

had been absorbed. After removal of the catalyst and concentration of the filtrate, there was obtained a colorless liquid mixture of α -glycols.

A portion of this liquid mixture of isomeric 6-methylbicyclo[4.3.0]nonan-7,8-diols, 142 mg., was dissolved in 11.7 g. of pure acetone containing 0.8 g. of freshly fused zinc chloride and the mixture was stored for 4 days at room temperature. A solution of 0.55 g. of potassium carbonate in 2.3 ml. of water was added with shaking, the precipitated basic zinc carbonate was removed by filtration, and the dried acetone solution was concentrated to about 5 ml. Fluffy, colorless crystals (0.025 g.) of the acetonide derived from one of the *cis*-glycols separated. After two recrystallizations from ethanol, an analytical sample of IV melted at 68–69°.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 74.25; H, 10.54. Found: C, 74.41; H, 10.40.

Oxidation of Liquid Acyloin (II) with Copper Acetate.—Liquid acyloin II (0.170 g.) was dissolved in 30 ml. of methanol, 2.0 g. of crystalline cupric acetate was added and the solution heated under reflux for one hour with occasional shaking. Red cuprous oxide precipitated almost immediately. After storage overnight, 300 ml. of ether was added and the ether solution washed successively with 0.5 *N* hydrochloric acid, 5% sodium bicarbonate and water, and then dried over sodium sulfate. The ether was evaporated, leaving 0.150 g. of a heavy yellow oil V which gave no reaction with Fehling solution, even when heated. After two recrystallizations from ethyl acetate, the 2,4-dinitrophenylosazone melted at 293–294°, and gave no depression of melting point when mixed with a sample of the 2,4-dinitrophenylosazone obtained directly from the acyloin II.

6-Methylbicyclo[4.3.0]nonan-7-one, *cis*- and *trans*-.—A mixture of 1.148 g. (0.0068 mole) of liquid acyloin II, 2.86 g. (0.044 mole) of zinc (20 mesh) in 2.5 g. of glacial acetic acid and 2.4 ml. of concentrated hydrochloric acid was heated for 160 minutes at 100°. Three additional 2.5-ml. portions of concentrated hydrochloric acid were added at 30-minute intervals. The red solution was poured into ice-water, extracted with ether, and the combined ether extracts washed with dilute sodium carbonate solution and water, dried over anhydrous sodium sulfate and the solvent

evaporated. The ether extracts did not reduce Fehling solution upon heating. The colorless liquid ketone (1.05 g., 83%) which had an odor reminiscent of camphor, was converted directly to the semicarbazone by treatment with 1.06 g. of semicarbazide hydrochloride and 1.55 g. of sodium acetate in 10 ml. of 95% ethanol and 8 ml. of water. No reaction was evident after 24 hours at room temperature and 18 hours at 0°. The contents of the flask were then heated on a steam-bath for one hour. After storage at 0°, 1.3 g. of colorless crystals deposited. The melting point was 201.6–206° after repeated crystallization from methanol-water.

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.01; H, 9.33; N, 20.01.

One gram of the semicarbazone obtained from the mixed methyl hydrindanones, m.p. 201.6–206°, was suspended in 250 ml. of water, 10.0 g. of oxalic acid dihydrate added, and the mixture distilled. The distillate was extracted with ether and the combined extracts dried and concentrated. The product was not obtained crystalline, but was converted to the 2,4-dinitrophenylhydrazones. The yellow needles, m.p. 112–126°, after two crystallizations from methanol, were dissolved in petroleum ether and the solution chromatographed over a 70 × 3 cm. column of alumina. By washing with petroleum ether a complete separation of two compounds was achieved. After elution with methanol the lower band yielded 150 mg. of short, yellow needles, m.p. 152.5–153.5°, of *trans*-6-methylbicyclo[4.3.0]nonan-7-one 2,4-dinitrophenylhydrazone, VIIb, which showed no depression of melting point when mixed with an authentic specimen,⁶ m.p. 152.5–153.5°.

Anal. Calcd. for $C_{11}H_{19}N_4O_4$: C, 57.81; H, 6.07. Found: C, 57.86; H, 6.08.

From the upper band there was obtained 350 mg. of *cis*-6-methylbicyclo[4.3.0]nonan-7-one 2,4-dinitrophenylhydrazone VIIa, m.p. 140–141°, which gave no depression of melting point upon mixture with an authentic sample,⁶ m.p. 140–141°.

Anal. Calcd. for $C_{11}H_{19}N_4O_4$: C, 57.81; H, 6.07. Found: C, 57.96; H, 6.04.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Synthesis of Two Seven-membered Ring Homologs of Demerol¹

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When the product obtained by condensation of phenyl- α -(β -dimethylaminoethyl)-acetonitrile, trimethylene chlorobromide and sodamide was heated, 1-methyl-4-phenyl-4-cyanohexamethylenimine was obtained. Phenyl- α -(β -diethylaminoethyl)-acetonitrile, trimethylene chlorobromide and sodamide yielded 1-ethyl-4-phenyl-4-cyanohexamethylenimine. The two nitriles were hydrolyzed to the corresponding acids, and the latter were esterified to produce the ethyl esters.

This paper deals with the synthesis of two seven-membered ring homologs V and XV of the analgesic Demerol.

Phenyl- α -(β -dimethylaminoethyl)-acetonitrile (I) was converted, with the aid of sodamide and trimethylene chlorobromide,⁴ into phenyl- α -(β -dimethylaminoethyl)- α -(γ -chloropropyl)-acetonitrile (II). The latter compound was not isolated but was converted, by heat, into 1-methyl-4-phenyl-4-cyanohexamethylenimine methochloride (III). This product, when heated, lost methyl

chloride with the formation of 1-methyl-4-phenyl-4-cyanohexamethylenimine (IV). Hydrolysis and esterification of IV yielded 1-methyl-4-phenyl-4-carbomethoxyhexamethylenimine (V) which was converted by lithium aluminum hydride into 1-methyl-4-phenyl-4-(hydroxymethyl)-hexamethylenimine (VI). The alcohol VI was characterized by the preparation of the acetate and the benzoate.

The structure of VI was confirmed by its synthesis from 4-phenyl-4-carbomethoxycyclohexanone (VII). The latter compound was converted by sodium azide and hydrochloric acid into δ -phenyl- δ -carbomethoxy- ϵ -caprolactam (VIII) which was reduced by lithium aluminum hydride to 4-phenyl-4-(hydroxymethyl)-hexamethylenimine. After formylation of the latter compound with chloral⁵ and reduction of the formyl derivative with lithium

(1) Abstract of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 15–19, 1953, p. 14L.

(2) This paper represents part of a dissertation submitted by Eu-Phang Tsao in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1952.

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(4) Ethylene chlorobromide was used by H. Kägi and K. Miescher (*Helv. Chim. Acta*, **33**, 2489 (1949)) for the preparation of Demerol and a number of its homologs.

(5) F. F. Blicke and Chi-Jung Lu, *THIS JOURNAL*, **74**, 3933 (1952).

1-Methyl-4-phenyl-4-cyano-hexamethylenimine (IV).—1-Methyl-4-phenyl-4-cyano-hexamethylenimine methochloride (10 g.),⁸ in a 50-cc. distillation flask, was heated in a metal-bath (275–280°) under 15 mm. pressure. Decomposition began almost immediately and was completed after 10 minutes. The distillates obtained, after 55 g. of the methochloride had been pyrolyzed, were combined, dissolved in ether and the solution filtered. After distillation, the product weighed 28.7 g. (65%), b.p. 133–135° (1 mm.).

The hydrochloride melted at 150–151° after recrystallization from methyl ethyl ketone.

Anal. Calcd. for $C_{15}H_{19}N_2Cl$: C, 67.03; H, 7.63; N, 11.18; Cl, 14.14. Found: C, 67.26; H, 7.39; N, 10.95; Cl, 14.17.

When excess methyl chloride, dissolved in ether, was added to an ethereal solution of the base the methochloride precipitated, m.p. 245–246° (dec.) after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{16}H_{21}N_2Cl$: Cl, 13.39. Found: Cl, 13.53.

The methobromide melted at 241–241.5° (dec.) after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{21}N_2Br$: N, 9.06; Br, 25.84. Found: N, 9.14; Br, 25.90.

The methiodide melted at 226.5–227° (dec.) after recrystallization from ethanol.

1-Methyl-4-phenyl-4-carbomethoxyhexamethylenimine (V) (A).—A mixture of 12.9 g. of IV and 40 cc. of concd. hydrochloric acid was refluxed for 40 hours. The solution was evaporated to dryness, the residue was dissolved in water and the solution made alkaline with sodium hydroxide. After the solution had been extracted with ether, it was acidified and evaporated to dryness. The gummy residue, the crude carboxylic acid hydrochloride, became solid when it was washed with ether. It was refluxed with 30 cc. of thionyl chloride for 1 hour. After removal of the excess thionyl chloride, the residue was refluxed with 150 cc. of absolute ethanol for 12 hours. The alcohol was removed and the residue was treated with water. After removal of an oily, water-insoluble material by extraction with ether, the aqueous solution was made alkaline and then extracted with ether. The ethereal solution was dried with sodium sulfate, the solvent removed and the residue distilled; b.p. 133–134° (1 mm.), yield 4.4 g. (28%).

The hydrochloride was obtained from an ethereal solution of the ester base and hydrogen chloride; m.p. 145.5–146.5° after recrystallization from methyl ethyl ketone.

Anal. Calcd. for $C_{16}H_{24}O_2NCl$: C, 64.54; H, 8.07; N, 4.71; Cl, 11.93. Found: C, 64.52; H, 7.89; N, 4.88; Cl, 12.14.

(B).—After 39 g. of nitrile had been converted into the crude carboxylic acid hydrochloride in the manner described above, the latter was dissolved in 400 cc. of absolute ethanol and the solution was filtered. After the filtrate had been saturated with hydrogen chloride, it was refluxed for 24 hours. The alcohol was removed, the residue dissolved in water, the solution then made alkaline, extracted with ether and the extract then dried with sodium carbonate. Upon distillation, 20.8 g. (43.7%) of ester was obtained; b.p. 127–129° (0.5 mm.). The hydrochloride melted at 145.5–146.5°.

(C).—In this instance the crude carboxylic acid, obtained by hydrolysis of 39 g. of the nitrile, was esterified by the use of diazoethane. The ester boiled at 128–130° (0.5 mm.); yield 30.0 g. (63%).

1-Methyl-4-phenyl-4-(hydroxymethyl)-hexamethylenimine (VI) from V.—Compound V (20.5 g.) dissolved in 30 cc. of anhydrous ether, was added, dropwise, to a stirred solution of 3.0 g. of lithium aluminum hydride in 150 cc. of anhydrous ether, and the mixture was refluxed for 12 hours. Water (6 cc.) was added carefully to the cooled mixture and the latter was stirred for one-half hour and then filtered. The solvent was removed from the filtrate and the residue was distilled. The product boiled at 161–163° (2 mm.), yield 14.2 g. (84.5%).

The methobromide precipitated when an ethereal solution of methyl bromide was added to an ethereal solution of the

base. The hygroscopic product was boiled with acetone to remove an impurity and was then recrystallized from isopropyl alcohol; m.p. 177–178.5°.

Anal. Calcd. for $C_{16}H_{24}ONBr$: C, 57.33; H, 7.64; N, 4.46; Br, 25.42. Found: C, 57.48; H, 7.53; N, 4.59; Br, 25.56.

Compound VI was obtained also from IX in the manner described below.

1-Methyl-4-phenyl-4-(acetoxymethyl)-hexamethylenimine.—A mixture of VI, 15 cc. of acetic anhydride and 10 cc. of ether was refluxed for 1 hour. The solution was poured into ice-water, made alkaline and extracted with ether. After the extract had been dried over sodium carbonate and the solvent removed, the residue was distilled; b.p. 153–156° (1.5 mm.), yield 4.6 g. (64%).

The hydrochloride was recrystallized from methyl ethyl ketone; m.p. 160–162°.

Anal. Calcd. for $C_{16}H_{24}O_2NCl$: C, 64.54; H, 8.07; N, 4.71; Cl, 11.93. Found: C, 64.63; H, 7.96; N, 4.59; Cl, 11.96.

1-Methyl-4-phenyl-4-(benzoyloxymethyl)-hexamethylenimine.—A mixture of the hydrochloride, obtained from 5 g. of VI, and 6 g. of benzoyl chloride was heated for 1 hour on a steam-bath. After the addition of water, the mixture was extracted with ether. The aqueous layer was made alkaline, extracted with ether, the extract dried over sodium carbonate and the solvent removed. The solid residue was recrystallized from methyl ethyl ketone; m.p. 170–171°. The product is hygroscopic.

Anal. Calcd. for $C_{19}H_{26}O_2N$: N, 4.33. Found: N, 4.31.

4-Phenyl-4-carbomethoxycyclohexanone (VII).—The crude γ -phenyl- γ -cyanopimelonitrile,⁹ obtained from 58.7 g. of phenylacetone, was washed with alcohol and then refluxed with 300 cc. of 48% hydrobromic acid for 40 hours. The γ -phenyl- γ -carboxypimelic acid which precipitated from the cold mixture, was recrystallized from water; m.p. 154–155°,¹⁰ yield 121.5 g. (87% based on phenylacetone).

Diethyl γ -phenyl- γ -carbomethoxypimelate was obtained from the acid by the use of diazoethane in 92.7% yield. The triethyl ester was converted into the diester, 4-phenyl-2,4-dicarbomethoxycyclohexanone, in the following manner.

To a stirred mixture of 16.2 g. of sodium hydride and 400 cc. of benzene in a 3-necked, liter flask, equipped with a stirrer, condenser and dropping funnel, there was added 2 cc. of ethanol and then 109 g. of the ester, dropwise. This operation was carried out in a nitrogen atmosphere. After the mixture had been refluxed for 4.5 hours, it was cooled, and 40.5 g. of acetic acid was added, followed by 37 cc. of water. The mixture was stirred for 30 minutes, filtered, the solvent removed and the residue distilled; b.p. 155–157° (0.05 mm.), yield 92.9 g. (97.4%).¹¹

A mixture of 77.2 g. of the diester, 150 cc. of acetic acid and 100 cc. of 20% sulfuric acid was refluxed for 5 hours. The mixture was extracted with ether and the extract neutralized with sodium hydroxide solution. The extract, which contained the 4-phenyl-4-carbomethoxycyclohexanone (VII), was dried with magnesium sulfate, the solvent removed and the residue distilled; b.p. 127–129° (0.2 mm.), yield 33.7 g. (56.4%).¹²

The aqueous, alkaline solution was acidified and extracted with ether. The acid, 4-phenyl-4-carboxycyclohexanone, obtained as a hydrate, weighed 16.0 g., m.p. 93–95° after recrystallization from water.

δ -Phenyl- δ -carbomethoxy- ϵ -caprolactam (VIII).—Sodium azide (20.4 g., 0.31 mole) was added in small portions to a stirred mixture of 63.4 g. (0.26 mole) of 4-phenyl-4-carbomethoxycyclohexanone (VII) and 170 cc. of concd. hydrochloric acid while the temperature was maintained at 28–33°. The mixture was stirred for 4 hours at room temperature and then made slightly alkaline with sodium hydroxide. The mixture was filtered and then extracted with chloroform. The extract was dried with potassium carbonate and the solvent was removed. The solid residue was recrystallized

(9) H. A. Bruson and T. W. Riener, *THIS JOURNAL*, **65**, 23 (1943).

(10) M. Rubin and H. Wishinsky (*ibid.*, **68**, 828 (1946)) found 153–154°.

(11) M. Rubin and H. Wishinsky (ref. 10), who effected the condensation with sodium sand, obtained a 65% yield.

(12) This process is a modification of one used by Rubin and Wishinsky (ref. 10).

(8) Compound IV was obtained in the same yield by the use of the methobromide or the mixture of methochloride and methobromide (m.p. 242–243°).

from a mixture of methyl ethyl ketone and petroleum ether (60–75°); m.p. 107–108°, yield 52.4 g. (78%).

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; H, 7.33; N, 5.36. Found: C, 68.97; H, 7.56; N, 5.37.

A compound, presumably the hydrochloride, precipitated when hydrogen chloride was passed into an ethereal solution of the lactam; m.p. 128–131°. When an attempt was made to recrystallize the salt from a mixture of methyl ethyl ketone and petroleum ether (90–100°), the lactam was obtained.

4-Phenyl-4-(hydroxymethyl)-hexamethylenimine (IX).—The lactam (VIII, 52.2 g.), dissolved in 350 cc. of dioxane, was added to a stirred mixture of 20 g. of lithium aluminum hydride and 400 cc. of anhydrous ether. The mixture was stirred and refluxed for 12 hours. It was cooled and 40 cc. of water was added, dropwise. The mixture was filtered and the solvents were removed. The solid residue was recrystallized from a mixture of ether and methyl ethyl ketone; m.p. 81.5–82.5°, yield 35.0 g. (85.4%).

Anal. Calcd. for $C_{15}H_{19}ON$: C, 76.07; H, 9.33; N, 6.82. Found: C, 75.50; H, 9.17; N, 6.71.

1-Methyl-4-phenyl-4-(hydroxymethyl)-hexamethylenimine (VI) from IX.—Chloral (30 g., 0.203 mole) was added slowly to 35.5 g. (0.173 mole) of IX dissolved in 100 cc. of chloroform. After 12 hours at room temperature, the solvent and excess chloral were removed, the residue was dissolved in 120 cc. of pure dioxane and the solution dropped into a stirred suspension of 7.0 g. (0.185 mole) of lithium aluminum hydride in 150 cc. of dry ether. The mixture was refluxed for 12 hours, cooled, 14 cc. of water added carefully and the mixture was filtered. The filtrate was evaporated to dryness and the residue was distilled; b.p. 142–144° (1 mm.), yield 28.8 g. (76%).

The methobromide was recrystallized from isopropyl alcohol; m.p. 178–179°, mixed m.p. 178–179°.

Anal. Calcd. for $C_{15}H_{21}ONBr$: C, 57.33; H, 7.64; Br, 25.42. Found: C, 57.22; H, 7.72; Br, 25.33.

1-Ethyl-4-phenyl-4-cyano-hexamethylenimine Methochloride (XII).—Phenylacetonitrile (94 g.), dissolved in 100 cc. of toluene, was allowed to react with 135 g. of β -diethylaminoethyl chloride, dissolved in 100 cc. of toluene, and 39 g. of sodamide by the procedure used for the preparation of I.⁸ After completion of the reaction, the mixture was filtered, but the reaction product X was not isolated. The filtrate was added, dropwise, to 39 g. of pulverized sodamide suspended in 200 cc. of toluene and the mixture was stirred for 5 hours. Trimethylene chlorobromide (158 g.) was added, dropwise, to the stirred mixture which was kept below 10°. After the mixture, maintained at 3°, had been stirred for 20 minutes, it was treated with ice-water, the organic layer which contained XI was separated and the aqueous layer was extracted with toluene. The combined extract and organic layer was refluxed for 15 hours. The precipitate was filtered and recrystallized from isopropyl alcohol; yield 60 g. This product was the methochloride (XII) contaminated with the methobromide.

1-Ethyl-4-phenyl-4-cyano-hexamethylenimine (XIII).—The crude product (22.5 g.) (XII) was pyrolyzed in the manner which has been described except that the bath temperature was maintained at 245–250°, b.p. 136–139° (1 mm.), yield 13.1 g.

The hydrochloride melted at 182–183° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{15}H_{21}N_2Cl$: C, 68.03; H, 7.99; N, 10.58; Cl, 13.39. Found: C, 68.03; H, 8.02; N, 10.55; Cl, 13.68.

Compound XIII was also obtained in the following man-

ner. Phenylacetonitrile (9.4 g., 0.08 mole), dissolved in 20 cc. of toluene, was added, dropwise, to a stirred suspension of 9.0 g. (0.23 mole) of sodamide in 100 cc. of toluene while the temperature was maintained at 35–40°. The mixture was stirred for 2 hours, and then a solution of 14.7 g. (0.08 mole) of ethyl- β -chloroethyl- γ -chloropropylamine (described below) in 100 cc. of toluene was added during a period of 3 hours. The mixture was refluxed for 2 hours, cooled and 50 cc. of water added. The organic layer was separated and the aqueous layer extracted with ether. The extract was combined with the organic layer and the solvents were removed. The product boiled at 137–139° (1 mm.), yield 3.6 g. (20%).

The hydrochloride melted at 182–183°, mixed m.p. 182–183°.

Ethyl- β -chloroethyl- γ -chloropropylamine.—A mixture of 36 g. of ethylethanolamine, 19.0 g. of trimethylene chlorohydrin and 30 cc. of water was heated on a steam-bath for 4 hours. Potassium hydroxide (13 g.) was added to the cold mixture, followed by 50 cc. of acetone. The precipitate was removed by filtration and the filtrate distilled. The ethyl- β -hydroxyethyl- γ -hydroxypropylamine boiled at 99–101° (1 mm.), yield 20.5 g. (69.7%).

The picrate precipitated when the base, dissolved in ethyl acetate, was treated with picric acid dissolved in the same solvent; m.p. 94–95°.

A solution of 17.7 g. of the hydroxyamine in 25 cc. of chloroform was added to a stirred solution of 45 g. of thionyl chloride in 50 cc. of the same solvent. The mixture was refluxed for 1 hour. After removal of the solvent and excess thionyl chloride, the residue was dissolved in water, the cold solution made alkaline and extracted with ether. The product boiled at 120–122° (31 mm.), yield 17.0 g. (77.2%).

The hydrochloride, prepared from an ethereal solution of the base and hydrogen chloride, melted at 105–106° after recrystallization from acetone.

Anal. Calcd. for $C_7H_{16}NCl_3$: Cl, 48.31. Found: Cl, 48.59.

1-Ethyl-4-phenyl-4-carboxyhexamethylenimine (XIV).—A mixture of 5.0 g. of XIII and 20 cc. of concd. hydrochloric acid was refluxed for 40 hours. The solution was made alkaline, extracted with ether, and the aqueous layer was acidified with hydrochloric acid. The solution was evaporated to dryness and the residue extracted with hot isopropyl alcohol. The solvent was removed from the extract and the residue, the acid hydrochloride, was recrystallized from isopropyl alcohol; m.p. 171–173°, yield 5.0 g. (80%).

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: C, 63.38; H, 7.81; N, 4.94; Cl, 12.50. Found: C, 63.78; H, 7.92; N, 4.80; Cl, 12.60.

One molar equivalent of a concd. sodium hydroxide solution was added to a saturated solution of the acid hydrochloride. The precipitated acid was recrystallized from ethanol; m.p. 188–189° (dec.).

Anal. Calcd. for $C_{15}H_{21}O_2N$: N, 5.66. Found: N, 5.60.

1-Ethyl-4-phenyl-4-carbomethoxyhexamethylenimine Hydrochloride (XV).—Excess diazoethane was added to an ethanolic solution of 5.0 g. of the hydrochloride of XIV. After 12 hours the solvent and excess diazoethane were removed, the residue was dissolved in ether and the solution was treated with hydrogen chloride. The precipitated hydrochloride was recrystallized from methyl ethyl ketone; m.p. 178–179°, yield 5.1 g.

Anal. Calcd. for $C_{17}H_{26}N_2Cl$: C, 65.44; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.80; H, 8.39; N, 4.57; Cl, 11.48.

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