tained. No separation of pure substances was possible. Therefore, 0.8 g. of the residue was treated with hydrogen peroxide in glacial acetic acid and 0.7 g. of diphenylsulfone isolated.

In order to prove the eventual presence of 1,2-diphenylethane in a qualitative manner, 1.8 g. of the sulfur-containing oil and 1.3 g. of dimethyl sulfate were heated on the water-bath. After one hour the mixture was poured into water and extracted with ether. The evaporation of the dried ethereal solution led to an oily residue which deposited crystals from ethanol. After two recrystallizations from ethanol these crystals melted at 51-52° (mixed m. p. with 1,2-diphenylethane 51-52°); yield 300 mg.

Acknowledgment.—We wish to express our thanks to the Rockefeller Foundation for a grant and to Dr. E. Giesbrecht and Dr. W. Safiotti for some authentic material they supplied for comparison.

Summary

1. Mixed thioethers are the main reaction products when thiobenzoic esters are refluxed in xylene solution in the presence of Raney nickel freed from hydrogen by previous heating at 200° *in vacuo.*

2. When hydrogen has not been completely removed, binuclear hydrocarbons such as diphenyl are formed.

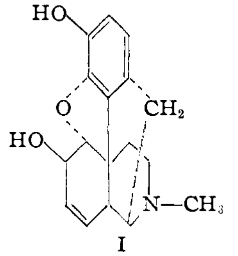
SÃO PAULO, BRASIL RECEIVED JUNE 23, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Angular Aryl Group. II. N-Methyl-10-phenyldecahydroisoquinoline

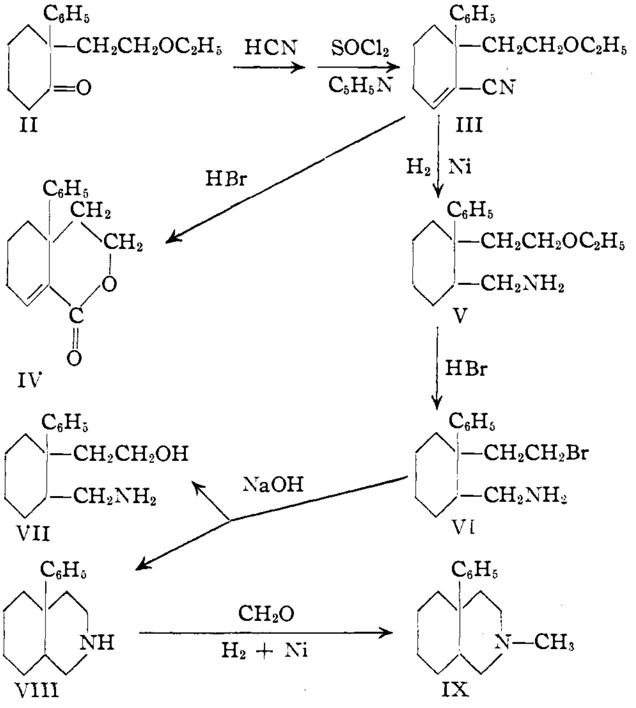
BY V. BOEKELHEIDE AND W. M. SCHILLING[1a,b]

In a previous publication[2] it was pointed out that the Gulland and Robinson formula for morphine may be regarded as a substituted octahydroisoquinoline having an angular aryl group.[3] This portion of the morphine skeleton is shown by solid lines in formula I. Although much work has been done on the synthesis of morphine analogs, the portion of the molecule outlined in I has not previously been synthesized and tested for analgesic activity.[4] The synthesis of N-methyl-10-phenyldecahydroisoquinoline has now been accomplished and the reaction scheme for its synthesis is outlined below.



I

The conversion of II to III was effected in 64% yield by addition of hydrogen cyanide followed by dehydration. The procedure for this was evolved using 2-phenylcyclohexanone as a model. An attempt was made to prepare the corresponding acid of III as a derivative, but hydrolysis did not occur readily and with 48% hydrobromic acid the corresponding lactone (IV) was formed.



Hydrogenation of III gave V in good yield. Cleavage of the ether linkage was accomplished with hydrobromic acid, and the crude bromoamine (VI) was cyclized directly to VIII. The cyclization product was impure and attempted purification resulted in the isolation of a product having the correct composition for VII. Since it was found that IX could be readily purified, the cyclization product, which consisted predominantly of VIII, was subjected directly to reductive alkylation. It was of interest that the picrate of IX was homogeneous, indicating that only one of the possible forms, presumably the

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[1] (a) Sherman Clarke Fellow, 1948-1949; (b) present address: University of Illinois, Urbana, Illinois.

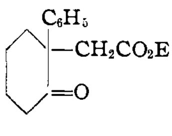
[2] Boekelheide, THIS JOURNAL, **69**, 790 (1947).

[3] Gulland and Robinson, *Mem. Proc. Manchester Lit. & Phil. Soc.*, **69**, 79 (1925).

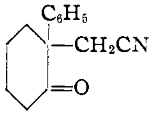
[4] Bergel and Morrison, *Quart. Rev.*, **2**, 349 (1948).

cis, was present.[5a,b] The complete carbon skeleton of morphine (N-methylmorphinan), which was recently synthesized by Grewe,[6] differs from IX by a methylene bridge. There are several possible ways in which the synthesis of IX might be extended to introduce this methylene bridge.

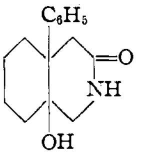
In exploratory work directed toward the synthesis of IX, both 2-carbethoxymethyl-2-phenylcyclohexanone (X) and 2-cyanomethyl-2-phenylcyclohexanone (XI) were investigated as possible starting materials.



X



XI



XII

Various attempts were made to effect cyanohydrin formation and reductive cyclization. The most successful of these efforts resulted in the conversion of X to XII. On slow distillation XII underwent dehydration as desired, but the yields in this approach were too low to favor further work. Although XI showed a carbonyl peak in its infrared absorption spectra, it did not give the usual carbonyl reactions and could not be usefully employed.

These and other exploratory investigations are outlined in the experimental sections B and C.

Experimental[7]

1-Cyano-2-phenylcyclohexanol-1.—To a solution of 25 g. of 2-phenylcyclohexanone[8] and 50 g. of potassium cyanide in 250 ml. of alcohol there was added dropwise 50 ml. of glacial acetic acid. The mixture was boiled under reflux for one hour and then poured into 650 ml. of water. The oil which separated solidified on standing and was collected. There was obtained 24.8 g. (89%) of a white solid which, after crystallization from petroleum ether (60–70°), melted at 117°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.48; H, 7.34.

1-Cyano-2-phenylcyclohexene-1.[9]—To a solution of 24.8 g. of 1-cyano-2-phenylcyclohexanol-1 in 40 ml. of dry pyridine immersed in an ice-bath, there was added dropwise 18.3 ml. of thionyl chloride. The mixture was boiled under reflux for one hour and was then poured onto a solution of ice and excess hydrochloric acid. The organic layer was extracted with ether, dried and distilled. There was obtained 9.0 g. (38%) of a colorless oil, b. p. 125–130° at 2 mm.; n^{20}D 1.5667. The oil crystallized on standing to yield large diamond-shaped crystals. After crystallization from a benzene–petroleum ether mixture, the crystals melted at 42–43°.

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.25; H, 7.10. Found: C, 85.51; H, 7.19.

2-Cyano-3-(β-ethoxyethyl)-3-phenylcyclohexene, III.—Although in the model study with 2-phenylcyclohexanone it was feasible to isolate the cyanohydrin, it was necessary to combine the two steps in the present case. A solution of 25.0 g. of 2-(β-ethoxyethyl)-2-phenylcyclohexanone[10] and three drops of a saturated potassium cyanide solution in about 40 g. of liquid hydrogen cyanide was allowed to stand at 0° for twelve hours. Three drops of concd. sulfuric acid was then added and the excess hydrogen cyanide was removed. The residual oil was subjected to dehydration as before using 32 ml. of dry pyridine and 24.0 g. of purified thionyl chloride. The product in this case was an oil and before distillation it was further purified by boiling an alcoholic solution of it for five hours with Raney nickel. On distillation there was obtained 16.1 g. (64%) of a colorless viscous oil, b. p. 153–154° at 0.9 mm., n^{21}D 1.5402.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.44; H, 8.14; N, 5.00.

2-Phenyl-2-(β-hydroxyethyl)-1-cyclohexenecarboxylic Acid Lactone (IV).—A solution of 1.00 g. of III in 7 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid was boiled under reflux for ninety-eight hours and was then poured into water. The product was extracted with ether, dried and the ether was removed. The dark residual oil slowly crystallized and, after recrystallization from a benzene–heptane mixture, it was obtained in poor yield as white crystals, m. p. 112–113°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 78.91; H, 7.13.

Attempts at hydrolysis under milder conditions gave no useful product. The above product was insoluble in cold base but dissolved on warming, indicating the presence of the lactone ring.

2-Aminomethyl-1-(β-ethoxyethyl)-1-phenylcyclohexane (V).—A mixture of 17.3 g. of III, 4 g. of Raney nickel catalyst and 35 ml. of a saturated ammoniacal ethanol solution was shaken at 130° for two hours under a pressure of *ca.* 180 atm. of hydrogen. After removal of the catalyst and solvent the residual oil was taken up in excess benzene and the amine portion was extracted with 0.6 *N* hydrochloric acid. The aqueous extract was made basic and the amine was extracted with benzene and distilled. There was obtained 13.8 g. (78%) of a colorless oil, b. p. 133–135° at 0.4 mm., n^{20}D 1.5395.

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.16; H, 10.42. Found: C, 78.17; H, 10.51.

The **picrate** of V was prepared from alcohol and obtained as yellow crystals, m. p. 160–161° (cor.).

Anal. Calcd. for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.17. Found: C, 56.54; H, 5.90.

10-Phenyldecahydroisoquinoline (VIII).—A solution of 8.0 g. of V in 125 ml. of hydrobromic acid was boiled under reflux for five hours. After removal of the hydrobromic acid *in vacuo*, a dark glassy substance remained which could not be purified and was cyclized directly. This was accomplished by taking it up in 1 l. of alcohol and adding this solution dropwise over a period of four hours to a well-stirred solution of 16.0 g. of sodium hydroxide in 1.5 l. of water and 500 ml. of alcohol. The mixture was maintained at 55° for sixteen hours. The solution was then made acidic and the volume was reduced by vacuum distillation to about 250 ml. Neutral material was extracted with ether and the solution was made basic. The amine fraction was taken up in ether, dried and distilled. There was obtained 4.6 g. (70%) of a colorless oil, b. p. 118–121° at 0.3 mm., n^{20}D 1.5602.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 82.27; H, 9.52.

The analysis indicated that the product was impure and purification was attempted through the picrate.

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(5) (a) Examination of models indicates that both *cis* and *trans* ring fusion is possible for IX but that *cis* ring fusion should be considerably easier than *trans* (see ref. 2). (b) Fieser and Fieser ("Natural Products Related to Phenanthrene," 3rd. ed., p. 24, Reinhold Publishing Corp., New York, N. Y., 1949) suggest that in morphine the octahydroisoquinoline ring fusion is *trans*. If so, IX probably differs from morphine in its manner of ring fusion. Possible evidence for this is the fact that IX shows low analgesic activity.

(6) Grewe, *Angew. Chem.*, **59**, 194 (1947).

(7) Analyses by Mrs. G. Sauvage and by the Micro-Tech Laboratories.

(8) Newman and Farbman, THIS JOURNAL, **66**, 1551 (1944).

(9) Also reported by St. Goldschmidt and Veer, *Rec. trav. chim.*, **67**, 489 (1948).

(10) Newman and Magerlein, THIS JOURNAL, **69**, 942 (1947).

From 2.0 g. of the crude oil from above there was obtained, after crystallization from alcohol, 1.0 g. of a yellow picrate, m. p. 227–228° (cor.). This picrate was then decomposed by heating it with a saturated solution of lithium hydroxide for ten minutes. The free amine was extracted with benzene and distilled using a molecular still. There was obtained 0.40 g. of an amber oil that slowly solidified. The white solid, m. p. 71–76°, was crystallized from a benzene–heptane mixture but its melting point did not change. Its composition indicates that it is VII and that the picrate procedure only effected isolation of the contaminant present.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.93. Found: C, 77.31; H, 9.34.

The **picrate** of VII was obtained as described above and melted at 227–228° (cor.).

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.55; H, 5.67. Found: C, 54.93; H, 5.46.

N-Methyl-10-phenyldecahydroisoquinoline (IX).—Freshly prepared formaldehyde was bubbled through a cold solution of 3.5 g. of a crude sample of VIII in 75 ml. of absolute ethanol for about ten minutes. Raney nickel catalyst was added and the mixture was shaken under 3-atm. pressure of hydrogen for three hours. The catalyst and solvent were removed and the residual oil was converted to the picrate. There was obtained 3.95 g. of yellow crystals which, after crystallization from alcohol, melted at 212–213° (cor.).

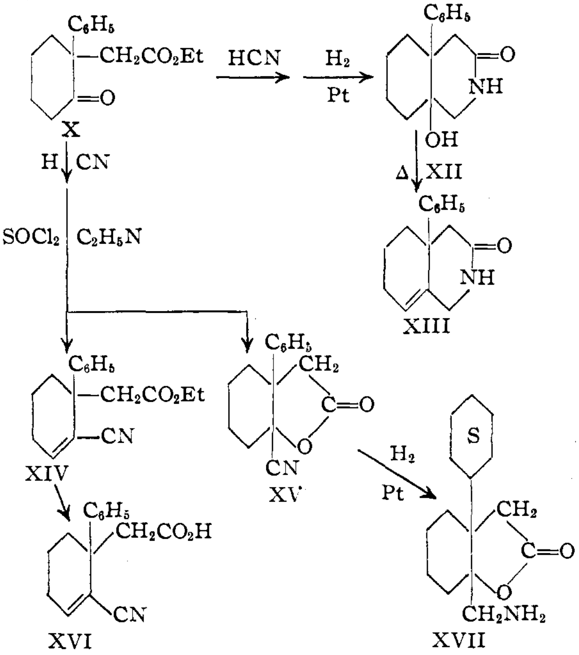
A 2.0-g. sample of the picrate was decomposed by heating it with 50 ml. of a saturated aqueous solution of lithium hydroxide for forty minutes. The free amine was extracted with benzene and distilled with a molecular-type still. There was obtained 0.75 g. of a colorless oil, b. p. 140–145° (bath temp.) at 0.5 mm., $n^{20}D$ 1.5530.

Anal. Calcd. for $C_{16}H_{23}N$: C, 83.77; H, 10.10; N, 6.13. Found: C, 83.54; H, 9.72; N, 5.90.

The **picrate** of IX as indicated above melted at 212–213° (cor.).

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: C, 57.63; H, 5.72. Found: C, 57.74; H, 5.73.

B. A summary of the reactions accomplished using X is given below.



2-Carbethoxymethyl-2-phenylcyclohexanone (X).—To a boiling suspension of 23.5 g. of sodamide[11] in 350 ml. of dry ether there was added dropwise over a period of one hour a solution consisting of 96.0 g. of 2-phenylcyclohexanone,[8] 185 ml. of dry ether and 80 ml. of dry thiophene-free benzene. The mixture was boiled under reflux until evolution of ammonia had ceased and then a solution of 141 g. of ethyl bromoacetate in 170 ml. of dry ether was added dropwise. The resulting solution was boiled under reflux for two hours, hydrolyzed with an excess of water, and the organic layer was separated. The volatile solvents and excess ethyl bromoacetate were removed *in vacuo*, and the residual oil was distilled. There was obtained 93 g. (65%) of a colorless oil, b. p. 150–155° at 2 mm., $n^{20}D$ 1.5278.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.84; H, 7.74. Found: C, 73.33; H, 7.95.

The **semicarbazone** of X was prepared and obtained, after crystallization from alcohol, as white crystals, m. p. 185–186°.

Anal. Calcd. for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.31. Found: C, 64.36; H, 7.10.

The use of sodium hydride in place of sodamide in the above reaction gave only a 37% yield.

2-Carboxymethyl-2-phenylcyclohexanone.—A solution of 1.0 g. of X in 25 ml. of a 10% aqueous sodium hydroxide solution was boiled under reflux for ninety minutes. The solution was then cooled and made acidic, and the organic layer was extracted with benzene. The benzene extract was decolorized with charcoal and the benzene was removed. The residual oil crystallized after three weeks of standing and was obtained from an alcohol–water mixture as white crystals, m. p. 130.5–131°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.61; H, 7.17.

9-Hydroxy-3-keto-10-phenyldecahydroisoquinoline (XII).—The cyanohydrin of X was prepared according to the procedure described by Butenandt and Schmidt-Thomé.[12] From 20 g. of X there was obtained 22 g. of a crude oily cyanohydrin.

This was taken up in 75 ml. of alcohol, 0.100 g. of platinum oxide catalyst was added, and the mixture was shaken under 3-atm. pressure of hydrogen overnight. The catalyst and solvent were removed and the residual oil was taken up in benzene and washed successively with dilute acid, water, dilute base and water. After removal of solvent, the residue was distilled yielding 8.0 g. of a colorless oil, b. p. 142–145° at 0.4 mm., $n^{24}D$ 1.5191.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.50; H, 7.91.

When the above sample was slowly distilled using a 10-in. column packed with glass helices, dehydration appeared to take place. After several distillations a small amount of a sample having the correct composition for XIII was obtained as a colorless oil, b. p. 133–135° at 0.5 mm., $n^{18}D$ 1.5478.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.27; H, 7.55. Found: C, 79.56; H, 7.82.

(2-Cyano-2-hydroxy-1-phenylcyclohexyl)-acetic Acid Lactone (XV).—In an attempt to prepare XIV the cyanohydrin of X was prepared and subjected to dehydration with thionyl chloride and pyridine as described for the preparation of III. From 25.0 g. of X there was obtained 11.0 g. of an oil, b. p. 130–135° at 0.4 mm., whose analysis indicated it to be a mixture of XIV and XV. When the oil was taken up in ether and treated with pentane, 1.5 g. of crystals separated. These crystals were soluble in hot base but not in the cold, indicating the presence of a lactone ring. After crystallization from an ether–pentane mixture, they were obtained as white crystals, m. p. 101.5–102.5°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 74.66; H, 6.27. Found: C, 74.55; H, 6.10.

2-Cyano-3-phenyl-3-carboxymethylcyclohexene (XVI).—The oil remaining after removal of the lactone (XV)

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(11) Vaughn and Niewland, This Journal, **56**, 2120 (1934).

(12) Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938).

was subjected to hydrolysis using 10% aqueous sodium hydroxide solution. From 1.0 g. of the oil there was obtained after acidification 0.7 g. of an amber oil which slowly crystallized. Recrystallization from an alcohol-water mixture gave white crystals, m. p. 234–235° (cor.).

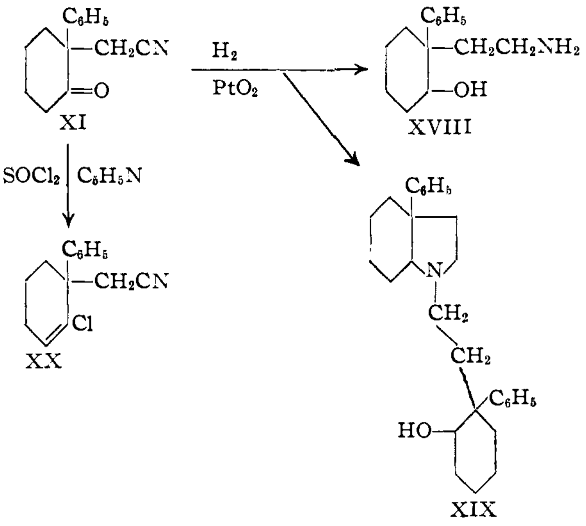
Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.62; H, 6.24.

Although it is possible that hydrolysis of XV could also yield the above acid, the relatively good yield on hydrolysis indicates that the bulk of the oil was XIV.

(2-Aminomethyl-2-hydroxy-1-(cyclohexyl)-cyclohexyl)-acetic Acid Lactone (XVII).—A suspension of 153 mg. of XV and 80 mg. of platinum oxide catalyst in 25 ml. of glacial acetic acid was shaken under 1 atm. of hydrogen overnight. The hydrogen uptake corresponded to five moles. The acetic acid was removed *in vacuo*, and the residue was taken up in water and made basic. The material, which separated, was extracted with ether and the ether was removed. There was obtained 60 mg. of a white solid which, after crystallization from an alcohol-water mixture, melted at 210–211°.

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03. Found: C, 71.75; H, 9.89.

C. A summary of reactions accomplished using XI is given below.



2-Cyanomethyl-2-phenylcyclohexanone (XI).—This was prepared in the same manner as was X except that chloroacetonitrile[13] was substituted for ethyl bromoacetate. From 66.0 g. of 2-phenylcyclohexanone there was obtained 53.5 g. (66%) of a colorless oil, b. p. 160–163° at 3 mm.; $n^{21}D$ 1.5418.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.87; H, 7.04. Found: C, 78.93; H, 7.22.

After several months standing the oil began to crystallize. When these crystals were used to seed a sample prepared several years earlier, this also crystallized. Recrystallization gave nice white crystals, m. p. 54–54.5°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.87; H, 7.04. Found: C, 78.68; H, 6.89.

Attempts to prepare a carbonyl derivative of XI were unsuccessful. However, the infrared absorption spectra of XI showed peaks at 1700 and 1444 cm.$^{-1}$ as would be expected for the carbonyl and nitrile groupings. Further evidence that the structure of XI is correct as assigned was the fact that acid hydrolysis of XI gave an oil which crystallized on being seeded with 2-carboxymethyl-2-phenylcyclohexanone.

2-(β-Aminoethyl)-2-phenylcyclohexanol-1 (XVIII).—Since it was desired to convert XI by the steps of cyanohydrin formation, dehydration, and reduction to the corresponding diamine, the reduction of XI itself was studied for reference purposes. A solution of 5.0 g. of XI in 100 ml. of a saturated solution of ammoniacal alcohol was shaken with 200 mg. of platinum oxide catalyst under 3 atm. of hydrogen pressure for sixteen hours. The catalyst and solvent were removed and the residue was taken up in ether. When the ethereal solution was treated with dilute hydrochloric acid, three layers resulted. The bottom layer, when made basic, yielded 0.62 g. of a solid amine (XVIII) which was recrystallized from heptane yielding white crystals, m. p. 91–92°.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.90; H, 9.33.

The picrate of XVIII was obtained, after crystallization from ether, as yellow crystals, m. p. 162–163°.

Anal. Calcd. for $C_{20}H_{24}N_4O_8$: C, 53.57; H, 5.39. Found: C, 54.01; H, 5.40.

The middle layer was separated, ether was added, and the solution was washed with base. Removal of the ether left 2.3 g. of an amber glass. A sample of this material was obtained by sublimation at 250° and at 2-mm. pressure. The analysis and molecular weight determinations fit most closely for a dimer such as XIX.

Anal. Calcd. for $C_{28}H_{37}NO$: C, 83.32; H, 9.24; N, 3.47; mol. wt., 403. Found: C, 82.31; H, 9.18; N, 3.65; mol. wt. (Rast), 421, 399.

2-Chloro-3-cyanomethyl-3-phenylcyclohexene (XX).—When XI was treated with hydrogen cyanide followed by dehydration with thionyl chloride and pyridine as described for the preparation of III, it was found that the product contained chlorine and was a solid, m. p. 79–80°. In view of the previous behavior of XI, it seemed possible that cyanohydrin formation had not occurred and therefore the action of thionyl chloride in pyridine on XI was studied.

To a solution of 3.0 g. of XI in 14 ml. of dry pyridine there was added 1.7 ml. of purified thionyl chloride. The solution was boiled under reflux for one hour and was then poured onto a mixture of ice and excess hydrochloric acid. Ether extraction yielded an amber oil which on treatment with methanol followed by cooling gave 1.1 g. of a solid. On recrystallization from methanol, white crystals, m. p. 79–80°, were obtained.

Anal. Calcd. for $C_{14}H_{14}ClNO$: C, 72.56; H, 6.09; Cl, 15.30. Found: C, 72.72, 72.60; H, 6.07, 5.98; Cl, 15.37.

The solid obtained in both procedures was the same and indicates that cyanohydrin formation did not occur. No good explanation for this reaction can be advanced but XX appears to be the most likely formula for the product.

Summary

The preparation of N-methyl-10-phenyldecahydroisoquinoline, which represents a portion of the morphine skeleton, has been accomplished.

Synthetic experiments utilizing 2-carbethoxymethyl-2-phenylcyclohexanone and 2-cyanomethyl-2-phenylcyclohexanone are described.

Rochester, New York Received July 5, 1949

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[13] Steinkopf, *Ber.*, **41**, 2540 (1908).