butyric acids has been shown to give 4-keto-1,2,-3,4-tetrahydroquinoline derivatives.

2. 4-Keto-1,2,3,4-tetrahydroquinolines may be dehydrogenated to 4-hydroxyquinolines in good yield with palladium in the presence of maleic acid.

3. The cyclic structure for the "aldol bases" of Miller and Plöchl has been confirmed.

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

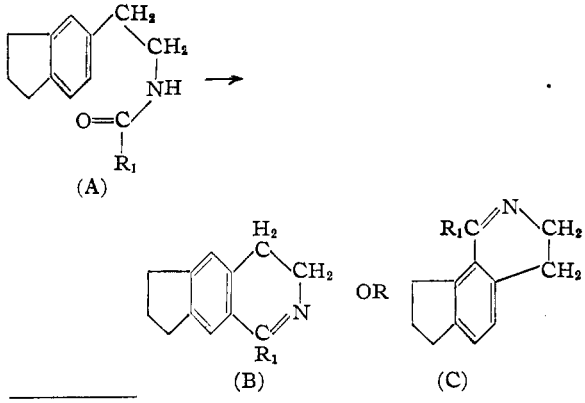
Synthetic Studies in the Isoquinoline Series

BY EVERETT M. SCHULTZ[1a,b] AND R. T. ARNOLD

Compounds having a 1-benzylisoquinoline structure occur in nature as minor constituents of opium. Of these, the most important is papaverine, 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline, which finds use as an antispasmodic. Synthetic isoquinolines that have been reported have most frequently carried alkoxy or methylenedioxy substituents, and but few having carbocyclic substituents have been described. Perhaps the most fruitful approach to the synthesis of 1-benzylisoquinoline is by the reaction of Bischler and Napieralski.[2] This reaction, which consists in cyclization through the dehydration of a substituted or unsubstituted β-arylethylamide, results in a 3,4-dihydroisoquinoline. The latter can be readily dehydrogenated catalytically by means of palladium[3] to yield an isoquinoline.

In the present work, a number of 1-benzyl-6,7-cyclopenteno- and 6,7-cyclohexeno-isoquinolines (Chart I) were synthesized by these methods in order to obtain compounds for physiological assay and to study the Bischler and Napieralski reaction in the hydrindene and tetralin series.

In the case of ring closure of a β-5-hydrindenyl- or β-6-tetralylethylamide (A), it is possible for cyclization to occur in one of two directions, one of which would lead to a 6,7-cycloalkeno-3,4-dihydroisoquinoline (B) and the other would lead to the 7,8-cycloalkeno-isomer (C).



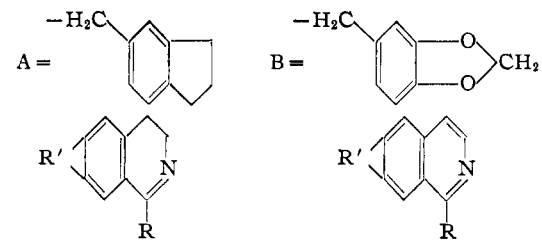
That cyclization led exclusively to structure B in both the hydrindene and tetralin series was demonstrated by nitric acid oxidation[4] of representative dihydroisoquinolines of both series. Such a degradation oxidizes the heterocyclic and alicyclic rings and yields a benzene tetracarboxylic acid. In both the hydrindene and tetralin series, the only product of the oxidation was 1,2,4,5-benzenetetracarboxylic acid. It must be concluded, therefore, that cyclization took place in such a direction as to form structure B exclusively.

The 3,4-dihydroisoquinolines, with one exception (III), were such extremely viscous, high-boiling sirups that rigorous fractionation was impossible and so analyses were made only on their picrates.

The amides of β-5- and 6-arylethylamines necessary for the synthesis of I through IX were obtained from the corresponding β-arylethylamines and a suitably substituted arylacetic acid or acetyl chloride. When the acid was used the amide was formed by dehydration of the amine carboxylic acid salt. If the acid chloride was employed, the amine and acid chloride were allowed to react in benzene solution in the presence of pyridine.

The β-arylethylamines and substituted acetic acids were obtained by reduction[5] or hydrolysis, respectively, of the proper nitriles. Compound VIII is probably the first example of a 1-substituted-6,7-benzoisoquinoline. Although Kindler, *et al.*,[6] have reported 1-phenyl-6,7-benzo-3,4-dihy-

CHART I



Dihydroisoquinolines

No.	R	R′
I	—A	—$(CH_2)_3$—
II	—B	—$(CH_2)_3$—
III	—A	CH_2O_2=
IV	—CH_3	—$(CH_2)_3$—
V	—$CH_2C_6H_5$	—$(CH_2)_4$—

Isoquinolines

No.	R	R′
VI	—B	—$(CH_2)_3$—
VII	—A	—$(CH_2)_3$—
VIII	—$CH_2C_6H_5$	—(CH=CH)₂—
IX	—A	CH_2O_2=

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(1b) Abstracted from a thesis presented to the faculty of the Department of Organic Chemistry, University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, July, 1944.

(2) Bischler and Napieralski, *Ber.*, **26**, 1903 (1893).

(3) Spaeth and Burger, *ibid.*, **60**, 704 (1927).

(4) Campbell, Soffer and Steadman, THIS JOURNAL, **64**, 425 (1942).

(5) Adkins and Schwoegler, *ibid.*, **60**, 408 (1938).

(6) Kindler, Peschke and Pludemann, *Arch. Pharm.*, **277**, 25 (1939).

droisoquinoline as the product obtained from the cyclization of N-β-(2-naphthyl)-ethylbenzamide, it is probable that their product was the 7,8-benzo isomer since Meyer and Schenko[7] showed that the cyclization of β-2-naphthylethylamine by the action of formaldehyde in hydrochloric acid yielded 7,8-benzotetrahydroisoquinoline.

Since chloromethylation of hydrindene is known to take place at position 5,[8] 5-hydrindenylacetonitrile (X) was obtained from chloromethylhydrindine by reaction with potassium cyanide.[9] On the other hand, pure 6-tetralylacetonitrile cannot be obtained directly from tetralin because it has been shown[10] that the chloromethylation of tetralin yields a mixture of the 5- and 6-isomers. However, acetylation of tetralin yields 6-acetyltetralin[10] and so the latter was used as the starting material. By means of the modified Willgerodt reaction,[11] 6-tetralylacetic acid was prepared. This readily yielded the corresponding ester which was converted to the amide and dehydrated to yield 6-tetralylacetonitrile. While this procedure is long, the yields in each step are good and no tedious purifications are necessary.

Piperonyl cyanide was prepared by known methods[12] and was hydrolyzed to homopiperonylic acid or hydrogenated catalytically to give homopiperonylamine. A more satisfactory preparation of the amine was found to be electrolytic reduction[13] of 3,4-methylenedioxy-ω-nitrostyrene.[14]

Experimental

5-Hydrindenylacetonitrile (X).—Eleven grams (0.226 mole) of sodium cyanide was dissolved in a minimum amount of hot water. While stirring and heating on a steam-bath, a solution of 30 g. (0.182 mole) of 5-chloromethylhydrindene[8] in 75 ml. of alcohol was added over a period of one-half hour. The mixture then was boiled for four hours. After removal of the alcohol by distillation, the water was separated and the organic layer was distilled, b. p. 113–115° (2.5 mm.); yield, 21.7 g. (73%).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.07; H, 7.00. Found: C, 84.09; H, 7.29.

β-5-Hydrindenylethylamine (XI).—To a solution of 19.0 g. (1.11 moles) of ammonia in 100 ml. of methanol, was added 58 g. (0.37 mole) of X and 4 g. of Raney nickel. The mixture was placed in a rocking autoclave under hydrogen, at an initial pressure of 1100 lb., and the nitrile was hydrogenated in four hours at a temperature of 110°. After removal of the catalyst and solvent, the product was distilled; b. p. 104–107° (4 mm.); yield, 59 g. (98%). The amine has little odor. It forms a carbonate very rapidly on exposure to air. For analysis, a derivative was prepared.

Phenylthiocarbamyl Derivative of XI.—This compound was prepared in the usual way; m. p., 96.5–97.5°, from benzene–hexane.

Anal. Calcd. for $C_{18}H_{20}N_2S$: C, 73.0; H, 6.82. Found: C, 73.1; H, 6.68.

5-Hydrindenylacetic Acid (XII) and Ethyl 5-Hydrindenylacetate (XIII).—In a mixture of 24 g. of absolute alcohol and 70 ml. of dry ether there was dissolved 75 g. (0.475 mole) of 5-hydrindenylacetonitrile (X). Hydrogen chloride (21 g.) was added and the mixture was allowed to stand at 5° for sixteen hours. The solid iminoether was precipitated by addition of more absolute ether, collected by filtration and air-dried. The dried salt was dissolved in water. After twenty-four hours, it has been hydrolyzed to the carboxylic acid ester (XIII). The ester was extracted with ether and worked up in the usual way. The yield was 40 g.; b. p., 122° (3 mm.); $n^{25}D$ 1.5201.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.5; H, 7.84. Found: C, 76.64; H, 7.77.

The ester was saponified by boiling for forty minutes with two equivalents of potassium hydroxide in a saturated methanolic solution. The acid was isolated in the usual manner and was distilled; b. p. 160–170° (bath temperature) at 4 mm. The distillate solidified and was crystallized from 50% acetic acid; m. p. 113–114°; yield 26 g. (76%). H. Arnold gives m. p. 112–114°.[14a]

Anilide (XIV).—M. p. 122.5–123.5°, from dilute alcohol.

Anal. Calcd. for $C_{17}H_{17}ON$: C, 81.26; H, 6.82. Found: C, 81.58; H, 7.01.

N-(β-5-Hydrindenylethyl)-5-hydrindenylacetamide (XV).—To a dry benzene solution of crude undistilled 5-hydrindenylacetyl chloride (19.4 g., 0.1 mole), that was prepared by the procedure of Bachmann,[15] was added dropwise, with shaking, a solution of β-5-hydrindenylethylamine (16.1 g., 0.1 mole) in pyridine (7.6 g.). The reaction mixture then was boiled for five minutes and allowed to cool. After washing with water, dilute hydrochloric acid, dilute sodium hydroxide solution and finally with water, the benzene layer was separated and dried over sodium sulfate. Upon evaporation of the benzene there remained a solid residue that was recrystallized from a benzene–hexane mixture. The product separated in fine needles; m. p. 99–100°; yield, 15 g. (47%).

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.76; H, 7.89. Found: C, 83.09; H, 8.19.

1-(5-Hydrindenylmethyl)-6,7-cyclopenteno-3,4-dihydroisoquinoline (I).—To 12 g. of phosphoric anhydride was added 6 g. of the amide (XV) in 65 ml. of hot xylene. The flask was set in a metal-bath and the mixture was boiled for twenty minutes. Then an additional 6 g. of phosphoric anhydride was added and the mixture was boiled for an additional half-hour. The xylene was decanted and 100 ml. of water was added cautiously to the yellow, gummy residue. The mixture then was heated on a steam-bath until the gum had dissolved. The residual xylene was steam distilled and the aqueous solution was extracted with ether. The aqueous layer then was made strongly basic with 10% potassium hydroxide solution[15a] and extracted with ether. The ether solution was dried over solid potassium hydroxide. Evaporation of the ether left a viscous, oily residue. The oil boiled at 235–240° (bath) (3 mm.). The product (4 g.) was a yellow, tacky sirup that showed no inclination to solidify. Since it was too viscous at all temperatures to purify by fractionation, the picrate was prepared for analysis.

The picrate, prepared in alcohol and recrystallized from absolute alcohol–benzene, melted at 196–197°.

Anal. Calcd. for $C_{28}H_{28}N_4O_7$: N, 10.58. Found: N, 10.82.

1-(5-Hydrindenylmethyl)-6,7-cyclopentenoisoquinoline (VII).—The above product (I) was transferred to a dehydrogenation flask[16] by means of ether and the ether was evaporated. To the residual oil was added 0.6 g. of 10%

(7) Meyer and Schenko, *Ber.*, **56**, 1412 (1923).
(8) Arnold, THIS JOURNAL, **61**, 1405 (1939).
(9) Adams and Thal, "Org. Syn.," Col. Vol. I, p. 101.
(10) Arnold and Barnes, THIS JOURNAL, **65**, 2393 (1942).
(11) Schwenk and Bloch, *ibid.*, **64**, 3051 (1942).
(12) Kobayashi, *Sci. Papers of the Inst. of Phys. and Chem. (Tokio)*, **6**, 165 (1927).
(13) Slotta, *J. prakt. Chem.*, [2] **137**, 339 (1933).
(14) Knoevenagel and Walter, *Ber.*, **37**, 4502 (1904).
(14a) H. Arnold, *ibid.*, **76B**, 777 (1943).
(15) Bachmann, THIS JOURNAL, **62**, 834, 2750 (1940).
(15a) Potassium hydroxide is preferable to sodium hydroxide since the potassium salts of the inorganic acids present are more soluble than the corresponding sodium salts.
(16) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath, Boston, Mass., p. 462.

palladium-charcoal catalyst. The charge was heated under a slow stream of carbon dioxide at 180–200° for forty-five minutes. The product was taken up in dry benzene, the catalyst was removed and the product was precipitated as the hydrochloride by addition of dry hydrogen chloride. The salt was collected by filtration and taken up in hot water. After filtering the solution the salt was precipitated by the addition of concentrated hydrochloric acid. The solid was added to 10% sodium hydroxide solution and the base thus liberated was extracted with ether and the ether solution was dried over solid potassium hydroxide. Upon evaporation of the ether, there remained a solid that crystallized from hexane in white needles; yield, 1.3 g., m. p. 91–92°.

Anal. Calcd. for $C_{22}H_{21}N$: N, 4.68. Found: N, 4.61.

Piperonyl Chloride.—While piperonyl chloride is a known compound, no specific directions for its preparation were found in the literature. To 27 g. (0.176 mole) of piperonyl alcohol in 200 ml. of dry benzene, 22 ml. (0.272 mole) of purified thionyl chloride was added slowly. The reaction mixture first became slightly warm and then became quite cool as evolution of gas began. After the addition of the thionyl chloride, the mixture was boiled for one hour. The solvent and excess thionyl chloride were removed by vacuum distillation at 40–50°. The oily residue solidified on cooling and melted at about 20°.[17] The product could not be distilled since polymerization occurred directly on heating.

Piperonyl Cyanide.—This compound was prepared from piperonyl chloride and mercuric cyanide by the procedure of Kobayashi.[12] The product boiled at 131–132° (4 mm.) and melted at 40–42° from alcohol; yield, 48%.

Homopiperonylic Acid (XVI).—Piperonyl cyanide was hydrolyzed by the method of Hahn and Schales.[18] There was obtained a 78% yield of the acid; m. p. 127–128°.

N-(β-5-Hydrindenylethyl)-homopiperonylamide (XVII).—In a 50-ml. round-bottomed flask having a neck 2 × 30 cm., there was heated at 160–170° for four hours, a mixture of 8.86 g. (0.055 mole) of 5-hydrindenylethylamine (XI) and 11 g. (0.0605 mole) of homopiperonylic acid. The water vapor that condensed in the neck of the flask was driven out by heating the neck with a small flame. The amide, which solidified on cooling, crystallized from alcohol in a mass of fine, tangled needles; 13.9 g. (77%); m. p. 110–117°. For analysis a sample was further crystallized from dilute alcohol and toluene–hexane. The pure compound melted at 119–120°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: N, 4.33. Found: N, 4.50.

1-(3,4-Methylenedioxybenzyl)-6,7-cyclopentenoisoquinoline (VI).—In a manner similar to that described for VII, 5.5 g. of the amide (XVII), was cyclized to give 1-(3,4-methylenedioxybenzyl)-6,7-cyclopenteno-3,4-dihydroisoquinoline (II) an unusually viscous, tacky oil that boiled at 170–180° (bath) at 10^{-5}–10^{-4} mm. The oil was at once dehydrogenated in the manner previously described. The product separated from hexane in small thick needles, m. p. 98–99°. The yield was 0.8 g.

Anal. Calcd. for $C_{20}H_{17}NO_2$: N, 4.62. Found: N, 4.92.

Homopiperonylamine (XVIII) was best prepared by the electrolytic reduction[13] of 3,4-methylenedioxy-ω-nitrostyrene[14] which was obtained in 95% yield from piperonal and nitromethane. The reduction led to a 62% yield of the desired amine, b. p. 108–110° (3 mm.); picrate, m. p. 175–176°.[19]

N-(β-3,4-Methylenedioxyphenylethyl)-5-hydrindenylacetamide (XIX).—The crude 5-hydrindenylacetyl chloride obtained from 17.6 g. (0.1 mole) of 5-hydrindenylacetic acid by the method of Bachmann[15] was dissolved in 100 ml. of benzene. To this solution 16.5 g. (0.1 mole) of homopiperonylamine and 7.6 g. (0.1 mole) of pyridine in 50 ml. of dry benzene was added slowly. The mixture then was boiled for ten minutes. Upon cooling, part of the product separated and was collected by filtration. Evaporation of the benzene yielded an additional amount of product. The fractions were combined and crystallized (Norit) from benzene–hexane (3:2), giving 19.7 g. (61%) of white needles; m. p. 122.5–123.5°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.5; N, 4.33. Found: C, 74.65; H, 6.5; N, 4.45.

1-(5-Hydrindenylmethyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (III).—Cyclization of the amide (XIX) (2 g.) in toluene in the presence of phosphorus pentoxide in the manner described above yielded III. The dihydroisoquinoline is a solid. It was crystallized from methanol from which it separated in blocks, m. p. 130.5–131° in an evacuated tube. Exposure to air results in the decomposition of the solid to a red oil. The yield was 0.7–0.8 g.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.68; H, 6.28. Found: C, 78.75; H, 6.48.

Picrate, m. p. 175–176°, from alcohol.

Anal. Calcd. for $C_{26}H_{22}N_4O_9$: C, 58.4; H, 4.12. Found: C, 58.52; H, 4.08.

1-(5-Hydrindenylmethyl)-6,7-methylenedioxyisoquinoline (IX).—The above compound (III) (5.9 g., 0.019 mole) and 1.3 g. of 10% palladium–charcoal catalyst were heated as described above for three and one-half hours at 155–200°. The hydrochloride was crystallized twice from methanol; m. p. 257–258°; yield 1.65 g. The free base obtained in the usual manner from the hydrochloride crystallized from methanol in flat hexagonal plates; m. p. 168–169° in an evacuated capillary tube; yield 1.22 g.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.20; H, 5.61. Found: C, 79.41; H, 5.87.

Picrate, m. p., 184–185°, from alcohol.

Anal. Calcd. for $C_{26}H_{20}N_4O_9$: C, 58.75; H, 3.78. Found: C, 58.89; H, 3.83.

1-Methyl-6,7-cyclopenteno-3,4-dihydroisoquinoline (IV) and 1,2,4,5-Benzene-tetracarboxylic Acid. (A) N-β-5-Hydrindenylethylacetamide (XX).—Acetyl chloride (2.57 g., 0.033 mole), β-5-hydrindenylethylamine (XI) (5.33 g., 0.033 mole) and pyridine (2.6 g., 0.033 mole) in benzene solution yielded, by the procedure described above, N-β-5-hydrindenylethylacetamide (XX); b. p. 170–185° (bath) (2 mm.); m. p. 77.5–78° (from hexane); yield 3 g.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.45. Found: C, 76.58; H, 8.28.

(B) The amide (XX) (2 g.) was cyclized to IV in the manner described for III using benzene or toluene as solvent. The oily product was not distilled but was purified through its picrate, m. p. 205°, from dilute alcohol; yield 1.33 g.

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: N, 13.52. Found; N, 13.35.

The picrate (1.3 g.) was decomposed by means of dilute ammonium hydroxide solution, the free base was taken up in ether and the solution was dried over sodium sulfate. After evaporation of the ether, the oily residue was transferred to a Carius tube, oxidized with nitric acid and the product esterified with diazomethane in the manner described by Campbell, Soffer and Steadman.[4] After one crystallization from methanol, the ester melted at 140–142°. The mixed m. p. with an authentic sample of methyl pyromellitate[20] was 139.5–141°. There was no indication of the presence of any other aromatic acid. Hence it must be concluded that cyclization in the hydrindene series occurs across the 5,6-positions of the hydrindene nucleus.

6-Tetralylthioacetomorpholide (XXI).—This compound was prepared by the modified Willgerodt reaction of Schwenk and Bloch.[11] 6-Acetyltetralin (50.9 g., 0.3 mole),[10] sulfur (10 g., 0.31 mole) and morpholine (26 g., 0.3 mole) were heated at 120–125° for eight and one-

(17) Decker and Koch, *Ber.*, **38**, 1731 (1905), give m. p. 23°.

(18) Hahn and Schales, *ibid.*, **67**, 1486 (1935).

(19) Decker, *Ann.*, **395** 291 (1913).

(20) We are indebted to Dr. L. I. Smith for authentic methyl pyromellitate.

half hours and then poured onto ice (100 g.). The tacky mass was transferred to warm water whereupon it solidified. The solid was crushed, washed with warm water, collected by filtration and dried in air; yield 74 g. (90%). For analysis a sample was crystallized from acetone-hexane and from 50% alcohol; m. p. 114.5-115.5°.

Anal. Calcd. for $C_{16}H_{21}NOS$: C, 69.79; H, 7.64. Found: C, 70.1; H, 7.70.

6-Tetralylacetic Acid (XXII).—The crude, dried thiomorpholide (XXI), (58.4 g., 0.212 mole) was suspended in one liter of 10% potassium hydroxide solution and the mixture was boiled for ten hours. The mixture was cooled and extracted with toluene and ether. The aqueous layer was acidified to congo red with concentrated hydrochloric acid. The solid that separated was collected and air-dried; yield 32 g. (79%).

For analysis, a sample of the acid was converted to the methyl ester, distilled and then saponified to the original acid; m. p. 95-96° from 50% acetic acid. The reported m. p.[21] is 97-97.5°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.74; H, 7.36. Found: C, 75.91; H, 7.56.

Methyl 6-Tetralylacetate.—The ester was prepared from the acid in the usual way in methanol with sulfuric acid as catalyst. From 100 g. (0.525 mole) of the acid, there was obtained 90 g. (84%) of the ester, b. p. 141-145° (2 mm.). The reported b. p. is 141-145° (4 mm.).[21]

6-Tetralylacetamide.—Methyl 6-tetralylacetate (59 g.), methanol (649 ml.) and concentrated ammonium hydroxide (477 ml.) were allowed to stand at 25-30° in a stoppered flask for seventy-two hours. The mixture was cooled to 0° and the amide that separated was collected by filtration and dried in a vacuum desiccator over solid potassium hydroxide and phosphorus pentoxide. The yield was 32.6 g. A further yield of 8.25 g. was obtained by concentrating the filtrate to 400 ml. and cooling to 0°. The combined product weighed 40.83 g. (83%), and after one crystallization from ethyl acetate melted at 168-169°. Further crystallization did not change the melting point.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 7.4. Found: N, 7.7.

6-Tetralylacetonitrile.—A solution of 6-tetralylacetamide (66.8 g., 0.35 mole) and purified thionyl chloride (150 g., 1.26 moles) in 200 ml. of benzene was heated to boiling on a steam-bath. The amide first dissolved; in a few minutes the mixture changed to a white, pasty mass. After about one hour of continued heating, the solid dissolved and the solution was refluxed four hours longer. After distilling off the benzene and excess thionyl chloride, 400 ml. of benzene was added. The reaction flask was cooled in an ice-bath and 200 ml. of water was added slowly with shaking. The benzene layer was separated, washed with water, shaken repeatedly with 5% sodium bicarbonate solution, dried over sodium sulfate and evaporated. The oily residue distilled at 144-147° (3 mm.); yield 40 g. (67%).

β-6-Tetralylethylamine.—6-Tetralylacetonitrile (40 g., 0.234 mole) was dissolved in 150 ml. of methanol containing 12 g. of liquid ammonia. Raney nickel (4 g.) was added, and hydrogenation was carried out as for XI; yield 38 g. (90%); b. p. 129-131° (2 mm.). Since the water-white product absorbed carbon dioxide from the air so rapidly a thio-carbamyl derivative was prepared for analysis.

1-[β-(6-Tetralyl)-ethyl]-3-phenylthiourea.—The derivative was prepared in the usual manner from the amine and phenyl isothiocyanate; m. p. 130-131°, from dilute ethanol.

Anal. Calcd. for $C_{19}H_{22}N_2S$: N, 9.02. Found: N, 9.09.

N-β-(6-Tetralyl)-ethylphenylacetamide (XXIII).—β-6-Tetralylethylamine (5 g., 0.0285 mole) and phenylacetic acid (4.25 g., 0.031 mole) were mixed and the resulting salt was heated in an open flask at 160-180° for three hours. The melt solidified on cooling. The product was crystallized once from a benzene-hexane mixture (1:3) to give fine white needles, m. p. 99-100°; yield 6.2 g. (74%). The m. p. was not changed by further recrystallization.

Anal. Calcd. for $C_{20}H_{23}NO$: N, 4.78. Found: N, 4.99.

1-Benzyl-6,7-cyclohexeno-3,4-dihydroisoquinoline (V).—The amide (XXIII) (5.15 g., 0.0175 mole) was cyclized to the dihydroisoquinoline in 75 ml. of toluene in the presence of phosphorus pentoxide (10 g.) in the manner previously described. There was obtained 3.75 g. of exceedingly viscous oil; b. p. (bath) 180-200° (10^{-4} mm.); that showed no inclination to solidify. To characterize the oil, the picrate was prepared.

Picrate.—This derivative was prepared in ethanol and recrystallized from 95% alcohol and from acetone. It melted at 193-194° (dec.).

Anal. Calcd. for $C_{26}H_{24}N_4O_7$: N, 11.20. Found: N, 11.39.

Proof of Structure of V.—Two grams of the dihydroisoquinoline was subjected to nitric acid oxidation as described in the case of oxidation of IV.[4] Esterification of the resulting acid gave 0.78 g. of methyl pyromellitate; m. p. 140-141.5°; which was identified by comparison with an authentic sample. Pyromellitic acid, or 1,2,4,5-benzenecarboxylic acid, can only be formed if the dihydroisoquinoline (V) is the 6,7-cyclohexeno isomer.

1-Benzyl-6,7-benzoisoquinoline (VIII).—The dihydroisoquinoline (V) (3.85 g.) was dehydrogenated by heating at 300-310° for four and one-half hours with 0.38 g. of 10% palladium-charcoal as described for the preparation of IX from III; yield, 1.5 g. of a dark oil.

Picrate.—Part of the oil obtained on working up the product was converted to the picrate in alcohol; it was crystallized from acetone, m. p. 211-212°.

Anal. Calcd. for $C_{26}H_{18}N_4O_7$: C, 62.65; H, 3.68; N, 11.26. Found: C, 62.74; H, 3.79; N, 11.39.

The remainder of the oil was taken up in 10 ml. of ethanol and the hydrochloride was precipitated by the addition of hydrogen chloride. The yellow solid that separated was collected by filtration, washed with ether and crystallized from 180 ml. of alcohol in which it has a strong green fluorescence. The free base was obtained by suspending the hydrochloride in water, adding concentrated ammonium hydroxide and extracting with ether. Evaporation of the ether left a tan solid, m. p. 107-110°, that was crystallized from hexane. The fine yellow needles so obtained (about 500 mg.) melted at 115-116°. In solution in organic solvents, the base shows a purple fluorescence.

Anal. Calcd. for $C_{20}H_{15}N$: C, 89.18; H, 5.61. Found: C, 89.02; H, 5.56.

Summary

A number of dihydroisoquinolines and isoquinolines of the hydrindene or tetralin series have been prepared by the Bischler–Napieralski synthesis.

The cyclization of β-5-hydrindenylethyl acetamides in the Bischler–Napieralski isoquinoline synthesis has been shown to lead to 1-substituted-6,7-cyclopenteno-3,4-dihydroisoquinolines.

In a like manner, the cyclization of β-6-tetralylethylacetamides has been shown to lead to 1-substituted-6,7-cyclohexeno-3,4-dihydroisoquinolines.

The synthesis of a number of aryl acetonitriles, arylacetic acids and β-arylethylamines in the hydrindene and tetralyl series is described.

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(21) Newman and Zahm, THIS JOURNAL, 65, 1097 (1943).