(30% yield) of white needles, m.p. 177–178° dec. An additional recrystallization from acetone-hexane gave the analytical specimen as white needles, m.p. 179–180° dec.; $[\alpha]_D$ +12° (c 0.1, chloroform); λ_{max} 235 mμ (ε = 16,100); λ_{max} 5.90, 6.00, 6.18 μ. Engel and Deghenghi[8a] recorded m.p. 169–170° dec.; $[\alpha]_D$ +12.1° (chloroform); λ_{max} 236–237 mμ (ε = 15,900). Mills and his associates[6] reported m.p. 180–181°, $[\alpha]_D$ +12° (chloroform) and λ_{max} 236 mμ (ε = 15,900).

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86; Br, 19.43; F, 4.62. Found: C, 61.02; H, 7.17; Br, 19.93; F, 4.77.

17α-Chloro-6α-fluoroprogesterone (IVb). The crude reaction product prepared from 2.000 g. of 3,20-diacetoxy-3,5,17(20)-pregnatriene (I) and perchloryl fluoride as described above was dissolved in acetone. The solution was treated with 5 ml. of a solution prepared by saturation of a 1*N* sodium bicarbonate solution with chlorine. Almost immediately following the addition, an aliquot of the reaction solution failed to give a color with starch-iodide paper. The crude product, isolated with chloroform, was dissolved in 50 ml. of glacial acetic acid that was previously saturated with hydrogen chloride. This solution was kept at room temperature for 16 hr. and then poured into saturated sodium acetate solution. The mixture was extracted with chloroform, and the organic extracts were washed successively with water, sodium bicarbonate solution and water, dried over magnesium sulfate and taken to dryness. The residue was adsorbed from benzene onto a column (1.8 × 36 cm.) that was prepared from silica gel and benzene. The column was washed with benzene-ether (99:1), 125-ml. fractions being collected. Removal of the solvent from fractions 8–24 gave crystalline material which was combined and recrystallized twice from acetone-hexane to give 0.815 g. (44% yield) of white blades, m.p. 192–196°. An additional recrystallization gave the analytical sample as blades, m.p. 195–197°; $[\alpha]_D$ +51° (c 0.1, chloroform); λ_{max} 237 mμ (ε = 16,700); λ_{max} 5.88, 6.00, 6.18 μ.

Anal. Calcd. for $C_{21}H_{28}ClFO_2$: C, 68.73; H, 7.69; Cl, 9.66; F, 5.18. Found: C, 68.61; H, 7.92; Cl, 9.94; F, 5.44.

6α-Fluoro-4,16-pregnadiene-3,20-dione (V). *Method A.* 17α-Bromo-6α-fluoroprogesterone (IVa) (150 mg.) was treated with 25 mg. of lithium chloride in 25 ml. of dimethylformamide as described previously.[8a] The product was obtained as white needles, m.p. 169–171°; $[\alpha]_D$ +157° (c 0.1, chloroform); λ_{max} 237 mμ (ε = 29,200); λ_{max}^{Nujol} 5.95, 6.00, 6.16, 6.29 μ. Engel and Deghenghi[8a] reported m.p. 162–163°, $[\alpha]_D$ + 158.4° (chloroform), and λ_{max} 238 mμ (ε = 22,000).

Anal. Calcd. for $C_{21}H_{27}FO_2$: C, 76.33; H, 8.24. Found: C, 76.21; H, 8.32.

Method B. 17α-Chloro-6α-fluoroprogesterone (IVb) (150 mg.) when treated in the same manner, gave after recrystallization from ether 57 mg. of white needles, m.p. 169–171°. The identity of this material with that of Method A was shown by mixture melting point and spectral comparisons.

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Stereochemistry of a 3-Phenylnorbornane-2-amine[1]

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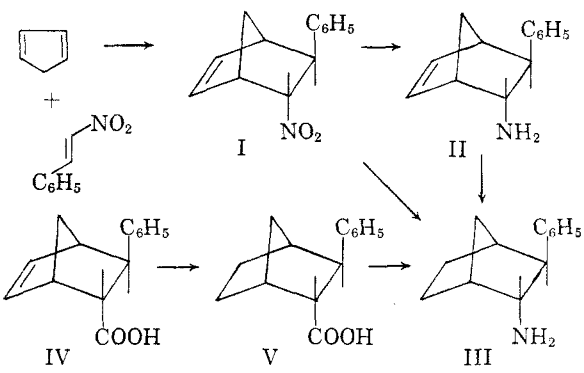
The reaction of cyclopentadiene and β-nitrostyrene leads to a 2-nitro-3-phenyl-5-norbornene. This had been reduced by iron and hydrochloric acid to a 3-phenyl-5-norbornene-2-amine which by hydrogenation over platinum gave a 3-phenylnorbornane-2-amine. This compound was also obtained directly by a Raney nickel catalyzed hydrogenation of the 2-nitro-3-phenyl-5-norbornene.[2] We have now determined the stereochemistry of these products and prepared some of their simple derivatives.

Consideration of the Alder rules[3] suggested that the initial adduct was *endo*-2-nitro-*exo*-3-phenyl-5-bornene, since interaction between the nitro group and the diene was felt to be stronger than similar interaction between the phenyl group and the diene. The success of iron and acetic acid[4] in reducing optically active nitro compounds to the corresponding amines with a high degree of retention of optical activity suggested that the same reagents would also reduce the 5-nitro-6-phenylnorbornene with retention of configuration. We have found that iron and acetic acid, iron and hydrochloric acid, or tin in acetic acid all gave the same 3-phenyl-5-norbornene-2-amine. Furthermore, catalytic reduction of this product gave the same 3-phenylnorbornane-2-amine that could be obtained by direct reduction of the initial adduct with hydrogen and Raney nickel. This implied that the saturated amine was *trans* with the amino group in an *endo* configuration.



In order to establish this, pure *exo*-3-phenylnorbornane-*endo*-2-carboxylic acid was prepared by reduction of *exo*-3-phenyl-5-norbornene-*endo*-2-carboxylic acid which had been purified by carrying it through the iodolactonization procedure.[5] This was converted to authentic *exo*-3-phenylnorbornane-*endo*-2-amine by use of the modified Curtius reaction which we have shown to proceed without

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[1] Presented in part at the Third Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., February 25, 1960. On presenting this work we discovered that several other laboratories had also investigated this problem, *i.e.*, Chester Trivette, Jr., Ph.D. thesis, Duke University, 1958; George Poos, McNeil Laboratories, personal communication.

[2] W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, **73**, 5068 (1951).

[3] See M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948) for a concise statement of them.

[4] N. Kornblum and L. Fishbein, *J. Am. Chem. Soc.*, **77**, 6266 (1955).

[5] C. S. Rondestvedt and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 4878 (1955).

change in configuration in a similar system.[6] The amine obtained in this way and the amine obtained by reduction of the nitro compound were identical.

EXPERIMENTAL[7]

exo-3-Phenyl-5-norbornene-endo-2-amine (II). To a suspension of 60 g. (0.5 mole) of tin granules in 150 ml. of glacial acetic acid was added dropwise a solution of 53.8 g. (0.25 mole) of 5-nitro-6-phenylnorbornene in 75 ml. of acetic acid. The mixture was then stirred vigorusly and heated on a steam bath for 1 hr. After cooling it was made basic with 40% sodium hydroxide and extracted four times with ether. The etherel layer was dried over sodium sulfate and on distillation gave 22.9 g. (49%) of an oil, b.p. 106–125° (0.7–1.0mm.).

A *maleic acid salt* was prepared from equimolecular amounts of maleic acid and the amine; the crude material had a melting point of 119–122°. After one recrystallization from an ethyl acetate–ethyl methyl ketone mixture, it melted at 129–130°. After two more recrystallizations from the same solvent mixture the melting point was constant at 150–151°.

Anal. Calcd. for $C_{13}H_{15}N \cdot C_4H_4O_4$: C, 67.76; H, 6.36. Found: C, 67.79, 67.55; H, 6.62, 6.47.

The *hydrochloride* was obtained as white crystals, m.p. 242–243° dec.

The same reduction was carried out with powdered iron in acetic acid; considerable difficulty was encountered in the work-up of this reaction mixture due to emulsification of the basic solution. Upon distillation a colorless liquid was obtained in 49% yield, b.p. 110–122° (1.5–2.5 mm.), $n_D^{21.5}$ 1.5620.

The *hydrochloride* of this oil, m.p. 242–245° dec., did not depress the melting point of the material obtained from the tin reduction and their infrared spectra were identical.

exo-3-Phenylnorbornane-endo-2-amine (III). A. *By reduction of I.* A solution of 10.7 g. (0.05 mole) of 5-nitro-6-phenylnorbornene in 100 ml. of absolute ethanol was shaken with one teaspoon of Raney nickel under 50 lbs. of hydrogen. When the uptake of hydrogen had stopped, the suspension was filtered, the filtrate concentrated *in vacuo* and the residual oil distilled. Distillation yielded a clear oil, b.p. 124° (1.7 mm.) n_D^{24} 1.5575.

The *hydrochloride* of this oil was prepared; on recrystallization from a methanol–ethyl acetate–ether mixture it gave 5.6 g. (59%) of a white solid, m.p. 203–204° dec.

Anal. Calcd. for $C_{13}H_{17}N \cdot HCl$: C, 69.78; N, 8.11. Found: C, 70.00; H, 8.21.

The *maleic acid salt* was also prepared and on recrystallization from an ethyl acetate–ether mixture gave white crystals, m.p. 165–167°.

Anal. Calcd. for: $C_{13}H_{17}N \cdot C_4H_4O_4$: C, 67.31; H, 6.98. Found: C, 67.08; H, 7.20.

The same maleate identified by infrared and mixed melting points was obtained when the reductions were carried out in acetic acid and 95% ethanol catalyzed by palladium-on-charcoal and in ethanol catalyzed by Raney cobalt.

B. *By reduction of* II. A suspension of 1.25 g. of *3-phenyl-5-norbornene-2-amine* in 60 ml. of ethanol and one-half teaspoon of Raney nickel was shaken under 50 lbs. of hydrogen for 5 hr. After removal of the catalyst by filtration, the reduction product was concentrated to give a yellow residue which was treated with 10% hydrochloric acid in isopropyl alcohol; the hydrochloride was precipitated by addition of ether and isolated as a white solid, m.p. 202–204° dec. A mixed melting point with a sample of 3-phenyl-norbornane-2-amine hydrochloride obtained by reduction of *3-phenyl-2-nitro-5-norbornene* in presence of Raney nickel did not show any depression.

C. *From the Curtius degradation of* V. A suspension of 6.07 g. (0.03 mole) of *exo*-3-phenyl-*endo*-2-norbornanecarboxylic acid in 7 ml. of water was dissolved in acetone. Then 5.06 g. (0.05 mole) of triethylamine in 90 ml. of acetone was added all at once and 5.5 g. (0.05 mole) of ethyl chloroformate in 20 ml. of acetone was added at such a rate that the temperature was maintained below 5°. After it stood for 30 min., 4.6 g. (0.07 mole) of sodium azide in 15 ml. of water was added to the reaction mixture. This was stirred for 1 hr., diluted with water, and extracted with ether. The ethereal layer was concentrated and the resulting residual oil was heated in toluene until the evolution of nitrogen ceased. The toluene was removed *in vacuo* and the residue was refluxed for 9 hr. in 60 ml. of 6*N* hydrochloric acid. After the resulting oil was dissolved in water and the aqueous solution was made basic, it was extracted twice with ether. The maleic acid salt was prepared from the ethereal solution, and on recrystallization from a methanol-ether mixture gave 7.3 g. (90%) of white crystals, m.p. 169–170°. This product did not show a melting point depression with the product obtained in A.

exo-3-Phenyl-endo-2-norbornane carboxylic acid (V). A mixture of 6.06 g. (0.03 mole) of *exo*-3-phenyl-5-norbornene-*endo*-2-carboxylic acid[5] and 0.15 g. of 10% palladium-on-charcoal in 50 ml. of ethanol was shaken under an atmosphere of hydrogen for 2 hr. The reaction mixture was filtered and the filtrate evaporated to dryness to give a solid which was recrystallized from a methanol-water mixture to give 5.8 g. (95%) of white crystals, m.p. 113.5–115°.

Anal.[8] Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.85; H, 7.84.

N-Methyl-exo-3-phenyl-endo-2-norbornanamine. A solution of 9.4 g. (0.05 mole) of *exo*-3-phenyl-*endo*-2-norbornanamine in 40 g. of ethylformate was refluxed for 6 hr. The solution was then concentrated *in vacuo* leaving a yellow oil. This was dissolved in 50 ml. of anhydrous ether and added slowly to a slurry of 2 g. of lithium aluminum hydride in 100 ml. of ether. After the initial reaction had subsided, the reaction mixture was heated to reflux for 2 hr., and then 20 ml. of a mixture of ethyl acetate and ether (1:3) was added followed by 10 ml. of water; stirring was then continued for another hour. The reaction mixture was filtered and the filtrate concentrated and distilled to give 7.75 g. (77%) of a liquid, b.p. 113–114° (1.2 mm.) $n_D^{25.3}$ 1.5472.

The *hydrochloride* melted at 201–203° after recrystallization from an ethyl acetate–ether mixture.

Anal. Calcd. for $C_{14}H_{19}N \cdot HCl$: C, 70.72; H, 8.48. Found: C, 71.01; H, 8.53.

The *maleic acid salt,* which was recrystallized from an ethyl acetate–ether mixture, was obtained as white crystals, m.p. 141–143°.

Anal. Calcd. for $C_{14}H_{19}N \cdot C_4H_4O_4$: C, 68.12; H, 7.30. Found: C, 67.86; H, 7.30.

N,N-Dimethyl-exo-3-phenyl-endo-2-norbornanamine. To 12 g. (0.25 mole) of 98% formic acid kept at 0° was added dropwise 9.36 g. (0.05 mole) of 3-phenyl-2-norbornanamine followed by 10 g. (0.1 mole) of 37% aqueous formaldehyde. The mixture was refluxed for 6 hr., allowed to stand at room temperature overnight and then 5 ml. of 12*N* hydrochloric acid was added. The excess formic acid and formaldehyde was eliminated *in vacuo*. The residue was diluted with water, made basic with 10% aqueous sodium hydroxide, and extracted with ether. After drying over magnesium sulfate the ethereal extract was concentrated and the residue distilled to give 8.6 g. (80%) of a colorless oil, b.p. 123° (3.6 mm.) $n_D^{24.5}$ 1.5421.

The *hydrochloride,* after recrystallization from an ethyl-acetate–ether mixture, was obtained as white crystals, m.p. 226.5–227.5°.

Anal. Calcd. for $C_{15}H_{21}N \cdot HCl$: C, 71.55; H, 8.81. Found: C, 71.32; H, 8.79.

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(6) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(7) We would like to thank Mrs. Doris Rolston and her staff for microanalytical work and Mr. F. Lanting for technical assistance.

(8) We would like to thank Mr. N. Hall for preparing this analytical sample.

N-Methyl-exo-3-phenyl-5-norbornene-endo-2-amine. A mixture of 23.1 g. (0.125 mole) of *exo*-3-phenyl-5-norbornene-*endo*-2-amine and 50 g. of ethyl formate was refluxed for 1.5 hr.; after 1 hr. a precipiate which had formed dissolved again. The reaction mixture was concentrated *in vacuo* and the residual oil was dissolved in ether and added dropwise to a slurry of 7.0 g. of lithium aluminum hydride in 150 ml. of ether. After refluxing for 2 hr., 100 ml. of a mixture of ether--ethyl acetate (1:2) was added, followed by 35 ml. of water and 2 g. of anhydrous sodium sulfate. The suspension was filtered and the filtrate distilled to give 20.5 g. (82%) of an oil, b.p 92–102° (0.07 mm.), n_D^{25} 1.5487.

A *maleic acid salt* was prepared and on recrystallization from ethyl methyl ketone was obtained as white crystals, m.p. 186–186.5°.

Anal. Calcd. for $C_{14}H_{17}N \cdot C_4H_4O_4$: C, 68 55; H, 6.71. Found: C, 68.48; H, 6.82.

N,N-Dimethyl-exo-3-phenyl-5-norbornen-endo-2-amine. To 12 g. (0.25 mole) of 98% formic acid at 0° were added dropwise 9.4 g. (0.05 mole) of *exo*-6-phenylnorbornen-*endo*-5-amine and 15 g. of 37% aqueous formaldehyde. The reaction mixture was refluxed for 6 hr. and then 6 ml. of hydrochloric acid was added. The excess of formic acid and formaldehyde was removed *in vacuo,* the residue diluted with water, made basic with 40% sodium hydroxide, and extracted with ether; the ethereal extract was dried over magnesium sulfate, filtered, and distilled. Two fractions were obtained: (1) b.p. 123–127° (1.2–1.4 mm.) $n_D^{24.3}$ 1.5458, 5.7 g. (54%); and (2) b.p. 167–169° (1.6 mm.) $n_D^{24.3}$ 1.5659, 3.3 g. (31%). Fraction II showed a strong absorption at 6 μ in its infrared absorption spectrum which indicated the presence of an amide carbonyl band; the fractions were combined, dissolved in 60 ml. of anhydrous ether and added to a suspension of 2.0 g. of lithium aluminum hydride in 100 ml. of ether. After 2 hr. of reflux 30 ml. of an ethyl acetate–ether mixture (1:2) was added followed by 10 ml. of water. The suspension was filtered and the filtrate on distillation yielded 5.1 g. (52%) of an oil, b.p. 114–119° (1.1 mm.) $n_D^{22.5}$ 1.5472.

The *maleic acid salt* was prepared and recrystallized from an ethyl acetate–ether mixture. It was obtained as white crystals, m.p. 148.5–149.5°.

Anal. Calcd. for $C_{15}H_{19}N \cdot C_4H_4O_4$: C, 69.28; H, 7.04. Found: C, 69.24; H, 7.16.

N-Methyl-exo-3-cyclohexylnorbornane-endo-2-amine. A suspension of 1 g. of *N*-methyl-*exo*-3-phenyl-5-norbornen-*endo*-2-amine, 1 ml. of 12*N* hydrochloric acid, 20 ml. of absolute ethanol, and 0.1 g. of platinum oxide was shaken under 50 lbs. of hydrogen for 3.5 hr. After the suspension was filtered, the filtrate was concentrated and the residue dissolved in water, made basic with 10% sodium hydroxide, and extracted with ether. The ethereal extract was dried, filtered, and concentrated to yield an oil.

The *maleic acid salt* was prepared and was isolated as a white solid, m.p 139–141°.

Anal. Calcd. for $C_{18}H_{29}NO_4$: C, 66 96; H, 8.99; N, 4.34. Found: C, 66 92; H, 9 01; N, 4.23.

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Physical Constants of 6-Methylenedihydrodesoxymorphine

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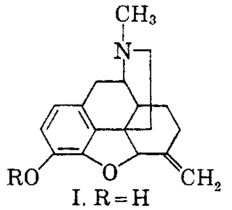
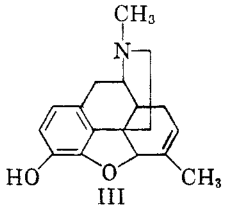
The synthesis of 6-methylenedihydrodesoxymorphine (I) has been described, and values have been reported for the melting point and specific rotation of the compound.[1] As the synthesis is based on the demethylation of 6-methylenedihydrodesoxycodeine (II) in the presence of an acidic catalyst. a possible by-product of the reaction is 6-methyl-Δ^6-desoxymorphine (III), resulting from the rearrangement of the exocyclic double bond of I to the more stable[2] endocyclic position.



I. R = H
II. R = CH_3



III

The results of investigations in our laboratories indicate that samples of I used in the abovementioned determinations of melting point and specific rotation may have been contaminated with III. A sample of I prepared in our laboratories by the method described below showed a constant specific rotation, $[\alpha]_D^{25}$ $-117°$, and melting point, 208.5–210.5°, after three successive crystallizations from acetone. The value of specific rotation previously reported[1] for I is $-140°$, which is between $-117°$, the value for pure I, and $-215°$, the value reported for III.[3,4] It was observed during the work described here that a sample of III[5] and an impure sample of I had absorption maxima at 6.66 μ, 7.57 μ, and 12.3 μ, while the purified sample of I did not.

The identity of purified I was established by converting the material to the original compound II with diazomethane.

EXPERIMENTAL[6]

6-Methylenedihydrodesoxymorphine (I). A dry, 1 × 8-in. test tube was charged with 7 g. (0.061 mole) of pyridine hydrochloride (Eastman Practical Grade) and fitted with a rubber stopper bearing a tube for introducing nitrogen beneath the surface of the salt. The pyridine hydrochloride was dried by heating the test tube in an oil bath at 220–230° while nitrogen was passed through the molten salt. While the nitrogen was still flowing, the tube was cooled, and 2 g. (0.0674 mole) of II was added. The mixture was heated at a temperature of 190–195° for 16 min. in the presence of nitrogen and cooled slightly, after which 30 ml. of water contain-

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(1) M. S. Chadha and H. Rapoport, *J. Am. Chem. Scc.,* **79,** 5730 (1957).

(2) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.,* **76,** 467 (1954); (b) R. Fleck, *J. Org. Chem.,* **22,** 439 (1957); (c) H. C. Brown, *J. Org. Chem.,* **22,** 439 (1957).

(3) H. D. Brown, I. M. Rasmussen, G. B. Payne, and K. Pfister III, *J. Am. Chem. Soc.,* **75,** 6238 (1953).

(4) The specific rotation reported in reference (3) was determined on material which melted at 225–229°, whereas material crystallized once more melted at 235–237°.

(5) We are indebted to Dr. Karl Pfister III of Merck and Co. for a sample of authentic 6-methyl-Δ^6-desoxymorphine.

(6) All melting points are corrected.