white solid, tinted green, was 7.0 g. The solid was washed with portions of ether until the melting point was constant, 128.5–129° with decomposition. Wieland[11] reports styrene pseudo-nitrosite to melt at 129° with decomposition. Fusion of the solid converted it into a bright green liquid which rapidly decomposes into a yellow oil. The molecular weight was determined by the Rast camphor method. Calcd. for $C_8H_8N_2O_3$: mol. wt., 180. Found: mol. wt., 235 (average of two determinations). The camphor solution exhibited a transitory bright green color on fusion.

ω-Nitroacetophenone Oxime.—Extraction of 7 g. of styrene pseudo-nitrosite with hot chloroform produced 6.1 g. of an oily solid which melted at 94.5–95.5° after recrystallization from carbon tetrachloride. Recrystallization of the styrene pseudo-nitrosite from hot water also produced white needles melting at 94.5–95.5°. The oxime is reported to melt at 96°.[10]

ω-Nitroacetophenone.—Refluxing a portion of either ω-nitroacetophenone oxime or styrene pseudo-nitrosite with dilute hydrochloric acid gave rise to white needles melting at 104.5–105.5° (literature,[19] m.p. 105–105.5°).

Reaction of N-(1-Phenyl-2-nitroethyl)-hydroxylamine with Benzoyl Chloride.—To 2 g. (0.011 mole) of N-(1-phenyl-2-nitroethyl)-hydroxylamine dissolved in 10 ml. of anhydrous pyridine, 2.8 g. (0.022 mole) of benzoyl chloride was added. The mixture was shaken and kept chilled. After 10 minutes, the mixture was poured into 50 ml. of cold water. A brown oil was obtained which was washed twice with water and then was dissolved in a minimum volume of methanol. After standing overnight, a solid separated which, on filtration and washing with cold methanol, yielded 1.1 g. of white solid. The yield was approximately the same when three equivalents of benzoyl chloride were used. The solid was recrystallized from methanol and then several times from benzene, m.p. 155.5–156°.

Anal. Calcd. for $C_{29}H_{22}N_2O_6$: C, 70.46; H, 4.48; N, 5.67. Found: C, 70.31; H, 4.36; N, 5.60.

A methanolic solution did not give a color with 1% ferric chloride. The compound was insoluble in 5% sodium hydroxide after 30 minutes. After a longer period the solid is soluble. Neutralization of the alkali with hydrochloric acid and treatment with 1% ferric chloride produced an intense red-violet coloration. Strong alkaline hydrolysis of 4.4 g. of the benzoylated product produced 2.4 g. of purified benzoic acid (m.p. 120.5–121.5°) corresponding to 2.2 moles of benzoic acid per mole of benzoylated product.

Acknowledgment.—Micro combustions for C, H and N were performed by J. Sorenson and C. White. This work was supported by a Commercial Solvents Corporation fellowship held by one of us (J. P.) during 1950–1951.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Mannich Reaction of Diphenylacetonitrile. Products and Derivatives

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RECEIVED AUGUST 7, 1952

Mannich type products have been prepared by the reaction of diphenylacetonitrile and formaldehyde with six secondary amines. Three of these α,α-diphenyl-β-substituted-amino-propionitriles have been hydrolyzed to the corresponding β-amino acids. A number of cleavage reactions of α,α-diphenyl-β-dimethylaminopropionitrile and of the corresponding carboxylic acid are described. Ester and amide derivatives of the dimethylamino acid have been prepared as general analogs of the active analgesic, Methadon.

Zief and Mason[1] have reported the reaction between benzyl cyanide and morpholinomethanol to give the expected amino nitrile $C_6H_5CH(CN)CH_2N$⟨O⟩ However, attempts to prepare the picrate resulted in cleavage of the molecule by a reverse Mannich reaction.

In the present work, the reaction of the analogous diphenylacetonitrile (I) and formaldehyde with the six secondary amines, dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine and N-methylpiperazine, respectively, is reported.[2] In all cases the expected products (II) were obtained, the first three in fair to good yields even at low reaction temperatures (40°) but the last three only in poor yields even at higher temperatures (80–120°).

$$(C_6H_5)_2CHCN \xrightarrow[R_2NH]{CH_2O} (C_6H_5)_2CCN$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_2NR_2$$

I

IIA, NR_2 = $N(CH_3)_2$; IID, NR_2 = piperidino
IIB, NR_2 = $N(C_2H_5)_2$; IIE, NR_2 = morpholino
IIC, NR_2 = pyrrolidino; IIF, NR_2 = N-methylpiperazino

In contrast to the instability of the salts of the Mannich product of benzyl cyanide observed by Zief and Mason, the product IIA obtained from dimethylamine formed a stable crystalline hydrochloride which underwent nearly quantitative reversal only on prolonged heating in water. On the other hand, when 75% sulfuric acid at 140° was employed as the hydrolytic agent, the corresponding β-amino acid IIIA was produced in a 64% yield. In like manner, the diethylamino (IIB) and piperidino (IID) nitriles were readily hydrolyzed to the corresponding carboxylic acids, IIIB and IIIC, respectively. The reason for this apparent anomaly—reversal in weakly acid or neutral solution and conversion of the nitrile to the carboxyl group in strong acid—probably lies in the intermediate formation in strong sulfuric acid of the following salt-like addition product[3]

$$\text{IIA,B,D} \longrightarrow (C_6H_5)_2CCOOH$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad CH_2NR_2$$

IIIA, NR_2 = $N(CH_3)_2$
IIIB, NR_2 = $N(C_2H_5)_2$
IIIC, NR_2 = piperidino

$$(C_6H_5)_2C(OSO_3H)-C=NH \longrightarrow (C_6H_5)_2C-C^+=NH + HSO_4^-$$
$$\qquad\qquad |\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\quad CH_2NR_2 \longleftarrow \qquad\qquad CH_2NR_2$$

This would have the effect of reducing the polariz-

(1) M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

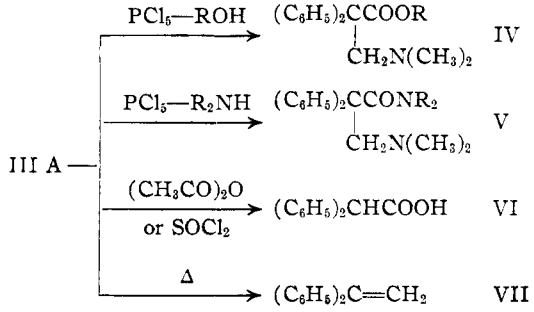
(2) After most of this work was completed, M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1948), reported the reaction of diphenylacetonitrile and formaldehyde with dimethylamine. However, few details were given and the product was not investigated extensively.

(3) Compare J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70**, 4045 (1948).

ability (electron withdrawal capacity) of the nitrile group and hence its tendency to promote the reverse Mannich reaction.

Other polarizability effects on the reverse Mannich reaction were also noted. When the nitrile IIA was treated with ethylmagnesium bromide, no water-insoluble basic material could be isolated. Here, apparently, the ketonic carbonyl group formed in the reaction induced spontaneous rupture of the Mannich product. Bockmühl and Ehrhart[2] also noted this cleavage reaction in attempting to prepare the same ketone from the Grignard reaction of the corresponding ester. These results are consistent with the observations[4] that 1,1-diphenylacetone undergoes Mannich substitution solely at the terminal methyl group and that ω-diphenylacetophenone does not react at all.

In a similar vein, when the carboxylic acid IIIA was heated with acetic anhydride, an 84% yield of diphenylacetic acid (VI) was obtained. Presumably a mixed anhydride between IIA and acetic acid was first formed, which then cleaved. Diphenylacetic acid also resulted on refluxing IIIA with thionyl chloride. Only when the acid IIIA was treated with phosphorus pentachloride in ether at 0° could an acid chloride be obtained, as indicated by its conversion without purification to a series of stable esters (IV) and amides (V) (Table I). All of these qualitative observations regarding the relative stabilities of these Mannich



type products are consistent with the following relative polarizabilities commonly ascribed[5] to carbonyl groups when present in different carbonyl functions:

$$-COR > -COCl \text{ (or anhydride)} > -COOR > -CONH_2 > -COO^-$$

When the acid IIIA was pyrolyzed at the relatively low temperature of 210°, not only carbon dioxide but dimethylamine also was evolved to give a 77% yield of 1,1-diphenylethylene (VII).

In addition to the preparation of several esters (IV) by reaction of the acid chloride of IIIA with alcohols, one ester IV (R = C_2H_5) was prepared by direct esterification of IIIA and three were made by treatment of the potassium salt of IIIA with an alkyl chloride. Since the potassium salt is soluble in non-polar solvents, this method proved to be the most convenient when relatively reactive halogen compounds were employed.

For the purpose of structure proof, the methyl ester IV (R = CH_3) was prepared independently by methylation of the known[6] methyl α,α-diphenyl-β-aminopropionate.

None of the compounds reported in the present work showed any interesting analgesic activity.

Acknowledgments.—The authors wish to thank Mr. E. F. Shelberg, Head of the Abbott Microanalytical Laboratory, and Mr. Robert Berg, Mr. Dan McCallum and Mr. Rodger Barron for the microanalyses reported in this paper. Grateful acknowledgment is also given to Dr. R. K. Richards and Mr. K. E. Kueter of the Abbott Pharmacological Research Department for the analgesic tests.

Experimental

α,α-Diphenyl-β-dimethylaminopropionitrile (IIA).—A solution of 269 g. of diphenylacetonitrile (I) in 400 cc. of dioxane was treated with 170 cc. of a 50% aqueous dimethylamine solution. Enough 95% ethanol was added to make a clear solution and then 125 cc. of a 40% aqueous formaldehyde solution was added in several portions. After each portion enough 95% ethanol to produce a clear solution was introduced into the mixture. In all, 100 cc. of ethanol was used, and the temperature of the mixture rose spontaneously to 45–50°. The homogeneous solution was then placed in a hot room (40°) for 33 days. Two layers formed in the reaction mixture after several days.

The reaction mixture was poured with stirring into a large volume of ice-water containing 190 cc. of concentrated hydrochloric acid. The acid-insoluble material (68 g.) soon formed a semi-solid precipitate which could be removed by filtration.

The acidic aqueous solution was made alkaline with 20% sodium hydroxide solution, maintaining a low temperature during the neutralization by the addition of ice. The separated oil was taken up in ether and the solution was washed with water. The ethereal extract was dried over anhydrous magnesium sulfate. Filtration and removal of the ether gave 240 g. of crude product which on vacuum distillation yielded 214 g. (61% conversion) of straw-colored oil, b.p. 142–147° (0.3 mm.), $n^{25}D$ 1.5662. The distilled product crystallized slowly and completely. Recrystallization of a sample from pentane gave colorless prisms, m.p. 44–45°.

Anal. Calcd. for $C_{17}H_{18}N_2$: N, 11.19. Found: N, 11.22.

Hydrochloride, shiny leaflets from methanol–ether, m.p. (rapid heating) 186–187° (dec.).[7]

Anal. Calcd. for $C_{17}H_{19}ClN_2$: C, 71.19; H, 6.68; N, 9.77. Found: C, 71.06; H, 6.85; N, 9.41.

The 68 g. of semi-solid non-basic material obtained as a by-product consisted mainly of a mixture of unreacted diphenylacetonitrile with an unstable material which gradually regenerated more diphenylacetonitrile together with formaldehyde. From the 68 g., 30 g. of pure diphenylacetonitrile could be recovered.

α,α-Diphenyl-β-diethylaminopropionitrile (IIB).—This preparation was similar to that of the dimethylamino analog, only equivalent liquid diethylamine in place of the aqueous dimethylamine was used. A 51% conversion to the aminonitrile was obtained after only five days at 40°, b.p. 143–148° (0.3 mm.), $n^{25}D$ 1.5550. Recrystallization of the solidified distillate from pentane gave large colorless prisms, m.p. 55–56°.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.54; H, 7.78; N, 10.04.

A crystalline hydrochloride could not be obtained.

α,α-Diphenyl-β-pyrrolidinopropionitrile (IIC).—Using pyrrolidine in place of dimethylamine and allowing the reaction to stand for 58 days at 40° gave the solid pyrrolidino nitrile in an 86.5% yield, m.p. 98–100°, after one recrystallization from Skellysolve C.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.77; H, 7.05; N, 10.28.

α,α-Diphenyl-β-piperidinopropionitrile (IID).—Substituting piperidine for the dimethylamine in the above procedure

(4) W. Wilson and Z. Kyi, *J. Chem. Soc.*, 1321 (1952).

(5) J. R. Johnson in Gilman, "Organic Chemistry," John Wiley and Sons Inc., New York, N. Y., 1943, Vol. II, p. 1847.

(6) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(7) Bockmühl and Ehrhart (ref. 2) report m.p. 160° for this hydrochloride.

TABLE I

α,α-DIPHENYL-β-DIMETHYLAMINOPROPIONIC ESTERS AND AMIDES $(C_6H_5)_2C(CH_2N(CH_3)_2)-COX$

X	M.p., °C.	Yield, %[a]	Formula	Nitrogen, % Calcd.	Found
		Esters IV			
$-OCH_3$[b]	178–179	66[c]	$C_{18}H_{22}ClNO_2$[d]	4.38	4.27
$-OC_2H_5$[b]	175–176	78[c]	$C_{19}H_{24}ClNO_2$[e]	4.20	4.29
$-OCH(CH_3)_2$	175–176	21[c]	$C_{20}H_{26}ClNO_2$	4.03	4.24
$-OCH_2C_6H_5$	165–170 (0.06 mm.)[f]	33[g]	$C_{24}H_{25}NO_2$[h]	3.90	3.97
$-OCH_2CH_2N(CH_3)_2$[i]	209–210	75[g]	$C_{21}H_{30}Cl_2N_2O_2$	6.78	6.80
$-OCH_2CH_2N(C_2H_5)_2$[i]	200–201	78[g]	$C_{23}H_{34}Cl_2N_2O_2$[j]	6.35	6.26
		Amides V			
$-NH_2$	156–157	69	$C_{17}H_{20}N_2O$	10.44	10.30
$-NHCH_3$	98–99.5	88	$C_{18}H_{22}N_2O$	9.92	10.05
$-N(CH_3)_2$	110–112	89	$C_{19}H_{24}N_2O$	9.45	9.42
$-NHC_2H_5$	71–73	96	$C_{19}H_{24}N_2O$	9.45	9.54
$-N(C_2H_5)_2$[b]	161–162	75	$C_{21}H_{29}ClN_2O$	7.76	7.84
-piperidino	95–97	90	$C_{22}H_{28}N_2O$	8.33	8.41
$-NHC_6H_5$	147–148	58	$C_{23}H_{24}N_2O$	8.13	8.06
$-NHCH_2CH_2N(CH_3)_2$	158–160 (0.1 mm.)[k]	38	$C_{21}H_{29}N_3O$	12.35	11.97
$-NHCH_2CH_2N(C_2H_5)_2$	187–190 (0.2 mm.)[k]	60	$C_{23}H_{33}N_3O$	11.43	11.40

[a] Yield based on amino acid. [b] Monohydrochloride. [c] Prepared through the acid chloride, method B. [d] Calcd.: C, 67.59; H, 6.94. Found: C, 67.93; H, 6.80. [e] Calcd.: C, 68.35; H, 7.25. Found: C, 68.90; H, 7.40. [f] Boiling point of free base, $n^{25}D$ 1.5241. [g] Prepared through the potassium salt, method C. [h] Calcd.: C, 80.19; H, 7.01. Found: C, 80.38; H, 6.77. [i] Dihydrochloride. [j] Calcd.: C, 62.58; H, 7.76. Found: C, 62.81; H, 7.56. [k] Boiling point of free base.

gave only a 16% yield of product after eight days at 40°. The procedure was therefore modified as follows:

To a solution of 42.6 g. (0.5 mole) of piperidine in 100 cc. of ice-cold 95% ethanol was added slowly with swirling 37.5 g. (0.5 mole) of 40% aqueous formaldehyde. To this mixture was added 19 g. (0.1 mole) of solid diphenylacetonitrile and the solution was refluxed for 18 hours. The ethanol was then removed by distillation *in vacuo* and the product was isolated from the residue by the procedure described above for the dimethylamino analog. Fractional distillation yielded 12.1 g. (42%) of the piperidino nitrile, b.p. 148–152° (0.3 mm.). Redistillation gave a colorless liquid, b.p. 146° (0.3 mm.), $n^{26}D$ 1.5652.

Anal. Calcd. for $C_{20}H_{22}N_2$: N, 9.65. Found: N, 9.80.

α,α-Diphenyl-β-(4-methyl-1-piperazino)-propionitrile (IIF).—Using 50 g. (0.5 mole) of N-methylpiperazine in place of piperidine in the above procedure gave 5.5 g. (18%) of the corresponding nitrile as a colorless oil, b.p. 163° (0.8 mm.), $n^{26}D$ 1.5606.

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.65; H, 7.59; N, 13.78.

α,α-Diphenyl-β-morpholinopropionitrile (IIE).—No product was obtained when the original low temperature (40°) procedure was attempted. The 18-hour ethanol reflux procedure described in the preparation of the piperidino analog gave only a 4% yield of product. When the ethanol was replaced by *n*-butanol and refluxing was continued for 114 hours, only a 6.8% yield of the morpholinopropionitrile was obtained in the form of colorless prisms, from evaporating ethereal solution, m.p. 132–134°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.12; H, 6.74; N, 9.82.

Unsuccessful Mannich Type Reactions.—Experiments using the described low temperature (40°) procedure with dimethylamine and, respectively, α-phenyl-α-cyclohexylacetonitrile, benzyl cyanide, ethyl diphenylacetate and diphenylacetic acid, all proved fruitless. Likewise, an attempt to prepare α,α-diphenyl-β-piperidinopropionitrile by the action of piperidinomethanol on diphenylacetonitrile, according to the method of Zief and Mason,[1] was unsuccessful.

Hydrolysis of α,α-Diphenyl-β-dimethylaminopropionitrile. Hydrochloride (IIA).—Three grams of IIA hydrochloride, m.p. 186–187°, was heated on the steam-bath with 60 cc. of water for five hours. The *p*H of the solution decreased from an initial value of 3.5 to a final value of 2.5. The oil which separated solidified on cooling. Filtration gave 1.83 g. (91% yield), m.p. 67–70°. Recrystallization from Skellysolve B raised the melting point to 72–74°. A mixed melting point with an authentic sample (m.p. 73–75°) showed the product to be diphenylacetonitrile (I).

α,α-Diphenyl-β-dimethylaminopropionic Acid (IIIA).—One hundred and six grams of the nitrile IIA was heated with stirring with 180 cc. of 75% sulfuric acid for two hours at 135–140° and then at 140–145° for two more hours, or until a test sample showed complete alkali-solubility. The hot solution was poured onto ice and made up to a volume of about three liters. Insoluble material was filtered off and discarded. The filtrate was heated nearly to boiling and neutralized by the addition of solid barium hydroxide. The progress of the neutralization was measured by use of Alkacid test paper. When the mixture began to give a green color (*p*H 8) with the test paper, filtered test samples of the mixture were treated with solutions of barium hydroxide and of sulfuric acid in order to attain the exact end-point. The nearly boiling suspension of barium sulfate was then filtered through a filter medium (Filtercel) and the barium sulfate cake was washed well with hot water. The combined washings and filtrate were concentrated *in vacuo* to a small volume (150–200 cc.) and cooled. Filtration of the crystallized material gave 73.3 g. (64% yield) of amino acid IIIA, m.p. 158–160° (dec.). Suspending in 200 cc. of ice-cold dry acetone and filtering gave 72.0 g., m.p. 164–165° (dec.). This product was pure enough for further use. For analysis it was recrystallized from isopropyl alcohol, white powder, m.p. 166° (dec.).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.07; H, 7.15; N, 5.37.

α,α-Diphenyl-β-dimethylaminopropionamide V (R = H).—When the above hydrolysis in 75% sulfuric acid was carried out for three hours at steam-bath temperature instead of at 140°, 75% of the starting material was recovered, together with a small amount of the amide V (R = H). This amide was separated from the nitrile II by washing with warm pentane and recrystallizing from aqueous ethanol, m.p. 156–157°. For nitrogen analysis see Table I.

α,α-Diphenyl-β-diethylaminopropionic Acid (IIIB).—α,α-Diphenyl-β-diethylaminopropionitrile (IIB) was subjected to the same hydrolytic conditions as were used for the preparation of the acid IIIA. Instead of precipitating the sulfate with barium hydroxide, the sulfuric acid was neutralized with sodium bicarbonate and the resulting solution was concentrated *in vacuo* to a small volume. The product sepa-

rated in poor yield and was purified by recrystallization, first, several times from acetone–ether, and finally from acetone alone, m.p. 121–122° (dec.).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.50; H, 7.53; N, 4.81.

α,α-Diphenyl-β-piperidinopropionic Acid (IIIC).—This product was prepared in poor yield, in the same way as the above diethylamino compound, from the corresponding piperidinonitrile (IID). It crystallized from dry acetone, m.p. 137–138° (dec.).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 78.16; H, 7.66; N, 4.52.

Reactions Leading to the Cleavage of α,α-Diphenyl-β-dimethylaminopropionic Acid (IIIA). A. Pyrolysis. Formation of 1,1-Diphenylethylene (VII).—Ten grams of the amino acid IIIA was placed in a vacuum distillation apparatus and heated in an oil-bath held at 210–215° under a 10 mm. vacuum. There was obtained as the distillate 5.25 g. (77% yield) of a colorless oil, b.p. 130–135° (9 mm.). Two more distillations gave a b.p. 138° (10 mm.), $n^{26}D$ 1.6057.

Anal. Calcd. for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.43; H, 6.74.

The identity of this product as 1,1-diphenylethylene was further established by conversion to the dibromide, m.p. 56–58°, which on heating evolved hydrogen bromide to give 1,1-diphenyl-2-bromoethylene.[8] Also, the maleic anhydride addition product was prepared, m.p. 276–278° (lit.[9] m.p. 279–281°).

B. Acetic Anhydride. Formation of Diphenylacetic Acid (VI).—A mixture of 5.4 g. of the amino acid IIIA and 20 cc. of acetic anhydride was heated on the steam-bath for four hours. The orange solution was poured into cold water and after excess acetic anhydride had decomposed, the solid product was filtered. Purification through the sodium salt gave 3.57 g. (84% yield) of diphenylacetic acid, m.p. 146–147° after recrystallization from dilute ethanol; mixed with an authentic sample of diphenylacetic acid, mixed m.p. 147–148°.

Preparation of α,α-Diphenyl-β-dimethylaminopropionamides (V) from the Amino Acid IIIA.—The general method used in the preparation of all the amides is illustrated by the following procedure employed in the synthesis of the simple amide V (R = H). The results obtained for the other amides are summarized in Table I.

A suspension of 5.4 g. (0.02 mole) of finely ground amino acid IIIA in 150 cc. of dry ether was stirred in an ice-bath with 6.8 g. of phosphorus pentachloride for three hours. The solvent was decanted from the insoluble product which was then washed by decantation with 250 cc. of cold dry ether in three portions. To the cold suspension of acid chloride hydrochloride was added slowly with stirring 150 cc. of a cold saturated solution of ammonia in dry ether, maintaining a temperature below 10°. Then ammonia gas was passed through the mixture until it was saturated, keeping the temperature below 15°. After several hours of stirring in an ice-bath, the mixture was allowed to stand overnight at room temperature.

The reaction mixture was poured into cold water and the ether layer was separated. The ether layer containing some undissolved product was washed and the ether removed. The residual solid was washed with a little cold dry ether and filtered; yield 3.75 g. (69% based on amino acid), m.p. 153–155°. Recrystallization from ethanol–water gave m.p. 156–157°. When mixed with a sample of the amide obtained by partial hydrolysis of the nitrile IIA it gave no depression of melting point.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51. Found: C, 76.35; H, 7.42.

Preparation of α,α-Diphenyl-β-dimethylaminopropionic Esters (IV).—Three methods were used for the preparation of these esters. Examples of each are given below. Results are summarized in Table I.

Method A. Direct Esterification. Preparation of the Ethyl Ester IV (R = C_2H_5).—A solution of 2.70 g. (0.01 mole) of the amino acid IIIA in 50 cc. of absolute ethanol was treated with 5.5 cc. of concentrated sulfuric acid. The solution was distilled slowly, replacing the lost alcohol with more dry ethanol. After four hours when about 250 cc. of alcohol had distilled, the alcohol coming over appeared to be anhydrous as tested by miscibility with kerosene. The solution was concentrated to about 25 cc. and poured into cold water. The clear aqueous solution was made alkaline with 20% sodium hydroxide and the separated oil was taken up in ether, washed and dried with anhydrous magnesium sulfate. Treatment of the dry solution with ethereal hydrogen chloride gave 1.45 g. (43% yield) of ethyl ester hydrochloride IV (R = C_2H_5), m.p. 173–176°. Recrystallization from acetone and then from ethanol–ether gave small prisms, m.p. 175–176° (dec.). For analyses, see Table I.

Method B. Esterification through the Acid Chloride. Preparation of the Methyl Ester IV (R = CH_3).—The acid chloride hydrochloride of the amino acid IIIA was prepared in exactly the same way as indicated above for the preparation of the amides. This acid chloride was treated with excess methanol and allowed to stand at room temperature overnight. The product was isolated in the same way as indicated under method A. The ester hydrochloride was obtained in the form of large prisms from methanol–ether; m.p. 178–179° (dec.), yield 66%. A sample mixed with the corresponding ethyl ester hydrochloride, m.p. 175–176°, gave a 10% depression of melting point. Likewise the isopropyl ester hydrochloride, m.p. 175–176°, gave similar melting point depressions when mixed separately with samples of the methyl and ethyl esters. For analyses, see Table I.

Method C. Esterification through the Potassium Salt. Preparation of the Diethylaminoethyl Ester IV (R = $(C_2H_5)_2NCH_2CH_2$-).—A solution of 5.4 g. (0.02 mole) of the amino acid IIIA in 100 cc. of methanol was neutralized with methanolic potassium hydroxide using phenolphthalein as an indicator. The filtered solution was then concentrated to dryness and the residue was dried in a vacuum desiccator overnight. The solid potassium salt was dissolved in 50 cc. of dry benzene and refluxed with 3 g. of freshly distilled diethylaminoethyl chloride for 20 hours. The benzene was then distilled and the residue was taken up in ether, washed with water and extracted with excess dilute hydrochloric acid. The acid extract was made alkaline with 20% sodium hydroxide. The separated oil was taken up in ether, washed and dried over anhydrous magnesium sulfate. Distillation of the ether gave 6.17 g. of a colorless oil which was dissolved in a small amount of dry ethanol and treated with excess ethereal hydrogen chloride. Addition of more dry ether precipitated 6.9 g. (78% yield) of the ester dihydrochloride, m.p. 200–201° (dec.). For analysis, a sample was crystallized from dry ethanol to give small colorless prisms with no change in melting point. See Table I for analytical results.

Structure Proof. Methylation of Methyl α,α-Diphenyl-β-aminopropionate.—The free methyl α,α-diphenyl-β-aminopropionate prepared from 1.45 g. (0.005 mole) of the hydrochloride[6] was refluxed for two hours with a mixture of 5 cc. of 90% formic acid and 0.33 g. (0.11 mole) of paraformaldehyde. The excess formic acid was removed *in vacuo* and the residue was treated with excess dilute hydrochloric acid. The aqueous solution was extracted with ether, which was discarded, and was made alkaline with 20% sodium hydroxide. The oil which separated was taken up in ether, washed and dried. The filtered ethereal solution was treated with an excess of an ether solution of hydrogen chloride. The hydrochloride which separated weighed 0.98 g., and melted at 169–172°. Recrystallization from acetone raised the melting point to 177–178° (dec.). Mixed with a sample of IV (R = CH_3) obtained from the amino acid IIIA, it gave no depression of melting point.

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