as it was formed by a water trap. Most of the toluene was then removed by distillation and the residue fractionated under reduced pressure; yield of anil, 97.5 g., 62%, b.p. 124–126° (5 mm.), $n^{25}D$ 1.5481.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.42; H, 9.09. Found: C, 83.34; H, 9.57.

N-Cyclohexylidene-*o*-toluidine.—In 200 g. of toluene, 89 g. of cyclohexanone, 107 g. of *o*-toluidine and 1 g. of anhydrous, powdered $ZnCl_2$ were allowed to react as above. Yield of the anil was 151.5 g., 81%, b.p. 124–126° (5 mm.) d^{25}_{25} 0.9829, $n^{25}D$ 1.5479.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.42; H, 9.09. Found: C, 83.02; H, 9.44.

N-Cyclohexylideneaniline.[9]—This compound was prepared as above in 51% yield.

Dehydrocyclization of N-2-Methylcyclohexylideneaniline to Acridine.—The catalyst used in all of the dehydrogenations was chromium–copper-on-charcoal catalyst no. 2 reported by Hansch, *et al.*[2] In each run 10 ml. of fresh catalyst was reduced as previously described.[2] In a typical run, 35 g. of the anil was processed at a space velocity of 538 at a temperature of 550°. A total of 11.5 liters of gas was evolved, 92% of which was hydrogen, 2% olefins and 6% saturated hydrocarbons. To the condensate was added 40 ml. of 6 *N* HCl and 15 ml. of acetone and this mixture cooled in the ice-box overnight. The acridine hydrochloride which crystallized out was filtered, washed thoroughly with ether and dried; yield, 11.7 g., 29%. The acridine obtained by treating the hydrochloride with dil. NaOH melted at approx. 108°, and at 109–110°[10] after recrystallization from ligroin. This product showed no melting point depression with an authentic sample of acridine. The picrate melted at the same point as that made from acridine.

Dehydrocyclization of N-Cyclohexylidene-*o*-toluidine to Acridine.—This molecule was dehydrogenated and the product worked up by the same procedure as that described above. Thirty-five grams of the anil gave 6.1 g. of acridine hydrochloride, 15.2%. In this reaction 10.3 liters of gas was evolved which consisted of 78% hydrogen, 5% olefins and 17% saturated hydrocarbons. Thus in this reaction, as indicated by the gaseous hydrocarbons, side reactions occurred to a much greater extent than in the dehydrogenation of N-2-methylcyclohexylideneaniline to acridine. In neither case did runs at 575° or 525° give higher yields of acridines. At the higher temperatures more decomposition occurred which poisoned the catalyst faster. No doubt higher yields could be obtained by using larger amounts of catalyst.

Dehydrocyclization of N-Cyclohexylideneaniline to Carbazole.—Over 10 ml. of catalyst was processed 31.5 g of anil at space velocity 408 and temperature of 575°. The liquid condensate was crystallized from ligroin, giving 3 g. of carbazole m.p. 243–245°,[6] 10% yield. The product gave a picrate m.p. 186–187° dec.[6] Runs at 550° and 600° gave slightly lower yields.

Acknowledgment.—This research was supported by the Office of Naval Research under contract NR-055-149. The carbon–hydrogen analyses reported were made by C. F. Geiger of Chaffey College, Ontario, California.

CLAREMONT, CALIFORNIA

(9) G. Reddelien and O. Meyn, *Ber.*, **53**, 345 (1920).

(10) O. Fischer and G. Korner, *ibid.*, **17**, 102 (1884).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Syntheses and Reactions of Acyclic N,N-Diacylglycines

BY JOHN C. SHEEHAN AND ELIAS J. COREY[1]

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Three acyclic N,N-diacylglycines have been prepared which represent possible intermediates in the synthesis of penicillin-like compounds. The acids were obtained in each case by hydrogenolysis of the corresponding benzyl esters. Synthesis of the benzyl esters was accomplished by three different routes: (1) acylation of an N-monoacylglycine benzyl ester, (2) alkylation of a diamide with a benzyl haloacetate and (3) formation and rearrangement of an O-acylisoamide. In sharp contrast to cyclic N,N-diacylamino acid chlorides, the acyclic N,N-diacylglycyl chlorides were found to be sufficiently stable to permit easy isolation in pure form *only* when the acyl groups were *aroyl*.

Recently a new method has been reported[2] for the preparation of fused β-lactam-thiazolidines involving interaction of protected amino acid chloride derivatives (such as succinylglycyl chloride) and thiazolines. Extension of the reaction to acyclic N,N-diacylglycyl chlorides and subsequent selective hydrolysis of one acyl group would lead to β-lactam-thiazolidines possessing the 6-acylamino substituent characteristic of the natural penicillins. A selective hydrolysis appears feasible since diamides are hydrolyzed rapidly to amides under mild conditions in the presence of base.[3] We are now reporting the preparation[4] of three acyclic diacylglycines and studies on the synthesis of the corresponding acid chlorides, N,N-diacetylglycyl chloride, N-acetylphenaceturyl chloride and N,N-dibenzoylglycyl chloride.

Catalytic esterification of aceturic acid with benzyl alcohol afforded, in 91% yield, benzyl aceturate (I), which when treated with acetic anhydride under conditions similar to those employed by Wiley and Borum[4] resulted in a 91% yield of N,N-diacetylglycine benzyl ester (II). The infrared spectrum of II (Fig. 1, curve A) contains bands at 5.70 and 5.85 μ due to the ester and diamide carbonyl groups, respectively, and no N–H stretching bands.[5] N,N-diacetylglycine (III) was obtained in 97% crude yield by catalytic hydrogenolysis of II. The acid, which was isolated as a colorless glass, could not be induced to crystallize, and it decomposed upon storage at room temperature. Exposure of III to laboratory air is sufficient to cause hydrolysis to aceturic acid. Attempts to convert III to the corresponding acid chloride led to unstable, non-crystalline products, the infrared spectra of which indicated the absence of the acid chloride function.

(1) Bristol Laboratories Fellow, 1948–1950.

(2) J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950).

(3) For example, diacetamide is almost completely hydrolyzed in one minute to acetamide by treatment with 0.1 *N* sodium hydroxide at 15° [A. W. Titherley and L. Stubbs, *J. Chem. Soc.*, **105**, 299 (1914)].

(4) At the time this work was initiated, no acyclic diacylamino acids or the corresponding acid chlorides were known. Recently two N,N-diacylamino acid esters have been described [R. H. Wiley, O. H. Borum and L. L. Bennett, THIS JOURNAL, **71**, 2899 (1949); R. H. Wiley and O. H. Borum, *ibid.*, **72**, 1626 (1950)].

(5) The shift in wave length of absorption of diamide carbonyl groups from the value usually found for acyclic amides (6.0 μ) is quite general, J. C. Sheehan and E. J. Corey, *ibid.*, **74**, 360 (1952).

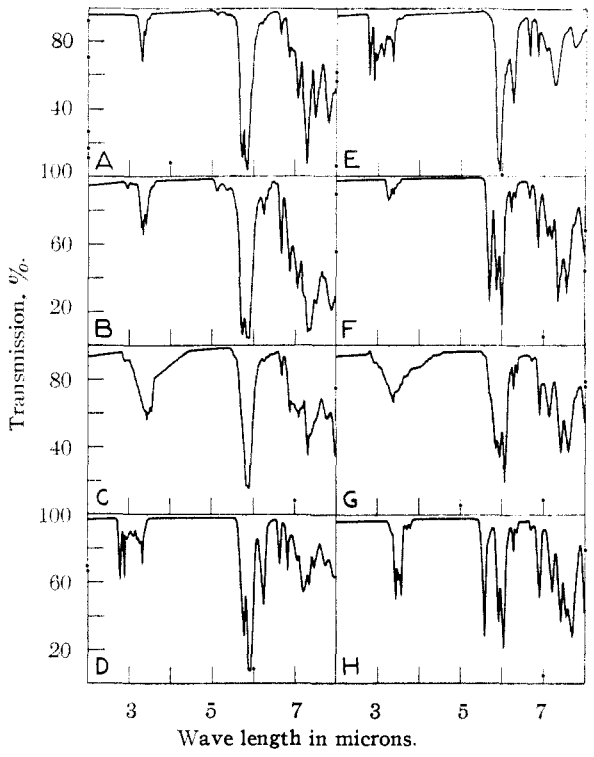


Fig. 1.—Infrared spectra: curve A, N,N-diacetylglycine benzyl ester (II), 5% in $CHCl_3$; B, benzyl N-acetylphenaceturate (VII) 5% in CCl_4; C, N-acetylphenaceturic acid (VIII), 5% in $Cl_2CHCHCl_2$; D, benzyl α-phenylsuccinamate (XI), 5% in $Cl_2CHCHCl_2$; E, phenylacetamide, 5% in $Cl_2CHCHCl_2$; F, N,N-dibenzoylglycine benzyl ester (XIII), 5% in CCl_4; G, N,N-dibenzoylglycine (XVI), 3.5% in $CHCl_3$; H, N,N-dibenzoylglycyl chloride (XVII), 5% in CCl_4.

The preparation of benzyl N-acetylphenaceturate was readily accomplished by the route used for the synthesis of the corresponding diacetyl compound II. Benzyl phenaceturate (IV) was prepared by three different procedures. The most practical route (88% yield) involved direct catalytic esterification of phenaceturic acid with benzyl alcohol. In an alternative procedure phenaceturic acid was converted to 2-benzyl-5-oxazolone hydrobromide by treatment with phosphorus tribromide, and the oxazolone hydrobromide was converted into benzyl phenaceturate by the action of benzyl alcohol–pyridine. The over-all yield by this route was 38%. A third synthesis involved phenylacetylation of glycine benzyl ester (V) in 92.5% yield. The hydrochloride of V was prepared in 32% yield by hydrazinolysis of phthaloylglycine benzyl ester (VI), which in turn was obtained from phthaloylglycyl chloride and benzyl alcohol in 88% yield. The preparation of glycine benzyl ester by hydrazinolysis of the phthaloyl derivative appears to represent the most practical route to this compound yet reported.

Treatment of benzyl phenaceturate with acetic anhydride afforded a 68% yield of N-acetylphenaceturic acid benzyl ester (VII). The acetylation of benzyl phenaceturate proceeded more slowly than that of benzyl aceturate. The infrared spectrum of VII (Fig. 1, curve B) was consistent with the assigned structure. Hydrogenolysis of VII yielded 97.5% of the theoretical N-acetylphenaceturic acid (VIII) as a colorless glass which, upon heating under reduced pressure to 70°, underwent decomposition to a sublimate of phenylacetic acid and a dark complex residue. An attempt to convert VIII to the acid chloride led to the formation of an unstable oil along with some phenylacetyl chloride. Little or none of the desired acid chloride was present in the crude product as judged by infrared spectrum.

The method used for the preparation of the N,N-diacylglycine derivatives II and VII could not be applied satisfactorily to the preparation of N,N-diphenylacetylglycine benzyl ester (IX). Several attempts to prepare IX from benzyl phenaceturate (IV) did not yield any isolable phenylacetylation product. Heating of IV with phenylacetic anhydride or phenylacetyl chloride alone and in the presence of bases resulted in extensive decomposition, although some starting material usually was recovered.

A second route to N,N-diphenylacetylglycine benzyl ester was investigated. N-Alkylation of α,α′-diphenyldiacetamide (X) with a benzyl haloacetate would yield the desired benzyl ester (IX). The diamide X was prepared in 70% yield from phenylacetonitrile and phenylacetic acid.[6] The reaction is reversible[7] and provides a good yield of X only when the equilibrium is disturbed by removal of the product at intervals. Treatment of X with sodium hydride in dioxane results in the formation of a soluble sodium salt which decomposes gradually on heating. Reaction of the sodium salt in dioxane with benzyl iodoacetate produced, after extensive chromatography, a low yield (3.6%) of the desired alkylation product IX along with a small amount (2%) of a product which proved to be benzyl α-phenylsuccinamate (XI). The structure of IX was proved by its facile hydrolysis to benzyl phenaceturate. The infrared spectrum of IX exhibits the same bands in the double bond region as do the analogous diamides, II and VII.

The by-product is isomeric with, but different from, benzyl phenaceturate, and the infrared spectrum strongly supports the assignment of structure XI. The spectrum, (Fig. 1, curve D) taken in tetrachloroethane solution, exhibits two sharp bands at 2.80 and 2.91 μ attributable to N–H stretching vibrations, a band at 5.77 μ due to the ester carbonyl, a band at 5.90 μ assignable to the primary amide carbonyl and a strong band at 6.27 μ due to the superposition of the weaker phenyl band with the more intense H–N–H bending band. The spectrum of the closely related phenylacetamide (Fig. 1, curve E) in solution shows identical bands at 2.80, 2.91, 5.92 and 6.27 μ due to the primary amide function. Basic hydrolysis of XI yielded phenylsuccinic acid.

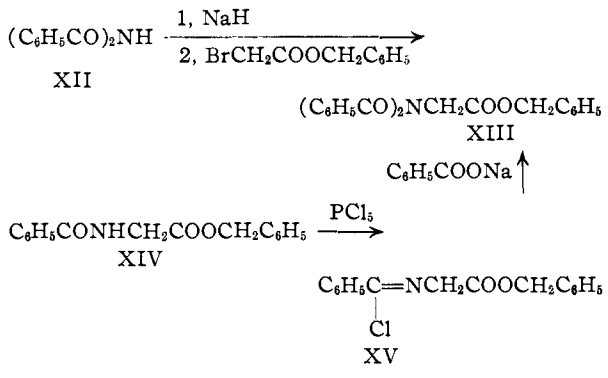
Attempted reaction of the sodium salt of α,α′-diphenyldiacetamide with benzyl chloroacetate, benzyl iodoacetate or potassium chloroacetate in toluene or methyl ethyl ketone yielded no isolable IX.

(6) C. Colbe and F. Dodge, *Am. Chem. J.*, **13**, 1 (1891).

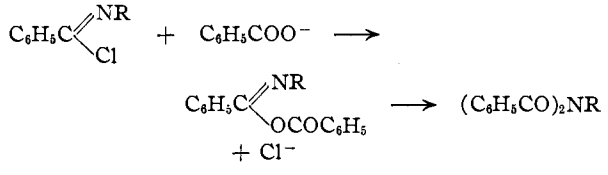
(7) R. H. Wiley and W. B. Guerrant, THIS JOURNAL, **71**, 981 (1949).

Treatment of dibenzamide (XII) with sodium hydride in ether resulted in formation of an insoluble sodium salt (soluble in dioxane). Removal of the ether and alkylation of the sodium salt with benzyl bromoacetate in methyl ethyl ketone produced N,N-dibenzoylglycine benzyl ester (XIII) in 40% yield.

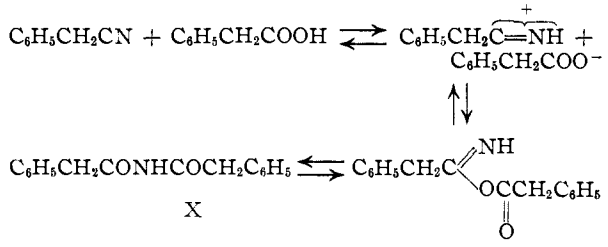
A more convenient route to XIII proved to be through benzyl hippurate (XIV) which was made from hippuric acid in 87% yield by the catalytic esterification process used in the preparation of benzyl aceturate. Treatment of benzyl hippurate with phosphorus pentachloride furnished the imido chloride (XV) which, when treated with dry sodium benzoate in dioxane, produced XIII in 70% over-all yield. This unusual reaction is patterned after one used by Mumm for the preparation of N-methyldibenzamide.[8]



The reaction probably involves production and rearrangement of an intermediate O-acylisoamide. The reversible formation of diamides



such as X from carboxylic acids and nitriles may well proceed by a similar O to N migration of an acyl group.



Upon hydrogenolysis of the benzyl ester XIII, N,N-dibenzoylglycine (XVI) was obtained as a crystalline solid in 94% yield. The acid is stable; a sample showed no signs of decomposition after storage at room temperature for one year. Treatment of XVI with phosphorus pentachloride provided the desired N,N-dibenzoylglycyl chloride (XVII) as a moderately stable oil which could be stored at 0° for several days without appreciable decomposition. The infrared spectrum of XVII (Fig. 1, curve H) is in complete agreement with that expected for the assigned structure. Reaction of XVII with benzyl alcohol–pyridine led to the starting benzyl ester XIV. Attempts to prepare a β-lactam from XVII by reaction with 2-phenyl-2-thiazoline yielded no crystalline products.

(8) O. Mumm, H. Hesse and H. Volquartz, *Ber.*, **48**, 388 (1915).

Experimental[9]

Benzyl Aceturate (I).—A mixture of 25.0 g. (0.214 mole) of aceturic acid,[10] 35.0 g. (0.325 mole) of benzyl alcohol, 0.5 ml. of concentrated sulfuric acid and 400 ml. of toluene in a flask surmounted by a soxhlet extraction apparatus containing *ca.* 200 g. of anhydrous barium oxide was heated to vigorous reflux for 16 hours. The barium oxide was then replaced by 200 g. of fresh oxide and the mixture was heated to reflux for an additional 32 hours. At the end of this time the solution was filtered, and concentrated under reduced pressure to a light yellow oil. Upon distillation of the crude liquid there was obtained 40.3 g. (91.0%) of IV, b.p. 175–180° (1–1.2 mm.), $n^{25}D$ 1.5250. After standing overnight at 4° the liquid crystallized to a colorless solid of m.p. 46.0–47.5°. Trituration of a small amount of this solid with petroleum ether followed by evaporative distillation at 130–140° (0.15 mm.) yielded a colorless oil which crystallized, m.p. 50.8–51.6°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.50; N, 6.86.

N,N-Diacetylglycine Benzyl Ester (II).—A solution of 35.0 g. (0.169 mole) of benzyl aceturate (I) in 200 ml. of acetic anhydride was heated under reflux for five hours. The acetic anhydride was removed under reduced pressure and the residual oil was evaporatively distilled at 140° (10 μ). The distillate, $n^{25}D$ 1.5200, crystallized completely on storage; m.p. 49–50° (38.2 g., 91%). Recrystallization from ether–ligroin afforded 33.0 g. of colorless needles, m.p. 50.6–51.2°. A second recrystallization from the same solvent did not affect the m.p.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.94; H, 6.37; N, 5.57.

N,N-Diacetylglycine (III).—A mixture of 1.00 g. (0.00402 mole) of II and 0.100 g. of palladium-on-Darco catalyst[11] in 5 ml. of dry dioxane was treated with dry hydrogen. Reduction was complete in three hours, the absorption of hydrogen being 97% of the theoretical. Removal of the catalyst by filtration (Super-Cel) and lyophilization of the filtrate yielded 0.620 g. (97.2% crude yield) of a colorless, viscous oil which could not be induced to crystallize. After storage at room temperature in a sealed container for several days, the oil became dark brown in color and the odor of acetic acid could be detected readily.

Anal. Calcd. for $C_6H_9NO_4$: C, 45.28; H, 5.70. Found: C, 46.38; H, 6.06.

Upon exposure of the oil to moist laboratory air a solid product formed rapidly which melted at 204 to 206° alone or mixed with aceturic acid.

Attempts to convert N,N-diacetylglycine to the corresponding acid chloride using phosphorus pentachloride, purified thionyl chloride, acetyl chloride, phosgene or oxalyl chloride (on the sodium salt) were unsuccessful.

Phthaloylglycine Benzyl Ester (VI).—A solution of 22.5 g. (0.10 mole) of phthaloylglycyl chloride[12] in 40 ml. of ethylene dichloride was added over a period of five minutes to a cold (5°) solution of 10.9 g. (0.10 mole) of benzyl alcohol and 8.0 g. (0.10 mole) of dry pyridine in 30 ml. of ethylene dichloride. The mixture was allowed to stand at room temperature for one hour and then washed with three 20-ml. portions of water, 20 ml. of 4 *N* hydrochloric acid and finally with 20 ml. of 5% potassium carbonate solution. The ethylene dichloride solution was dried by filtration and evaporated under reduced pressure to an almost colorless

(9) All melting points are corrected. Infrared spectra were measured with a Baird Infrared Recording Spectrophotometer, Model B. The cell thickness used with solutions was 0.10 mm. We are indebted to Dr. S. M. Nagy and associates for the microanalyses and infrared spectra.

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., second edition, 1943, p. 11.

(11) M. Newman, THIS JOURNAL, **65**, 1097 (1943).

(12) J. C. Sheehan and V. S. Frank, *ibid.*, **71**, 1856 (1949).

solid, m.p. 101.7–102.7°, 26.0 g. (88%). Recrystallization from ethanol–water yielded 24.2 g. of pure ester, m.p. 102.8–103.1°

Anal. Calcd. for $C_{17}H_{18}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.90; H, 4.60; N, 4.83.

Glycine Benzyl Ester Hydrochloride.—To a solution of 6.0 g. (0.0203 mole) of VI in 30 ml. of commercial absolute ethanol and 3 ml. of glacial acetic acid heated to reflux was added over a period of 45 minutes 20 ml. of *M* hydrazine hydrate in absolute ethanol. The mixture was heated under reflux for an additional 15 minutes and then concentrated to dryness under reduced pressure at a bath temperature of 50°. The residual solid was treated with 20 ml. of water and the insoluble phthalhydrazide was removed by filtration and washed with warm water. The combined filtrate and washings were cooled to 5°, treated with 7 g. of potassium carbonate and extracted with five 20-ml. portions of cold ether. The ethereal solution after drying (potassium carbonate) and treatment with dry hydrogen chloride furnished 1.30 g. (32.3%) of glycine benzyl ester hydrochloride m.p. 135.0–136.0° (reported 139–140°)[13] as colorless needles.

Benzyl Phenaceturate (IV). A.—The procedure followed was the same as that described for the preparation of benzyl aceturate (I). From 50.0 g. (0.259 mole) of phenaceturic acid, 100 g. (0.925 mole) of benzyl alcohol and 1 ml. of concentrated sulfuric acid in 600 ml. of toluene there was obtained, after a 16-hour heating period and evaporation of the solvent, a light yellow oil consisting of crude product and benzyl alcohol. The liquid was caused to solidify by trituration with five 500-ml, portions of lukewarm water and 500 ml. of ice-cold water. The resulting oily solid was triturated with 500 ml. of water–methanol (4:1) to remove most of the remaining benzyl alcohol and collected by filtration. The crisp solid was washed with water–methanol, dried, and recrystallized from benzene–ligroin to yield 65.0 g. (89.8%) of colorless needles, m.p. 94.2–94.6°. Recrystallization of a small amount of this product from chloroform–ligroin provided analytically pure benzyl phenaceturate, m.p. 94.5–95.0°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.82; H, 6.15; N, 5.00.

B.—To an ether suspension of 2-benzyl-5-oxazolone hydrobromide[14] prepared from 5.50 g. (0.0285 mole) of phenaceturic acid and 7.1 g. (0.026 mole) of phosphorus tribromide was added 2.25 ml. (0.026 mole) of dry pyridine. The resulting mixture was shaken for a few minutes and then filtered. The insoluble solid was washed with ether and the filtrate plus washings treated with 3.0 ml. (0.025 mole) of benzyl alcohol. After standing for 1.5 hours, the solution was evaporated to a light yellow oil which crystallized to an oily solid upon storage in a refrigerator. Two recrystallizations of the crude product from chloroform–ligroin (Norit) yielded 3.0 g. (38%) of VII, m.p. 94.5–95°.

C.—To a solution of 2.01 g. (0.01 mole) of glycine benzyl ester hydrochloride and 2 ml. (1.96 g., 0.0248 mole) of dry pyridine in 25 ml. of dry methylene chloride was added 1.5 ml. (1.75 g., 0.0114 mole) of phenacetyl chloride (Eastman Kodak Co.). After 15 minutes at room temperature, the methylene chloride solution was washed with 20-ml. portions of water, 2 *N* hydrochloric acid and 5% sodium carbonate solution and dried by filtration. Evaporation of the methylene chloride under reduced pressure led to an almost colorless solid. Recrystallization of the crude product from benzene–ligroin (Norit) gave 2.62 g. (92.5%) of benzyl phenaceturate, m.p. 94–94.6°.

N-Acetylphenaceturic Acid Benzyl Ester (VII).—A solution of 2.83 g. (0.01 mole) of benzyl phenaceturate in 15 ml. of acetic anhydride was heated under reflux for 15 hours. The acetic anhydride was evaporated under reduced pressure and the colorless residue was triturated with cold, dry ether–petroleum ether solution (1:3). The solid mass which resulted was recrystallized from ether–petroleum ether, giving 1.50 g. of colorless needles, m.p. 61–62°. A second crop of product, m.p. 61–62°, was obtained by evaporation of the filtrate under reduced pressure and recrystallization of the semi-solid residue from ether–petroleum ether (Norit). The total yield of VII was 2.40 g. (68%). Two recrystallizations of 0.80 g. of this material yielded 0.43 g. of pure VII, m.p. 63.8–64.2°.

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.40; H, 5.88; N, 4.28.

N-Acetylphenaceturic Acid (VIII).—A mixture of 0.340 g. (0.001047 mole) of VII and 0.045 g. of palladium-on-Darco catalyst in 3.0 ml. of pure dioxane was treated with dry hydrogen at atmospheric pressure. After three hours the absorption of hydrogen had ceased and corresponded to 99% of the theoretical. The catalyst was removed by filtration (Super-Cel) and the filtrate was lyophilized. The residue, which was obtained as a colorless glass, weighed 0.240 g. (97.5%).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.45; H, 5.63; N, 6.05.

Upon heating a small portion of this acid at 70° and 2.5 mm. a colorless solid slowly collected on the walls of the tube, m.p. 75–76°, undepressed upon admixture with phenylacetic acid.

An 0.140-g. sample of VIII in 4 ml. of pure dioxane was treated with 0.124 g. of phosphorus pentachloride at 10°. The phosphorus pentachloride slowly reacted and a clear, colorless solution was formed. The dioxane and phosphorus oxychloride were removed by lyophilization, leaving a slightly yellow, oily residue. The strong, characteristic odor of phenylacetyl chloride was detected in the Dry Ice-trap. The infrared spectrum of the oil did not exhibit the band at 5.55 μ which is characteristic of acid chlorides.

Alkylation of α,α'-Diphenyldiacetamide (X).[6]—A mixture of 5.28 g. (0.0208 mole) of X and 0.500 g. (0.0208 mole) of finely powdered sodium hydride in 100 ml. of purified dioxane was stirred in an atmosphere of nitrogen for 15 minutes. To the resulting clear solution was added 5.70 g. (0.0206 mole) of benzyl iodoacetate, which had been freshly prepared from benzyl chloroacetate and sodium iodide in dry acetone, dissolved in 40 ml. of dioxane. The reaction mixture was stirred at room temperature for 14 hours and finally for four hours at 70–80°. The mixture was allowed to cool to room temperature, and the insoluble inorganic salt was collected by filtration. The filtrate was evaporated under reduced pressure to a straw-colored sirup, which was triturated with petroleum ether and treated with 30 ml. of hot carbon tetrachloride. After one day the cooled mixture was filtered, yielding a residue of 1.0 g., m.p. 185–190° alone or admixed with X. The filtrate was chromatographed using a 25 × 1 cm. column of activated alumina (alcoa, 48–100 mesh). Evaporation of the fractions individually, furnished straw-colored sirups which were triturated with petroleum ether and stored at room temperature. After 13 days several of the fractions had partially crystallized and the solid material was freed of oil in each case by trituration with carbon tetrachloride. The solid products, m.p. 104–108°, were combined and amounted to 0.302 g. (3.6%). One recrystallization from carbon tetrachloride–ether–petroleum ether (after treatment of the solution with a mixture of Norit and activated alumina) provided fine, colorless needles of N,N-diphenylacetylglycine benzyl ester(IX), m.p. 107.8–108.4°. Another recrystallization from the same solvent did not raise the m.p.

Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.60; H, 5.95; N, 3.79.

A small portion of this product (*ca.* 30 mg.) was dissolved in acetone and the solution was treated with 1.5 ml. of 0.1 *N* sodium hydroxide. After 5 minutes the solution was diluted with water and extracted with methylene chloride. The methylene chloride extract was evaporated to a faintly yellow solid which, upon recrystallization from ligroin, had a m.p. of 93–94°, undepressed upon admixture with benzyl phenaceturate.

Further washing of the column of alumina afforded a small amount (0.072 g.) of a product, m.p. and mixed m.p. with phenylacetamide 158–159° after recrystallization from chloroform–carbon tetrachloride.

The carbon tetrachloride soluble oils were combined and, after removal of the carbon tetrachloride, were dissolved in benzene–petroleum ether (4:1) and passed through a 25 × 1 cm. column of activated alumina. The column was eluted with 25-ml. portions of benzene (fraction 1), benzene–carbon tetrachloride (fraction 2), carbon tetrachloride (fraction 3), ether (fraction 4), dioxane–carbon tetrachloride (2:1), (fraction 5), dioxane (fraction 6) and dioxane (fraction 7). From fractions 5, 6 and 7 there was obtained after concen-

(13) C. R. Harington and T. H. Mead, *Biochem. J.*, **30**, 1609 (1936).

(14) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, chapter XXI, p. 781.

tration, trituration with petroleum ether and recrystallization from methylene chloride–carbon tetrachloride 0.118 g. of XI as a colorless solid, m.p. 98–100.5°. Further recrystallization from carbon tetrachloride yielded analytically pure material, m.p. 99.5–101°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.14; N, 5.20.

A small portion of this product (0.035 g.) was treated with boiling 10% sodium hydroxide solution for 15 minutes. The odors of both benzyl alcohol and ammonia were detected. The basic solution was cooled, acidified with 12 *N* hydrochloric acid and extracted with ether. The ether solution was evaporated and the residual solid was recrystallized from ether–benzene to yield *ca.* 0.012 g. of phenylsuccinic acid, m.p. 166–167°.

Benzyl Hippurate (XIV).—This preparation was carried out essentially by the procedure described for benzyl phenaceturate. From 90.0 g. (0.50 mole) of hippuric acid 81.0 g. (78 ml., 0.75 mole) of benzyl alcohol in 300 ml. of toluene and 1 ml. of concentrated sulfuric acid after heating under reflux for ten hours there was obtained as colorless needles 117 g. (87%) of pure product, m.p. 87.0–89.0° (reported 91–92°).[15]

N,N-Dibenzoylglycine Benzyl Ester (XIII). A.—To a suspension of 0.300 g. (0.0125 mole) of finely powdered sodium hydride in 25 ml. of dry ether was added 2.25 g. (0.010 mole) of dibenzamide.[16] A vigorous reaction took place immediately, subsiding after about 15 seconds. The resulting mixture was stirred for one hour to ensure complete formation of the sodium salt and then the ether was evaporated and replaced by 25 ml. of dry methyl ethyl ketone. A solution of 4.0 g. (0.176 mole) of benzyl bromoacetate in 20 ml. of methyl ethyl ketone was added together with 1.5 g. (0.01 mole) of dry sodium iodide. The reaction mixture was heated at reflux for 22 hours. To the cooled mixture was added 100 ml. of ether, and the insoluble inorganic salts were removed by filtration. The filtrate was concentrated under reduced pressure to a yellow sirup which solidified after trituration with three 40-ml. portions of ether–petroleum ether. The crude, oily solid weighed 2.60 g. (fraction 1). The ether–petroleum ether solution upon standing yielded 0.20 g. of an almost colorless solid (fraction 2), m.p. 111–113°. Fraction 1 was triturated with 20 ml. of ether and the insoluble solid (1.60 g.) was recrystallized from methylene chloride–methylcyclohexane to yield 1.20 g. of pale yellow prisms, m.p. 105.5–113° (fraction 3). The ether solution was evaporated to a semi-solid residue which, after trituration with petroleum ether and recrystallization from methylene chloride–methylcyclohexane, furnished 0.30 g. of almost colorless solid, m.p. 107–113° (fraction 4). Fractions 2, 3 and 4 were combined and recrystallized from methylene chloride–methylcyclohexane (Norit). The yield of XIII as colorless prisms, m.p. 114.0–115.3°, was 1.51 g. (40.5%). A small sample was further purified for analysis by evaporative distillation at 145° (5 μ). The material so obtained had a m.p. of 114.5–115.5°.

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.48; H, 5.13; N, 3.75. Found: C, 73.78; H, 5.22; N, 3.77.

The yields of XIII ranged from 11% when the alkylation was carried out in dioxane to 27% when acetone was used as the solvent. The product in both cases was not isolated in pure condition as readily as in the procedure described.

B.—To a solution of 32.4 g. (0.120 mole) of benzyl hippurate dissolved in 50 ml. of dry dioxane was added 200 ml. of anhydrous ether and 25.0 g. (0.120 mole) of phosphorus pentachloride. The mixture was swirled until the phosphorus pentachloride had dissolved (10 minutes) and the resulting clear yellow solution was evaporated under reduced pressure (25 mm., bath temperature not over 50°) to remove the dioxane and phosphorus oxychloride present. To the residual yellow liquid was added 20 ml. of toluene and the toluene, along with the last traces of phosphorus oxychloride, was removed by distillation at 25 mm.

A solution of the imido chloride in 100 ml. of dry dioxane was added to a stirred suspension of 28.0 g. of dry sodium benzoate in 100 ml. of dioxane. The mixture was heated to 65° with stirring for 12 hours and then heated to reflux for an additional four hours. After cooling, the insoluble solid was removed by filtration and washed well with dioxane. Evaporation of the filtrate under reduced pressure afforded a light yellow sirup which soon crystallized. The solid was triturated with 45 ml. of ether and ground to a powder. The mixture was filtered and the powder was washed with four 20-ml. portions of ether–petroleum ether (7:3). The almost colorless product, m.p. 111.6–114.0°, weighed 32.0. The filtrate and washings were concentrated to an oil which yielded 1.70 g. of XIII, m.p. 112–114°, after trituration with petroleum ether and recrystallization of the residue from ether–methylcyclohexane. Recrystallization of the combined crude products from methylene chloride–methylcyclohexane yielded a first crop of XIII weighing 26.8 g., m.p. 114.0–115.0°, and a second crop of 4.50 g., m.p. 113.5–114.5° (70%). An additional amount of less pure XIII was obtained from the filtrate.

Reaction of the imido chloride XV in ether with an aqueous solution of sodium benzoate resulted in a 35% yield of XIII. Reaction in dimethylformamide led to a low yield (28%) of a product which was difficult to purify.

N,N-Dibenzoylglycine (XVI).—A mixture of 10.0 g. (0.0268 mole) of the benzyl ester XIII and 1.00 g. of palladium-on-Darco catalyst in 45 ml. of dry dioxane was shaken with hydrogen at three atmospheres. Consumption of hydrogen was complete after five hours and the absorption was approximately the theoretical. The catalyst was removed by filtration (Super-Cel) and washed with five 5-ml. portions of dioxane. The filtrate and washings were combined and then were concentrated under reduced pressure to a colorless oil which crystallized upon trituration with 20 ml. of dry ether. The solid, m.p. 136–137.2°, was collected by filtration, weight 5.60 g. From the filtrate there was obtained an additional 1.53 g. of solid upon slow evaporation. The total yield of analytically pure product was 7.13 g. (94.5%).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.62; N, 4.95. Found: C, 67.78; H, 4.76; N, 5.02.

N,N-Dibenzoylglycyl Chloride (XVII).—A mixture of 0.100 g. (0.354 millimole) of N,N-dibenzoylglycine and 0.074 g. (0.354 millimole) of phosphorus pentachloride in 2 ml. of dry dioxane was allowed to react at room temperature. After the phosphorus pentachloride had completely dissolved, the dioxane and phosphorus oxychloride were removed by lyophilization and the oily residue was taken up in 2.0 ml. of dry carbon tetrachloride. The spectrum of the acid chloride was determined using a portion of this solution.

To 1.5 ml. of the above solution of XVII at 0° was added a solution of 0.035 g. (0.324 millimole) of benzyl alcohol and 0.025 g. (0.317 millimole) of dry pyridine in 4 ml. of carbon tetrachloride. The resulting mixture was allowed to stand for 12 hours and then filtered to remove the insoluble pyridine hydrochloride. The filtrate was evaporated under reduced pressure to a yellow oil which solidified upon trituration with methylcyclohexane–ether (2:1) and seeding. The residue was recrystallized from methylene chloride–methylcyclohexane to yield 0.060 g. (*ca.* 60%) of colorless prisms, m.p. 114.5–115.0°, undepressed upon admixture with pure N,N-dibenzoylglycine benzyl ester.

Larger scale preparations of the acid chloride were carried out by the same procedure. Upon storage for a few days at room temperature N,N-dibenzoylglycyl chloride underwent extensive decomposition with the formation of a dark, viscous mixture containing benzoyl chloride, which was detected by odor. Benzoyl chloride also resulted when a small sample of the acid chloride was heated to 70° in a sublimation apparatus at 13 mm. Addition of aniline to the almost colorless distillate resulted in the formation of benzanilide, m.p. 162–163°.

No crystalline product could be isolated upon addition of triethylamine under high-dilution conditions to a solution of the acid chloride XVII and 2-phenyl-2-thiazoline in methylene chloride. Addition of a cold (−70°) solution of the acid chloride XVII and triethylamine in methylene chloride to a solution of 2-phenyl-2-thiazoline likewise did not lead to crystalline material, even after extensive chromatography.

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