd. for $C_9H_{13}NO \cdot HCl$: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 58.09; H, 7.65; N, 7.62; Cl, 18.71.

The salt was dissolved in a little water, and the solution was treated with excess 50% aqueous sodium hydroxide. The oily product was extracted with chloroform; the extract was dried over magnesium sulfate, and the solvent was distilled. The hydroxymethyl compound was crystallized from acetone, m.p. 87.0–88.5°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.27; H, 8.66; N, 9.21.

The infrared spectrum in chloroform solution was different from that of the isomer IV, and the dissociation constant in water (pK'_a = 7.10) also differed from that of IV (pK'_a = 7.30).

2,3,6-Trimethyl-4-hydroxymethylpyridine (IV) **by Hydrogenolysis of 2,6-Dimethyl-3,4-di-(hydroxymethyl)-pyridine.**[1]—The glycol (1.0 g.) was hydrogenated for three hours at 50 pounds per square inch pressure in 50 ml. of glacial acetic acid using 1.0 g. of 5% palladium-on-carbon catalyst. The catalyst was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in water, the excess sodium hydroxide was added. The product was extracted with three 20-ml. portions of chloroform, and the extracts were dried over magnesium sulfate and concentrated. The product was crystallized from acetone; yield 0.35 g. (39%), m.p. 127–128°. A mixture melting point with a sample obtained by lithium aluminum hydride reduction of the diester[1] I was not depressed.

(6) Melting points are uncorrected.

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Potential Anti-viral Agents. I. N,N-Dimethyl-N'-isopropyl-N'-(2-nitroisobutyl)-ethylenediamine Hydrochloride

BY FREDERICK LEONARD AND FLOYD E. ANDERSON

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In recent years, increasing attention has been focused on the anti-viral and anti-rickettsial properties of a variety of nitro compounds. Chloram-