[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Syntheses Utilizing γ-Cyano-γ-phenylpimelonitrile

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Procedures for obtaining many derivatives from γ-cyano-γ-phenylpimelonitrile have been developed. An overall idea of the reactions studied is best obtained by examination of charts I to VII in the experimental part of this paper.

When Bruson and Riener reported[1] that benzyl cyanide and acrylonitrile reacted to form γ-cyano-γ-phenylpimelonitrile in good yield, it was at once apparent that the product afforded easy syntheses of interesting compounds distantly related to morphine. An investigation of the synthetic possibilities was begun, but it was interrupted in 1944 by the war. Since attempts to convert nitrogenous substances in the series to amines by sodium and alcohol were failures, the work was not published. However, in view of recent interest in some of the compounds involved,[2,3] it appears advisable to report the old synthetic work. It is planned to resume the study now, and to take advantage of the reducing properties of the metal hydrides.

In the interest of brevity, only positive results are presented. This is done in Charts I to VII. Cross references between important compounds depicted in the charts and descriptions in the text are made by parenthesized numbers. It has been found conducive to clarity to preserve numerical rather than chemical sequence in the text, so that in reading, one should follow the order indicated by arrows in the charts.

Many of the analytical results were obtained by the author. It is a pleasure to acknowledge help by Roger Amidon, Mrs. R. A. Barnes, J. S. Buckley, Mrs. O. Hamarston, W. C. Kuryla, and S. A. Sundet for others.

EXPERIMENTAL

(1) A mixture of 1 g. of (5) and 10 ml. of 5% sodium hydroxide was boiled for 5 min., then cooled and acidified. The resulting *γ-carbamyl-γ-phenylpimelic acid* formed prisms from water, m.p. 178–179° with foaming; reported[3] 177–178°, dec. 179°.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; neut. equiv., 138. Found: C, 60.4; H, 6.23; neut. equiv., 139.

(2) A paste made from 75 ml. of sulfuric acid and 25 g. of (5) at 10° was kept at 10–15° while a mixture of 25 ml. of nitric acid (1.42) in 25 ml. of sulfuric acid was stirred in during 45 min. After 15 min. more, the mixture was poured on ice, and the solid product was removed and washed well with water (28.7 g. = 98%). Crystallization from 110 ml. of 10% acetic acid gave 25.4 g. of *3-p-nitrophenyl-2,6-piperidinedione-3-propionic acid*, colorless prisms, m.p. 176–178°.

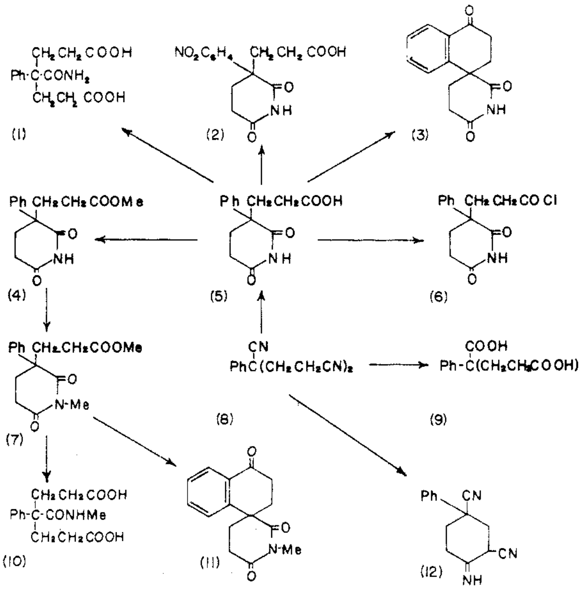

Chart I

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.9; H, 4.61. Found: C, 55.0; H, 4.69.

Hydrogenation of 10 g. of this nitro compound in 70 ml. of alcohol using platinum oxide took place rapidly. The product crystallized when it was kept for a week with ethyl acetate, and then became nearly insoluble in ethyl acetate, even hot. Recrystallization from water with very slow cooling gave 6.7 g. of *3-p-aminophenyl-2,6-piperidinedione-3-propionic acid*, yellowish prisms, m.p. 186–188°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.84. Found: C, 60.6; H, 5.99.

A solution of 0.5 g. of the amino acid in 5 ml. of water containing 0.5 ml. of sulfuric acid was treated at 0° with 0.2 g. of sodium nitrite. After a few minutes a solution of 1 g. of potassium iodide was added, and the mixture was boiled. The resulting oil (0.7 g.) crystallized when it was rubbed with ether; recrystallization from dilute acetic acid gave yellow plates, m.p. 182–184°, *3-p-iodophenyl-2,6-piperidinedione-3-propionic acid.*

Anal. Calcd. for $C_{14}H_{14}INO_4$: C, 43.4; H, 3.62. Found: C, 43.4; H, 3.80.

(3) A mixture of 200 g. of (5) and 500 ml. of sulfuric acid was heated on a boiling water bath for 1.25 hr., then cooled and poured on ice slowly and with stirring so that the product separated directly as a crystalline powder. This was pressed on a filter and washed with 2 × 500 ml. of cold water. (The combined mother liquors deposited 9 to 13 g. of crude product on keeping for several days.) The main part of the material was suspended in cold water and stirred while dilute sodium carbonate was added to slightly basic reaction. This gave a nearly pure product in 77–82% yield. Recrystallization from acetone gave spiro-*1,2,3,4-tetrahydro-4-naph-*

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[1] H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, 65, 23 (1943).

[2] A. D. Campbell, *J. Chem. Soc.*, 1377 (1954).

[3] J. M. D. Blair and D. H. Hey, *J. Chem. Soc.*, 2921 (1957).

thalenone-[1:3']-2',6'-piperidinedione, needles, m.p. 201–202° (β-form); when the melt was kept at 202° it solidified during 5 min. and then melted at 204–205°. The higher melting α-form separated directly from 25% acetic acid as plates. (Only one form has been reported,[2] m.p. 198°.)

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.39. Found: (β) C, 69.1; H, 5.67; (α) C, 69.2; H, 5.52.

A solution of 1.2 g. of (3) in 5 ml. of alcohol and 5 ml. of acetic acid was treated with 0.5 g. of phenylhydrazine, warmed for 5 min., then diluted with water and cooled. Recrystallization from 50 ml. of dilute alcohol gave 1.3 g. of the phenylhydrazone, nearly colorless needles, m.p. 180–182°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.0; H, 5.74. Found: C, 71.9; H, 6.03.

When 1.5 g. of the above phenylhydrazone was boiled for a few minutes with 20 ml. of 2% sodium hydroxide, a pale yellow solution was formed. The product was precipitated with acetic acid and crystallized from 100 ml. of acetic acid by diluting the hot solution with water, giving 1.3 g. of the *phenylhydrazone of 4-carbamyl-1,2,3,4-tetrahydro-1-naphthalenone-4-propionic acid,* bronze prisms, m.p. 230° with effervescence, soluble immediately in cold dilute sodium carbonate.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.4; H, 6.02. Found: C, 68.7; H, 6.12.

(4) A solution of 100 g. of (5) and 25 ml. of sulfuric acid in 250 ml. of methanol was boiled for 3 hr., then cooled and treated with water and ether. Acidic material was removed by washing with dilute sodium carbonate, but the neutral product formed a colorless glass (99 g.) that did not crystallize when it was kept under ether-ligroin during 4 winter months. Pure *methyl 3-phenyl-2,6-piperidinedione-3-propionate* was obtained as a colorless glass by distillation, b.p. 251° at 9 mm. After about a year, the compound crystallized, then formed prisms from ether-ligroin, m.p. 75–76°.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.5; H, 6.22. Found: C, 65.5; H, 6.43.

(5) When a mixture of 175 g. of (8) with 400 ml. of water and 500 ml. of concd. hydrochloric acid was boiled and stirred, the organic material became crystalline after 1.5 hr. After 2.5 hr., the mixture was cooled, and the product was removed and washed with water; yield 91–98%, m.p. 169–171°. Recrystallization from 15 volumes of water gave *3-phenyl-2,6-piperidinedione-3-propionic acid* in the form of plates, m.p. 170–171°; (reported 165°,[2] 167–169°[3]).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.3; H, 5.91.

(6) When 2 ml. of thionyl chloride was added to 1 g. of (5), rapid evolution of gas took place. The mixture was kept at 35° for 15 min., then excess thionyl chloride was removed at 50° under reduced pressure. The residue crystallized when it was rubbed with a little ether; recrystallization from benzene-ligroin gave *3-phenyl-2,6-piperidinedione-3-propionyl chloride* in nearly quantitative yield; m.p. 101–103°.

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.1; H, 5.01. Found: C, 60.1; H, 5.10.

(7) A solution of 0.6 g. of sodium in 15 ml. of methanol was treated with 6.1 g. of (4) and then with 5 ml. of methyl iodide; after the spontaneous reaction was over, the mixture was boiled for 15 min., until it became neutral. Methanol was removed under reduced pressure, and the residue was taken up in ether and washed with dilute sodium hydroxide. Distillation gave *methyl 1-methyl-3-phenyl-2,6-piperidinedione-3-propionate,* a colorless viscous oil, 5.2 g., b.p. 232–235° at 9 mm.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.62. Found: C, 66.0; H, 6.61.

(8) γ-Cyano-γ-phenylpimelonitrile was prepared by the method of Bruson and Riener[1] and used without recrystallization; m.p. 70–72°; yield 85–95% in 2-mol. batches. About 12 kg. of the compound was used in the present research.

(9) Four hundred ml. each of water and concd. sulfuric acid were mixed in a 3-liter two necked flask fitted with a condenser and a stopper. The mixture was heated to boiling, the source of heat was removed, and 200 g. of γ-cyano-γ-phenylpimelonitrile was introduced in 50-g. portions, the mixture being swirled by hand after each addition. About 5 min. was allowed between each portion, so that the exothermic first stage of the hydrolysis might be completed. The mixture was boiled for 5 hr., then poured into 500 ml. of water, stirred until the original oily precipitate was completely crystalline, and kept overnight. The product was pressed out on a suction filter, using nitrated filter paper, and washed with a cold mixture of 40 ml. of water and 60 ml. of concd. hydrochloric acid. The still moist filter cake was dissolved in 300 ml. of warm water, 400 ml. of concd. hydrochloric acid was added, and the solution was stirred and cooled slowly, finally to 0°, so that the product separated crystalline directly. It was washed on a filter with 100 ml. of 1:1 hydrochloric acid and dried at 80°, giving 220–230 g. (88–92%) of pure γ-hydroxy-γ-phenylpimelic acid, m.p. 155–157° (reported[4] 153–154°).

(10) A mixture of 1.5 g. of (7) and 5 ml. of 10% sodium hydroxide gave a clear solution when it was boiled for 10 min.; boiling was continued to 20 min., and the solution was then acidified. The oily precipitate crystallized when it was rubbed with ether. Recrystallization from water gave 1.7 g. of *γ-N-methylcarbamyl-γ-phenylpimelic acid,* prisms, m.p. 182–183° with gas evolution.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.53. Found: C, 61.6; H, 6.81.

(11) A solution of 1 g. of (7) in 3 ml. of sulfuric acid was heated at 95° for 40 min., then cooled and poured on ice. The product was taken up in ethyl acetate and washed with dilute sodium carbonate. It crystallized slowly when it was rubbed with ethyl acetate–ligroin, and was then recrystallized from 50% alcohol, giving 0.6 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-1'-methyl-2',6'-piperidinedione,* coarse white needles, m.p. 142–143°; another preparation (14).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.88. Found· C, 70.1; H, 6.19.

(12) To a solution of 2.3 g. of sodium in 25 ml. of absolute alcohol was added 22.3 g. of γ-cyano-γ-phenylpimelonitrile. The thick paste became yellow-brown and fluid when it was heated on a water bath, and after about 10 min. crystals started to form. Heating was continued for 30 min., until the mixture had nearly completely solidified. A solution of 6 g. of acetic acid in 50 ml. of water was then added, and the crystalline material was removed and washed with water, alcohol, and ether. Crystallization from 50% alcohol containing a few drops of ammonia gave 12 g. of *2,4-dicyano-4-phenylcyclohexanonimine,* large nearly colorless plates and needles, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.3; H, 5.87; N, 18.8. Found: C, 75.4; H, 5.85; N, 18.7.

(13) A mixture of 12 g. of (17), 60 ml. of acetic acid, 6 g. of butyl nitrite, and 1 ml. of hydrochloric acid was warmed to 50°, whereupon a slightly exothermic reaction took place and the solid dissolved. After it had been kept overnight, the mixture deposited 7.1 g. of spiro-*3-oximino-1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-2',6'-piperidinedione,* small tan prisms, that darkened above 200° and melted at 238° with gas evolution and blackening.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.7; H, 4.44. Found: C, 62.0; H, 4.55.

(14) A solution of 1 g. of sodium in 25 ml. of absolute alcohol was treated with 10 g. of (17) and then with 5.5 g. of methyl sulfate. A vigorous reaction took place and the sodio derivative dissolved. Addition of water gave an oil which crystallized when it was seeded; washing with ether and crystallization from dilute alcohol gave 5.3 g. of spiro-

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(4) M. Rubin and H. Wishinsky, *J. Am. Chem. Soc.*, **68**, 828 (1946).

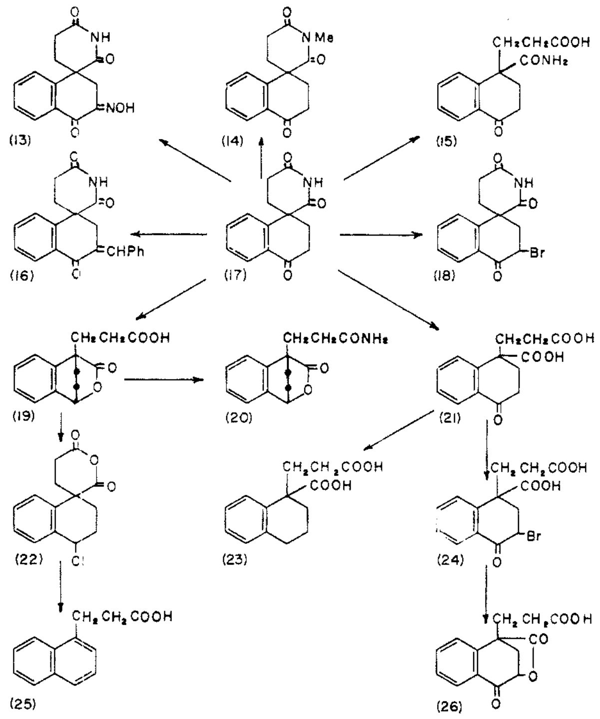

Chart II

1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-1′-methyl-2′,6′-piperidinedione, m.p. 142–143°, identical with (11).

(15) A suspension of 0.3 g. of (17) in 6 ml. of cold water dissolved immediately when 1 ml. of 40% sodium hydroxide was added. If the solution was acidified at once, unchanged (17) precipitated, but if it was boiled for 2 min., then cooled and acidified, no immediate precipitate was formed. When the acidified solution was kept, 0.25 g. of coarse needles slowly separated. Recrystallization from water gave *4-oxo-1,2,3,4-tetrahydro-1-naphthalenecarboxamide-1-propionic acid,* m.p. 197–198° with gas evolution.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.6; H, 5.80.

(16) A solution of 1 g. of (17) in 10 ml. of 2% sodium hydroxide was treated with 0.6 g. of benzaldehyde, boiled for 5 min., then cooled and acidified. The precipitate was removed, dried, and boiled for 2 min. with 5 ml. of acetic anhydride. Addition of water and crystallization from dilute acetic acid gave 0.55 g. of spiro-*3-benzal-1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2,6-piperidinedione,* faintly yellow plates, m.p. 228–230°.

Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.1; H, 5.17. Found: C, 76.3; H, 5.19.

(17) See (3), Chart I.

(18) A solution of 12.1 g. of (17) in 60 ml. of acetic acid was treated with 8 g. of bromine and then warmed to 60°. The solution was then cooled, giving 14.1 g. of crystalline product. Recrystallization from dilute acetic acid gave spiro-*3-bromo-1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′,6′-piperidinedione,* colorless prisms, m.p. 208–210° with gas evolution.

Anal. Calcd. for $C_{14}H_{12}BrNO_3$: C, 52.2; H, 3.73. Found: C, 52.2; H, 3.81.

(19) A solution of 1 g. of (26) in 20 ml. of 1% sodium hydroxide was treated successively with two 6-g. portions of 3% sodium amalgam. After 1 hr., the solution was acidified. When it was heated, the solution deposited an oil. Extraction with ether removed a gum (0.7 g.) which furnished 0.2 g. of material m.p. 164–168°.

Large scale preparations were made as follows. A solution of 24 g. of (17) in 100 ml. of 10% sodium hydroxide was boiled for 15 min. while ammonia and 25 ml. of water were allowed to distil. The solution was cooled, treated with 3 g. of Raney nickel and shaken under hydrogen at 40 p.s.i. for 24 hr., or until one equivalent of hydrogen had been absorbed. The mixture was filtered, treated with 10 ml. of sulfuric acid, and heated to boiling. Addition of 45 ml. of acetic acid gave a clear solution, which deposited 7.8 g. of crystals when it was cooled and seeded. The mother liquor was boiled under reflux for 30 min., then cooled and seeded, giving an additional 5.6 g. of crystalline product. Recrystallization from 20% acetic acid (charcoal) gave 11.4 g. of pure *4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionic acid,* colorless prisms, m.p. 167–168°. For another preparation, see (47).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.73; neut. equiv., 246. Found: C, 68.3; H, 5.96; neut. equiv., 240.

A solution of 6.6 g. of (19) and 5 ml. of sulfuric acid in 30 ml. of methanol was boiled for 1 hr., then cooled and treated with ether and water. The ether solution was washed with dilute sodium carbonate and evaporated at 100° and 20 mm., leaving 6.8 g. of a colorless oil that could not be crystallized. *Methyl 4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionate* was obtained by distillation, b.p. 220–223° at 17 mm., as a colorless viscous oil.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.20. Found: C, 69.3; H, 6.90.

(20) A mixture of 0.5 g. of (19) and 3 ml. of thionyl chloride was kept at room temperature for 15 min., then warmed to 45° under reduced pressure. The residue was taken up in dry ether and shaken for 1 min. with iced ammonium hydroxide, giving an oil which rapidly crystallized. Recrystallization from water containing a few drops of acetic acid gave 0.4 g. of *4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionamide,* colorless prisms, m.p. 168–169°. The amide was not soluble in 10% sodium carbonate, and a mixture with (19) had m.p. 140–150°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.16. Found: C, 68.8; H, 6.04.

(21) A solution of 12 g. of (17) and 6 g. of sodium hydroxide in 30 ml. of water was boiled for 4 hr., then cooled and acidified. The resulting red oil solidified when it was rubbed with a little ether. Washing with ether and then recrystallization from water gave 6.5 g. of pink crystals, m.p. 165–170°. This was treated with charcoal in ethyl acetate, then recrystallized from water, giving 5.5 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid,* m.p. 170–171°. A better preparation is described in (46). The form m.p. 135–136°, then 167°[2] was not encountered in the present work.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.38; neut. equiv., 131. Found: C, 64.0; H, 5.33: neut. equiv., 132.

(22) A mixture of 22.5 g. of (19) with 45 ml. of thionyl chloride was boiled for 2 hr., and then excess reagent was removed at 100° under reduced pressure. The brown solid residue was recrystallized from benzene containing a few drops of acetyl chloride, giving 6.3 g. of spiro-*4-chloro-1,2,3,4-tetrahydronaphthalene-[1:3′]-2′,6′-pyrandione,* colorless needles, m.p. 163–165° with gas evolution.

Anal. Calcd. for $C_{14}H_{13}ClO_3$: C, 63.5; H, 4.95. Found: C, 63.5; H, 5.00.

When 0.5 g. of this chloro anhydride was boiled for 15 min. with 6 ml. of 5% sodium carbonate, it gave a clear solution. Acidification in the cold gave no precipitate, but boiling 5 min. caused separation of an oil that slowly solidified. Recrystallization from 10% acetic acid gave 0.2 g. of lactone-acid (19).

(23) Five grams of (21) and 5 g. of amalgamated zinc were boiled for 4 hr. with excess hydrochloric acid. The organic product was distilled at 20 mm. and the resulting anhydride was boiled with dilute sodium carbonate until it dissolved. Crystallization from dilute acetic acid gave *1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid,* colorless prisms, m.p. 148–149°; yield 60%. The compound was reported[2] as "semisolid."

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.50. Found: C, 68.0; H, 6.57.

(24) When a solution of 8.7 g. of (21) in 10 ml. of acetic acid was treated with 5.4 g. of bromine and warmed gently, the bromine rapidly disappeared. Keeping the solution for 30 min. gave a nearly solid mass of gray crystals, which were removed and washed with acetic acid and water; 9.6 g. = 85%. Recrystallization from acetic acid led to decomposition, but crystallization from ethyl acetate–ligroin (charcoal) gave 6.9 g. of *3-bromo-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid,* faintly yellow plates, m.p. 183–185° with blackening and gas evolution.

Anal. Calcd. for $C_{14}H_{13}BrO_5$: C, 49.3; H, 3.82; Br, 23.4. Found: C, 49.1; H, 4.03; Br, 23.4.

(25) One-half gram of (22) was heated at 190° until hydrogen chloride evolution stopped, and the brown residue was distilled at 20 mm. The partly crystalline distillate was boiled out with 5% sodium carbonate, neutral material being discarded. The acidic product, 0.1 g., was identified as 1-naphthalenepropionic acid by comparison with an authentic sample kindly furnished by Dr. R. T. Arnold.

(26) Several small-scale preparations were carried out using purified (24), but for larger ones the following procedure was more convenient. A solution of 26 g. of (21) in 30 ml. of acetic acid was treated with 16 g. of bromine and kept for 2 hr. Then 50 ml. of 50% acetic acid was added, and the crystalline bromo compound was removed, washed with 25 ml. of 50% acetic acid, and finally with water. The moist product was boiled for 1 hr. with 300 ml. of water containing 30 ml. of acetic acid. When the resulting solution was kept overnight, it deposited 13.8 g. of orange crystals of nearly pure lactone. Recrystallization from dilute acetic acid (charcoal) gave *3-hydroxy-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionic acid,* coarse needles, m.p. 185–187°.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.6; H, 4.65. Found: C, 64.7; H, 4.90.

The *oxime*, obtained by boiling a solution of 0.5 of (26) and 0.5 g. of hydroxylamine sulfate in a slight excess of aqueous sodium carbonate, formed tan plates from dilute alcohol, m.p. 205° with blackening and gas evolution.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.1; H, 4.73. Found: C, 61.4; H, 5.08.

The *methyl ester*, from (26) in methanol with ethereal diazomethane or from (26) in aqueous sodium carbonate with methyl sulfate, or from (26) by boiling 15 min. with 5% methanolic hydrogen chloride, crystallized after it had been distilled, b.p. 240° at 15 mm.; it formed coarse needles from methanol, m.p. 115–116°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.15. Found: C, 65.6; H, 5.46.

(27) A mixture of 3.1 g. of (30) with 3.5 ml. of 85% hydrazine hydrate, 3.5 ml. of water, and 2 ml. of alcohol became homogeneous when it was heated on a water bath for 10 min. After 10 min. more, the mixture was evaporated at 100° under reduced pressure; 10 ml. of alcohol was added and the evaporation was repeated. The resulting glassy froth was dissolved in absolute alcohol, treated with ether to turbidity and kept for several days, when it deposited 3.1 g. of colorless crystals that melted at 88–90° to a bubble-filled froth. This was a solvated form of *3-carbamyl-3-phenylpimelanilide hydrazide.*

Anal. Calcd. for $C_{20}H_{24}N_4O_3 + C_2H_6O$: C_2H_6O, 11.1. Found, loss in weight at 75°/25 mm., 9.95.

The solvent-free residue formed a white powder, m.p. 104–107°.

Anal. Calcd. for $C_{20}H_{24}N_4O_3$: C, 65.2; H, 6.53. Found: C, 65.3; H, 6.80.

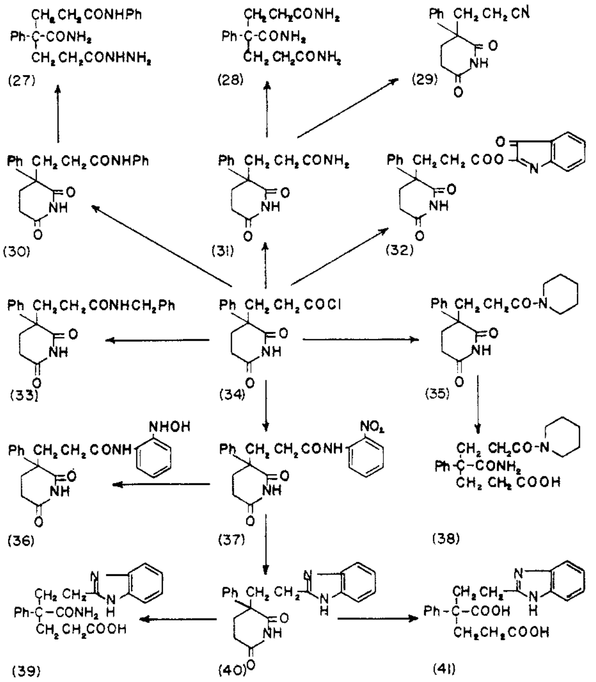

Chart III

Many fruitless experiments to carry out a Curtius degradation led only to liberation of hydrazoic acid from the intermediate amide-anilide-azide. But when the amide-anilide-hydrazide was treated with piperonal in alcohol, it was converted quantitatively into an *amide-anilide-piperonalhydrazide,* colorless prisms from ether or alcohol, m.p. 128–130°.

Anal. Calcd. for $C_{28}H_{28}N_4O_5$: C, 67.2; H, 5.6. Found: C, 68.3; H, 5.90.

(28) A suspension of 0.5 g. of (31) in 4 ml. of ammonium hydroxide became clear when it was kept for 20 hr. Evaporation at 100° under reduced pressure left a viscous oil which crystallized when it was kept moist with nitromethane for several days. Recrystallization from a small volume of water followed by washing with a little alcohol and then ether gave *3-carbamyl-3-phenylpimelamide,* colorless prisms m.p. 215–218° with gas evolution.

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.6; H, 6.91. Found: C, 60.3; H, 6.95.

(29) When a mixture of 3.8 g. of (31) with 8 ml. of thionyl chloride was boiled for 45 min., a clear solution resulted. The mixture was evaporated at 100° under reduced pressure and treated with water and ether, giving 2.8 g. of crude crystalline product. Recrystallization from dilute alcohol and then water gave 1.4 g. of pure *3-phenyl-2,6-piperidinedione-3-propionitrile,* colorless plates, m.p. 131–132°.[5]

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.83. Found: C, 69.4; H, 6.00.

(30) A solution of 6.9 g. of (34) in benzene was treated with 7 g. of aniline. The product was removed by filtration and washed with dilute hydrochloric acid, dilute sodium carbonate, and ether giving 8.3 g. of fine white crystals. Recrystallization from alcohol gave pure *3-phenyl-2,6-piperidinedione-3-propionanilide,* shining plates, m.p. 205–206°.

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.4; H, 5.99. Found: C, 71.2; H, 5.89.

(31) A solution of 6.5 g. of (34) in 25 ml. of toluene was shaken with 25 ml. of iced ammonium hydroxide for a few minutes; the product was then removed by filtration and washed with water and ether; yield 5.9 g. of nearly pure material. Crystallization from water gave *3-phenyl-2,6-piperidinedione-3-propionamide,* m.p. 201–203°.

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(5) This confirms Blair and Hey's opinion[3] that their compound $C_{14}H_{14}N_2O_2$, m.p. 201°, does not have this nitrile structure.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.20. Found: C, 64.4; H, 6.18.

(32) To a suspension of 1.4 g. of isatin in 5 ml. of chloroform and 1 ml. of pyridine was added a solution of 2.6 g. of (34) in 5 ml. of chloroform. After 30 min., the resulting deep red solution was shaken with dilute hydrochloric acid; the aqueous layer and a small amount of flocculent material were separated by centrifugation. On keeping, the chloroform deposited 1.7 g. of crystalline product. Crystallization from 35 ml. of acetic acid gave 0.9 g. of the *O-isatin ester of 3-phenyl-2,6-piperidinedione-3-propionic acid,* fine yellow needles that sintered and darkened above 220°, m.p. *ca.* 235°. Formulation as an *O*- rather than *N*- derivative was indicated by action of several different bases, which yielded only γ-carbamyl-γ-phenylpimelic acid and isatin, and not a quinolone.

Anal. Calcd. for $C_{22}H_{18}N_2O_5$: C, 67.6; H, 4.65. Found: C, 67.4; H, 4.88.

(33) A solution of 2.6 g. of (34) in 5 ml. of benzene was added to 2.5 g. of benzylamine in benzene. After 3 min., water was added resulting in the formation of 3 liquid layers. The middle layer was taken up in ethyl acetate, washed with dilute bicarbonate and with dilute hydrochloric acid, and evaporated at 100° under reduced pressure. The resulting glass crystallized when it was kept for several days under ether containing a little ethyl acetate. Recrystallization from dilute alcohol gave 2.5 g. of the *benzylamide of 3-phenyl-2,5-piperidinedione-3-propionic acid,* poorly formed prisms, m.p. 143–144°. In later preparations when seed were available, the middle liquid layer crystallized directly and better yields (2.9–3.0 g.) were obtained.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.33. Found: C, 72.1; H, 6.77.

When 0.5 g. of (33) was boiled with 5 ml. of 4% sodium hydroxide for 1 min., then cooled and acidified, *γ-carbamyl-γ-phenylpimelic acid monobenzylamide* precipitated, plates from 10% acetic acid, m.p. 164–165°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.4; H, 6.57. Found: C, 68.4; H, 6.73.

(34) See (6), Chart I.

(35) A solution of 2 g. of (34) in 20 ml. of benzene was treated with 2 g. of piperidine and kept for 1 hr. The product was washed with dilute hydrochloric acid and with sodium carbonate and crystallized from dilute alcohol, giving 2 g. of the *piperidide of 3-phenyl-2,6-piperidinedione-3-propionic acid,* small prisms, m.p. 164–166°.

Anal. Calcd. for $C_{19}H_{24}N_2O_3$: C, 69.5; H, 7.37. Found: C, 69.4; H, 7.58.

(36) A suspension of 3.8 g. of (37) and 0.1 g. of platinum oxide in 25 ml. of alcohol shaken with hydrogen at 35 p.s.i. took up 1.5 lb. (calcd. 2.1 lb.) of the gas during 4 hr., and the reaction had stopped. The reaction mixture contained a thick suspension of nearly colorless needles. The product was removed and crystallized from alcohol, giving a nearly quantitative yield of *3-phenyl-2,6-piperidinedione-3-propion-o-hydroxylaminoanilide,* faintly yellow needles, m.p. 165° with gas evolution and darkening. The compound gave a black resin when it was treated with warm dilute aqueous hydrochloric acid, or with cold methanolic hydrogen chloride.

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.4; H, 5.76. Found: C, 66.0; H, 5.77.

(37) A solution of 56 g. of (34) in 50 ml. of benzene was treated dropwise with 28 g. of *o*-nitroaniline and 20 ml. of pyridine in 50 ml. of benzene. After it had been shaken for 1 hr., the mixture was treated with excess dilute hydrochloric acid and cooled. The yellow crystalline product was removed and washed with water and ether, yield 69.5 g. Recrystallization from acetic acid gave pure *3-phenyl-2,6-piperidinedione-3-propion-o-nitroanilide,* yellow needles, m.p. 155°.

Anal. Calcd. for $C_{20}H_{19}N_3O_5$: C, 63.0; H, 5.0. Found: C, 63.1; H, 5.29.

(38) The piperidide (35) dissolved immediately when it was added to 4 ml. of 5% sodium hydroxide. The solution was boiled for 30 sec., then cooled and acidified. The product was washed with water, and then triturated with 5% sodium bicarbonate, 0.2 g. of (35) remaining undissolved. Acidification of the bicarbonate extract gave the *acid piperidide of γ-carbamyl-γ-phenylpimelic acid,* solvated needles from 20% alcohol that fell to a white powder when dried at 150°; m.p. 200–203°.

Anal. Calcd. for $C_{19}H_{26}N_2O_4$: C, 65.8; H, 7.57. Found: C, 65.9; H, 7.72.

(39) When 0.5 g. of (40) was warmed with 3 ml. of 5% sodium hydroxide for 1 min. it gave a bright yellow solution. This was cooled and acidified with hydrochloric acid, and the yellow resin resulting was caused to crystallize by rubbing with ethyl acetate. Recrystallization from alcohol by adding ether gave pure *ε-(2-benzimidazolyl)-γ-carbamyl-γ-phenyl caproic acid hydrochloride,* colorless needles, m.p. 165–167° to a bubble-filled liquid.

Anal. Calcd. for $C_{20}H_{21}N_3O_3 + HCl$: C, 62.2; H, 5.72. Found: C, 62.0; H, 5.68.

(40) A solution of 69 g. of (37) in 750 ml. of hot 35% acetic acid was treated with 50 g. of iron filings. A smooth reaction took place which was completed by warming and stirring for 2 hr. The mixture was cooled and filtered, and the filtrate was neutralized with ammonium hydroxide, and the brown crystalline precipitate was removed and dried (61.3 g.). This was crystallized from 200 ml. of alcohol using a Soxhlet extractor, giving 53 g. of *3-(β-2-benzimidazolylethyl)-3-phenyl-2,6-piperidinedione,* faintly tan plates, m.p. 260–262°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.0; H, 5.74. Found: C, 71.7; H, 6.04.

The *picrate* formed yellow needles from alcohol, m.p. 184–185°.

Anal. Calcd. for $C_{26}H_{22}N_6O_9$: C, 55.5; H, 3.94. Found: C, 55.8; H, 4.19.

(41) A mixture of 2 g. of (40) with 3 ml. of water and 10 g. of 85% potassium hydroxide was heated at 185–190° for 10 min., ammonia being evolved during the first 5 min. The mixture was cooled to about 100° and treated with enough water to allow the inorganic material to be separated by decantation. The potassium salt was dissolved in a little water and acidified strongly with hydrochloric acid. The *hydrochloride* precipitated and was purified by crystallization from alcohol-ether; tan needles, m.p. 173–175° with gas evolution; yield 1.0 g.

Anal. Calcd. for $C_{20}H_{20}N_2O_4 + HCl$: C, 61.6; H, 5.40. Found: C, 61.0; H, 6.01.

ε-(2-Benzimidazolyl)-γ-carboxy-γ-phenylcaproic acid was obtained by treating an aqueous solution of the hydrochloride with sodium acetate. Crystallization from formamide gave colorless crystals that fell to a powder at 100°, sintered at 160°, then resolidified and melted again at 192–194° with gas evolution.

Anal. Calcd. for $C_{20}H_{20}N_2O_4 + H_2O$: C, 64.9; H, 5.99. Found: C, 65.0; H, 6.21.

(42) A solution of 3 g. of (46) and 1 ml. of sulfuric acid in 10 ml. of methanol was boiled for 1 hr. and then concentrated to 0.5 volume under reduced pressure. Addition of water gave a gum which was taken up in ether and separated with dilute sodium carbonate into a neutral part (0.8 g.) and an acid (2.0 g.). The latter was crystallized from ether-ligroin giving *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionate,* fine needles, m.p. 92–93°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.3; G, 6.15.

The neutral part was (43), b.p. 244–246° at 19 mm., described below.

(43) By solution in the calculated amount of *N*-sodium hydroxide and precipitation with silver nitrate, 3.0 g. of (46) was converted into the silver salt (Found: Ag, 44.3; $C_{14}H_{12}O_5Ag_2$ requires Ag, 45.3). Five grams of this salt and 5 g. of methyl iodide were heated together in 25 ml. of

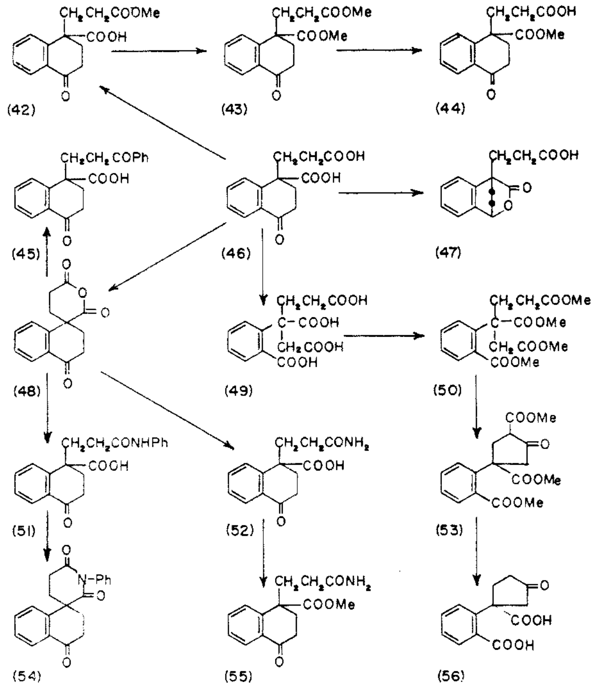

Chart IV

benzene for 30 min. The neutral product, 2.8 g., was *dimethyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionate,* b.p. 242–244° at 18 mm. with no forerun or residue.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.25. Found: C, 66.3; H, 6.44.

(44) When 0.7 g. of (43) was boiled with 0.2 g. of sodium hydroxide in 2.5 ml. of water and 0.5 ml. of alcohol, a clear solution was formed in 2 min. Acidification gave an oil that was obtained crystalline with some difficulty. Recrystallization from nitromethane gave *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionic acid,* minute rosettes, m.p. 166–167° to a red liquid.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 64.7; H, 5.37.

(45) A suspension of 4.1 g. of (48) and 8 g. of aluminum chloride in 30 ml. of benzene was boiled for 1 hr., then decomposed with iced hydrochloric acid. The acidic product was extracted with sodium carbonate, crystallized by keeping with ether-ligroin, and dried (4.2 g.). Washing with ether and recrystallization from 70% acetic acid gave 2.3 g. of *1-(β-benzoylethyl)-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid,* coarse needles, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.63; neut. equiv., 322. Found: C, 74.38; H, 5.67; neut. equiv., 322.

(46) A mixture of 232 g. of (9) with 925 ml. of concd. sulfuric acid was stirred and heated on a boiling water bath for 45 min., then poured into 2500 ml. of water (not ice) and cooled. The crystalline product was recrystallized from 300 ml. of water, giving 191 g. of pure 4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid, identical with (21).

(47) A solution of 10.5 g. of (46) in 35 ml. of 10% sodium hydroxide was treated with 3 g. of Raney nickel and shaken with hydrogen at 40 p.s.i. for 16 hr. Acidification gave an oil which soon crystallized, 9.3 g. Recrystallization from 35 ml. of 30% acetic acid gave 6.6 g. of 4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid-lactone-1-propionic acid, m.p. 167–168°, identical with (19).

(48) A mixture of 5 g. of (46) with 10 ml. of acetyl chloride was boiled for 15 min. and then evaporated at 100° under reduced pressure. Crystallization of the residue from toluene (charcoal) gave 3.7 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′,6′-dioxopyran,* m.p. 151–152°.

In another preparation, the same anhydride was obtained in 80% yield from the dibasic acid obtained as described before (21). The anhydride was also obtained using propionyl chloride.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 4.95. Found: C, 68.7; H, 5.22.

When 2 ml. of piperidine was added to 0.5 g. of (48) an exothermic reaction took place. The product was isolated by adding ethyl acetate and dilute hydrochloric acid, and it was caused to crystallize by rubbing with ether. Crystallization from dilute alcohol gave fine white needles which changed to well formed prisms on keeping under the mother liquor; *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionpiperidide* had m.p. 151°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04. Found: C, 69.2; H, 7.24.

(49) A solution of 10 g. of (46) in 50 ml. of hot water was kept boiling while 25 ml. of nitric acid was added dropwise during 30 min.; nitrous fumes were evolved. The solution was evaporated at 100° under reduced pressure; 25 ml. of water was added and the evaporation was repeated. When the resulting yellow glass was treated with a little ether, it slowly crystallized. Recrystallization from water (charcoal) gave nearly colorless prisms of *β-carboxy-β-(o-carboxyphenyl)-adipic acid,* that melted indefinitely above 120°, with loss of water and formation of an *anhydride.* ($C_{14}H_{14}O_8$ requires: H_2O, 5.8; found: H_2O, 5.9.) The dried (100°, 5 hr.) substance formed nearly colorless prisms from nitromethane, m.p. 178–179°; yield 8–8.5 g. In subsequent experiments it was found easier to remove the yellow color from the crude acid by boiling its solution in 1:1 hydrochloric acid with a little amalgamated zinc.

Anal. Calcd. for $C_{14}H_{12}O_7$: C, 57.5; H, 4.55. Found: C, 57.5; H, 3.99.

The *silver salt* formed an amorphous white powder, insoluble in water and stable to light.

Anal. Calcd. for $C_{14}H_{10}O_8Ag_4$: Ag, 58.5. Found: Ag, 59.0.

(50) A solution of 34 g. of (49) and 10 ml. of sulfuric acid in 125 ml. of methanol was boiled under a Soxhlet extractor containing calcium carbide for 20 hr. Addition of water gave a gum which was taken up in ether and separated with dilute sodium carbonate into 17.3 g. of crude neutral ester and 18.6 g. of crude acid-ester. The latter, with 50 ml. of methanol and 5 ml. of sulfuric acid, boiled for 20 hr., gave 8.5 g. of neutral ester and 7.6 g. of acid-ester. The latter treated again with 25 ml. of methanol and 3 ml. of sulfuric acid gave 2.2 g. of neutral ester and 3.5 g. of acid ester. The combined neutral ester fractions were distilled, giving 26.2 g. of *methyl β-carbomethoxy-β-(o-carbomethoxyphenyl)-adipate,* b.p. 270–275° at 20 mm.

Anal. Calcd. for $C_{18}H_{22}O_8$: C, 59.0; H, 6.05. Found: C, 59.0; H, 5.55.

The distilled ester had a saponification equivalent of 80.0 (calcd. 77.5) and gave back the tetrabasic acid when it was boiled for 5 min. with excess 30% sodium hydroxide.

(51) A mixture of 1.2 g. of (48) with 5 ml. of aniline was warmed at 100° for 5 min., then treated with ether and dilute hydrochloric acid. Removal of the ether left a glass which crystallized on rubbing with ether-ligroin. Recrystallization from dilute alcohol gave 1.6 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionanilide,* fine needles, m.p. 199–200° with gas evolution.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.68. Found: C, 71.4; H, 5.96.

(52) A mixture of 5 g. of (48) and 40 ml. of 15% ammonia was warmed gently until solution took place, then evaporated to dryness at 100° under reduced pressure. Addition of water and dilute hydrochloric acid gave an oil which crystallized when it was kept with ethyl acetate–ligroin. Crystallization from water (charcoal) gave 3.7 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionamide,* m.p. 170–172° with gas evolution.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.2; H, 5.96.

(53) A solution of 25 g. of (50) in 40 ml. of toluene was added to sodium methoxide prepared from 2 g. of powdered sodium and 3 ml. of methanol in 25 ml. of toluene. The mixture was heated for 1 hr. in a bath at 100°, then cooled and acidified with acetic acid. Extraction with 5% sodium carbonate removed 13.8 g. of a dark brown gum, which gave back 7 g. of (49) when it was boiled with 20% sodium hydroxide. The neutral material crystallized when it was kept with a little ether. Recrystallization from methanol (charcoal) gave 6.5 to 7.5 g. of *3,5-biscarbomethoxy-3-(o-carbomethoxyphenyl)cyclopentanone*,[6] square pink plates, m.p. 110–112°.

Anal. Calcd. for $C_{17}H_{18}O_7$: C, 61.1; H, 5.43. Found: C, 61.2; H, 5.71.

(54) When 1 g. of (51) was heated in a bath at 245° for 10 min. and the glassy residue was kept for several days under ether, crystals were obtained. Recrystallization from dilute alcohol gave 0.4 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-1′-phenyl-2′,6′-piperidinedione*, flat needles, m.p. 125°.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.2; H, 5.37. Found: C, 75.7; H, 5.67.

(55) The *silver salt* of (52) formed a nearly insoluble resin, that was powdered, washed with water, and dried at room temperature.

Anal. Calcd. for $C_{14}H_{14}NO_4Ag$: Ag, 29.4. Found: Ag, 30.1.

A suspension of 3 g. of this silver salt in 15 ml. of benzene was treated with 3 ml. of methyl iodide and boiled for 1 hr. Filtration and removal of benzene gave a gum which became crystalline when it was kept under ether for one week. Recrystallization from ethyl acetate–ligroin gave 0.4 g. of *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionamide*, m.p. 139–140°. An additional 0.4 g. of the same substance was obtained by extracting the silver iodide with methanol and rubbing the gummy extracted material with dilute sodium carbonate and ether.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.22. Found: C, 65.4; H, 6.21.

(56) When 0.5 g. of (53) was boiled for 30 min. with 5 ml. of 10% sodium hydroxide, it yielded a partial hydrolysis product, probably *6-carbomethoxy-3-carboxy-3-(o-carboxyphenyl)cyclopentanone* on the basis of its analysis and its giving a strong purple ferric chloride test. The compound was isolated by acidification and ether extraction; it crystallized slowly when rubbed with ether-ligroin at −75°, and was then recrystallized from water, yielding rosettes, m.p. 163–164° with gas evolution.

Anal. Calcd. for $C_{15}H_{14}O_7$: C, 58.8; H, 4.61. Found: C, 58.7; H, 5.07.

In order to get complete hydrolysis, it was necessary to combine acidic and basic hydrolysis as follows. A mixture of 0.5 g. of (53) with 5 ml. of 20% hydrochloric acid was boiled for 1 hr. and then evaporated at 100° under reduced pressure. The solid residue was then boiled for 1 hr. with 5 ml. of 10% sodium hydroxide. Crystallization from water (charcoal) gave 0.3 g. of *3-carboxy-3-(o-carboxyphenyl)cyclopentanone*, colorless needles, m.p. 161–162°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.9; H, 4.87. Found: C, 63.0; H, 5.55.

The *dimethyl ester* was obtained when 2.4 g. of (56) was boiled for 30 min. with 10 ml. of methanol containing 0.5 ml. of sulfuric acid. The product was taken up in ether, washed with dilute sodium carbonate, and distilled; b.p. 210–220° at 12 mm.; yield, 2.2 g.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.2; H, 6.02.

When 0.7 g. of (56) was dissolved in 5 ml. of 10% sodium hydroxide, treated with 0.7 g. of benzaldehyde and boiled, nearly all of the aldehyde dissolved during 10 min. The remainder was removed with steam, and the solution was acidified. The resulting yellow gum (0.9 g.) crystallized slowly when it was kept with ether-ligroin. Recrystallization from dilute acetic acid gave a *monobenzal derivative*, yellow prisms, m.p. 200–201° with gas evolution.

Anal. Calcd. for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.47; H, 5.05.

(57) See (9), Chart I.

(58) A mixture of 200 g. of (57), 750 ml. of methanol, and 50 ml. of sulfuric acid was boiled for 45 min., then cooled and stirred into 2 l. of ice water. The product was removed, ground to a paste, and washed with water, giving 207 g. of diester, m.p. 89–93°, suitable for further use. Pure *methyl γ-carboxy-γ-phenylpimelate*, obtained by extraction with $N/10$ sodium hydroxide, precipitation, and crystallization from ether-ligroin, had m.p. 95–97°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54; neut. equiv., 308. Found: C, 62.4; H, 6.79; neut. equiv., 311.

The corresponding *diethyl ester*, obtained similarly in 95% crude yield from 275 g. of (9), 600 ml. of absolute ethanol, and 60 ml. of sulfuric acid formed a sirup.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.3; H, 7.19; neut. equiv., 336. Found: C, 64.0; H, 7.34, neut. equiv., 351.

(59) The *silver salt* of methyl γ-carboxy-γ-phenylpimelate was obtained by titrating a suspension of 207 g. of (58) in 500 ml. of hot water with 10% sodium hydroxide (phenolphthalein), precipitation with 10% silver nitrate, and drying for 2 days at 50° under reduced pressure over sulfuric acid; yield 294 g. (105%).

Anal. Calcd. for $C_{16}H_{19}O_6Ag$: Ag, 25.3. Found: Ag, 26.0.

The silver salt was suspended in 1500 ml. of dry benzene (the salt dissolved almost completely, and the solution rapidly set to a gel) and stirred while 150 g. of methyl iodide was added as rapidly as the exothermic reaction would permit. The mixture was stirred and heated for an additional 15 min. and then filtered, the silver iodide being washed with 100 ml. of benzene. The product was washed with dilute sodium carbonate and then distilled, giving 175 g. of pure *methyl-γ-carbomethoxy-γ-phenylpimelate*, b.p. 237–242° at 22 mm.; prisms from ligroin, m.p. 52–54°.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.3; H, 6.88. Found: C, 63.3; H, 7.13.

Methyl γ-carbethoxy-γ-phenylpimelate, obtained similarly using ethyl iodide, had b.p. 240–242° at 20 mm. and could not be obtained crystalline.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.3; H, 7.19. Found: C, 64.4; H, 7.30.

When the silver salt of ethyl γ-carboxy-γ-phenylpimelate (Found: Ag, 30.0; $C_{18}H_{23}O_6Ag$ requires Ag: 24.4) (350 g.) was treated with 175 g. of ethyl iodide in benzene, there was obtained 238 g. of *ethyl γ-carbethoxy-γ-phenylpimelate*, b.p. 227–229° at 9 mm.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.9; H, 7.74. Found: C, 65.27; H, 7.68.

An apparently better preparation of this ethyl ester has been reported by Rubin and Wishinski.[4]

Partial hydrolysis of (59) was effected when 0.5 g. of it was boiled for 5 min. with 2 ml. of 10% sodium hydroxide and 1 ml. of alcohol. The resulting solution was evaporated and then treated with water and dilute hydrochloric acid, giving *γ-carbomethoxy-γ-phenylpimelic acid*, coarse needles from water, m.p. 147–148°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.17. Found: C, 61.3; H, 6.53.

Similar partial hydrolysis of either methyl or ethyl γ-carbethoxy-γ-phenylpimelate gave *γ-carbethoxy-γ-phenylpimelic acid*, prisms from 5% acetic acid, m.p. 126–127°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54; neut. equiv., 154. Found: C, 62.3; H, 6.51; neut. equiv., 153.

The *silver salt* of γ-carbethoxy-γ-phenylpimelic acid gave no useful product when it was treated with bromine in carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{18}O_6Ag_2$: Ag, 41.4. Found: Ag, 41.4.

(60) A boiling solution of 2.5 g. of (63) in 8 ml. of water was treated dropwise with 3.5 ml. of nitric acid, and boiling

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(6) Formulated as a cyclopentanone rather than a tetralone, because the latter would yield (63) on hydrolysis and decarboxylation.

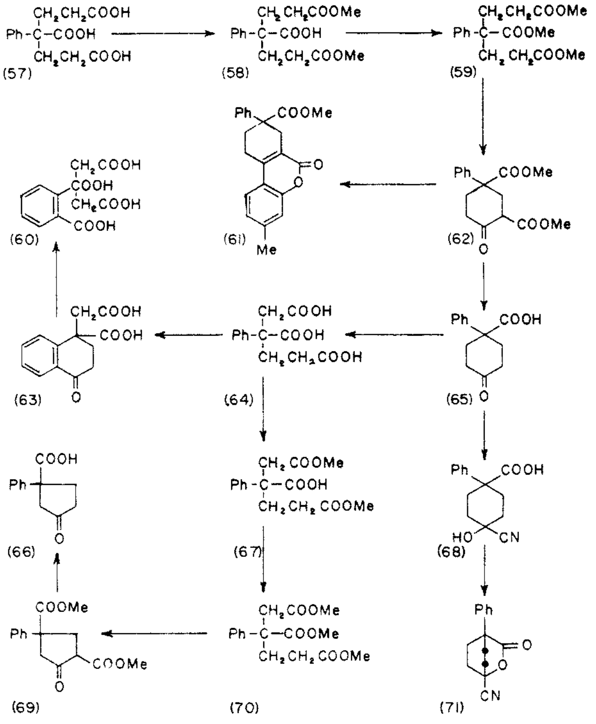

Chart V

was continued for 15 min. Filtration of the cooled mixture removed a red tar, and evaporation of the filtrate at 100° under reduced pressure left 1.2 g. of yellow crystals. The product was boiled for 15 min. with charcoal in 6 ml. of 20% hydrochloric acid, then recovered by evaporation and recrystallized from ethyl acetate–ligroin and then from water. *β-o-Carboxyphenyltricarballylic acid* formed transparent prisms that became opaque on drying at 100° and then analyzed as an anhydride, m.p. 237–239° with gas evolution.

Anal. Calcd. for $C_{13}H_{10}O_7$: C, 56.1; H, 3.62. Found: C, 56.2; H, 3.30.

(61) A mixture of 10 g. of (62) (methyl ester) and 5 g. of *m*-cresol was added to 15 ml. of sulfuric acid containing 3 ml. of water, external cooling being used to keep the mixture at 30–35°. The mixture was kept at room temperature for 2 hr., then poured on ice. The resinous precipitate became crystalline (11.0 g.) when it was boiled with water; recrystallization from 75% acetic acid gave 9.8 g. of *8-carbomethoxy-3-methyl-8-phenyl-7,8,9,10-tetrahydro-6-dibenzo[b,d]pyrone*, prisms, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.8; H, 5.79. Found: C, 75.8; H, 5.85.

(62) A mixture of 400 ml. of toluene and 10 g. of sodium was boiled and stirred vigorously while 18 ml. of methanol was added dropwise. When the sodium had all reacted, 100 g. of methyl γ-carbomethoxy-γ-phenylpimelate was added. The mixture was boiled and stirred for 1 hr., then cooled and stirred while 500 ml. of 5% acetic acid was added. The organic layer was separated, washed with sodium bicarbonate solution, and evaporated under reduced pressure at 100°. The residue (89 g., 98%) was nearly pure *2,4-biscarbomethoxy-4-phenylcyclohexanone*, m.p. 88–90°. The compound separated from methanol in the form of prisms, m.p. 91–92°; it gave a purple ferric chloride test.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.25. Found: C, 66.6; H, 6.45.

2,4-Biscarbethoxy-4-phenylcyclohexanone, obtained similarly from ethyl γ-carbethoxy-γ-phenylpimelate in 94% yield, crystallized only after it had been distilled, forming prisms from alcohol, b.p. 216–218° at 10 mm., m.p. 53–55°; it gave a deep purple color with alcoholic ferric chloride. The compound has been reported[4] as an oil, b.p. 165–175° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.9; H, 6.97. Found: C, 68.2; H, 7.38.

The ethyl ester formed a sodio derivative easily soluble in benzene, but difficultly soluble in water. Its *copper derivative* formed yellow-green needles from toluene-ligroin, m.p. 192–193°.

Anal. Calcd. for $C_{36}H_{42}O_{10}Cu$: C, 61.9; H, 6.03; Cu, 9.12. Found: C, 61.6; H, 6.06; Cu, 8.85.

(63) A solution of 5.6 g. of (64) in 25 ml. of sulfuric acid was heated for 20 min. on a boiling water bath, then cooled and poured into water. The product was extracted with ether and crystallized from water, giving 2.5 g. of tan needles m.p. 140–147°. Recrystallization from water gave *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-acetic acid*,[7] colorless needles, m.p. 148–149°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.9; H, 4.87. Found: C, 63.0; H, 4.90.

(64) To a mixture of 100 ml. of water and 20 ml. of nitric acid (d. 1.42) boiling under a good condenser, there was added 24.5 g. of (65) in 3- to 4-g. portions. A vigorous reaction with a short induction period took place after each addition. The mixture was finally boiled for 10 min., then cooled and seeded (seed were obtained by evaporating a similar reaction mixture to dryness under reduced pressure, and rubbing the product with ether-ligroin), giving a semisolid crystalline paste. The product was washed with 2 × 5 ml. of water and dried at 60°, giving 22.3 g. of nearly pure *β-carboxy-β-phenyladipic acid*. Recrystallization from ethyl acetate–ligroin gave small prisms, that sintered at 160° and melted at 168–169° with gas evolution.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.30. Found: C, 58.8; H, 5.23.

(65) A mixture of 100 g. of (62) (methyl ester), 1000 ml. of water and 45 g. of sodium hydroxide was boiled for 30 min., then distilled to half volume during 90 min. Acidification gave an oil which soon solidified, and recrystallization from benzene gave a partly solvated material m.p. 113–119° (73–75 g., 97%). Pure *4-carboxy-4-phenylcyclohexanone*, m.p. 120–121° (reported[4] m.p. 118.5–119.5°), was obtained by drying at 100° under reduced pressure followed by crystallization from ether-ligroin and drying at 75° for 2 hr.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.6; H, 6.47; neut. equiv., 218. Found: C, 71.8; H, 6.61; neut. equiv., 220.

The *silver salt* of (65), colorless needles from hot water, was quite sensitive to light (Found: Ag, 33.1; $C_{13}H_{13}O_3Ag$ requires Ag, 33.2). When 15 g. of this silver salt suspended in 30 ml. of dry toluene was treated with 10 g. of ethyl iodide and boiled for 15 min., there was obtained 11 g. of *4-carbethoxy-4-phenylcyclohexanone*, b.p. 200–205° at 16 mm. (reported[4] b.p. 144–146° at 0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.1; H, 7.37. Found: C, 72.9; H, 7.35.

2,6-Bisbenzylidene-4-carboxy-4-phenylcyclohexanone was obtained when 0.5 g. of (65), 0.5 g. of benzaldehyde, and 10 ml. of 1% sodium hydroxide were shaken together for 10 min. at 60–65°, then boiled for 0.5 min. and finally cooled and acidified. It formed yellow prisms from acetic acid, m.p. 273–276°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.2; H, 5.62. Found: C, 82.3; H, 5.40.

(66) A suspension of 13 g. of (69) in 30 ml. of boiling water was treated dropwise during 30 min. with 30 ml. of 20% sodium hydroxide. Boiling was continued 30 min. more, and the solution was then cooled and acidified. The precipitated colorless oil became crystalline when it was rubbed with ether, yield 6.6 g. Crystallization from ethyl acetate–ligroin and then from water gave 4 g. of *3-oxo-1-*

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(7) Formulated as a tetralone rather than a hydrindone on general principles and on the belief that oxidation of the latter would yield a thermally unstable malonic acid.

phenylcyclopentanecarboxylic acid, small prisms, m.p. 159–160°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.92. Found: C, 70.6; H, 6.01.

The *oxime,* prepared in aqueous sodium carbonate, formed a fine white powder, m.p. 202° with blackening.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.8; H, 5.98. Found: C, 65.8; H, 6.09.

(67) A solution of 24 g. of (64) and 10 ml. of sulfuric acid in 100 ml. of methanol was boiled for 1 hr., then cooled and treated with water and ether. The product was separated into a neutral part (3.9 g.) and an acidic part (18.8 g.) by washing the ether solution with dilute sodium carbonate. The neutral part was the trimethyl ester (70), prepared in quantity as described below. The acidic part was *methyl β-carboxy-β-phenyladipate;* it crystallized after it had been dried at 100° under reduced pressure and then allowed to stand without solvent for several days at room temperature. All solvents tried depressed its m.p. considerably, and it had to be recrystallized by allowing a methanol-water solution to stand at room temperature in a desiccator containing water. It formed colorless prisms, m.p. 93–95°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.17. Found: C, 61.2; H, 6.13.

(68) Ten grams of (65) was added in portions to a solution of 5 g. of potassium cyanide in 25 ml. of water with cooling to 25°. Then 0.5 g. of acetic acid was added and the solution was kept for 3 hr. Addition of hydrochloric acid gave an oil which soon solidified. The cyanohydrin mixture was ground and washed with water and dried (11.2 g.). Crystallization from nitromethane gave 5.2 g. of solvated *α-*(OH *cis* to COOH)*-4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid,* needles that became opaque when dried at 120°; m.p. 170–173°; the compound crystallized nicely from water, forming coarse needles, m.p. 170–173°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.16. Found: C, 68.6; H, 6.42.

The nitromethane mother liquor was evaporated at 100° and reduced pressure; the residue, crystallized from nitromethane-benzene, gave 4.2 g. m.p. 145–155° (solvated). Recrystallization from 30 ml. of 20% acetic acid gave 2.2 g. of poorly formed solvated prisms that melted at 82–86°, then resolidified and melted again at 161–164°. A portion crystallized again from 10% acetic acid and dried for 2 hr. at 65° under reduced pressure gave pure *β-*(OH *trans* to COOH)*-4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid,* colorless prisms, m.p. 165–168°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.16. Found: C, 68.4; H, 6.57.

When 1 g. of the α-cyanohydrin was boiled with 2 ml. of water and 3 ml. of hydrochloric acid, an oil was slowly formed and this later solidified in the boiling mixture. After 2.5 hr., the mixture was cooled and filtered giving 0.9 g. of *4-carboxy-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone,* coarse needles from ethyl acetate–ligroin, m.p. 199–200°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.73. Found: C, 68.3; H, 6.04.

When 1 g. of the α-cyanohydrin was boiled for 3 hr. with 5 ml. of methanol containing 0.5 ml. of sulfuric acid, it gave 1 g. of *4-carbomethoxy-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone,* b.p. 230–235° at 17 mm., needles from dilute methanol or prisms from benzene-ligroin, m.p. 103–105°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.20. Found: C, 69.2; H, 6.54.

When 1 g. of the β-cyanohydrin was boiled with 2 ml. of water and 3 ml. of hydrochloric acid, separation of solid after 30 min. caused such severe bumping that 2 ml. of acetic acid, 1 ml. of water, and 1 ml. of hydrochloric acid had to be added. After 2.5 hr., the mixture was cooled, and the product (0.9 g.) was recrystallized from acetic acid. *1-Hydroxy-4-phenyl-1,4-cyclohexanedicarboxylic acid* formed small prisms m.p. 248° with gas evolution. It was nearly insoluble in ethyl acetate.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.10. Found: C, 63.6; H, 6.23.

(69) When 15.4 g. of (70) was added under hydrogen to a suspension of sodium methoxide from 1.2 g. of powdered sodium and 2 ml. of methanol in 25 ml. of toluene, only slight temperature rise took place, but the base dissolved during 2 min. Six ml. of solvent (containing 3.5 ml. of methanol) was removed by distillation, and the remaining clear solution was cooled and treated with 40 ml. of 10% acetic acid. The toluene solution was washed with sodium bicarbonate and evaporated, leaving 14 g. of a honey-like oil that could not be crystallized. For analysis, a portion was distilled at 15 mm., b.p. 205–215° with some decomposition giving *2,4-biscarbomethoxy-4-phenylcyclopentanone* as a colorless oil that gave a purple color with alcoholic ferric chloride.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.2; H, 6.06.

The *copper salt* precipitated as a green oil when the keto ester was treated with copper acetate in methanol. Crystallization from methanol gave yellow-green needles that sintered and darkened at 225°, m.p. 235° dec.

Anal. Calcd. for $C_{30}H_{30}O_{10}Cu + CH_3OH$: C, 57.6; H, 5.27; Cu, 9.85. Found: C, 57.9; H, 5.14; Cu, 9.95.

(70) A suspension of 22.8 g. of (67) in 50 ml. of water was neutralized with 10% sodium hydroxide and then treated with 15 g. of silver nitrate in 60 ml. of water. The resulting silver salt was washed and dried, giving 30 g. of a tan powder. A suspension of 29 g. of this silver salt in 50 ml. of benzene was treated with 15 g. of methyl iodide and boiled for 1.5 hr. Filtration, and distillation of the filtrate gave 17.5 g. of *methyl β-carbomethoxy-β-phenyladipate,* b.p. 218–219° at 15 mm. The distillate soon solidified; from dilute methanol the ester formed prisms, m.p. 56–58°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54. Found: C, 62.5; H, 6.77.

(71) When 1 g. of the β-cyanohydrin (68) was dissolved in 3 ml. of acetic acid containing 0.1 g. of sulfuric acid and boiled for 2 min., it was recovered unchanged. But when the α-cyanohydrin was treated in this way it was converted into *4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone,* 2-cm.-long needles from dilute acetic acid, m.p. 191°; the cyanolactone distilled at 15 mm. without decomposition.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77. Found: C, 74.3; H, 5.79.

(72) See (65), Chart V.

(73) A solution of 2.2 g. of (72) in 25 ml. of 2% sodium hydroxide took up the calculated amount of hydrogen when it was shaken at 35 p.s.i. with 2 g. of Raney nickel for 16 hr. Acidification gave 2.0 g. of crystalline material; fractional crystallization from nitromethane gave 0.75 g. of the α-form (OH and COOH *cis*) of *4-hydroxy-1-phenylcyclohexanecarboxylic acid,* plates m.p. 194–196° with gas evolution.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32; neut. equiv., 220. Found: C, 70.8; H, 7.08; neut. equiv., 222.

The *silver salt* formed fine needles from hot water, in which it was very difficultly soluble.

Anal. Calcd. for $C_{13}H_{15}O_3Ag$: Ag, 32.9. Found: Ag, 32.9.

Evaporation of the nitromethane mother liquors left a crystalline residue. Extraction with hot water and recrystallization from water gave 0.6 g. of the β-form (OH and COOH *trans*) of *4-hydroxy-1-phenylcyclohexanecarboxylic acid,* m.p. 154–158°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32. Found: C, 71.1; H, 7.45.

(74) When 0.5 g. of β-(73) in 3 ml. of acetic acid containing 2 drops of sulfuric acid was boiled for 1 min. and the solution was then diluted with water and cooled, the β-acid was recovered unchanged. But when α-(73) was treated in the same way, it gave 0.3 g. of *4-hydroxy-1-phenylcyclo-*

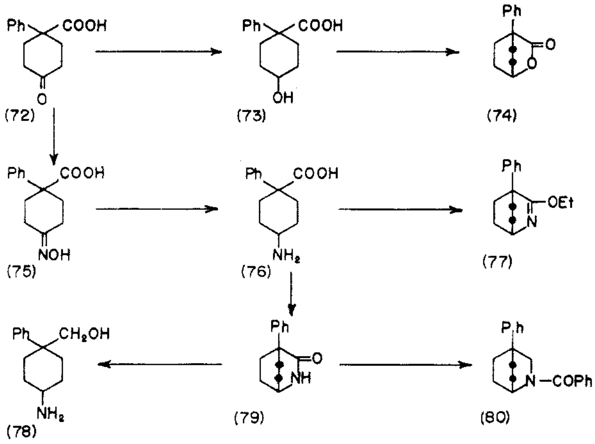

Chart VI

hexanecarboxylic acid lactone, plates from dilute acetic acid, m.p. 140–141°, not soluble in hot dilute sodium carbonate.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.98. Found: C, 77.1; H, 7.15.

From the mother liquors of the lactonization of the α-(73), there was recovered about 50 mg. of the β-acid. Whether this was present in the α-(73) used or was formed by inversion was not determined.

(75) A solution of 20 g. of (72) in 100 ml. of 10% sodium carbonate was treated with 10 g. of hydroxylamine sulfate, boiled for 10 min. and then acidified. Crystallization of the precipitate from dilute alcohol gave 17.5 g. of coarse transparent needles that sintered at 120°, then melted at 157–159°. After drying at 100°, then 115°, then 138° under reduced pressure, *4-oximino-1-phenylcyclohexanecarboxylic acid* formed a powder, m.p. 160–161° (reported[4] 155.5–156.5°).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48. Found: C, 67.3; H, 6.58.

The *silver salt* formed fine white difficultly soluble crystals that darkened when heated under the mother liquor.

Anal. Calcd. for $C_{13}H_{14}NO_3Ag$: Ag, 31.8. Found: Ag, 32.4.

(76) A solution of 2.3 g. of (75) in 40 ml. of 5% sodium hydroxide and 100 ml. of ammonium hydroxide was shaken with hydrogen at 35 p.s.i. and 2 g. of Raney nickel for 16–20 hr. The solution was boiled to remove ammonia, and then neutralized with acetic acid. The resulting precipitate (1.15 g.) was insoluble in boiling ethylene glycol, but easily soluble in dilute sodium hydroxide or dilute hydrochloric acid. It was obtained in the form of fine white plates by precipitation from an acid solution with sodium acetate; m.p. above 275° dec. Behavior of the substance towards phosphorus pentachloride (below) indicated that the substance was a mixture of *cis-* and *trans-4-amino-1-phenylcyclohexanecarboxylic acids.*

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.82. Found: C, 69.8; H, 7.68.

The amino acid was recovered unchanged after 0.9 g. of it was boiled for 2 hr. with 10 ml. of alcohol containing 1 ml. of sulfuric acid, or after it was treated with excess sodium butoxide in dry butyl alcohol.

(77) Compound (76) (1.1 g.) was treated with phosphorus pentachloride as in preparation (79) but the residue was boiled with 5 ml. of absolute alcohol instead of water for 10 min. Dilute sodium hydroxide was then added to *p*H 8, and the mixture was distilled with steam. Ether extraction removed 0.25 g. of *2-ethoxy-1-phenyl-3-aza-*Δ^2*-bicyclo-[2,2,2]-octane,* colorless crystals that were too soluble to be recrystallized; b.p. 170° at 15 mm., m.p. 72–75°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.6; H, 8.35. Found: C, 78.9; H, 8.54.

(78) A solution of 0.8 g. of (79) in 15 ml. of hot dry butyl alcohol was treated with 1 g. of sodium. After the metal had dissolved, dilute hydrochloric acid was added and the butyl alcohol was removed with steam. Filtration removed 0.3 g. of unchanged (79), and addition of potassium hydroxide precipitated 0.45 g. of basic material, m.p. 120–130°. 4-Hydroxymethyl-4-phenylcyclohexylamine had b.p. 190° at 13 mm., but was analyzed only as its *hydrochloride,* crystals from alcohol-ether, m.p. 257–258°.

Anal. Calcd. for $C_{13}H_{19}NO + HCl$: C, 64.7; H, 8.3. Found: C, 64.7; H, 8.55.

(79) A mixture of 3.0 g. of (76) with 3 ml. of phosphorus oxychloride and 3 g. of phosphorus pentachloride was heated on a water bath for 30 min., then evaporated under reduced pressure. The residue was treated with water and dilute sodium carbonate, giving a crystalline precipitate. Extraction of this with dilute hydrochloric acid removed 0.7 g. of (76) and left 0.85 g. of neutral material. Sublimation of the latter at 15 mm. and crystallization from alcohol furnished *4-amino-1-phenylcyclohexanecarboxylic acid lactam* as large rhombs, m.p. 263–264°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.6; H, 7.51. Found: C, 77.6; H, 7.69.

The recovered amino acid was probably pure *trans* (76), since, although it was otherwise indistinguishable from starting material, retreatment with phosphorus pentachloride gave it back unchanged. It was analyzed as its *hydrochloride,* coarse needles from water, not melted at 285°.

Anal. Calcd. for $C_{13}H_{17}NO_2 + HCl$: C, 61.1; H, 7.5. Found: C, 60.83; H, 7.35.

(80) The hydrochloride remaining in the alcohol-ether mother liquors from (78) contained a small amount of a different substance which could not be separated as such. Treatment with aqueous sodium carbonate and benzoyl chloride followed by fractional crystallization from ether-ligroin and then dilute alcohol gave 40 mg. of colorless plates, m.p. 138–139°, probably *3-benzoyl-1-phenyl-3-azabicyclo-[2,2,2]-octane.*

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.4; H, 7.26. Found: C, 82.2; H, 7.28.

(81) See (65), Chart V.

(82) A solution of 21.8 g. of (81) in 75 ml. of sulfuric acid and 10 ml. of chloroform was treated during 1 hr. with 7 g. of sodium azide added in portions and with stirring and cooling. Gas was evolved even at 10°, but the mixture had to be warmed at 40° at intervals to break the froth, in which stirring was ineffective. After an additional hour, the mixture was poured on ice; the product was pulverized, washed with water, dried, and then washed with hot ethyl acetate; yield, 21.5 g. of nearly pure material. A sample of *5-phenylhexahydro-2-azepinone-5-carboxylic acid,* crystallized from water in dendrites that melted with vigorous effervescence when introduced into a bath at 170°.

Anal. Calcd. for $C_{13}H_{15}NO_3 + H_2O$: C, 62.1; H, 6.82. Found: C, 61.6; H, 6.92.

The anhydrous form of the acid, obtained by long drying at 100° under reduced pressure, was apparently amorphous, it sintered at 160° and flowed at 175°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48. Found: C, 66.5; H, 6.85.

(83) *Methyl 5-phenylhexahydro-2-azepinone-5-carboxylate,* obtained by treatment of a suspension of (82) in methanol-ether with ethereal diazomethane, formed small prisms from methanol or benzene, m.p. 150–151°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93. Found: C, 67.8; H, 6.89.

(84) A mixture of 19.5 g. of (82), 20 ml. of water, and 30 ml. of hydrochloric acid was boiled for 1 hr. and then evaporated under reduced pressure at 100°. The residue was treated with 50 ml. of water and evaporated again, then dissolved in 60 ml. of water and treated with a solution of 20 g. of hydrated sodium acetate in 20 ml. of water. Cooling and scratching gave 17.3 g. of *α-(2-aminoethyl)-α-*

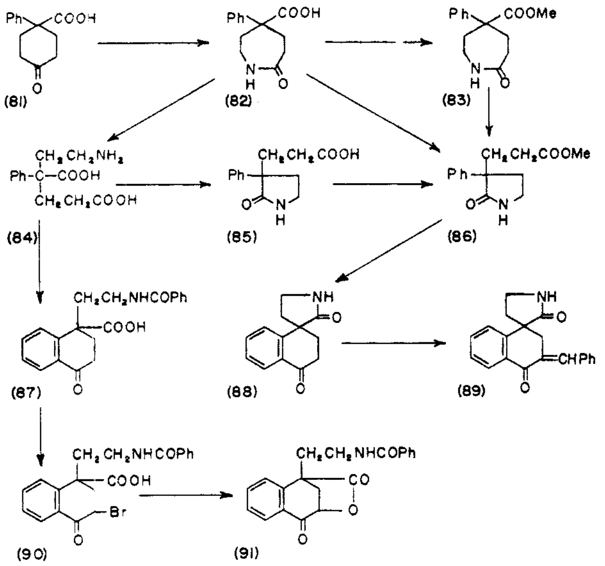

Chart VII

phenylglutaric acid, colorless crystals, m.p. 208–209° with gas evolution.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.82. Found: C, 62.1; H, 6.96.

(85) When (84) was heated at 220° for 5 min. it left a glass that crystallized when rubbed with ether; purification of the product by crystallization alone was successful but inefficient. A pure product was easily obtained through esterification.

Fourteen and one-half grams of (84) was added in portions to a flask heated in a bath at 225°. The melt was cooled and dissolved in 45 ml. of methanol containing 3.5 g. of hydrogen chloride. The solution was boiled 45 min., then distilled to half volume and cooled, giving 12.2 g. of (86), m.p. 118–119°. This was boiled for 5 min. with 200 ml. of 5% sodium carbonate, then acidified and cooled. The precipitate was recrystallized from water, giving 8.9 g. of pure *3-phenyl-2-pyrrolidone-3-propionic acid,* m.p. 150–151°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.0; H, 6.48. Found: C, 67.0; H, 6.66.

(86) A solution of 1.5 g. of (83) in 10 ml. of 25% methanolic hydrogen chloride was boiled for 1 hr. and then evaporated. The residue was treated with water and 0.5 g. of (83) was removed by filtration. Addition of dilute sodium hydroxide gave an oily precipitate (amino diester?) which was soluble in dilute hydrochloric acid when tested at once, but which became insoluble when it was allowed to stand or when warmed. Recrystallization from 5% methanol and then benzene-ligroin gave *methyl 3-phenyl-2-pyrrolidone-3-propionate,* prisms, m.p. 118–119°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93. Found: C, 67.8; H, 6.90.

The same compound was obtained similarly from (82) and from (85).

(87) A solution of 20 g. of (84) in 80 ml. of sulfuric acid was heated in a water bath for 30 min., then cooled, poured on ice and nearly neutralized with 40% sodium hydroxide. The mixture was cooled to 10°, treated with 10 ml. of benzoyl chloride and 100 ml. of 40% sodium hydroxide and shaken for 10 min. Acidification gave a gum which crystallized when it was rubbed with ether. Recrystallization from ethyl acetate gave 26 g. of a solvated product that melted at 113–114° with gas evolution, resolidified when held at 120° and remelted at 154–155°. Crystallization from dilute alcohol gave solvent-free *1-(β-benzoylaminoethyl)-4-oxo-1,2,3,4 tetrahydro-1-naphthoic acid,* m.p. 154–155°; yield 22 g.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.68. Found: C, 71.0; H, 5.94.

The *oxime,* prepared in aqueous sodium carbonate solution, formed small plates from alcohol, m.p. 200–203° with gas evolution.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.2; H, 5.69. Found: C, 68.5; H, 6.20.

(88) A solution of 10 g. of (86) in 40 ml. of sulfuric acid was heated in a water bath for 45 min., then poured on ice. The crystalline precipitate (8.1 g.) was recrystallized from water; spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′-pyrrolidone* formed colorless flat needles, m.p. 196–197°. The compound was recovered unchanged after it had been boiled for 1 hr. with excess 48% hydrobromic acid.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.09. Found: C, 72.7; H, 6.32.

The *oxime* formed colorless prisms from alcohol that darkened at 235°, m.p. 245–250° dec. It was soluble in 10% sodium hydroxide, whereas (88) was not.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.8; H, 6.13. Found: C, 67.7; H, 6.00.

(89) A solution of 0.5 g. of (88) and 0.4 ml. of benzaldehyde in 3 ml. of alcohol was made basic with a few drops of 20% sodium hydroxide and boiled for 0.5 min. Addition of water gave an oil which was taken up in ether and washed with sodium bisulfite and with sodium carbonate. Removal of the ether left a glass which crystallized on keeping for several days with ether-ligroin. Recrystallization from alcohol gave 0.2 g. of spiro-*3-benzal-1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′-pyrrolidone,* yellow prisms m.p. 190–191°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.2; H, 5.65. Found: C, 78.8; H, 5.83.

(90) A solution of 16.5 g. of (87) in 40 ml. of acetic acid at 60° was treated with 8 g. of bromine and then exposed to strong light, causing rapid reaction. The mixture was then treated with 25 ml. of water at 70° and seeded, giving a nearly quantitative yield of crystalline *1-(β-benzoylaminoethyl)-3-bromo-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid,* m.p. 177–179° with foaming.

Anal. Calcd. for $C_{20}H_{18}BrNO_4$: C, 57.7; H, 4.33; Br, 19.2. Found: C, 57.6; H, 4.33; Br, 19.5.

(91) A mixture of 20 g. of (90), 200 ml. of water and 20 g. of sodium acetate was boiled for 2 hr. The crystalline product was removed and dried (14.5 g.) and then recrystallized from dilute alcohol giving *1-(β-benzoylaminoethyl)-3-hydroxy-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid lactone,* colorless plates, m.p. 180°. The compound was insoluble in warm dilute sodium carbonate, slowly soluble with blackening in boiling 10% sodium hydroxide.

Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.6; H, 5.11. Found: C, 71.9; H, 5.36.

The *oxime,* prepared in alcohol, formed faintly green needles from dilute alcohol, m.p. 210–212° dec.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.6; H, 5.18. Found: C, 68.9; H, 5.44.

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