[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Intramolecular Reaction of Acid Chloride and Tertiary Amine Groups

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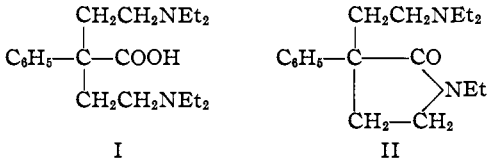
In a recent paper by Gardner, Easton and Stevens[2] reporting some new compounds related to methadone, the authors noted that γ-dimethylamino-α,α-diphenylvaleric acid is converted to 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone on refluxing with thionyl chloride. Likewise γ-dimethylamino-α,α-diphenyl-β-methylbutyric acid is converted to 1,4-dimethyl-3,3-diphenyl-2-pyrrolidone. We wish to report the results of our independent studies of this type of reaction.

In the course of attempts to make the ethyl ester of α,α-bis-(diethylaminoethyl)-phenylacetic acid (I) through the corresponding acid chloride, it was noted that 1-ethyl-3-(β-diethylaminoethyl)-3-phenyl-2-pyrrolidone (II) was formed and none of the desired ester isolated. This interesting reaction has been explored and its scope and some of its limitations noted.



I

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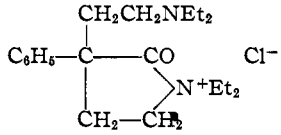
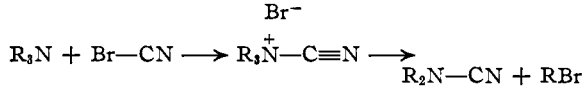


III

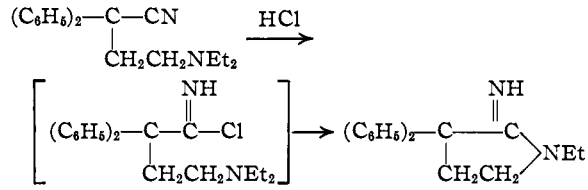
When the acid (I) is dissolved in cold thionyl chloride and the solution is warmed, acid chloride formation begins around 30° and can be completed below 60°. At 60–80° a second reaction is initiated in the solution, ethyl chloride is evolved and the pyrrolidone (II) is formed. The reaction can be driven to completion by refluxing the thionyl chloride solution (87–90°). The amino acid chloride hydrochloride is an intermediate in this reaction and can be isolated. The acid chloride appears to go through a transitory quaternary amide form (III) which then decomposes with the elimination of a molecular equivalent of alkyl halide. Either the free amino acid or its hydrochloride can be used as the starting material.

The reaction described here has been found to be applicable to a wide variety of compounds and can be classed as "general." This is of interest in view of the small number of general reactions for the cleavage of the carbon–nitrogen bond.

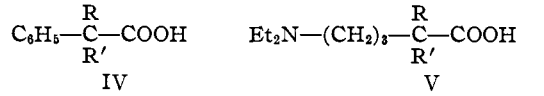
Hess[3] has reported an intermolecular reaction in which benzoyl chloride reacts with dimethylaniline to produce N-benzoyl-N-methylaniline and methyl chloride. This intermolecular reaction requires 180° for completion and appears to be an isolated instance. The von Braun reaction of tertiary amines with cyanogen bromide[4] is somewhat related in that a quaternary nitrogen is adjacent to a negative group in the intermediate complex and this decomposes to give a molecule of alkyl halide.



Blicke and Zambito[5] have reported an intramolecular reaction accomplishing the conversion of the hydrochloride salts of γ-dialkylaminonitriles to iminopyrrolidones which can be hydrolyzed to the corresponding pyrrolidones. Presumably an iminochloride intermediate is involved.



In order to determine the relative facility with which various alkyl groups are cleaved from the nitrogen atom in the reaction studied, two mixed amino acids were prepared. Treatment of IV, in which R is β-diethylaminoethyl and R′ is β-dimethylaminoethyl, with thionyl chloride yielded a mixture of approximately 75% methyl



IV V

chloride and 25% ethyl chloride. When R is β-dimethylaminoethyl and R′ is β-di-*n*-butylaminoethyl, the cleavage product was methyl chloride exclusively. Thus there is indication that the smaller alkyl group attached to the nitrogen is eliminated preferentially.

In a study of the effects of substituents on ring closure in a γ-dialkylaminobutyric acid, it was found that sulfurous products predominate if both alpha positions are not substituted when thionyl chloride is used as the acid chloride forming reagent. These substituents may be either aliphatic or aromatic. If phosphorus trichloride is used to obtain the acid chloride, this complica-

(1) Present address: Gillette Safety Razor Co., Boston, Mass.

(2) Gardner, Easton and Stevens, THIS JOURNAL, **70**, 2906 (1948).

(3) Hess, *Ber.*, **18**, 685 (1885).

(4) J. v. Braun, *ibid.*, **33**, 1438 (1900).

(5) Abstracts, 111th meeting of the American Chemical Society, 1947, p-3K.

TABLE I

NITRILES RR'C(C_6H_5)CN

R	R'	B. p. °C.	Mm.	$n^{25}D$	Yield, %	Nitrogen, %[f] Calcd.	Found
$Me_2N-(CH_2)_2$	H	100–102	0.3	1.5056	51	7.44	7.26
$Me_2N-(CH_2)_2$	$Et_2N(CH_2)_2$	124–131	.3	1.5018	58	9.74	9.53
$Me_2N-(CH_2)_2$	$Bu_2N(CH_2)_2$	148–152	.15	1.4915	75	8.16	8.24
$Et_2N-(CH_2)_2$[a]	H	100–105	.15	1.5004	72	6.46	6.38
$Et_2N-(CH_2)_2$	$Et_2N-(CH_2)_2$	137–138	.08	1.4978	81	8.88	8.69
$Et_2N-(CH_2)_2$[b]	C_6H_5	160–163	.55	1.5490	69	4.79	4.63
$Et_2N-(CH_2)_3$	$Et_2N(CH_2)_3$	172–175	.3	1.4940	80	8.15	8.28
$Et_2N-(CH_2)_3$[c]	C_6H_5	154–156	.15	1.5427	75	4.57	4.62
$C_4H_8N-(CH_2)_2$[d]	C_6H_5	M. p. 72–73			69	4.85	4.85
$C_5H_{10}N-(CH_2)_2$[e]	C_6H_5	M. p. 73–74			65		

[a] Eisleb, *Ber.*, **74B**, 1433 (1941). [b] A. J. Zambito, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich. [c] Confirms unpublished work, Bill Elpern, Sterling-Winthrop Research Institute, Rensselaer, N. Y. [d] Confirms work unpublished, A. W. Ruddy, Sterling-Winthrop Research Institute, Rensselaer, N. Y. [e] Bockmühl and Ehrhart, U. S. Patent 2,230,774. [f] Basic nitrogen determined by titration with perchloric acid in acetic acid.

TABLE II

ACIDS RR'R"CCOOH

R	R'	R"	M. p., ° C. Impure	Yield, %	Hydrolysis time in hours from nitrile[f]	Nitrogen, % Calcd.	Found
$Me_2N-(CH_2)_2$	$Et_2N-(CH_2)_2$	C_6H_5	Gum	85	2	...	...
$Me_2N-(CH_2)_2$	*n*-$Bu_2N-(CH_2)_2$	C_6H_5	197–198	62	40	7.73	7.64
$Et_2N-(CH_2)_2$[a]	Et	Et	149–151[b]	30[d]	60	16.50[c]	16.69
$Et_2N-(CH_2)_2$	H	C_6H_5	93–96	49	8	5.95	5.70
$Et_2N-(CH_2)_2$	$Et_2N-(CH_2)_2$	C_6H_5	175–178[e]	85	2	8.39	8.21
$Et_2N-(CH_2)_2$	C_6H_5	C_6H_5	178–179.5	84	30	4.49	4.43
$Et_2N-(CH_2)_3$	$Et_2N-(CH_2)_3$	C_6H_5	102–105[g]	76	65	7.73	7.59
$Et_2N-(CH_2)_3$	C_6H_5	C_6H_5	132–133	67	30	4.30	4.12
$C_4H_8N-(CH_2)_2$	C_6H_5	C_6H_5	204–205	47[d]	65	4.53	4.41
$C_5H_{10}N-(CH_2)_2$	C_6H_5	C_6H_5	227–230	60	65	4.33	4.04
$OC_8H_4N-(CH_2)_2$	C_6H_5	C_6H_5	216–217 (d.)	57	70	4.30	4.23

[a] Prepared from the corresponding nitrile which is known: Ziegler and Ohlinger, *Ann.*, **495**, 84–112 (1932). [b] Melting point of the hydrochloride salt. [c] Chlorine analysis. [d] This yield is low due to mechanical difficulties. [e] This is the melting point observed when the sample is heated from room temp. If placed in bath at 160° it melts, resolidifies, and then remelts at 175–176°. [f] Several of these hydrolyses were allowed to proceed over week-ends and the times given thus are not significant except to indicate a working limit. [g] The dihydrochloride salt of this acid melts at 128–132°.

tion is removed and no substituents are necessary in the alpha positions. Yields appear to be lower with the latter reagent. Table III presents the pyrrolidones which have been prepared. Phosphorus trichloride was used in the preparation of the first, second and the eighth compounds listed. Thionyl chloride was used in the preparation of the remainder.

For some unknown reason this pyrrolidone ring formation occurs at a higher temperature when phosphorus trichloride is used instead of thionyl chloride. In every case where thionyl chloride was used, pyrrolidone formation occurred in the refluxing thionyl chloride solution whereas each time that phosphorus trichloride was used, the excess reagent had to be removed and the solid acid chloride heated to 160° or higher. The first compound in Table III was formed at 160°, the second at 180° and the eighth at 250°.

Three piperidones were prepared by this method from δ-dialkylaminovaleric acids. When the acid chloride from the acid (V) where R and R' are phenyl, prepared using thionyl chloride, was heated to 150–170°, ethyl chloride was evolved and 1-ethyl-3,3-diphenyl-2-piperidone was formed. It is of interest that the formation of 1-ethyl-3,3-diphenyl-2-pyrrolidone occurred at 80–85° using the same reagent, thionyl chloride. That a 70–90° elevation in temperature above that required for a five-membered ring should be required to close a six-membered ring is surprising. This same trend was apparent in the formation of 1-ethyl-2-piperidone from the acid chloride of (V) where R and R' are hydrogen, a temperature of 190–200° being required. The corresponding pyrrolidone, 1-ethyl-2-pyrrolidone, formed at 150–160°. In this latter comparison phosphorus trichloride was the reagent used.

When the acid chloride of (V), where R is phenyl and R' is γ-diethylaminopropyl, was heated to 205–210°, 1-ethyl-3-phenyl-3-(γ-diethylaminopropyl)-2-piperidone was formed. Another sample of this intermediate acid chloride was refluxed with alcohol and the corresponding ester, ethyl α,α-bis-(γ-diethylaminopropyl)-phenylacetate, was isolated.

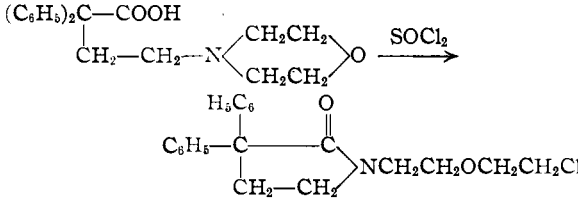
TABLE III

1-R-3-R′-3-R″-2-PYRROLIDONES

R	R′	R″	B. p. °C.	Mm.	$n^{25}D$	M. p. HCl salt, °C.	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Et[a]	H	H	211–214	784	1.4647	.....	54					12.37[b]	12.10
Et	H	C_6H_5	M. p. 47–48	..	....	.....	30	76.16	76.55	7.97	7.57	7.40[b]	7.43
Et	Et	Et	60–61	0.23	1.4601	.....	48	....	...	....	...	8.28[b]	8.12
Me	$Et_2N(CH_2)_2$	C_6H_5	126–128	.03	1.5180	.....	68[f]	73.80	73.92	9.29	9.52	10.76[b]	11.05
Et	$Et_2N(CH_2)_2$	C_6H_5	130–133	.07	1.5204	178–180	70	66.54[c]	66.77	8.69	8.85	10.92[d]	10.76
Me	n-$Bu_2N(CH_2)_2$	C_6H_5	139–142	.04	1.5120	.....	76	76.31	76.00	10.37	10.26	4.24[c]	4.26
Et[g]	C_6H_5	C_6H_5	M. p. 108–109	..	....	.....	41	....	...	....	...	5.28[b]	5.19
Me	$Cl(CH_2)_2$	H	78–79	.11	1.4902	.. ....	24	....	...	....	...	8.67[b]	8.51
Me	$Cl(CH_2)_2$	C_6H_5	158–160	.22	1.5538	.....	72	....	...	14.93[d]	14.59	5.88[b]	5.82
Me	$Me_2N(CH_2)_2$	C_6H_5	M. p. 66.5–68[h]	..	1.5364	.....	81	73.11	73.34	9.00	9.08	11.37[b]	11.32
$C_6H_5CH_2$	$Cl(CH_2)_2$	C_6H_5	184–187	.07	1.5790	.....	50[k]	72.72	72.72	11.37[d]	11.28	4.46[b]	4.66
$C_6H_5CH_2$	$Me_2N(CH_2)_2$	C_6H_5	192–193	.22	1.5632	.....	79	78.23	78.20	8.13	8.11	8.68[b]	8.65
$Cl(CH_2)_4$	C_6H_5	C_6H_5	200–210	.09	1.5825	.....	63	....	...	10.82[d]	10.59	4.27[b]	4.21
$Me_2N(CH_2)_4$	C_6H_5	C_6H_5	200–201	.2	1.5635	160–161.5	70	78.51	78.38	8.39	8.50	4.16[c]	4.18
$Cl(CH_2)_5$	C_6H_5	C_6H_5	M. p. 58–59[i]	..	1.5760	.....	48	....	...	....	...	10.39[d]	10.42
$Me_2N(CH_2)_5$	C_6H_5	C_6H_5	197–198	.2	1.5591	105–106	70	71.39[e]	71.61	8.08	8.01	9.16[d]	8.93
$Cl(CH_2)_2O(CH_2)_2$	C_6H_5	C_6H_5	M. p. 76–78[j]	..	....	.....	52	69.85	69.85	6.45	6.17	10.31[d]	10.10
$Me_2N(CH_2)_2O(CH_2)_2$	C_6H_5	C_6H_5	178–181	.1	1.5626	125–127	78	67.92[e]	67.80	7.25	7.50	9.13[d]	8.90

[a] Prepared from γ-diethylaminobutyric acid hydrochloride, *Beilstein*, **4** (506). [b] Nitrogen analysis by Kjeldahl method. [c] Nitrogen analysis by titration with perchloric acid in acetic acid. [d] Chlorine analysis. [e] Analysis of the hydrochloride salt. [f] Per cent. yield of hydrochloride salt before liberation of the free base. [g] See footnote 5. [h] Boiling point, 137–138° (0.25 mm.). [i] Boiling point, 170–173° (0.001 mm.). [j] Boiling point, 180–182° (0.15 mm.). [k] Low due to mechanical loss.

Since this reaction involves the cleavage of a carbon–nitrogen bond, it was of interest to see if it could be applied to the opening of nitrogen containing heterocyclic compounds. The three compounds studied were γ-pyrrolidyl-, γ-piperidyl- and γ-morpholinyl-α,α-diphenylbutyric acids. In each case the ring was opened to give an ω-chloroalkyl side-chain attached to the nitrogen atom of the pyrrolidone produced. This is illustrated by the following example.



As an extension to these studies it was decided to heat the acid chloride of 1-methylpiperidine-4-carboxylic acid with the expectation that methyl chloride would be evolved and a bicyclic amide, 7-keto-1-azabicyclo[2,2,1]heptane, would be produced. The product isolated contained chlorine and proved to be 1-methyl-3-β-chloroethyl-2-pyrrolidone. The cleavage of the ring here should be contrasted with examples noted above where, with non-cyclic substitution on the nitrogen atom, the smallest group is cleaved. Apparently in this case, the strain imposed by closure of the pyrrolidone ring caused preferential cleavage of a carbon–nitrogen bond in the existing ring structure. This same type of cleavage was noted when 1-methyl-4-phenylpiperidine-4-carboxylic acid and 1-benzyl-4-phenylpiperidine-4-carboxylic acid were employed.

The chlorine atoms in all the ω-chloro compounds described above were replaced by dimethylamino groups and the resulting basic pyrrolidones are being tested by pharmacological activity.

Appreciation is extended to Mr. S. J. Marsala and Mrs. H. D. Carter for technical assistance in this work.

Experimental

α,α-bis-(β-Diethylaminoethyl)-phenylacetonitrile.[6]—In a 2-liter, round-bottomed flask fitted with a stirrer, thermometer and reflux condenser was placed 117 g. (1 mole) of benzyl cyanide, 305 g. (2.25 moles) of β-diethylaminoethyl chloride, and 1 liter of toluene. This mixture was warmed to 50° and 97.5 g. (2.5 moles) of sodamide added, in portions, at such a rate that, with cooling, the temperature of the mixture was held between 50 and 70°. The time for addition was approximately forty-five minutes.

The mixture was stirred and refluxed for ten hours, then cooled and 75 ml. of alcohol added to decompose any traces of free sodium originally present in the sodamide. The toluene solution was decanted from a small solid residue, washed with two 150-ml. portions of saturated aqueous sodium chloride solution, and dried over anhydrous potassium carbonate.

The toluene and alcohol were removed by distillation under reduced pressure and the oil residue fractionated. The product, 256 g. (81%) boiled at 135–138° (0.08 mm.). Analyses and further constants are given in Table I.

α,α-bis-(β-Diethylaminoethyl)-phenylacetic Acid.[7]—To a cold solution of 287 ml. of concentrated sulfuric acid in 196 ml. of water (70% sulfuric acid by weight) was added

(6) The method described here was used in the preparation of all the nitriles reported in Table I.

(7) All the acids reported in Table II were prepared by this method except for the 4th in the list. Its preparation is described separately.

196 g. (0.62 mole) of α,α-bis-(β-diethylaminoethyl)-phenylacetonitrile. The resulting solution was heated at 145° (gentle reflux) for two hours,[8] cooled, and poured into a mixture of 500 g. of ice and 750 ml. of water. This mixture was made strongly alkaline with 35% sodium hydroxide. The sodium salt of the amino acid separated partially at this point due to salting out effects and was filtered.[9] The filtrate was adjusted to a *p*H of 7 with hydrochloric acid and the free amino acid which separated was filtered, washed with water and dried. The sodium salt, separated above, was dissolved in a maximum of water and the *p*H adjusted to 7. The precipitated amino acid was filtered, washed with water and dried. The total quantity of slightly impure amino acid isolated thus was 174 g. (84%). A sample, after one recrystallization from water, melted at 175–178° when heated from room temperature but when put into the bath at 165°, the solid melted, resolidified, and then melted at 175–176°. The crude material was satisfactory for this work.

γ-Diethylamino-α-phenylbutyric Acid.—A solution of 50 g. of γ-diethylamino-α-phenylbutyronitrile in 250 ml. of concentrated hydrochloric acid was refluxed for eight hours. The reaction mixture was then made alkaline to phenolphthalein with 35% sodium hydroxide and heated on a steam-bath until no more ammonia was evolved. The solution was then made neutral and evaporated to dryness. The water must be completely removed since the product is very soluble in water.[10] The residue was then taken up in hot chloroform, the chloroform extract filtered free of salt, the chloroform evaporated and the residue dissolved in hot benzene. The solid, 17 g., m. p. 90–92°, which separated from the cold solution was filtered and the filtrate evaporated to dryness. After two weeks the residue had crystallized to some extent. It was filtered free of oil, washed with benzene and combined with the first crops of crystals giving a total of 30 g. of acid. An additional benzene recrystallization of the combined product gave 26.5 g. of acid, m. p. 90–92°. Several more benzene recrystallizations were necessary to give an analytically pure sample, m. p. 92–95°.

δ-Diethylaminovaleric Acid Hydrochloride.—A mixture of 48.4 g. (0.177 mole) of diethyl α-(γ-diethylaminopropyl)-malonate,[11] 20 g. of sodium hydroxide in 100 ml. of water and 25 ml. of alcohol was refluxed for two hours, made strongly acid with concd. hydrochloric acid and refluxed for ten hours to effect decarboxylation to the acetic acid. After removing the solvents, the pasty δ-diethylaminovaleric acid hydrochloride was warmed with 200 ml. of alcohol and cooled. The sodium chloride was filtered and the filtrate evaporated to give an oil which solidified to a mush after standing for one week. Addition of 50 ml. of acetone to this produced a filterable material. Addition of ether to the filtrate precipitated a further quantity of solid. The solid product was recrystallized from a benzene–alcohol mixture and dried at 80°. The impure product melted at 195–199°; yield 15 g. (40%).

Anal. Calcd. for $C_9H_{18}NO_2 \cdot HCl$: Cl, 17.4. Found: Cl, 16.5.

N-Methylisonipecotic Acid Hydrochloride.—This compound was prepared from isonicotinic acid in two steps without isolating the intermediate isonipecotic acid. A mixture of 125 g. (1.02 moles) of isonicotinic acid, 400 ml. of glacial acetic acid, 300 ml. of water and 2.5 g. of platinum oxide catalyst was placed in an autoclave and subjected to a hydrogen pressure of 1000 lb. at 25°. Six hundred thirty pounds of hydrogen was absorbed in eighteen hours. The autoclave was opened and 0.5 g. of platinum oxide added. Re-introduction of hydrogen into the autoclave resulted in the consumption of 120 lb. of hydrogen. This 750 lb. represents 90% of the theoretical uptake of hydrogen. The catalyst was removed by filtration.

A palladium-on-charcoal catalyst, made from 4.1 g. of palladous chloride and 33 g. of Darco G60, was added to the above solution of reduced isonicotinic acid and then 108 g. of 40% formaldehyde. This mixture was subjected to hydrogenation at room temperature and 340 lb. (110%) of hydrogen was consumed.

The palladium catalyst was filtered and the filtrate evaporated to an oil. After the addition of 100 ml. of concentrated hydrochloric acid, the liquids were evaporated under reduced pressure on a steam-bath to give a pasty solid. Trituration of this with 300 ml. of acetone gave 151 g. of N-methylisonipecotic acid hydrochloride. Recrystallization from isopropyl alcohol yielded 130 g. (71%) of product which melted at 223–225° (cor.).

Anal. Calcd. for $C_7H_{13}NO_2.HCl$: Cl, 19.74. Found: Cl, 20.15.

1-Ethyl-3-(β-diethylaminoethyl)-3-phenyl-2-pyrrolidone.[12]—To 75 ml. (1 mole) of thionyl chloride cooled to 5–10° was added slowly and with vigorous stirring 58 g. (0.17 mole) of α,α-bis-(β-diethylaminoethyl)-phenylacetic acid. No reaction occurred. The flask was attached to a reflux condenser. To the top of the latter were connected in series two scrubbers filled with 20% potassium hydroxide, a calcium chloride filled drying tube and finally a test-tube trap cooled by a Dry Ice–methylene chloride mixture.

When the reaction mixture was heated to 25–30°, acid chloride formation began. This reaction was completed below 60°. At 70–80° ethyl chloride evolution began and 7.7 g. (70%) was collected; b. p. 12.5–13°; $n^{4.8}D$ 1.3762. An authentic sample showed $n^{4.8}D$ 1.3761. After the thionyl chloride solution had been refluxed (85–88°) for one and one-half hours, the reaction appeared complete.

The excess thionyl chloride was removed on a steam-bath with the aid of an aspirator and the residue dissolved in water. This solution was made strongly alkaline and the pyrrolidone extracted with ether. After drying the ether solution over potassium carbonate and removing the ether, the residual liquid was fractionated and 35 g. (70%) of the pure pyrrolidone collected at 130–133° (0.07 mm.).

1-Ethyl-2-pyrrolidone.[13]—A mixture of 30 g. (0.15 mole) of γ-diethylaminobutyric acid and 50 ml. of phosphorus trichloride was refluxed for forty-five minutes in a 200-ml. round-bottomed flask connected to a condenser and gas collecting train as described in the preparation of the pyrrolidone above. No ethyl chloride was evolved. The excess phosphorus trichloride was removed by distillation under reduced pressure on a steam-bath and the residue heated further while attached to the original system. At 145° ethyl chloride began to be evolved and the reaction appeared complete after it had been heated for one hour at 155–160°.

The mixture was cooled somewhat and poured into 100 ml. of water with stirring. Complete solution occurred. This water solution was saturated with potassium carbonate and extracted five times with 75-ml. portions of ether. After the combined ether extracts were dried over potassium carbonate, the ether was distilled on a steam-bath and the residue fractionated at atmospheric pressure. The 1-ethyl-2-pyrrolidone boiled at 211–214°.[14]

1-Ethyl-2-piperidone.—The compound was prepared from δ-diethylaminovaleric acid hydrochloride using the procedure described immediately above. In this case it was necessary to heat the acid chloride to 190–200° before ethyl chloride was evolved. The product boiled at 120–

(8) See Table II for hydrolysis times required for other nitriles.

(9) With some of the acids studied, the sodium salt failed to solidify. In such cases the solution was diluted until the salt dissolved, but the resulting volumes were undesirably large and reduced the yields.

(10) This surprising solubility in water is unexplained.

(11) Marvel, Zartman and Bluthardt, THIS JOURNAL, **49**, 2299–2303 (1927).

(12) All of the pyrrolidones in Table II except the first, second and eighth were prepared by this method.

(13) The first, second and eighth compounds of Table III were prepared by this method, heating at 160, 180 and 250°, respectively, being necessary.

(14) B. p. 218° (751 mm.) reported by Tafel and Stern, *Ber.*, **33**, 2235 (1900).

122° (27 mm.). The yield was 20%. Its hydrochloride salt melted at 107–108°. This compound is reported[15] to boil at 109° (12 mm.) and its hydrochloride to melt at 108°.

1-Ethyl-3,3-diphenyl-2-piperidone.—In 35 ml. of cold thionyl chloride was dissolved 16 g. (0.05 mole) of δ-diethylamino-α,α-diphenylvaleric acid. This solution was refluxed for thirty minutes while attached to a train described earlier for the trapping of ethyl chloride. Acid chloride formation occurred but no ethyl chloride was evolved. Excess thionyl chloride was removed from the mixture by warming under vacuum and the residual liquid heated gradually to 150° at which point ethyl chloride began to be evolved. When the temperature was then raised to 175° over a period of twenty minutes the reaction appeared complete. Considerable blackening of the mixture occurred. The product was dissolved in ether, and the resulting solution washed with water and dried over potassium carbonate. The solvent was evaporated and the residue dissolved in alcohol, treated twice with charcoal, and recovered from the alcohol by evaporation of this solvent. After recrystallization once from Skelly C and once from a methanol–water mixture, it melted at 119–119.5°. The yield was 4 g. (30%).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01. Found: C, 82.01; H, 7.32; N, 4.88.

3-(γ-Diethylaminopropyl)-1-ethyl-3-phenyl-2-piperidone.—To 50 ml. of cold thionyl chloride was added 25 g. (0.057 mole) of α,α-bis-(γ-diethylaminopropyl)-phenylacetic acid dihydrochloride. The resulting solution was refluxed on a steam-bath for ninety minutes and the excess thionyl chloride removed by distillation on a steam-bath under reduced pressure. The yellow solid acid chloride dihydrochloride residue was heated to 190° before darkening and melting began. At 205–210° ethyl chloride was evolved and the reaction approached completion in thirty minutes. Finally the mixture was heated to 225° for fifteen minutes.

The cooled mixture was dissolved in water, non-basic impurities removed by three ether extractions, the solution made alkaline, and the liberated oil separated by three extractions with ether. The combined extracts were dried over potassium carbonate, the solvent removed, and the product distilled under reduced pressure. It boiled at 150–153° (0.04 mm.), $n^{25}D$ 1.5238. The yield was 13.2 g. (73%).

Anal. Calcd. for $C_{20}H_{32}N_2O$: C, 75.89; H, 10.10; N, 8.84. Found: C, 75.89; H, 9.99; N, 8.78.

Ethyl α,α-bis-(γ-Diethylaminopropyl)-phenylacetate.—To 30 ml. of cold thionyl chloride was added 15 g. (0.041 mole) of α,α-bis-(γ-diethylaminopropyl)-phenylacetic acid. This mixture was refluxed for one hour, the excess thionyl chloride removed on a steam-bath under 10 mm. pressure and the solid residue refluxed with 75 ml. of alcohol for one hour. The alcohol was removed under reduced pressure on a steam-bath, the solid residue dissolved in water, and the solution made alkaline. The liberated oil was diluted with ether, separated, the solution dried over potassium carbonate, the ether evaporated, and the residue fractionated. The yield of ester, b. p. 149–151° (0.05 mm.), $n^{25}D$ 1.4902, was 11.2 g. (70%).

Anal. Calcd. for $C_{24}H_{42}N_2O_2$: N, 7.18. Found: N, N, 7.35. This ester was converted to its dihydrochloride which melted at 220–222° (dec.).

Anal. Calcd. for $C_{24}H_{42}N_2O_2 \cdot 2HCl$: C, 62.17; N, 9.57; Cl, 15.30. Found: C, 62.48; H, 9.72; Cl, 15.45.

(15) C. Räth, *Ann.*, **489**, 107–118 (1931).

Summary

An intramolecular reaction between acid chlorides and tertiary amines, with the simultaneous elimination of a molecular equivalent of alkyl halide, has been noted.

This reaction has been applied to the syntheses of pyrrolidones and piperidones.

A novel method for opening heterocyclic nitrogen rings is presented.

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Pyrolysis of Some Amino Acids

BY ROBERT L. CLARKE AND ARAM MOORADIAN

It has been noted by Le Sueur[1] that pyrolysis of a mixture of ethyl α,α′-dibromoadipate and monoethylaniline at 185–195° produced ethyl 1-phenylpyrrolidine-2,5-dicarboxylate (62.5% yield) and diethylaniline. The intermediate was demonstrated to be ethyl α,α′-bis-(N-ethylanilino)-adipate which then decomposed with evolution of diethylaniline.

With the idea that ethyl α,α-bis-(β-diethylaminoethyl)-α-phenylacetate might be pyrolyzed to produce ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate (the ethyl analog of "Demerol") and triethylamine, Clarke, *et al.*,[2] attempted to make the necessary ester and failed because the acid chloride obtained was transformed into a pyrrolidone.

Since the preparation of ethyl α,α-bis-(β-diethylaminoethyl)-α-phenylacetate was found to be difficult, it seemed of interest to determine whether the acid instead of the ester might be pyrolyzed to give a piperidine carboxylic acid. Pyrolysis of α,α-bis-(β-diethylaminoethyl)-α-phenylacetic acid at 180-200° did not cause separation of any of the expected triethylamine, but gave an excellent yield of diethylamine (91%). From the residue α-diethylaminoethyl-α-phenylbutyrolactone was obtained in 84% yield.

In order to determine whether diethylamine was eliminated in this pyrolysis to produce α-diethylamino-α-vinyl-α-phenylacetic acid which then lactonized or the hydrogen of the carboxyl group was eliminated in the diethylamine, a sample of α,α-bis-(β-diethylaminoethyl)-α-phenyl acetonitrile which contained no carboxyl hydrogen was heated at its boiling point near 300°. There was no evidence of decomposition. In order to exclude the possibility that the decomposition

(1) Le Sueur, *J. Chem. Soc.*, **95**, 273 (1909); **97**, 173 (1910).

(2) Clarke, Mooradian, Lucas and Slauson, THIS JOURNAL, **71**, 2821 (1949).