[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

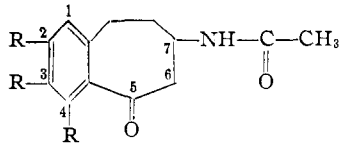
Seven-membered Ring Compounds. VII.[1] 7-Acetamidobenzosuberone and α-Amino-γ-3,4,5-trimethoxyphenylbutyric Acid

BY W. J. HORTON AND GRANT THOMPSON[2]

RECEIVED OCTOBER 30, 1953

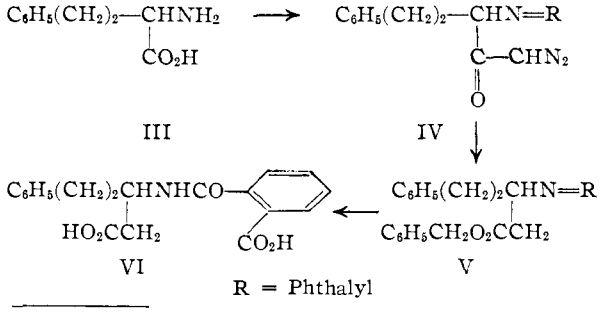
The synthesis of 7-acetamidobenzosuberone (I) is reported. An attempt to prepare the 2,3,4-trimethoxy derivative of I by an analogous route was terminated with α-phthalimido-γ-3,4,5-trimethoxyphenylbutyric acid which could not be converted to the needed valeric acid.

In a synthetic route[3] to colchicine *via* a benzosuberone the compound II was wanted as an intermediate.[4] 7-Acetamidobenzosuberone (I) was sought in initial exploratory experiments. β-



I, R = H
II, R = CH_3O

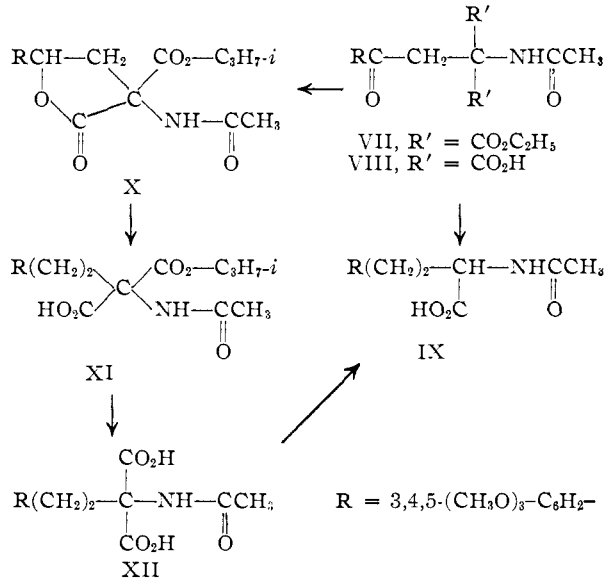
Phenylethyl bromide was added to sodium acetamidomalonic ester to give, after the conventional treatment, α-amino-γ-phenylbutyric acid (III). The amino group of III was blocked by a phthalyl group[5] so as to allow the preparation of the acid chloride and thus the diazoketone (IV). The latter rearranged on heating in benzyl alcohol[6] to V. Saponification of V gave the phthalamic acid (VI). Further hydrolysis with acid produced the salt of β-amino-δ-phenylvaleric acid, which after acetylation of the amino group and cyclization in polyphosphoric acid, gave I. Apparently the alternatively possible closure to a seven-membered nitrogen-containing ring similar to a Bischler–Napieralski cyclization was slow as compared to



R = Phthalyl

the homocyclic ring closure since the product obtained was not acidic and formed an oxime.

The above scheme was used in an attempt to obtain II. In place of the phenylethyl bromide, 3,4,5-trimethoxyphenacyl bromide was condensed with sodium acetamidomalonic ester to produce VII. Saponification of VII with alkali gave the malonic acid (VIII) with retention of the acetyl group.[7] Pyrolysis followed by catalytic reduction[8] afforded IX.



VII, R′ = $CO_2C_2H_5$
VIII, R′ = CO_2H

The acetamidobutyric acid (IX) was obtained from VII *via* a second route. Aluminum isopropoxide reduction of VII gave X in which transesterification as well as lactonization occurred.[9] Support for this formulation was found in the analytical data and in the subsequent reaction on X. On catalytic reduction of X[8] an acidic compound XI, m.p. 141–142° with gas evolution, was obtained. Saponification of XI gave XII, m.p. 80–85°, which could not be purified. The malonic acid (XII) lost carbon dioxide when heated to produce IX, identical to that previously prepared.

By acid hydrolysis, α-amino-γ-3,4,5-trimethoxyphenylbutyric acid was obtained from IX and the amino group then was blocked by formation of the phthalimido derivative. A diazoketone apparently formed in the attempted homologation since nitrogen evolution was noted on heating with

(1) Paper VI, *J. Org. Chem.*, in press.

(2) Public Health Service Research Fellow of the National Cancer Institute, 1951–1953. A part of the doctoral research of Grant Thompson.

(3) This general attack toward colchicine, with final closure of the C ring, is suggested also in the work of H. Rapoport and J. E. Campion, THIS JOURNAL, **73**, 2239 (1951); E. C. Horning and J. Koo, *ibid.*, **73**, 5830 (1951); D. S. Tarbell, *et al.*, *ibid.*, **74**, 6263, 6266 (1952); A. G. Anderson, Jr., and H. F. Greef, *ibid.*, **74**, 5203 (1952); J. Koo, *et al.*, *ibid.*, **75**, 720, 1625 (1953). An alternate attack in which the B ring is the final ring closed is that of C. D. Gutsche, *et al.*, *ibid.*, **73**, 786 (1951); **75**, 2579 (1953); V. Boekelheide and F. C. Pennington, *ibid.*, **74**, 1558 (1952); T. Nozoe, *et al.*, *Proc. Jap. Acad.*, **28**, 32, 291 (1952); D. Ginsberg and R. Pappo, THIS JOURNAL, **75**, 1094 (1953).

(4) Note that 2,3-dimethoxy-9-benzamidobenzosuberyl acids have been reported: J. Koo, *ibid.*, **75**, 723 (1953).

(5) K. Balenović and D. Fleš, *J. Org. Chem.*, **17**, 347 (1952).

(6) A. L. Wilds and A. L. Meader, Jr., *ibid.*, **13**, 763 (1948).

(7) H. R. Snyder and C. W. Smith, THIS JOURNAL, **66**, 350 (1944).

(8) E. C. Horning and D. B. Reisner, *ibid.*, **71**, 1036 (1949).

(9) This behavior with γ-ketoesters is known: R. Adams, ed., "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 191–192.

benzyl alcohol. All attempts to isolate material after saponification of the supposed benzyl ester of the aminovaleric acid failed.

The assistance of a Frederick Gardner Cottrell Grant is gratefully acknowledged.

Experimental[10]

α-Amino-γ-phenylbutyric Acid (III).—A solution containing 3.72 g. (0.162 mole) of sodium in 300 cc. of absolute ethanol and 35.4 g. (0.163 mole) of acetamidomalonic ester[11] (m.p. 96–98°) was refluxed for 15 minutes. β-Phenylethyl bromide (30.0 g., 0.162 mole) was added and refluxing was continued for 12 hours. The hot alcoholic solution was filtered from sodium bromide, acidified with acetic acid and the alcohol was removed by distillation at 40 mm. pressure. The residue was treated with water until no more oil separated and crystallization occurred after several minutes. The colorless ethyl α-acetamido-α-carbethoxy-γ-phenylbutyrate weighed 23.7 g. (0.074 mole, 45%) and melted at 110–114°. Recrystallization five times from aqueous ethanol gave colorless needles, m.p. 115.5–117.5°.

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21. Found: C, 63.75; H, 7.32.

The crude ester (23.7 g.) was refluxed with 200 cc. of 6 *N* hydrochloric acid for 4 hours. Neutralization of the cooled solution with ammonia precipitated a white powder which was filtered and washed with alcohol. Dried *in vacuo*, the product weighed 11.8 g. (0.066 mole, 89%), m.p. 290–293° dec.; reported[12] m.p. 305–306° cor.

α-Phthalimido-γ-phenylbutyric Acid.—A well powdered mixture of 5.0 g. (0.028 mole) of the aminoacid and 4.15 g. (0.028 mole) of phthalic anhydride following a reported procedure[5] gave 7.4 g. of product (0.24 mole, 85%) from benzene which melted at 139.5–142°. Repeated crystallization from ethyl acetate–petroleum ether (70–90°) gave clusters of tiny needles, m.p. 142.5–144°.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89. Found: C, 70.04; H, 4.87.

β-(*o*-Carboxybenzamido)-δ-phenylvaleric Acid (VI).—The acid chloride of the phthalimidobutyric acid was prepared from 8.0 g. (0.026 mole) of the acid and 8 cc. (0.11 mole) of purified thionyl chloride.[5] The oily acid chloride in 30 cc. of dry benzene was added over a 40-minute period to an ice-cold ether solution of diazomethane (from 15 g. of N-nitrosomethylurea) with mechanical stirring. After 60 minutes at 0° and 60 minutes stirring while the solution came to room temperature, the ether and excess diazomethane were distilled *in vacuo* leaving the diazoketone (IV) as a yellow oil.

A solution containing 40 cc. of benzyl alcohol and 40 cc. of γ-collidine was added to the diazoketone and the flask was immersed in a pre-heated oil-bath at 180–190°.[6] After 20 minutes, evolution of nitrogen ceased. The product was cooled and dissolved in ether, the solution was washed with dilute hydrochloric acid and water and the solvent was removed by distillation. The benzyl ester V was saponified directly by refluxing with 40 cc. of methanol and 40 cc. of 40% potassium hydroxide. The methanol was removed by distillation and the ether-washed alkaline solution was acidified. A sticky brown solid separated. It dissolved in 10% sodium bicarbonate and, after treatment with carbon, reprecipitated on acidification as a tan solid, m.p. 90–115° dec.; 4.7 g. Purification from ethyl acetate gave 2.0 g., m.p. 149.5–150.5° dec. Recovery (using ethyl acetate) of 1.3 g. from the mother liquor from the brown sticky solid brought the total yield of VI from the phthalimidobutyric acid to 37%.

After three additional recrystallizations from ethyl acetate, VI was obtained as colorless rosettes, m.p. 150.5–151° (slight gas evolution).

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61. Found: C, 66.73; H, 5.61.

β-Amino-δ-phenylvaleric Acid.—The acid VI (3.3 g., 0.0097 mole) was refluxed for 12 hours with 60 cc. of 6 *N* hydrochloric acid. The cooled solution was extracted four times with ether and the aqueous solution was evaporated to dryness. The tan hydrochloride was dissolved in hot absolute ethanol, filtered and the alcohol was distilled as benzene was added. On cooling, 1.9 g. (0.0083 mole, 86%) of colorless needles, m.p. 178–180° dec., was obtained and an additional 100 mg., m.p. 165–167° dec., was recovered from the filtrate. After five recrystallizations from ethanol–benzene it melted at 185–187°.

Anal. Calcd. for $C_{11}H_{16}NO_2Cl$: C, 57.51; H, 7.02. Found: C, 57.41; H, 7.02.

From 1.7 g. (0.0074 mole) of recrystallized hydrochloride in 6 cc. of water there was obtained by the addition of concentrated ammonia to a *p*H 6, 1.2 g. of a colorless solid, m.p. 216–217° dec. An additional 80 mg. from the filtrate gave a total yield of 89%. The compound, recrystallized three times from hot water, formed plates, m.p. 220–221° dec.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.32; H, 7.83.

The crude amino acid (1.2 g., 0.0062 mole) in 2.1 cc. of 3 *N* sodium hydroxide at 0° was treated with 1.0 cc. (0.011 mole) of acetic anhydride and 3.9 cc. of 3 *N* sodium hydroxide, added over a 30-minute period. After standing at room temperature for 1 hour, the solution was acidified. The colorless **N-acetyl derivative** separated, 1.15 g. (0.0049 mole, 79%), m.p. 120–123°. After four crystallizations from water, long thin needles, m.p. 122–124°, were obtained.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.29. Found: C, 66.65; H, 7.27.

7-Acetamidobenzosuberone (I).—A solution of 400 mg. (0.00170 mole) of the acetamidovaleric acid in 8.0 g. of polyphosphoric acid was heated for 20 minutes in an oil-bath at 125°. The slightly cooled dark cherry-red solution was treated with ice and water and then extracted five times with ethyl acetate. The ethyl acetate solution was washed with 5% sodium bicarbonate and with water. Distillation of the ethyl acetate gave 280 mg. (0.00129 mole, 76%) of a yellow oil which crystallized, m.p. 99–103°. After five recrystallizations from ethyl acetate–petroleum ether (65–110°) the melting point was 109.5–110.5°. After drying at 0.1 mm. for 8 hours at 55° it melted at 117.5–118.5°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 71.37; H, 7.02.

The **oxime**[13] was obtained in 62% yield and after repeated recrystallization from methanol, melted at 240–241° dec.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.40; H, 6.93.

3,4,5-Trimethoxyphenacyl Bromide.—3,4,5-Trimethoxyacetophenone was obtained from 3,4,5-trimethoxybenzoyl chloride and sodium malonic ester[14] followed by hydrolysis.[15]

A solution of 6.0 g. (0.029 mole) of the acetophenone in 280 cc. of anhydrous ether at 0° was treated with 5.4 g. (0.0034 mole) of bromine in 180 cc. of dry ether, also at 0°. The mixture was swirled in an ice-bath and exposed to a 150-watt light bulb. The solution was colorless after 5 minutes. After 1 hour at 0°, the ether solution was washed with water, dried and the ether removed by distillation. The solid after recrystallization from ethanol gave 7.2 g. (0.025 mole, 86%) of colorless needles, m.p. 63–67°; reported[16] m.p. 64°, 51.2°.

Ethyl α-Acetamido-α-carbethoxy-β-3,4,5-trimethoxybenzoylpropionate (VII).—Sodium ethoxide was prepared by refluxing with stirring 380 cc. of dry benzene and 5.8 cc. of absolute ethanol with 2.02 g. of sodium hydride for 1 hour. A warm solution containing 18.4 g. of acetylaminomalonic ester in 190 cc. of dry benzene was added and the refluxing was continued for 3.5 hours. After the addition of 22.9 g. (0.0793 mole) of the above phenacyl bromide and refluxing with stirring for 16.5 hours, the cooled solution was treated with water and concentrated hydrochloric acid. The aqueous layer was twice extracted with ethyl acetate and the

(10) Melting points are uncorrected.

(11) Conveniently available from oximinomalonic ester, prepared according to ref. 7, and reductively acetylated following J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, p. 370.

(12) V. du Vigneaud and O. J. Irish, *J. Biol. Chem.*, **122**, 349 (1938).

(13) W. E. Bachmann and C. H. Boatner, THIS JOURNAL, **58**, 2097 (1936).

(14) H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, *ibid.*, **70**, 4181 (1948).

(15) H. G. Walker and C. R. Hauser, *ibid.*, **68**, 1386 (1946).

(16) K. Hayashi, *Acta Phytochim. (Japan)*, **8**, 65 (1934); W. Baker, W. M. Morgans and R. Robinson, *J. Chem. Soc.*, 374 (1933).

combined organic layers, after washing with water, were distilled to dryness. The residue after digestion with petroleum ether (60–90°) weighed 29.4 g. (0.0717 mole, 90.4%), m.p. 138–150°. Repeated purification from ethyl acetate–petroleum ether (65–110°) gave colorless needles, m.p. 152–153°.

Anal. Calcd. for $C_{20}H_{27}NO_9$: C, 56.46; H, 6.39. Found: C, 56.82; H, 6.40.

α-Acetamido-β-3,4,5-trimethoxybenzoylpropionic Acid.—A solution containing 8.5 g. (0.02 mole) of the alkylation product in 100 cc. of 10% potassium hydroxide and 30 cc. of ethanol was refluxed for 3 hours. After distillation of the alcohol at 20 mm. pressure and extraction with ether, the alkaline layer was acidified with dilute hydrochloric acid. The solid obtained (VIII) weighed 6.6 g. (0.018 mole, 89%) and melted at 132–134° (dec.). It decomposed during attempted recrystallization.

By heating at 160° under nitrogen, 6.0 g. (0.016 mole) of the malonic acid gave 5.0 g. (0.015 mole, 95%) of solid, m.p. 168.5–170°. By treatment with charcoal and recrystallization from water, colorless needles were obtained, m.p. 169.5–170.5°.

Anal. Calcd. for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.88. Found: C, 55.27; H, 5.69.

α-Acetamido-γ-3,4,5-trimethoxyphenylbutyric Acid (IX).—Reduction of 9.0 g. (0.028 mole) of the above keto acid in 75 cc. of acetic acid with 3.0 g. of 5% palladium–carbon[8] at 30 lb. pressure and 55° gave 7.5 g. (0.024 mole, 87%) of the butyric acid, m.p. 174–176°. After five crystallizations from water, the compound melted at 175–176.5°.

Anal. Calcd. for $C_{15}H_{21}NO_6$: C, 57.86; H, 6.80. Found: C, 58.06; H, 6.58.

A mixture with the keto acid melted at 152–162°.

α-Acetamido-α-carboisopropoxy-γ-hydroxy-γ-3,4,5-trimethoxyphenylbutyric Acid Lactone (X).—A solution containing 5.3 g. (0.012 mole) of VII in 20 cc. of isopropyl alcohol was added to a solution of aluminum isopropoxide (from 0.5 g. of aluminum) in 10 cc. of isopropyl alcohol. After 18.5 hours of refluxing, no additional acetone formation could be detected.[17] The residue after distillation of the solvent at 20 mm. pressure was acidified with dilute hydrochloric acid. The solid which precipitated and material obtained by benzene extraction of the filtrate were combined and recrystallized from ethyl acetate. The first crop, m.p. 181–184° (2.95 g.), and a second, m.p. 180–183° (0.55 g.), brought the yield to 73%. Six recrystallizations from ethyl acetate gave colorless plates, m.p. 183–184.5°. The compound was insoluble in cold 5% sodium hydroxide but dissolved on warming.

Anal. Calcd. for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37. Found: C, 58.13; H, 6.44.

α-Acetamido-α-carboisopropoxy-γ-3,4,5-trimethoxyphenylbutyric Acid (XI).—Hydrogenation of 1.0 g. (0.0025 mole) of the lactone (X) with 5% palladium–carbon as above gave 0.9 g. (0.0023 mole, 89%) of colorless crystals, m.p. 136–138° dec. After four recrystallizations from aqueous ethanol, colorless plates, m.p. 141–142° dec., were obtained. The compound was soluble in aqueous sodium bicarbonate.

Anal. Calcd. for $C_{19}H_{27}NO_8$: C, 57.42; H, 6.85. Found: C, 57.52; H, 7.27.

α-Acetamido-γ-3,4,5-trimethoxyphenylbutyric Acid (IX).—A solution containing 0.7 g. (0.0018 mole) of the malonic half-ester in 10 cc. of 5% sodium hydroxide was refluxed for 1 hour. On acidification 0.4 g. (0.0011 mole, 64%) of the malonic acid (XII), m.p. 80–85° dec., was obtained.

The crude malonic acid (0.2 g., 0.00056 mole) after 15 minutes at 140° (20 mm.) gave a glassy solid which dissolved in hot water. On cooling, 0.12 g. (0.00039 mole, 68%) of colorless needles was obtained, m.p. 156–168°. Further crystallization from water gave material, m.p. 169–172°, which melted at 172.5–175.5° when mixed with IX above.

α-Amino-γ-3,4,5-trimethoxyphenylbutyric Acid.—A solution containing 3.0 g. (0.0096 mole) of IX in 15 cc. of 3 *N* hydrochloric acid was refluxed for 1 hour. The ice-cold solution was adjusted to *p*H 6 by addition of ammonia. The colorless precipitate which then appeared weighed 2.1 g. (0.0078 mole, 78%), m.p. 223–226° dec. After further purification from water colorless needles were obtained, m.p. 225.5–227.5° dec.

Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11. Found: C, 58.20; H, 7.15.

α-Phthalimido-γ-3,4,5-trimethoxyphenylbutyric Acid.—A mixture of 2.0 g. (0.0074 mole) of the aminoacid and 1.1 g. of phthalic anhydride was heated for 15 minutes in a bath at 145°. The residue (2.8 g., 0.0070 mole, 94%) melted at 190–196° and after four recrystallizations from ethanol, at 197.5–199°.

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30. Found: C, 63.41; H, 5.41.

The phthalimidobutyric acid was submitted to the Arndt–Eistert reaction[6] analogous to the model compound above. After saponification, the expected valeric acid could not be purified.

(17) Reference 9, p. 203.

SALT LAKE CITY 1, UTAH

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Unsymmetrical Quaternary Carbon Compounds. II. The Comparative 1,4-Additions of Grignard Reagents to Several Conjugated Systems[1]

BY FRANKLIN S. PROUT, ELIZABETH P.-Y. HUANG, ROBERT J. HARTMAN AND CHARLES J. KORPICS

RECEIVED OCTOBER 28, 1953

The reactions of *n*-alkyl, aryl and benzyl organometallic reagents with five isopropylidene conjugated systems have been compared. The 1,4-addition products were major products in all cases except one. Grignard additions to ethyl isopropylidenecyanoacetate were most dependable. Additions with organocadmium compounds were poor with alkyl and aryl reagents but excellent with dibenzylcadmium.

The work of Alexander, McCollum and Paul[2] and the results reported in the first paper of this series[3] implied that the *sec*-alkylidenecyanoacetic esters were the most effectively alkylated of this class of compounds.[4] In order to test this conclusion we have examined the 1,4-addition to five conjugated isopropylidene compounds—ethyl isopropylidenecyanoacetate, ethyl isopropylidenemalonate, isopropylidenemalononitrile, isopropylidenecyanoacetic acid and potassium isopropylidenecyanoacetate—with *n*-butylmagnesium bromide, phenylmagnesium bromide, benzylmagnesium chloride and some organocadmium compounds. Furthermore, the addition reactions of ethyl *sec*-butylidenecyanoacetate were extended to aryl and benzyl Grignard reagents.

(1) Abstracted in part from the thesis for Master of Science of Elizabeth P.-Y. Huang, June, 1953, and from the theses for Bachelor of Science of Robert J. Hartman and Charles J. Korpics, June, 1952.

(2) E. R. Alexander, J. D. McCollum and D. E. Paul, THIS JOURNAL, **72**, 4791 (1950).

(3) F. S. Prout, *ibid.*, **74**, 5915 (1952).

(4) See reference 3 for a bibliography of examples of this reaction.