and when mixed with the tetraacetate made by acetylation of the bis-hydroquinone (IV).

Ultraviolet Absorption Data.—The ultraviolet absorption characteristics for seven of the compounds are summarized in Table I. A Beckman quartz spectrophotometer, model DU, with a hydrogen discharge lamp and 1 cm. quartz cells was used. The solvent was 95% ethanol in all cases.

The $\lambda_{max.}$ at 244 mμ ($\epsilon = 2.65 \times 10^4$) for the diquinone diester (VII) is in good agreement with the value of 250 mμ ($\epsilon = 1.95 \times 10^4$) found for 2-methyl-1,4-naphthoquinone.[12] The agreement with the value of 239 ± 5 mμ found to be characteristic of α,β-disubstituted-α,β-unsaturated ketones is also satisfactory.[13] With compound XII the absorption peak at 285 mμ agrees closely with value found for related cyclic β-diketones.[14] The monoester (XII) has considerably greater absorption than the diester (VII) suggesting that in XII the conjugation extends through both naphthalene moieties as in the structure shown. As previously pointed out it is apparent that the two diacetates (the third and last compounds tabulated) are not identical.

(12) L. F. Fieser, D. M. Bowen, W. P. Campbell, E. M. Fry and M. D. Gates, Jr., THIS JOURNAL, **61**, 1927 (1939).

(13) R. B. Woodward, *ibid.*, **63**, 1123 (1941).

(14) E. R. Blout, V. W. Eager and D. C. Silverman, *ibid.*, **68**, 566 (1946).

COLLEGE PARK, MARYLAND RECEIVED AUGUST 9, 1950

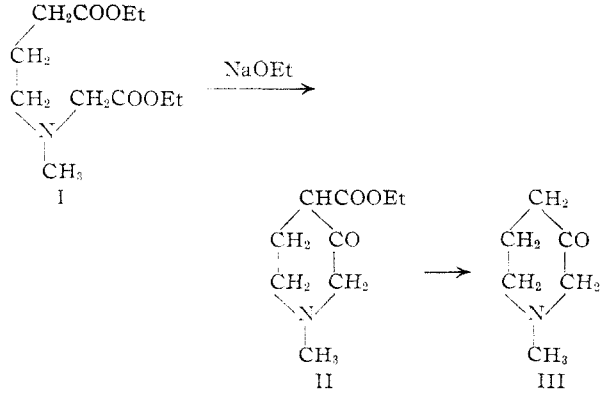
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXIV. 1-Methyl-4-phenyl-3-piperidone and Related Products

BY S. M. McELVAIN AND PAUL M. LAUGHTON[1]

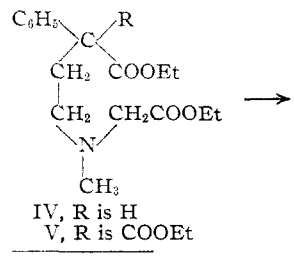
The Dieckmann cyclizations of the amino esters IV and V with dry sodium ethoxide yield the corresponding 2-carbethoxy-4-phenyl-3-piperidones, VI and VII, with the evolution of approximately two equivalents of ethyl alcohol. With IV the cyclization proceeds better with sodium hydride as the condensing agent. The decarbethoxylation of VI gives good yields of 1-methyl-4-phenyl-3-piperidone (VIII); however, a similar decarbethoxylation of VII gives very low yields of VIII because of extensive ring opening to produce the amino diacid corresponding to IV. The preparations of the amino esters IV and V from phenylmalonic ester, together with those of certain incidental compounds, are described.

In an earlier paper from this Laboratory the Dieckmann cyclization of the 3-azoheptanedioic ester I to a carbethoxy-3-piperidone, which yielded 1-methyl-3-piperidone (III) on decarbethoxylation, was reported.[2] The 4-carbethoxy structure (II) was assigned to the intermediate keto ester in preference to the isomeric 2-carboethoxy structure because of earlier observations that certain amino diesters, in which the methylene group involved in the reaction carried an amino substituent, reacted very sluggishly or not at all under the conditions of the Dieckmann cyclization. Later, however, the self-condensation of piperidinoacetic ester with dry sodium ethoxide to the corresponding diperidinoacetoacetic ester was effected[3] readily and in high yield, and the earlier failures to obtain reaction with this type of amino ester were ascribed to adverse surface or solubility effects or to the use of alkali metals, rather than to any inherent unreactivity of the α-aminomethylene group.



The present paper reports a study of the cyclization of the aminoesters IV and V. Aside from interest in the analgesic properties of the resulting products, a cyclization of either of these esters by sodium ethoxide would of necessity involve the amino methylene group of V and most probably that of IV, unless the hydrogen on the tertiary carbon of the latter ester is sufficiently activated by the phenyl and carbethoxy groups to react with the base to yield ethyl alcohol. If the cyclization of IV occurred in this latter manner the resulting keto ester would not be expected to form a sodium enolate. An alternative course of cyclization of V would involve the elimination of ethyl carbonate,[4] but the resulting keto ester would also be incapable of forming a sodium enolate.

The cyclizations of both IV and V were effected by either sodium ethoxide or sodium hydride. With the former base the course of the cyclization was followed by collecting the volatile material. From the diester IV only alcohol (94%) was evolved from the cyclization; from the triester V the volatile material was mainly alcohol (90%) with less than 5% of ethyl carbonate. This latter result was noteworthy in view of the previously noted facile cleavage of phenylmalonic esters to the corresponding acetic esters and ethyl carbonate by sodium ethoxide.[5] The cyclization of both IV and V yielded a sodium enolate which fixes the structure of the corresponding cyclic keto esters as VI and VII.



IV, R is H
V, R is COOEt

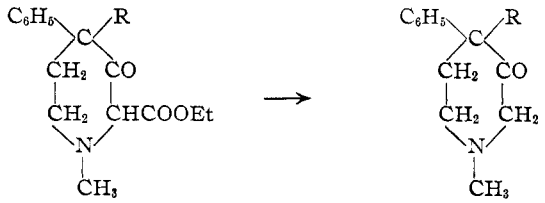
(1) Wisconsin Alumni Research Foundation Research Assistant, 1947–1950.

(2) E. A. Prill and S. M. McElvain, THIS JOURNAL, **55**, 1233 (1933).

(3) W. B. Thomas and S. M. McElvain, *ibid.*, **56**, 1806 (1934).

(4) *Cf.* S. M. McElvain, *et al.*, *ibid.*, **57** (a) 1133, (b) 1443 (1935).

(5) A. C. Cope and S. M. McElvain, *ibid.*, **54**, 4319 (1932).



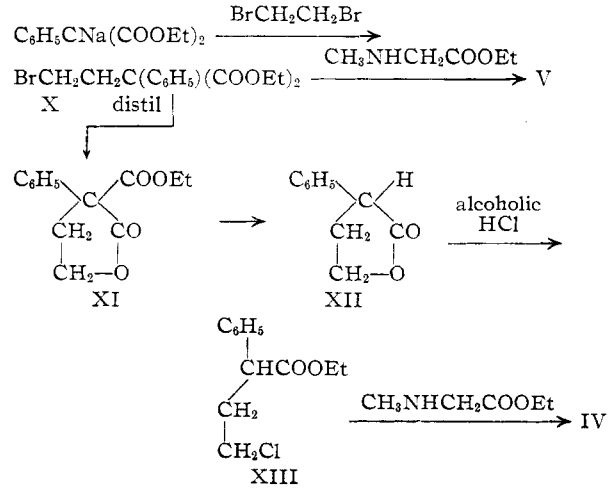
VI, R is H
VII, R is COOEt

VIII, R is H
IX, R is COOEt

The cyclization of IV to VI proceeded better with sodium hydride than with sodium ethoxide. With the latter base the reaction temperatures required to cause 94% of two equivalents of alcohol to distil from the reaction produced considerable decomposition of the sodium enolate of VI. With sodium hydride as the cyclizing agent, VI was obtained as an unstable free base, which was characterized as a methiodide and by decarbethoxylation to the unstable, solid 1-methyl-4-phenyl-3-piperidone (VIII). The lower limit of the yield of this cyclization was established by the conversion of IV to the purified piperidone (VIII) in 73% yield.

The cyclization of V appeared to proceed better with sodium ethoxide; its reaction with sodium hydride was sluggish and not reproducible. The sodium enolate of VII was soluble in both benzene and ether, but could be separated by precipitation with petroleum ether. The keto diester VII was obtained as a red oil in 47% yield from a cyclization that was carried to 70% completion, as measured by the amount of evolved alcohol. On decarbethoxylation in acid solution, VII yielded only one equivalent of carbon dioxide and 5–15% of the piperidone VIII; no material corresponding to the expected 4-carbethoxy derivative IX could be isolated. The principal product from the decarbethoxylation of VII was an acidic material (soluble in sodium bicarbonate). On esterification this material yielded the amino diester IV in an amount equivalent to 40% of the keto diester that was decarbethoxylated. It thus appears that the conditions generally used for the ketonic cleavage of carboethoxypiperidones causes the dicarbethoxypiperidone VII to undergo an acid cleavage with ring opening.

The amino esters IV and V were obtained by the reaction of the appropriate halogeno ester X and XIII with two equivalents of sarcosine ester. The bromo ester X was obtained in *ca.* 59% yields, together with 15–25% yields of diethyl α,α'-dicarbethoxy-α,α'-diphenyladipate, from the reaction of an excess of ethylene dibromide with the sodium enolate of phenylmalonic ester. As all attempts to distil X converted it to ethyl bromide and the lactone XI,[6] it was used as it was obtained for the reaction with sarcosine ester. The carbethoxy lactone XI was readily decarbethoxylated to the lactone XII, which gave an 89% yield of the chloroester XIII on treatment with an alcoholic solution of hydrogen chloride.[7]



Experimental

Sarcosine Ester.—The hydrochloride of this ester was prepared by the following modification of the procedure of Staudt.[8] A solution of 350 g. (5 moles) of methylammonium chloride in 700 ml. (*ca.* 9 moles) of 37% formalin prepared with ice cooling was treated very slowly with a chilled solution of 270 g. (5 moles) of sodium cyanide in 500 ml. of water. The reaction temperature was *kept below 10°* during this addition, otherwise the desired product was not obtained. After an additional half-hour of stirring, sarcosine nitrile separated as a pale brown oil, which was taken up in 100 ml. of ether. After drying, the solution was treated with 600 ml. of absolute ether saturated at 0° with hydrogen chloride (*ca.* 4.5 moles), the white gum taken up in 1 l. of absolute alcohol at 65°, and the solution allowed to crystallize. The crude sarcosine nitrile hydrochloride (m.p. 102–105°) so obtained weighed 290 g. (53%); it was slowly added with cooling and stirring to 1400 ml. of absolute alcohol saturated with dry hydrogen chloride at 0° and then stirred overnight without cooling. The iminoester hydrochloride so formed was converted directly to the ester by stirring 24 hours after adding the theoretical quantity (48 ml.) of water. The ammonium chloride containing some sarcosine hydrochloride was filtered off, the solution concentrated under reduced pressure and taken up in 1 l. of hot acetone, yielding 180 g. of sarcosine ester hydrochloride as white grains, m.p. 113–123°; after one recrystallization from acetone, it melted at 122–123°. The major contaminant of the material m.p. 113–123° is sarcosine hydrochloride, which does not interfere with the next procedure.

If the temperature of the reaction was allowed to rise as high as 25°, even for a few minutes, during the addition of the sodium cyanide solution an oil of the usual appearance separated and was collected. On distillation only a small amount of material that distilled below 150° (17 mm.) was obtained; the main reaction product was a greenish liquid, b.p. 153–154° (18 mm.), $n^{25}D$ 1.4498, which was identified as **methylene - N,N' - bis - (N - methylaminoacetonitrile)**, $CH_2(N(CH_3)CH_2CN)_2$, which was obtained in yields as high as 54%.

Anal. Calcd. for $C_{17}H_{12}N_4$: C, 55.25; H, 7.95; N, 36.9. Found: C, 54.88; H, 8.19; N, 36.9.

A sample of this material after boiling to small volume with concentrated hydrobromic acid deposited sarcosine hydrobromide as a mass of white needles, m.p. 181–185°, which after recrystallization from ethanol melted at 185–190° (dec.).

A 31-g. sample of ester hydrochloride was dissolved in the minimum amount of liquid ammonia, which was then allowed to evaporate. Three 25-ml. absolute ether extracts of the solid residue were combined and distilled to yield 22.5 g. (95%) of sarcosine ester, b.p. 55° (19 mm.), $n^{25}D$ 1.4107, with practically no distillation residue. The fine yellow picrate from alcohol melted at 147.5–148.5°.[9]

A useful derivative for the detection of sarcosine ester in aqueous solution is **nitrososarcosine ester**, readily prepared in high yield with nitrous acid, followed by ether extraction, b.p. 70–73° (0.3 mm.), $n^{25}D$ 1.4471.

(6) G. S. Skinner, THIS JOURNAL, **59**, 322 (1937).

(7) This reaction is in marked contrast to a similar cleavage of α-alkyl-γ-butyrolactones, which yield γ-hydroxy esters (see ref. 4b).

(8) Staudt, *Z. physiol. Chem.*, **146**, 287 (1925).

(9) E. Fischer, *Ber.*, **34**, 452 (1901).

Anal. Calcd. for $C_5H_{10}N_2O_3$: C, 41.09; H, 6.89. Found: C, 41.04; H, 7.16.

The thermal stability of sarcosine ester is shown by the following experiment. A 5.5-g. sample of sarcosine ester was heated six hours at the reflux temperature (155°). A yield of 0.5 g. (23%) of ethanol distilled over, but upon distillation of the residue, 3.0 g. (55%) of sarcosine ester was recovered. The distillation residue consisted of 1.4 g. (35%) of white flakes identified as sarcosine anhydride (1,4-dimethyl-2,5-diketopiperazine), b.p. 304–306°, m.p. after recrystallization from ethyl acetate, 145–146°.[10] This anhydride sublimes at 120° (0.35 mm.). Samples of this amino ester retained in the distillation receiver or transferred by pouring appeared stable for weeks at room temperature, but samples transferred with ether or catalyzed by a trace of acetic acid deposited large prisms of the anhydride in a few days.

N-Ethylsarcosine Ester.—This model compound was prepared in order to test the nucleophilic displacing activity of sarcosine ester at the elevated temperatures required for reaction with the halogenoesters X and XIII. A solution of 19 g. (0.165 mole) of sarcosine ester and 8.7 g. (0.080 mole) of ethyl bromide in 20 ml. of benzene was heated 16 hours at 100° in a sealed tube. Upon chilling and opening the tube, a honey-like mass of sarcosine ester hydrobromide (98%) separated. The benzene layer was decanted and distilled; 4.3 g. (36%) of N-ethylsarcosine ester, a clear colorless liquid, was collected at 51–53° (9 mm.). The material was purified by recovery in high yield from cold aqueous solution after treatment with nitrous acid (which gave no detectable quantity of nitrososarcosine ester) and refractionation with little loss at 69–70° (24 mm.), $n^{25}D$ 1.4158.

Anal. Calcd. for $C_7H_{15}NO_2$: N, 9.64. Found: N, 9.59.

Ethyl γ-Bromo-α-carbethoxy-α-phenylbutyrate (X).—The sodium enolate of diethyl phenylmalonate[11] was prepared from 12.0 g. (0.50 mole) of 97% sodium hydride, 118 g. (0.50 mole) of the ester and 50 ml. of dry toluene in a standard-taper flask fitted with a mercury-seal Hershberg stirrer and reflux condenser. With vigorous stirring the evolution of hydrogen had ceased in 20 minutes. Then 760 g. (4.0 moles) of ethylene bromide was added and stirring continued at a bath temperature of 106° for 4 hours. A small additional volume of hydrogen was evolved during this reaction. After cooling, the suspension was filtered with suction, the removed solid cautiously dissolved in ice-water, the resulting mixture extracted with benzene, and this extract added to the liquid filtrate. Analysis of the aqueous solution (Volhard) indicated the presence of 95–100% of the expected bromide ion.

The low-boiling materials were distilled from the filtrate under reduced pressure; from them 610 g. of ethylene bromide was recovered on refractionation. In earlier attempts to purify the bromoester from the crude residue at this stage, it was found that ethyl bromide was evolved before all the phenylmalonic ester was removed, even with an initial pressure of 0.02 mm. Accordingly, the residue was freed of ethylene bromide by evaporation for two hours at 0.2 mm. over a steam-bath. After cooling, the remaining 136 g. of clear red viscous liquid was filtered to remove 12 g. of white grains, m.p. 114–116° (see below). A Stepanov analysis of the filtrate showed the presence of 0.295 equivalent of bromine (101 g. (59%) calcd. as the bromoester X).

The solid, identified as **diethyl α,α′-dicarbethoxy-α,α′-diphenyladipate**, melted at 116–116.5° on recrystallization from alcohol, and gave a saponification equivalent of 122 (theory, 124.5).

Anal. Calcd. for $C_{28}H_{34}O_8$: C, 67.42; H, 6.88; C_2H_5O, 36.2. Found: C, 67.35; H, 6.84; C_2H_5O, 35.6.

α,α′-Diphenyladipic acid was prepared from this tetraester. After 12 hours in refluxing alkali, 125 g. of the crude tetraester yielded 76.6 g. of crude acid on removal of the alcohol, filtration, precipitation with hot sulfuric acid and drying at 160°. Recrystallization to constant melting point from dioxane gave colorless prisms, which decrepitated under vacuum to a white powder, m.p. 250–253°, neutral equivalent 151 (theory, 149).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.49; H, 6.08. Found: C, 72.34; H, 6.10.

Ethyl γ-Diethylamino-α-carbethoxy-α-phenylbutyrate.—As a model experiment a 28.3-g. sample of crude bromoester X containing 0.0577 equivalent of bromine (calcd. as 19.8 g. of X) was heated 22 hours at steam temperature in a steel bomb with 10 g. (0.137 mole) of diethylamine and 20 ml. of dry benzene. After chilling in ice, the brown liquid was filtered free of 8.3 g. (94%) of diethylammonium bromide,[12] m.p. 212–216°, after washing with ether.

The combined ether and benzene solution was extracted with dilute hydrochloric acid, and the dissolved basic materials recovered by treatment with excess alkali and ether extraction. Distillation of the dried ether solution yielded 14.5 g. (80% yield) of ethyl γ-diethylamino-α-carbethoxy-α-phenylbutyrate, a colorless oil, b.p. 148–149° (0.25 mm.). A sample refractionated for analysis boiled at 129–130° (0.10 mm.), $n^{25}D$ 1.4910, d^{25}_4 1.0363, sapn. equiv. 330 (calcd.,[13] 335).

Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.74; N, 4.18; C_2H_5O, 26.8. Found: C, 68.06; H, 8.74; N, 4.14; C_2H_5O, 25.4.

The methiodide of this amino ester, recrystallized from ethanol and ethyl acetate, melted at 107–109°.

Anal. Calcd. for $C_{20}H_{27}INO_4$: C, 50.30; H, 6.76; I, 26.58. Found: C, 50.03; H, 6.96; I (gravimetric), 26.49.

Ethyl γ-(N-Carbethoxymethyl-N-methylamino)-α-carbethoxy-α-phenylbutyrate (V).—A 58.2-g. sample of crude bromoester X containing 0.125 equivalent of bromine (calcd. 43 g. of X) was heated 24 hours at 100° in a steel bomb with 28.0 g. of sarcosine ester and 50 ml. of benzene. After chilling and filtering the reaction mixture, 18.5 g. (75%) of **sarcosine ester hydrobromide**, m.p. 70–75°, was obtained. After recrystallization from alcoholic ethyl acetate this salt melted at 74–77°. An authentic sample was prepared from sarcosine ester with ethereal hydrogen bromide, and recrystallized from acetone.

Anal. Calcd. for $C_5H_{12}BrNO_2$: Br, 40.3. Found: Br, 40.1.

A water extract of the benzene filtrate showed an additional 0.023 equivalent of bromide ion to make a total of 0.117 equivalent (97% reaction).

The remaining benzene solution was extracted with dilute acid to remove the basic material. The neutral material remaining in the benzene was fractionated to give 8.5 g. of phenylacetic and phenylmalonic esters, 16 g. of carbethoxylactone XI, and 2.5 g. of the solid tetraester.

Treatment of the acid solution with alkali liberated 28 g. of a red oil, which was fractionated into a small forerun, 17.7 g. (39%) of the amino triester V, b.p. 174° (0.4 mm.) −190° (0.9 mm.), $n^{25}D$ 1.4911, and 7 g. of a viscous, higher-boiling product that was not identified. A sample of the main fraction, refractionated for analysis, boiled at 175–176° (0.4 mm.), $n^{25}D$ 1.4910, d^{25}_4 1.0994, sapn. equiv. 189 (calcd.,[13] 189.7).

Anal. Calcd. for $C_{20}H_{29}NO_6$: C, 63.31; H, 7.70; N, 3.70; C_2H_5O, 35.6. Found: C, 63.32; H, 7.77; N, 3.79; C_2H_5O, 32.3.

The methiodide of V, after recrystallization from ethyl acetate, melted at 130–131.5°.

Anal. Calcd. for $C_{21}H_{32}INO_6$: C, 47.94; H, 6.17; I, 24.34. Found: C, 48.38; H, 6.17; I (gravimetric), 24.65.

A small additional amount of V can be recovered from the salt by-products in this preparation. The hydrobromide occasionally failed to crystallize; however, free sarcosine ester could be obtained in high recovery by the liquid ammonia method.

α-Phenyl-γ-butyrolactone (XII).—A mixture containing bromoester X prepared as described above from 118 g. of phenylmalonic ester was distilled and then refractionated under reduced pressure to give 1.7 g. of ethyl phenylacetate, 21.7 g. (18.5%) of phenylmalonic ester, and 59 g. (50%) of ethyl α-phenyl-α-carbethoxy-γ-butyrolactone[6] (XI), b.p. 170–173° (3 mm.), $n^{25}D$ 1.5193; 7.4 g. of diethyl α,α′-

(10) Mylius, *Ber.*, **17**, 287 (1884).

(11) This ester was kindly supplied by Dr. V. H. Wallingford, Mallinckrodt Chemical Works, St. Louis, Missouri.

(12) Wagner, *Z. Kryst. Min.*, **43**, 164 (1907).

(13) Using phenolphthalein as the indicator in this determination, the excess alkali and the amino group are titrated; the sapn. equiv. is therefore related to the number of carbethoxy groups in excess of one in the amino ester.

dicarbethoxy-α,α'-diphenyladipate was recovered from the residues, making the total yield of this product 32.0 g. (26%); 9.2 g. of ethyl bromide was recovered from the Dry Ice trap.

The identity of the lactone VII was confirmed by its properties[6]: b.p. 146° (0.3 mm.), $n^{25}D$ 1.5190, d^{25}_4 1.1829, and by its carbon, hydrogen and ethoxyl content.

The lactone XII was prepared by saponification of 30 g. of XI under a column until alcohol ceased to distil, followed by addition of excess hydrochloric acid (vigorous foaming) and distillation until constant boiling hydrochloric acid began to distil (110°). After dilution, the residue was extracted with three portions of ether; the ether solution was dried and distilled to yield as the only product, 20.3 g. (97%) of XII,[14] a colorless liquid b.p. 131–134° (0.3 mm.). This material on redistillation boiled at 116° (0.2 mm.), $n^{25}D$ 1.5436, d^{25}_4 1.1604, sapn. equiv. 160 (calcd., 162).

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 73.99; H, 6.29. Found: C, 73.70; H, 6.28.

Ethyl α-Phenyl-γ-chlorobutyrate (XIII).—A solution of 26.5 g. (0.163 mole) of the lactone XII in 150 ml. of absolute ethanol was saturated with dry hydrogen chloride without cooling. After two days standing, the solution was concentrated under reduced pressure, poured onto ice and the water extracted with ether. The dried extracts on distillation yielded as the sole product 30.6 g. (82%) of pure XIII as a clear, colorless liquid, b.p. 100–105° (0.5 mm.), $n^{25}D$ 1.5050, d^{25}_4 1.1092, sapn. equiv. 119 (theory, 113).

Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.66; Cl, 15.65; C_2H_5O, 19.9. Found: C, 63.77; H, 6.73; Cl, 15.30; C_2H_5O, 20.3.

Ethyl γ-(N-Carbethoxymethyl-N-methylamino)-α-phenylbutyrate (IV).—A mixture of 52.6 g. (0.45 mole) of sarcosine ester and 51 g. (0.225 mole) of the chloroester XIII was heated with mechanical stirring for 3 hours at 130°. After partial cooling, dry ether was added with stirring while the lower layer crystallized. The ether solution was separated from 40 g. of pale yellow crystals, which were washed with ether.

The combined ether extracts yielded 5.0 g. (10%) of sarcosine ester followed by 14.6 g. (25%) of chloroester (XIII) containing a few prisms of sarcosine anhydride. The main fraction, 42.3 g. of a pale yellow oil b.p. 137–145° (0.35 mm.), $n^{25}D$ 1.4915, was the amino diester IV. From the crystalline reaction product 15.8 g. of sarcosine ester, 1.0 g. of sarcosine anhydride and 4.5 g. of amino diester were recovered after treatment with liquid ammonia. Total yield of IV was 46.8 g. (92% on the chloroester not recovered). The amino diester on refractionation was obtained as a water-white liquid b.p. 130–131° (0.15 mm.), $n^{25}D$ 1.4911, d^{25}_4 1.0554, neut. equiv. (methyl red and brom cresol green indicator) 309; sapn. equiv. 288 (calcd.,[13] 307.4).

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56; C_2H_5O, 29.3. Found: C, 66.44; H, 8.20; N, 4.64; C_2H_5O, 28.7.

The methiodide of IV was recrystallized from alcoholic ethyl acetate, m.p. 151–153°.

Anal. Calcd. for $C_{18}H_{28}INO_4$: C, 48.12; H, 6.31; I, 28.25. Found: C, 48.05; H, 6.63; I (gravimetric), 28.13.

Cyclization of the Amino Diester (IV). The Methiodide of VI.—A 20.6-g. (0.067-mole) sample of IV was added to a suspension of 3.17 g. (0.132 mole) of sodium hydride grains under nitrogen in 150 ml. of dry benzene. Under gentle reflux hydrogen evolution ceased after 3 hours; the reaction mixture suddenly gelled after 2.5 hours. After cooling, 8.0 g. of glacial acetic acid was added, followed by 6.5 ml. of water and a seed of sodium acetate trihydrate. Ether washings of the solid were added to the benzene filtrate, which was evaporated under reduced pressure to yield 18.1 g. of an amber oil, $n^{25}D$ 1.527, which gave a strong blue-green test[15] with alcoholic ferric chloride and contained 14.4% ethoxyl (calcd. for VI, 17.25%). This oil rapidly turned red on standing in the refrigerator, distilled with decomposition at about 150° (1 mm.) to give poor recovery of product, and generally yielded tars in attempts to prepare crystalline derivatives (salts, phenylpyrazolone, copper complex). However, it yielded a methiodide, which crystallized reluctantly from alcoholic ethyl acetate and ether as white grains, which turned to buff after a day in the refrigerator, m.p. 140–141° (dec.).

Anal. Calcd. for $C_{16}H_{22}INO_3$: C, 47.66; H, 5.50; I, 31.52. Found: C, 47.73; H, 5.78; I (gravimetric), 31.9.

In one run using powdered rather than granular sodium hydride the reaction began with uncontrollable violence almost immediately on mixing the reagents at room temperature.

Inferior reaction products were obtained using dry sodium ethoxide instead of sodium hydride for this cyclization. Up to 94% of the theoretical two moles of alcohol was obtained by heating the reaction mixture at 145–155° (0.2 mm.) for 6 hours, but the free base obtained from the enolate was dark red and only in one case could it be converted to a crystalline methiodide. The following decarbethoxylation experiment gave less satisfactory results with the ketoester obtained from sodium ethoxide cyclizations.

1-Methyl-4-phenyl-3-piperidone (VIII).—Under a 10-plate Fenske column attached through a condenser to an apparatus for collecting carbon dioxide, 13.2 g. of crude ketoester VI, as obtained above, was refluxed with 50 ml. of 18% hydrochloric acid under nitrogen. Evolution of carbon dioxide, first order with respect to ester, was slow after 5 hours and ceased after 7 hours. The extent of decarboxylation was 85% on the basis of evolved gas, and 75% on the basis of the alcohol collected by distillation. The clear solution was neutralized with sodium bicarbonate, made basic with sodium hydroxide and extracted with ether. On drying and evaporation of the ether solution under reduced pressure, 7.0 g. of an amber oil, $n^{25}D$ 1.5400, which solidified to a waxy solid, was obtained. Treatment of this material with ethereal hydrogen chloride and ethyl acetate yielded 5.6 g. of the hydrochloride of VIII, m.p. 156–160° (dec.). An additional 2.0 g. of VIII was recovered from the mother liquor by treatment with base and distillation. An analytical sample of the piperidone VIII, obtained by distillation from a small modified Claisen flask, boiled at 111–113° (0.3 mm.), $n^{25}D$ 1.5417; it gave a negative ferric chloride test and showed no ethoxyl content. This distillate solidified completely on standing, m.p. by melting curve 38–41°, but began to liquefy after a day in the refrigerator.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.07; H, 8.05; N, 7.00.

The melting point of the hydrochloride was raised to 162–164° (dec.) by recrystallization from a mixture of alcohol and ethyl acetate, and ether.

Anal. Calcd. for $C_{12}H_{16}ClNO$: Cl, 15.7. Found: Cl, 15.2.

The methiodide was solid but rapidly decomposed; all attempts to prepare other derivatives were unsuccessful.

1-Methyl-4-phenyl-2,4-dicarbethoxy-3-piperidone (VII).—In a flask equipped for stirring and distillation under diminished pressure, 11.0 g. (0.029 mole) of the amino triester V was added under nitrogen to 2.1 g. (0.031 mole) of sodium ethoxide, which had been heated at 205° (0.1 mm.) for 2–4 hours. After 2 hours of stirring at 125°, all of the ethoxide was in solution. The pressure was lowered to 0.15 mm. while the reaction was continued for an additional 2 hours and the evolved alcohol collected in a cold trap; it amounted to 1.84 g. (70%) on distillation and only 0.05 g. of residue and holdup was left. In other runs up to 5% yield of ethyl carbonate was detected by saponification of this residue and in one case a trace of the ester was isolated.

The sodium enolate of VII was obtained as a white powder from the red, glassy reaction product by precipitating it three times from its solution on 200 ml. of boiling absolute ether by the addition of 200 ml. of petroleum ether (60–68°), distillation of the diethyl ether and centrifugation. The combined petroleum ether solutions contained 1 g. of the solid enolate, 1.2 g. of the amino diester and a trace of piperidone VIII.

The white powder was stirred with an excess of ethereal acetic acid, centrifuged free of sodium acetate, and the solution extracted rapidly with cold sodium bicarbonate solution. The dried ether extract was evaporated, yielding 4.55 g. (47%) of VII as a transparent red oil, $n^{25}D$ 1.5038; this compound shows no coloration with ferric chloride.

(14) B. Rothstein (*Bull. soc. chim.*, [5] **2**, 80 (1935)) reports $n^{22}D$ 1.5400 and d^{22}_4 1.1603 for this compound.

(15) *Cf.* H. Henecka, *Chem. Ber.*, **81**, 179 (1948).

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.89; H, 6.95; N, 4.20; C_2H_5O, 27.0. Found: C, 64.45; H, 7.29; N, 4.02; C_2H_5O, 27.1.

Distillation of this material was accompanied by considerable decomposition and resulted in oils with wide ranges of boiling points, refractive indexes, and ethoxyl content. All efforts to prepare derivatives of VII resulted in intractable oils.

Acid Hydrolysis of VII.—A 2.10-g. sample (0.0063 mole) of the keto diester (VII) was dissolved under nitrogen in 20 ml. of 18% hydrochloric acid and the resulting solution maintained at a slow distillation rate under a 12-inch Vigreux column. In 3 hours, 0.0063 mole of carbon dioxide had been collected at a rate slightly higher than first order and the evolution of the gas had ceased; 64% of two equivalents of alcohol (b.p. and $n^{25}D$) was refractionated from the distillate.

The non-acidic material, 0.51 g., was separated by treatment of the remaining acidic solution with base and extraction with ether. From this 0.13 g. of the piperidone VIII was distilled, b.p. 115–120° (0.3 mm.), $n^{25}D$ 1.5483; hydrochloride, m.p. 155–160°, both alone and after mixing with the hydrochloride of VIII; the residue of this distillation was a tar. The basic solution from which the piperidone VIII was extracted was acidified with hydrochloric acid and evaporated to dryness. The salt residue was extracted with alcohol and the resulting solution evaporated to yield 1.05 g. of a hydrochloride, which, after esterification with alcoholic hydrogen chloride and treatment with sodium bicarbonate, yielded 0.9 g. of the amino diester IV, of which 0.75 g. (40%) was collected on distillation at 140–145° (0.5 mm.); this product gave a methiodide, m.p. 151–153°, both alone and when mixed with an authentic sample of the methiodide of IV.

MADISON, WISCONSIN RECEIVED JULY 20, 1950

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Asymmetric Enzymatic Synthesis of Amino Acid Anilides

BY NOEL F. ALBERTSON

A number of acyl-DL-amino acids have been converted to acyl-L-amino acid anilides in the presence of papain.

If an acyl derivative of a DL-amino acid, I, is treated with aniline in the presence of papain at the proper *p*H the L-amino acid reacts to form an insoluble anilide, II, whereas the D-form does not react, but remains in solution.[1]

$$\underset{\text{I}}{\text{DL—RCONHCHR'COOH}} + C_6H_5NH_2 \longrightarrow \underset{\text{II}}{\text{L—RCONHCHR'CONHC}_6\text{H}_5} + H_2O + \text{D—RCONHCHR'COOH}$$

It had been suggested that this method might be used as a "general method for resolution of amino acids,"[2] but apparently the first L-amino acid to be obtained by hydrolysis of its acylated anilide was methionine in 1948.[3a,b] The appearance of this paper by Dekker and Fruton prompted us to investigate this method of resolution.

The present paper summarizes the data obtained in the preparation of a number of amino acid anilides. Since all experiments were carried out under comparable conditions, data have been included in Table II even for those anilides which have been previously reported.

It is known that the rate of formation of the anilide, II, is considerably influenced by the nature of R and R' of I. It was noted that when R was phenyl and the *p*H was 5, the rate increased as R' went from hydrogen to methyl to ethyl. The rate for *n*-propyl was about the same as for ethyl, but the rate then decreased when R' was *n*-butyl.

The effect of varying R may be noted in the case of phenylalanine; the formyl derivative gave 0% yield in 96 hours, the acetyl derivative gave 18% yield in 163 hours and the benzoyl derivative gave 93% in 48 hours. The variation in *p*H was not sufficient to account for this difference.

Fox and co-workers[4a,b] pointed out that the *p*H optimum for enzymatic activity may vary with the substrate. Additional confirmatory data, obtained in this investigation, are shown in Table I. It is interesting to note that although benzoylalanine forms no anilide at *p*H 5.6 in 16 hours, benzoyl-2-aminobutyric acid gives a 50% yield under the same conditions. On the other hand, benzoylnorleucine will give a 20% yield in 16 hours at *p*H 6.4 whereas benzoyl 2-aminobutyric acid will not react.

TABLE I

L-Acyl amino acid anilide	Time, hr.	Initial *p*H	Yield, %
Benzoylalanine	22	5.97	0
		5.58	1
		5.13	33
		4.87	48
		4.58	63
Benzoyl-2-aminobutyric	16	6.26	1
		5.72	39
		5.56	54
		5.02	91
Benzoylnorleucine	16	6.38	20
		6.01	36
		5.61	53
		4.73	64
		4.18	25
Acetyltryptophan	66	5.15	20
		4.87	40
		4.60	53
		4.21	36
		3.90	12

Inasmuch as the anilides listed in Table II were prepared from DL-amino acids it has not been shown that they are entirely free of D-isomers. However, incubation of benzoyl-D-alanine with papain and cysteine for one month gave no anilide. On the other hand, the anilide prepared from

(1) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

(2) J. Fruton, G. Irving and M. Bergmann, *ibid.*, **133**, 703 (1940).

(3) (a) C. Dekker and J. Fruton, *ibid.*, **173**, 471 (1948); (b) the referee called our attention to the resolution of 3-fluorotyrosine; C. Niemann and M. Rapport, THIS JOURNAL, **68**, 1671 (1946).

(4) (a) S. Fox and C. Pettinga, *Archiv. Biochem.*, **25**, 13 (1950); (b) S. Fox, C. Pettinga, J. Halverson and H. Wax, *ibid.*, p. 21.