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Amine Adducts of β -Benzoylacrylic Acid and Its Methyl Ester. Hydrogenation Products

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Catalytic hydrogenation of the amine adducts of β -benzoylpropionic acid in glacial acetic acid employing palladium-on-charcoal produces the α -amino- γ -phenylbutyric acids while the sodium borohydride reaction of these materials in aqueous base gives either α -amino- γ -hydroxy- γ -phenylbutyric acid or the α -amino- γ -phenyl- γ -butyrolactones. Catalytic hydrogenation with palladium-on-charcoal in benzene or isopropyl ether solutions of methyl α -amino- β -benzoylpropionates led to methyl α -amino- γ -hydroxy- γ -phenylbutyrates, which react with amines to produce α -amino- γ -hydroxy- γ -phenylbutyramides.

In an earlier investigation¹ evidence was presented which supports the assignment of the α -amino- β -benzoylpropionic acid and methyl α -amino- β -benzoylpropionate structures to the amine adducts of β -benzoylacrylic acid and its methyl ester. Catalytic hydrogenation of methyl α -morpholino- β -benzoylpropionate in methanol apparently produced methyl α -morpholino- γ -hydroxy- γ -phenylbutyrate which on distillation or treatment with hydrogen chloride gave α -morpholino- γ -phenyl- γ -butyrolactone,¹ the first member of an interesting new series of lactones.²

Acid catalysis is often necessary to reduce a carbonyl group directly to a methylene group by catalytic hydrogenation.³ Since it was found that the α -amino- β -benzoylpropionic acids were reasonably stable in acetic acid, several of these compounds were subjected to catalytic hydrogenation in this solvent employing palladium-on-charcoal (Pd/C) as a catalyst. In this way α -morpholinol, α -benzylamino, and α -methylamino γ -phenylbutyric acids were prepared from the corresponding α -amino- β -benzoylpropionic acids. These keto-amino acids, which were prepared by the previously reported technique,¹ were unstable in some solvents and thus were difficult to purify for analysis. On the other hand, the hydrochlorides of the α -amino- β -benzoylpropionic acids were readily obtained in analytical form. The α -morpholino- γ -phenylbutyric acid, as prepared in this way, was identical with a sample obtained by treating α -bromo- γ -phenylbutyric acid with morpholine. These experiments definitely establish the structures of these amine

adducts of β -benzoylacrylic acid and its methyl ester as the α -amino and not the β -amino⁴ products.

α -Amino and α -morpholino- γ -phenylbutyric acids were obtained by the catalytic (Pd/C) hydrogenation of the corresponding β -benzoylpropionic acids in methanol containing dry hydrogen chloride.

The hydrogenation of methyl α -benzylamino β -benzoylpropionate in benzene containing a small amount of glacial acetic acid also produced the α -benzylamino- γ -phenylbutyric acid, while similar experiments in the absence of any acid produced the methyl α -morpholino and α -piperidino- γ -hydroxy- γ -phenylbutyrates from the corresponding α -amino- γ -ketoesters.

By analogy with the previously reported studies¹ α -dimethylamino- β -benzoylpropionate was reduced with lithium aluminum hydride to 3-dimethylamino-phenyl-1,4-butandiol which was found to be a solid with a surprisingly high melting point for an amino diol of this type.¹

Reduction of the α -amino- β -benzoylpropionic acids with sodium borohydride in aqueous base produced either the α -amino- γ -hydroxy- γ -phenylbutyric acids or their dehydration products, the α -amino- γ -phenyl- γ -butyrolactones, which were usually isolated as the hydrochlorides. α -Piperidino- γ -hydroxy- γ -phenylbutyric acid was dehydrated to the lactone on heating under vacuum, but the corresponding α -cyclohexylamino hydroxy acid resisted all attempts to ring-close it to a lactone. Both the α -piperidino and α -cyclohexylamino- γ -phenyl- γ -butyrolactones were isolated as their hydrochlorides after the hydrogenation (Pd/C) of the corresponding methyl α -amino- β -benzoylpropionates were carried out in methanol and isopropyl ether, respectively.

Methyl α -piperidino- γ -hydroxy- γ -phenylbutyrate reacted readily on heating with dimethylamine or piperidine to produce the corresponding

(1) N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956).

(2) After our investigations (K. E. Cook, Ph.D. thesis, University of Nebraska, July 1957) had been completed, W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1560 (1957), reported that the aniline adduct of β -benzoylacrylic acid may be reduced with sodium borohydride to give α -anilino- γ -phenyl- γ -butyrolactone which was then hydrogenated to α -anilino- γ -phenylbutyric acid with palladium-on-charcoal in abs. ethanol. This latter amino acid was identical with the product from the reaction of aniline with α -bromo- γ -phenylbutyric acid.

(3) W. H. Hartung and R. Simonoff, *Org. Reactions*, **VII**, 268 (1953).

(4) The β -amino structure was tentatively proposed by P. Chabrier, *et al.*, *Compt. rend.*, **226**, 1378 (1948); **228**, 1952 (1949); **230**, 212 (1950); **232**, 2326 (1951); **233**, 1367 (1951); **234**, 2541 (1952); **237**, 66, 1420 (1953).

N,N-disubstituted α -piperidino- γ -hydroxy- γ -phenylbutyramides.

Infrared absorption spectra. The α -morpholino, α -benzylamino, and α -methylamino γ -phenylbutyric acids showed ionized COO^- bands at 1628, 1610, and 1587 cm^{-1} , respectively, in their solid state infrared spectra. The latter two secondary amino acids also showed NH^+ bands between 3050 and 3100 cm^{-1} . The methyl α -amino- γ -hydroxy- γ -phenylbutyrates had ester carbonyl bands between 1720 and 1730 cm^{-1} and associated OH bands from 3210 to 3462 cm^{-1} . 3-Dimethylamino-1-phenyl-1,4-butandiol had a highly associated OH band at 3310 cm^{-1} . The α -amino- γ -phenyl- γ -butyrolactone hydrochlorides all show lactone carbonyl bands between 1765 and 1800 cm^{-1} , with the parent α -amino compound showing two such bands in this region. The *N,N*-disubstituted α -piperidino- γ -hydroxy- γ -phenylbutyramides showed amide carbonyl bands at 1610–1613 cm^{-1} and associated OH bands between 3390 and 3420 cm^{-1} .

EXPERIMENTAL

Methyl α -amino- β -benzoylpropionates. The procedure previously described¹ was used for the preparation of these compounds from the addition of the corresponding amines to methyl β -benzoylacrylate. The yields of the α -morpholino, α -piperidino, and α -benzylamino products ranged from 90–98%. The methyl α -dimethylamino- β -benzoylpropionate was obtained in 77% yield, m.p. 43–45°. This material was unstable and decomposed to dimethylamine and methyl- β -benzoylacrylate on standing in the solid form at room temperature.

α -Amino- β -benzoylpropionic acids and hydrochlorides. The previously described¹ procedures were used for the preparation of these acids. The yield of the crude parent α -amino acid⁴ was 79% while those of the α -morpholino and α -piperidino acids¹ were nearly quantitative. The hydrochlorides of the various α -amino- β -benzoylpropionic acids were prepared by passing dry hydrogen chloride gas into methanol suspensions of the acid. After the solid material had dissolved the methanol was removed under reduced pressure and the residues recrystallized from methanol and ether mixtures. The yields were nearly quantitative.

α -Benzylamino- β -benzoylpropionic acid, yield 98%, m.p. 165° (dec.); *hydrochloride*, m.p. 144–146° (dec.).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{NO}_3\text{Cl}$: N, 4.38. Found: N, 4.30.

α -Piperidino- β -benzoylpropionic acid hydrochloride, m.p. 202–204°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{Cl}$: N, 4.70. Found: N, 4.43.

α -Cyclohexylamino- β -benzoylpropionic acid, yield 87%, m.p. 167°; *hydrochloride*, m.p. 177–180°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_3\text{Cl}$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.79; H, 7.23; N, 4.60.

α -Methylamino- β -benzoylpropionic acid. A 10 g. sample of β -benzoylacrylic acid was dissolved in a mixture of 8 ml. of aqueous 40% methylamine and 200 ml. of water. The solution was evaporated to dryness and the residue digested with 25 ml. of cold 95% ethanol. Filtration left 7.75 g. (66% yield) of nearly colorless material, m.p. 181°; *hydrochloride*, m.p. 193–196°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{NO}_3\text{Cl}$: C, 54.21; H, 5.79; N, 5.75. Found: C, 54.29; H, 5.73; N, 5.76.

α -Dimethylamino- β -benzoylpropionic acid. Following the procedure used for the α -methylamino acid, this product was obtained in 76% yield, m.p. 140°; *hydrochloride*, m.p. 147–150°.

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{Cl}$: C, 55.92; H, 6.26; N, 5.44. Found: C, 55.71; H, 6.07; N, 5.43.

α -Amino- γ -phenylbutyric acids. Ten-gram samples of the various α -amino- β -benzoylpropionic acids were dissolved in 130 ml. of glacial acetic acid and shaken with 1 g. of 10% palladium-on-charcoal under 45 lbs./in.² of hydrogen at room temperature for 4 to 7 hr.

α -Morpholino- γ -phenylbutyric acid, m.p. 185–187°, yield 42%, recrystallized from 95% ethanol. Infrared spectrum⁵ (Nujol): $\nu(\text{COO}^-)$, 1628 cm^{-1} ; $\nu(\text{C}_6\text{H}_5)$, 1610 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.53; H, 7.70; N, 5.84.

(a) This product was also prepared by refluxing 2.0 g. of α -bromo- γ -phenylbutyric acid⁶ with 1.5 ml. of morpholine in 10 ml. of benzene for 2 hr. Morpholine hydrobromide was removed by filtration and the benzene solution concentrated to produce a 50% yield of the amino acid, m.p. 186–187°, identical with the material described above.

(b) Hydrogenation of α -morpholino- β -benzoylpropionic acid (5.0 g.) using 10% palladium-on-charcoal in a 100 ml. methanol solution containing excess dry hydrogen chloride produced the crude hydrochloride of α -morpholino- γ -phenylbutyric acid, m.p. 220–225°. This material was converted with aqueous sodium carbonate to the amino acid which was crystallized from aqueous ethanol; wt. 2.4 g. (51% yield); m.p. 185°.

α -Amino- γ -phenylbutyric acid. This known amino acid was obtained in a 63% yield as the hydrochloride, m.p. 152–155°, following procedure (b), used for α -morpholino- γ -phenylbutyric acid. This hydrochloride was converted to the amino acid, m.p. 291–293°, with aqueous ammonia.

α -Benzylamino- γ -phenylbutyric acid. (a) Following the general procedure in glacial acetic acid this compound was obtained in 64% yield and recrystallized from glacial acetic acid, m.p. 222–224°. Infrared spectrum (hexachlorobutadiene, LiF optics): $\nu(\text{N}=\text{H})$, 3050 cm^{-1} ; $\nu(\text{COO}^-)$, 1610 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.60; H, 7.11; N, 5.72.

(b) A 5.0 g. sample of methyl α -benzylamino- β -benzoylpropionate¹ in 75 ml. of benzene and 1 ml. of glacial acetic acid was shaken under 40 lbs./in.² of hydrogen in the presence of 1.0 g. of 10% palladium-on-charcoal for 3.5 hr. The product, which had precipitated from the solution during the hydrogenation, was recrystallized from glacial acetic acid, m.p. 223–224°; wt. 2.6 g. (57% yield). A mixed melting point determination with the product from procedure a showed no depression.

α -Methylamino- γ -phenylbutyric acid. Hydrogenation in glacial acetic acid produced a 56% yield of this acid, m.p. 239–241°, recrystallized from 50% ethanol. Infrared spectrum (Nujol): $\nu(\text{N}=\text{H})$, 3100 cm^{-1} ; $\nu(\text{OH})$, 1587 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.37; H, 8.03; N, 7.36.

Methyl α -morpholino and α -piperidino- γ -hydroxy- γ -phenylbutyrates. The methyl α -amino- β -benzoylpropionates (8 g.) were shaken under 40 lbs./in.² of hydrogen in benzene (60 ml.) solution in the presence of 10% palladium-on-charcoal catalyst for 4.0 hr. The catalyst was removed by filtration and the solution concentrated under vacuum at room temperature and petroleum ether added to precipitate the products. Recrystallization from ether and petroleum ether mixtures produced analytical samples.

Methyl α -morpholino- γ -hydroxy- γ -phenylbutyrate, m.p. 64–67°, 83% yield. Infrared spectrum (Nujol): $\nu(\text{OH})$, 3462 cm^{-1} ; $\nu(\text{C}=\text{O})$, 1730 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.68; H, 7.71; N, 5.03.

Warming this material with concd. hydrochloric acid gave

(5) All infrared spectra were determined over the range of 4000–400 cm^{-1} with a Perkin-Elmer double beam instrument, Model 21, employing NaCl optics unless otherwise indicated.

(6) C. L. Stevens and W. Holland, *J. Org. Chem.*, **18**, 1112 (1953).

(7) F. Knopp and H. Hoessli, *Ber.*, **39**, 1479 (1906).

α -morpholino- γ -phenyl- γ -butyrolactone hydrochloride, m.p. 243°.

Methyl α -piperidino- γ -hydroxy- γ -phenylbutyrate, m.p. 72.5–74°, 87% yield. Infrared spectrum (Nujol): $\nu(\text{OH})$, 3210 cm^{-1} ; $\nu(\text{C}=\text{O})$, 1720 cm^{-1} ; $\nu(\text{C}_6\text{H}_5)$, 1602 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.64; H, 8.43; N, 5.06.

This same product resulted in 85% yield when isopropyl ether was substituted for benzene as solvent in the catalytic hydrogenation.

β -Dimethylamino-1-phenyl-1,4-butanediol. A 5.0 g. sample of methyl α -dimethylamino- β -benzoylpropionate was reduced with lithium aluminum hydride by the procedure previously¹ described for analogous preparations. A 23% yield of a colorless product, slightly soluble in cold ether, but readily recrystallized from benzene was obtained, m.p. 137.5–139°. Infrared spectrum (Nujol): $\nu(\text{OH})$, 3310 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 69.32; H, 8.95; N, 6.21.

Reduction of α -amino- β -benzoylpropionic acids with sodium borohydride. A 0.019-mole amount of the α -amino- β -benzoylpropionic acid was dissolved in a solution of 0.85 g. of potassium hydroxide in 25 ml. of water. To this solution was added 0.36 g. (0.0095 mole) of sodium borohydride in one lot. After standing at room temperature for 48 hr., the solution was made acidic with concd. hydrochloric acid and evaporated to dryness on a steam bath under slight vacuum. The residue was extracted with hot 95% ethanol. Cooling of the ethanol solution produced the products described as follows.

α -Morpholino- γ -phenyl- γ -butyrolactone hydrochloride, m.p. 243°, yield 37%. Infrared spectrum (hexachlorobutadiene, LiF optics): $\nu(\text{C}=\text{O})$, 1780 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_2\text{Cl}$: C, 59.26; H, 6.39; N, 4.94. Found: C, 59.45; H, 6.63; N, 4.79.

α -Amino- γ -phenyl- γ -butyrolactone hydrochloride, m.p. 236°; yield, 70%; Infrared spectrum (Nujol): $\nu(\text{C}=\text{O})$, 1800, 1786 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{NO}_2\text{Cl}$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.17; H, 5.66; N, 6.83.

α -Benzylamino- γ -phenyl- γ -butyrolactone hydrochloride, yield 88%, m.p. 223–224° (dec.), after recrystallization from glacial acetic acid. Infrared spectrum (Nujol): $\nu(\text{C}=\text{O})$, 1765 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{NO}_2\text{Cl}$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.41; H, 6.08; N, 4.62.

α -Cyclohexylamino- γ -hydroxy- γ -phenylbutyric acid. A 10 g. (0.036 mole) sample of α -cyclohexylamino- β -benzoylpropionic acid and 3.2 g. of sodium bicarbonate were dissolved in 100 ml. of water and 0.7 g. (0.019 mole) of sodium borohydride added. This mixture was stirred for 3 hr. After standing for 48 hr. at room temperature the precipitated material was filtered, wt. 4.44 g., m.p. 180–210°. This crude product was recrystallized, first from glacial acetic acid and then from 95% ethanol to give colorless crystals, m.p. 236–236.5° (yield 45%). Infrared spectrum (Nujol): $\nu(\text{OH}/\text{NH})$, 3350, 3160 cm^{-1} ; $\nu(\text{COO}^-)$, 1595 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.43; H, 8.26; N, 5.38.

This γ -hydroxy- α -amino acid resisted all attempts to dehydrate it to the α -aminolactone. Heating with concd. hydrochloric acid gave no change. When a portion was heated in a solids distillation flask at 0.3-mm. pressure and 180°, material sublimed which when recrystallized from benzene had a m.p. 142–145° and showed no infrared spectrum (Nujol) bands between 1700 and 1850 cm^{-1} , but a weak band at 1660 cm^{-1} . This product was not investigated further.

α -Piperidino- γ -hydroxy- γ -phenylbutyric acid. A 1.0-g. (0.0038 mole) sample of α -piperidino- β -benzoylpropionic acid and 0.5 g. of sodium bicarbonate were dissolved in 20 ml. of water and 0.1 g. of sodium borohydride added. After standing at room temperature for 20 hr. the mixture was made acidic with concd. hydrochloric acid and evaporated to dryness on a steam bath under slight vacuum. The residue was extracted with hot 95% ethanol. The ethanol solution on cooling produced a 43% yield of the product, m.p. 244° (dec.). Infrared spectrum (Nujol): $\nu(\text{OH})$, 3225 cm^{-1} ; $\nu(\text{COO}^-)$, 1618 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.86; H, 8.55; N, 5.35.

α -Piperidino- γ -phenyl- γ -butyrolactone. A 1.0-g. sample of α -piperidino- γ -hydroxy- γ -phenylbutyric acid was heated to 230° at a pressure of 0.2 mm. with a flow of nitrogen gas. A small amount of material distilled over and was recrystallized from a mixture of benzene and petroleum ether, m.p. 68–69°; infrared spectrum (CCl_4): $\nu(\text{C}=\text{O})$, 1752 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: N, 5.71. Found: N, 5.50.

α -Piperidino- γ -phenyl- γ -butyrolactone hydrochloride. A 5.0-g. (0.018 mole) sample of methyl α -piperidino- β -benzoylpropionate was dissolved in 50 ml. of methanol and shaken with 0.5 g. of 10% palladium-on-charcoal under 15 lbs./in.² of hydrogen for 3 hr. The catalyst was removed by filtration and the methanol by distillation. The residue was dissolved in ether and treated with dry hydrogen chloride gas to precipitate a gummy material which was crystallized from methanol and ether mixtures; m.p. 211–215°, yield 66%. Infrared spectrum (Nujol) $\nu(\text{C}=\text{O})$, 1765 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}_2\text{Cl}$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.65; H, 7.21; N, 5.16.

α -Cyclohexylamino- γ -phenyl- γ -butyrolactone hydrochloride. A 9.85-g. (0.034 mole) sample of methyl α -cyclohexylamino- β -benzoylpropionate was dissolved in 75 ml. of isopropyl ether and shaken with 1.5 g. of 10% palladium-on-charcoal under 45 lbs./in.² of hydrogen for 3 hr. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was dissolved in concd. hydrochloric acid and the solution evaporated to dryness. The residue was recrystallized from methanol to give 5.0 g. of colorless crystals, m.p. 270°. Infrared spectrum (Nujol): $\nu(\text{C}=\text{O})$, 1774 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{Cl}$: C, 64.96; H, 7.50; N, 4.74. Found: C, 65.03; H, 7.45; N, 4.92.

Reaction of methyl α -piperidino- γ -hydroxy- γ -phenylbutyrate with amines. A 1.0-g. sample of the hydroxyaminoester was mixed with an excess of the amine and heated (with piperidine for 4 hr. under reflux; with dimethylamine for 12 hr. at 70° in a sealed tube).

α -Piperidino- γ -hydroxy- γ -phenylbutyropiperidide, 41% yield, m.p. 106–108°, recrystallized from benzene and petroleum ether. Infrared spectrum (Nujol): $\nu(\text{OH})$, 3420 cm^{-1} ; $\nu(\text{C}=\text{O})$, 1610 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.64; H, 9.10; N, 8.18.

N,N-Dimethyl- α -piperidino- γ -hydroxy- γ -phenylbutyramide, 76% yield, m.p. 105.5–106.5°, recrystallized from ether. Infrared spectrum (Nujol): $\nu(\text{OH})$, 3390 cm^{-1} ; $\nu(\text{C}=\text{O})$, 1613 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.35; H, 8.93; N, 9.36.

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LINCOLN, NEB.