(85%), melted at 50–51°. A mixture melting point with a sample of 2-N-ethylaminopyrimidine prepared by procedure *A* gave no depression, m.p. 50–51°. The picrate prepared from ethereal picric acid and recrystallized from ethyl alcohol melted at 160–161°. A mixture melting point with the picrate prepared from procedure *A* gave no depression, m.p. 159–160°.

Preparation of 2-N-ethylaminopyrimidine picrate from I. To 2.5 g. (0.01 mole) of I dissolved in 5 ml. of ethyl alcohol was added an excess of ethereal picric acid. A yellow crystalline solid precipitated immediately. The picrate was filtered and recrystallized from ethyl alcohol, 3.17 g. 90.0%), m.p. 160–161°. A mixture melting point with 2-N-ethylaminopyrimidine picrate, m.p. 160–161°, prepared from procedure *A* gave no depression, m.p. 160–161°.

Preparation of 2-N-n-butylaminopyrimidine. This compound was prepared by procedure *A* and *B* given for 2-N-ethylaminopyrimidine. The iodide (II) recrystallized from ethyl alcohol was obtained in 55.0% yield and melted at 144–146°.

Anal. Calc'd for $C_8H_{14}IN_3$: C, 34.4; H, 5.0; N, 15.1. Found: C, 34.1; H, 5.2; N, 15.0.

The *free base* was obtained from II in 87% yield, b.p. 75–80° (2 mm.), n_D^{20} 1.5328, and by the reaction of 2-chloropyrimidine with *n*-butylamine in 69.0% yield, b.p. 76–78° (2 mm.), n_D^{20} 1.5330.

Anal. Calc'd for $C_8H_{13}N_3$: C, 63.5; H, 8.6; N, 27.8. Found: C, 63.4; H, 8.4; N, 27.5.

The *picrate* prepared from the free base and II respectively was recrystallized from ethyl alcohol and melted at 126–127°, (128–129°).[7]

MADISON, WISCONSIN

(7) Behnisch and Mietzsch, German Patent 889,445, September 10, 1953 (*Chem. Abstr.*, **48**, 12813[e]). The *picrate* was prepared from the condensation product of propargylaldehyde with *n*-butylguanidine sulfate.

N-Substituted 1-, 2-, and 4-Aminofluorene Derivatives[1]

EUGENE SAWICKI[2] AND BARBARA CHASTAIN[3]

Received March 29, 1956

The procedure for the preparation of 1-aminofluorene usually involves 6 steps starting with fluoranthene.[4,5] In attempting to prepare a large quantity of 1-aminofluorene for cancer research studies it was found that the reduction of 1-fluorenonecarboxylic acid to 1-fluorenecarboxylic acid was the weak link in the synthesis. In our hands difficult-to-purify mixtures and unsatisfactory yields resulted when attempts were made to prepare large quantities of 1-fluorenecarboxylic acid by hydrazine,[4] sodium amalgam,[6] or zinc amalgam reduction.[7] Dissatisfaction with the reduction procedure has also been expressed by Gutmann and Albrecht.[8] Ring-reduced by-products were obtained in the sodium amalgam reduction and 3-hydroxy-1,2-diazofluoranthene[9] was isolated from the hydrazine reduction procedure.

A simplified 5-step preparation resulting in higher yields of 1-aminofluorene has been developed. This method depends on carrying out the reduction at a later stage in the synthesis. As each step has been repeated at least 8 times, the procedure is believed to be reliable. Essentially the sequence consists of fluoranthene → 1-(9-fluorenone)carbonyl azide → 1-acetylamino-9-fluorenone → 1-aminofluorene.

The effect of N-acyl groups on the biological properties of biologically important amines is worthy of more intensive study since 2-trifluoroacetylamino fluorene has been reported to be much more carcinogenic[10] to Buffalo rats than is the well-known 2-acetylaminofluorene.[11,12] For this reason N-substituted fluoroacetyl, difluoroacetyl, trifluoroacetyl, and perfluoropropionyl derivatives of the carcinogenic 2-aminofluorene[11,13] as well as of the 1- and 4-isomers were prepared. Included in Table I are other acyl derivatives and Schiff bases. 4-Aminofluorene was prepared by a six step procedure starting from phenanthrene.[14]

EXPERIMENTAL[15]

1-(9-Fluorenone)carbonyl azide. Reaction between 1-(9-fluorenone)carbonyl chloride, m.p. 130–131°, dissolved in acetone and sodium azide in water solution gave a 90% yield of crude product, dec. 86°. Lit. m.p. 90–91°.[16] Recrystallization from heptane gave a 62% yield of yellow needles, m.p. 148–150°. The infrared spectrum in chloroform had a very strong band at 4.88 μ which is apparently due to the azido group.

1-Acetylamino-9-fluorenone. A solution of 2.49 g. of dry 1-(9-fluorenone)carbonyl azide, m.p. 142–146°, in 33 ml. of acetic anhydride was refluxed for 4 hours and allowed to

(1) This investigation was supported by research grant C-1066 from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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(3) Taken in part from a thesis to be presented by Barbara Chastain in partial fulfillment of the requirements for the M.S. Degree.

(4) Bergmann and Orchin, *J. Am. Chem. Soc.*, **71**, 1111 (1949).

(5) Weisburger and Weisburger, *J. Org. Chem.*, **18**, 864 (1953).

(6) Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

(7) Forrest and Tucker, *J. Chem. Soc.*, 1140 (1948).

(8) Gutmann and Albrecht, *J. Am. Chem. Soc.*, **77**, 175 (1955).

(9) Campbell and Stafford, *J. Chem. Soc.*, 299 (1952).

(10) Morris, *J. Natl. Cancer Inst.*, **15**, 1535 (1955).

(11) Wilson, DeEds, and Cox, *Cancer Research*, **1**, 595 (1941).

(12) Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, Fed. Sec. Agency, Washington, 1951.

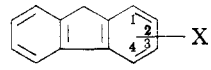
(13) Morris, Dubnik, and Johnson, *J. Natl. Cancer Inst.*, **10**, 1201 (1950).

(14) Sawicki, Ray, and Glocklin, *J. Org. Chem.*, **21**, 243 (1956).

(15) Melting points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Florida.

(16) Cook and Moffatt, *J. Chem. Soc.*, 1160 (1950).

TABLE I

FLUORENE DERIVATIVES,  —X

X	M.P., °C.	Cryst. Solvent	Yield %	Formula	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
1-NHCOOCH$_2$CH$_2$F	123–125	[a]	55	$C_{16}H_{14}FNO_2$			5.17			5.20
1-NHCOCH$_2$F	186–187	[b]	85	$C_{15}H_{12}FNO$			5.81			5.71
1-NHCOCHF$_2$[c]	146–147	[b]	95	$C_{15}H_{11}F_2NO$			5.41			5.28
1-NHCOCF$_3$[c]	154–155	[a]	98	$C_{15}H_{10}F_3NO$			5.05			5.11
1-NHCOC$_2$F$_5$[c]	150–151	[a]	95	$C_{16}H_{10}F_5NO$	58.7	3.05		58.5	3.22	
1-N=CHC$_6$H$_5$	84–86	[d]	80	$C_{20}H_{15}N$			5.20			5.25
1-N=CH(4-C$_6$H$_4$NO$_2$)	198–199	[e]	45	$C_{20}H_{14}N_2O_2$			8.92			9.02
2-NHCO-α-Furyl	198–199	[f]	88	$C_{18}H_{13}NO_2$			5.09			5.13
2-NHCO(4-C$_6$H$_4$OCH$_3$)	236–237	[g]	85	$C_{21}H_{17}NO_2$	80.0	5.40		80.5	5.45	
2-NHCOOCH$_2$CH$_2$Cl	122	[b]	90	$C_{16}H_{14}ClNO_2$	66.7	4.86		66.4	4.92	
2-NHCOCCl$_3$	193–194	[h]	85	$C_{15}H_{10}Cl_3NO$	54.9	3.05		55.2	3.23	
2-NHCO(4-Pyridyl)	223–224	[g]	83	$C_{19}H_{14}N_2O$			9.79			9.60
2-NHCONHC$_2$H$_5$	236 dec	[h]	95	$C_{16}H_{16}N_2O$			11.1			10.7
2-NHCOOCH$_2$CH=CH$_2$	110–111	[b]	38	$C_{17}H_{15}NO_2$	77.0	5.66		77.1	5.72	
2-N=CH(α-Naphthyl)	126–127	[b]	85	$C_{24}H_{17}N$	90.3	5.33		90.1	5.30	
2-N=CHC$_6$H$_3$O$_2$CH$_2$[j]	179–180	[b]	90	$C_{21}H_{15}NO_2$	80.5	4.79		80.7	5.00	
2-N=CH(4-C$_6$H$_4$CH$_3$)	158–159	[b]	85	$C_{21}H_{17}N$	89.0	6.01		88.7	5.90	
2-N=CH(4-C$_6$H$_4$ iso-C$_3$H$_7$)	158–159	[b]	85	$C_{23}H_{21}N$	88.7	6.75		88.4	6.51	
2-N=CH(4-C$_6$H$_4$NHAc)	227–230 dec	[g]	70	$C_{22}H_{18}N_2O$	81.0	5.52		80.7	5.37	
4-NHCOCH$_2$F	175–176	[b]	90	$C_{15}H_{12}FNO$	74.7	4.97		74.5	5.08	
4-NHCOCHF$_2$[c]	172–173	[i]	95	$C_{15}H_{11}F_2NO$			5.41			5.31
4-NHCOCF$_3$[c]	153–154	[a]	97	$C_{15}H_{10}F_3NO$	65.0	3.61		65.1	3.56	
4-NHCOC$_2$F$_5$[c]	144–145	[b]	95	$C_{16}H_{10}F_5NO$	58.7	3.06		58.4	3.14	
4-NHCONHC$_2$H$_5$	253–254	[h]	90	$C_{16}H_{16}N_2O$			11.1			10.8
4-N=CHC$_6$H$_5$	124–125	[a]	88	$C_{20}H_{15}N$	89.2	5.57		89.1	5.40	
4-CONH iso-C$_3$H$_7$	157–158	[b]	78	$C_{17}H_{17}NO$	81.3	6.77		81.5	6.80	
4-CONH-n-C$_4$H$_9$	136–137	[b]	75	$C_{18}H_{19}NO$	81.5	7.17		81.7	7.25	
4-CON(C$_2$H$_5$)$_2$	72–73	[d]	82	$C_{18}H_{19}NO$			5.28			5.35
4-CONHC$_2$H$_5$	138–139	[b]	72	$C_{16}H_{15}NO$	81.0	6.30		81.1	6.38	

[a] Hexane. [b] Heptane. [c] Acid anhydrides were used to prepare these compounds while acid chlorides were used to prepare the remainder of the acylamino derivatives. [d] Pentane. [e] Aqueous Methyl Cellosolve (2-Methoxyethanol). [f] Benzene. [g] Xylene. [h] Methanol. [i] Aqueous methanol. [j] 2-Piperonylideneaminofluorene.

cool. The yellow crystals of *sym*-bis-(9-fluorenonyl) urea[17] m.p. 260–280°, were filtered. The addition of water to the mother liquid gave an approximately 90% yield of a mixture, m.p. 110–118°, probably containing the 1-mono- and 1-di-acetylaminofluorenones. Crystallization of a small amount of this product from aqueous acetic acid gave yellow needles of the monoacetylamino derivative, m.p. 137–138°. Lit. m.p. 138.0–138.3.[18] The infrared spectrum in chloroform showed the presence of a C=O stretching band at 5.89 μ with an inflection at 5.82 μ and an N—H stretching band at 3.0 μ.

The *urea derivative* was crystallized from benzene to give a 10% yield of yellow needles, m.p. 283–285°.

Anal. Calc'd for $C_{27}H_{16}N_2O_3$: N, 6.73. Found: N, 6.63.

1-Aminofluorene. A solution of 2.79 g. of the crude acetylamino-9-fluorenone, m.p. 110–118°, and 1.4 g. of sodium hydroxide in 35 ml. of ethylene glycol and 4 ml. of 85% hydrazine hydrate was refluxed for 2½ hours. The condenser was removed and the solution was evaporated until its temperature was 205°. The mixture then was refluxed 3 hours longer and finally was poured into excess water. Crystallization from hexane gave a 65% yield (based on 1-(9-fluorenone)carbonyl azide) of colorless needles, m.p. 124–125°. Lit. m.p. 124–125°.[5]

General procedure for the preparation of the acylaminofluorenes. To a warm solution of 0.002 mole of aminofluorene in 10 ml. of benzene and 0.2 ml. of pyridine was cautiously added 0.0022 mole of the acid chloride or acid anhydride. The mixture was warmed for 5–10 minutes and excess water was added. The benzene was steam-distilled and the product was crystallized from the appropriate solvent, Table I. The urethans were prepared in a similar fashion from alkyl chlorocarbonates, Table I.

General procedure for the preparation of the Schiff bases. A hot solution of 0.002 mole of the aldehyde in a small volume of alcohol was added to 0.002 mole of the aminofluorene dissolved in 5 ml. of alcohol. The mixture was refluxed for one hour, excess water was added, and it was allowed to cool. The precipitate was crystallized from the appropriate solvent, Table I.

General procedure for the preparation of 4-carbamoylfluorene derivatives. Two molar-equivalents of an aliphatic amine were added to a solution of a molar-equivalent of 4-fluorenecarbonyl chloride in acetone. The mixture was refluxed for 15 minutes and then excess dilute sulfuric acid was added. The precipitate was crystallized from the appropriate solvent, Table I.

Preparation of 1-(1'- or 4'-fluorenyl)-3-ethylurea. To a 0.01 mole of the aminofluorene dissolved in 20 ml. of ben-

(17) This compound was apparently derived from the rearrangement of a small portion of the carbonyl azide to the isocyanate. Some of the isocyanate reacted with water to give the amine which then reacted with the isocyanate to form the symmetrical urea.

(18) Huntress, Pfister, and Pfister, *J. Am. Chem. Soc.*, **64**, 2845 (1942).

zene was added 0.01 mole of ethyl isocyanate. The mixture solidified. Crystallization from the appropriate solvent gave the pure compound, Table I.

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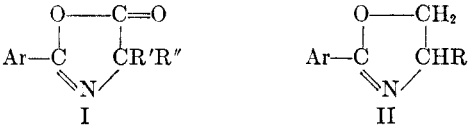
Azidocarbonyl Compounds. IV. Acid Catalysis of α-Azido-Carboxylic Acids and Their Esters[1]

J. H. BOYER AND J. STOCKER

Received April 20, 1956

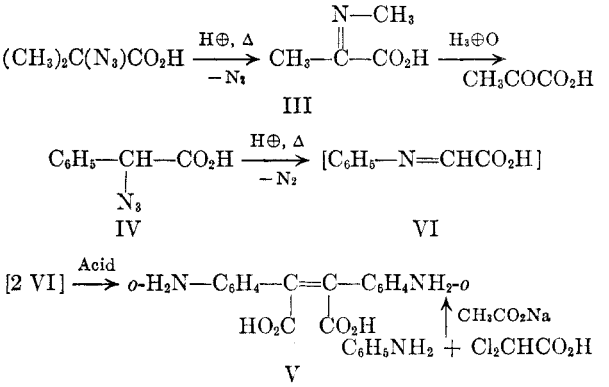
An interest in 5-ketoöxazolines (I) (azlactones) was a natural outgrowth of the discovery of the formation of oxazolines (II) from certain aromatic aldehydes and azidohydrins.[2] In order to determine the possibility of realizing an acid-catalyzed reaction between aldehydes and α-azidoacids, combinations of benzaldehyde containing sulfuric acid with α-azidoacetic, with α-azidoisobutyric, and with α-azido-α-phenylacetic acids were studied. Azlactones were not detected in the reaction products which were investigated not only for the oxazolone itself but also for its hydrolysis products as well as possible condensation products with benzaldehyde, present in excess. Apparently the presence of the aldehyde was unimportant since each azide gave the same product in acid-catalyzed reactions carried out in the absence of benzaldehyde.



I II

Acid catalysis resulted in the evolution of nitrogen with the apparent migration of methyl carbanion from carbon to nitrogen and the formation of the Schiff's base (III) from α-azidoisobutyric acid. Subsequent hydrolysis allowed the formation of pyruvic acid, isolated as its dinitrophenylhydrazone.

Competition between the migration of hydrogen and of the phenyl group apparently favored the latter in the case of α-azido-α-phenylacetic acid (IV) and its ethyl ester.[3] The product, *o,o'*-diaminostilbenedicarboxylic acid (V) (both geometric isomers assumed present) was previously obtained from the anil (VI) of glyoxylic acid upon warming in acetic acid and from treating aniline with dichloroacetic acid in a warm sodium acetate solution.[4]



III

IV VI

V

The infrared spectrum of a sample of the product (V) obtained from α-azido-α-phenylacetic acid was identical with that from a sample obtained from dichloroacetic acid and aniline.

EXPERIMENTAL[5]

Acid decomposition of α-azido-α-phenylacetic acid and its ethyl ester. α-Azido-α-phenylacetic acid[6] (1.02 g., 0.006 mole) or the ethyl ester[3] (1.021 g., 0.005 mole) was dissolved in 20 ml. of warm benzene and added dropwise to a mixture of 1.4 ml. of concentrated sulfuric acid and 15 ml. of benzene, the latter maintained at *ca.* 75° and stirred mechanically. When the reaction appeared complete, the entire mixture was poured into 20–25 g. of ice and water. The mixture was filtered by suction to remove traces of scum, and the aqueous layer was separated. Solid sodium carbonate was added in small portions, with frequent stirring, to adjust the solution to *p*H 2–3 (maximum precipitation). The yellow-brown precipitate was filtered, thoroughly water-washed, and dried in a vacuum for 24 hours. Additional material was obtained by evaporation of the filtrate, crude yield 54%. The m.p. was indeterminate, darkening of the material began about 180°, deepening to a black sintered product about 300°.[4]

The product obtained either by Heller's procedure[4] or by the present procedure was poorly soluble in water, slightly soluble in alcohol, very soluble in aqueous base (0.1 *N* or greater), including pyridine (insoluble in anhydrous pyridine). Solutions in all bases, organic or inorganic, required the addition of acid for reprecipitation. It was very soluble in dimethylformamide from which it was not easily recovered, very slightly soluble or insoluble in ethyl ether, benzene, acetone, and chloroform. Solution of the material, crude or otherwise, in 0.1 *N* sodium hydroxide and reprecipitation with dilute hydrochloric acid yielded a product with apparently unchanged properties.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 64.41; H, 4.73; N, 9.39. Calc'd for $C_{16}H_{14}N_2O_4 \cdot {}^1/_2H_2O$: C, 62.53; H, 4.92; N, 9.12. Found: C, 62.88; H, 5.51; N, 9.42. Repeat: C, 62.41; H, 4.96; N, 8.80.

The following medium to strong absorption peaks in cm.$^{-1}$ for the product (V) from either aniline and dichloroacetic

(1) A grant from the American Association of Arts and Sciences is gratefully acknowledged.

(2) J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955).

(3) Only hydrogen migration was detected from pyrolysis of ethyl α-azido-α-phenylacetate (J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, **75**, 1642 (1953)).

(4) G. Heller, *Ann.*, **332**, 268 (1904); **358**, 354 (1907); **375**, 266 (1910).

(5) Melting points are corrected. Elemental analyses by Microtech laboratories, Skokie, Illinois. Infra-red analyses by S. P. Sadtler and Son, Inc., Philadelphia, Pa. and by Mr. R. T. O'Connor, Southern Regional Research Laboratory, New Orleans, Louisiana.

(6) A. Darapsky, *J. prakt. Chem.*, 99, 179 (1919).