m. p. 165°, after crystallization from an alcohol–ether mixture. Even after it had been dried at 100° the product, on analysis, appeared to contain solvent of crystallization.

Anal. Calcd. for $C_{19}H_{21}N_2Cl\cdot 0.5H_2O$: C, 70.90; H, 6.89. Found: C, 71.12; H, 7.01.

α-Ethyltryptamine.—This was prepared according to the procedure of Snyder and Katz.[15]

The **picrate** of α-ethyltryptamine was obtained as scarlet prisms, m. p. 223–224°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59. Found: C, 52.18; H, 4.68.

(15) Snyder and Katz, THIS JOURNAL, **69**, 3140 (1947).

Attempts to effect cyclization by incubating α-ethyltryptamine with formaldehyde under various different conditions of *p*H and temperature similar to that employed by Späth and Lederer[14] gave no useful product.

Summary

A number of salts of β- and γ-carboline have been prepared and found to possess curariform activity.

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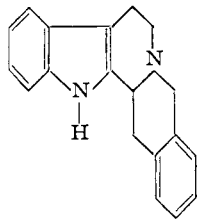
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

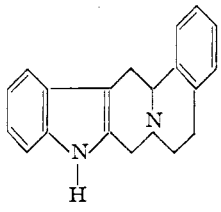
Curariform Activity and Chemical Structure. VII. Some 1-Skatylisoquinoline Derivatives and a Novel Method for their Synthesis[1,2]

BY V. BOEKELHEIDE AND C. AINSWORTH[3]

Investigation of the highly potent calabash curare alkaloids has led to speculation that certain of



I

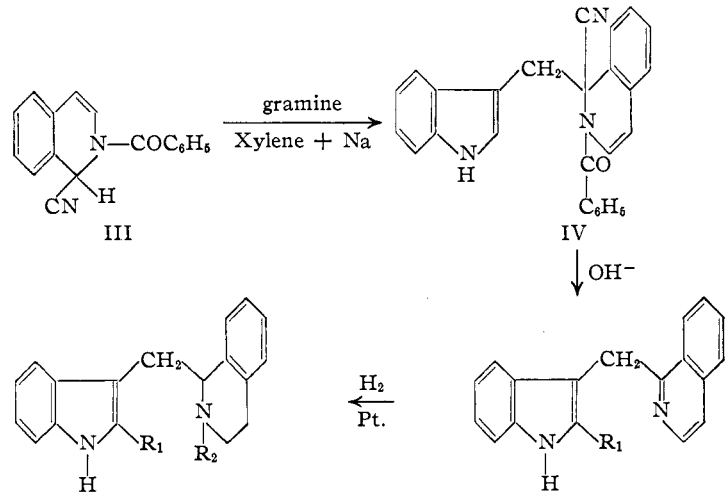


II

these alkaloids may contain a hexahydrobenzoindoloquinolizine nucleus.[4a,b,5] The only simple hexahydrobenzoindoloquinolizine known is I, which was prepared by Clemo and Swan in their investigation of yobyrine.[6] However, as yet, nothing has been reported on the curariform activity of the quaternary salts of I. Because of the desirability of having synthetic samples of hexahydrobenzoindoloquinolizines for physiological testing and for comparison studies, we have prepared some 1-skatylisoquinoline derivatives and attempted their conversion to II.

For the synthesis of 1-skatylisoquinoline a new method has been employed. Reissert's compound[7] (III), which is well known for its acid hydrolysis to benzaldehyde and isoquinaldinic acid,[8] was alkylated with gramine in the presence of sodium to give IV in fair yield. On basic hydrolysis IV was readily converted to 1-skatylisoquinoline (V) in quantitative yield. The two-step combination of alkylation and basic hydrolysis appears to have promise as a general method for preparing 1-substituted isoquinolines.

In the hydrolysis of IV with dilute sodium hydroxide the other products formed in addition to V were sodium cyanide and sodium benzoate. To explain the formation of these products and the ease of hydrolysis we suggest that the reaction



VII, R_1 = —H, R_2 = —H
VIII, R_1 = —H, R_2 = —CH_2OH
IX, R_1 = —CO_2Et, R_2 = —H
X, R_1 = —CH_2OH, R_2 = —H
XI, R_1 = —H, R_2 = —CH_3

V, R_2 = — H
VI, R_1 = —CO_2Et

proceeds by attack of a hydroxyl ion or a water molecule at the amide linkage which results in the shift of a pair of electrons and loss of a cyanide ion

(1) Aided by a grant from the National Foundation for Infantile Paralysis.

(2) For paper VI of this series, see Boekelheide and Ainsworth, THIS JOURNAL, **72**, 2132 (1950).

(3) Present address, Department of Chemistry, University of Colorado, Boulder, Colorado.

(4) For leading references on the chemistry of calabash curare, see (a) Schmid and Karrer, *Helv. chim. acta*, **30**, 2101 (1947); (b) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

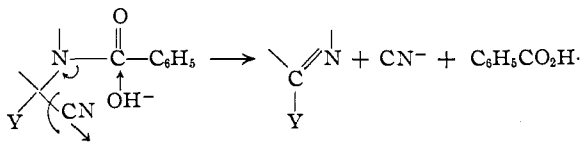
(5) For speculation on the presence of the hexahydrobenzoindoloquinolizine nucleus in certain C-curare alkaloids, see ref. 4b and Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).

(6) Clemo and Swan, *J. Chem. Soc.*, 617 (1946).

(7) Reissert, *Ber.*, **38**, 3427 (1905).

(8) Padbury and Lindwall, THIS JOURNAL, **67**, 1268 (1945).

as illustrated below. The driving force for the reaction is probably derived from aromatization of the pyridine ring.[9]



The catalytic reduction of 1-skatylisoquinoline to the corresponding tetrahydro derivative (VII) occurred smoothly using platinum oxide as catalyst in acid media. The same product was obtained by reduction with sodium and butyl alcohol but in poor yield.

It was hoped that treatment of VII with formaldehyde would effect ring closure and yield the desired compound (II). However, the usual conditions for such ring closures were tried without success. When VII was incubated with formalin for twenty hours at a *p*H of 5.0–5.5 and at a temperature of 37°, the resulting compound appeared to be the corresponding N-hydroxymethyl derivative (VIII). As would be expected for a compound having structure VIII, it underwent hydrolysis with aqueous acid to regenerate VII. Attempts to effect conversion of VIII to II were without success.

A synthesis of II was also attempted by repeating the same general reaction scheme with 2-carbethoxy-3-diethylaminomethylindole instead of gramine. The preparation of 2-carbethoxy-3-diethylaminomethylindole was accomplished by Hegedus' method,[10] although the yields were improved somewhat by several modifications. When Reissert's compound (III) was alkylated with 2-carbethoxy-3-diethylaminomethylindole and the product was subjected to brief alkaline hydrolysis, 1-(2′-carbethoxy-3′-indolyl)-methylisoquinoline (VI) resulted. In this case, though, VI was obtained in better yield when the hydrolysis was allowed to go to completion and the resulting amino acid was re-esterified.

Catalytic reduction of VI yielded the corresponding tetrahydro derivative (IX). This result was rather surprising since it was expected that lactamization would accompany hydrogenation. Several experiments were undertaken in attempts to utilize IX. Reduction of IX was tried with lithium aluminum hydride in the hope that cyclization might occur under these conditions to yield II, but the product isolated had the properties to be expected for the corresponding carbinol (X). When IX was heated in boiling tetralin, lactamization did occur and a neutral yellow product, m. p. 310–312°, resulted. On the basis of its composition and the similarity of its properties and ultraviolet absorption spectra (see Fig. 1) to those of

(9) For the mechanism of the acid catalyzed hydrolysis of Reissert compounds, see McEwen and Hazlett, THIS JOURNAL, **71**, 1949 (1949).

(10) Hegedus, *Helv. chim. acta*, **29**, 1499 (1946).

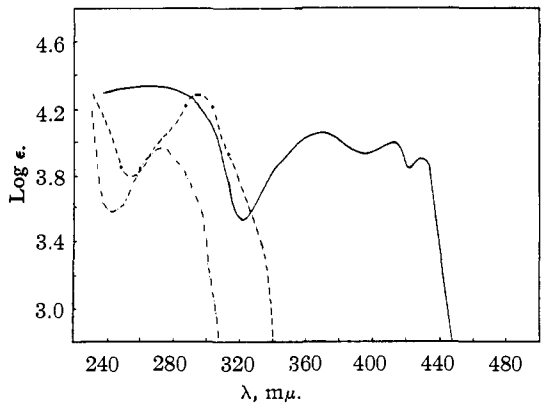
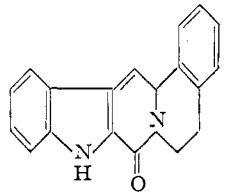


Fig. 1.—Ultraviolet absorption spectra of 1-skatyltetrahydroisoquinoline, VII (—·—·); 1-(2′-carbethoxy-3′-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline, IX (----); and XII (——) in ethanol.

ketoyobyrine[11,12,13,14,15] and of 7,8-benzo-1,2-(2,3-indolo)-3,4-dihydro-6-quinolizone,[6,16,17] we have tentatively assigned structure XII to this yellow material. No useful product has been obtained from attempts to convert XII to II.



XII

Incidental to this work the methiodide of XI was prepared and tested for physiological activity. In preliminary tests with frogs it showed typical curariform activity and was about one-fifth as effective as *d*-tubocurarine chloride.[18]

Experimental[19]

1-Cyano-1-skatyl-2-benzoyl-1,2-dihydroisoquinoline, IV.—To a solution of gramine[20] (8.6 g., 0.05 mole) and 1-cyano-2-benzoyl-1,2-dihydroisoquinoline[8] (13.0 g., 0.05 mole) in 100 ml. of xylene there was added a small piece of sodium. The mixture was boiled under reflux under a nitrogen atmosphere whereupon it turned red and dimethylamine was rapidly evolved. After the solution had boiled for three hours, it was filtered, cooled, and allowed to stand at 5° for two days. The solid, which

(11) Woodward and Witkop, THIS JOURNAL, **70**, 2409 (1948).

(12) Schlittler and Speitel, *Helv. chim. acta*, **31**, 1199 (1948).

(13) Julian, Karpel, Magnani and Meyer, THIS JOURNAL, **70**, 2834 (1948).

(14) Raymond-Hamet, *Compt. rend.*, **226**, 1379 (1948).

(15) Clemo and Swan, *J. Chem. Soc.*, 487 (1949); Swan, *ibid.*, 1720 (1949).

(16) Schlittler and Allemann, *Helv. chim. acta*, **31**, 128 (1948); see also Jost, *ibid.*, **32**, 1297 (1949).

(17) Edwards and Marion, THIS JOURNAL, **71**, 1664 (1949).

(18) We are indebted to Dr. Ernest Wright, Dept. of Physiology, University of Rochester School of Medicine and Dentistry, Rochester, New York, for the physiological testing.

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

(20) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

precipitated, was collected and crystallized from ethanol to give 9.0 g. (46%) of fine white prisms, m. p. 175–176°.

Anal. Calcd. for $C_{26}H_{19}N_3O$: C, 80.18; H, 4.92. Found: C, 80.51; H, 4.87.

1-Skatylisoquinoline, V.—A mixture of 1-cyano-1-skatyl-2-benzoyl-1,2-dihydroisoquinoline (3.9 g., 0.01 mole), 10 ml. of 10% aqueous sodium hydroxide, and 200 ml. of methanol was boiled under reflux for two hours. The solution was then concentrated, 50 ml. of water was added, and the aqueous layer was extracted three times with 50-ml. portions of ether. The ether extracts were combined and the ether removed. The resulting residue was crystallized from ethanol yielding 2.6 g. (quant.) of white prisms, m. p. 171–172°.

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.73; H, 5.46. Found: C, 84.08; H, 5.62.

The **picrate** of 1-skatylisoquinoline was obtained from alcohol as golden plates, m. p. 163–165°, dec.

Anal. Calcd. for $C_{24}H_{17}N_5O_7$: C, 59.14; H, 3.52. Found: C, 59.13; H, 3.85.

The **methiodide** of 1-skatylisoquinoline was prepared in alcohol and was obtained after crystallization from an alcohol–ether mixture as yellow prisms, m. p. 227–228°, dec.

Anal. Calcd. for $C_{19}H_{17}N_2I$: C, 57.01; H, 4.28. Found: C, 57.53; H, 4.53.

When the aqueous layer from the ether extraction above was made acidic with sulfuric acid, a second ether extraction gave benzoic acid in the expected amount. Also steam distillation of the acidic aqueous solution into a dilute solution of silver nitrate gave a white precipitate having the properties of silver cyanide. The odor of hydrogen cyanide was apparent.

1-Skatyl-1,2,3,4-tetrahydroisoquinoline, VII. (a) By Catalytic Reduction.—A solution of 1-skatylisoquinoline (2.58 g., 0.01 mole) in 100 ml. of glacial acetic acid containing 0.3 g. of prereduced Adams catalyst was shaken at room temperature under an atmospheric pressure of hydrogen until two molar equivalents of hydrogen had been adsorbed. The catalyst was removed, 100 g. of ice was added, and the solution was made basic with ammonium hydroxide. The solid, which separated, recrystallized with difficulty but was obtained from methanol as 1.3 g. (50%) of white prisms, m. p. 139–140°. This product gave a positive test for the indole nucleus when treated with Ehrlich reagent.

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68. Found: C, 82.51; H, 6.76; N, 10.46.

The **picrate** of 1-skatyl-1,2,3,4-tetrahydroisoquinoline was obtained from alcohol as dark yellow needles, m. p. 210–211° dec.

Anal. Calcd. for $C_{24}H_{21}N_5O_7$: C, 58.65; H, 4.31. Found: C, 58.67; H, 4.00.

The **hydrochloride** of 1-skatyl-1,2,3,4-tetrahydroisoquinoline was obtained by treating the free base in ether with dry hydrogen chloride. Crystallization from absolute ethanol gave white needles, m. p. 248–250°.

Anal. Calcd. for $C_{18}H_{19}N_2Cl$: C, 72.35; H, 6.41. Found: C, 72.57; H, 6.49.

(b) By Reduction with Sodium and Butanol.—To a solution of 0.50 g. of 1-skatylisoquinoline in 50 ml. of *n*-butyl alcohol there was added 4.0 g. of sodium in separate additions of small pieces. The butanol was then removed, the residue was taken up in ether, and the ethereal solution was washed with water and then concentrated. The resulting oil did not crystallize and was therefore converted directly to the picrate, m. p. 208–211° dec. The picrate was decomposed by treating it with 1% hydrochloric acid and extracting the picric acid with benzene. When the aqueous solution was made basic, a small amount of solid separated which, after crystallization from methanol, melted at 138–140°. A mixture of this and the product of catalytic reduction showed no depression of melting point.

1-Skatyl-2-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline, VIII.—Although a number of attempts were made to effect ring closure by the reaction of VII with formaldehyde, the experiments cited below are the only ones which gave a definite product other than starting material.

To a solution of 10 g. of 1-skatyl-1,2,3,4-tetrahydroisoquinoline hydrochloride in 100 ml. of water there was added 4 ml. of formalin and sufficient sodium acetate solution (1 *M.*) to give the final solution a *p*H of 5.0 to 5.5. After the solution had been heated at 37° for twenty hours it was made basic and the precipitate was collected. The solid product was dried and then crystallized from methanol to yield 0.67 (60%) of white prisms, m. p. 169–170°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89. Found: C, 77.81; H, 6.82.

When VIII was boiled for one hour with a 1% aqueous sulfuric acid solution, the product isolated on making the solution basic was 1-skatyl-1,2,3,4-tetrahydroisoquinoline.

2,2-Dimethyl-1-skatyl-1,2,3,4-tetrahydroisoquinolinium Iodide.—A solution of 1.0 g. of 1-skatyl-2-methylisoquinolinium iodide and 0.10 g. of platinum oxide in 30 ml. of alcohol was shaken at room temperature under an atmospheric pressure of hydrogen until two molar equivalents of hydrogen had been absorbed (15 min.). The catalyst and solvent were removed, the residue was taken up in 20 ml. of water, and then this was made basic with dilute sodium hydroxide. The gummy mass, which separated, could not easily be purified and it was converted directly to the methiodide, by treating it with an excess of methyl iodide in alcohol. The product was crystallized from an ethanol–ether mixture and was obtained as a pale yellow, hygroscopic solid, m. p. 122–124°.

Anal. Calcd. for $C_{20}H_{23}N_2I$: C, 57.42; H, 5.54. Found: C, 57.10; H, 5.21.

2-Carbethoxy-3-diethylaminomethylindole.—The procedure employed by Hegedus was modified as described below. This simpler procedure gave an over-all yield of 46% from ethyl β-diethylaminoethylacetoacetate as compared to the 26% over-all yield reported by Hegedus.[10]

Ethyl γ-diethylamino-α-(phenylhydrazono)-butyrate hydrochloride was obtained by the reaction of benzenediazonium chloride with ethyl β-diethylaminoethylacetoacetate as reported.[10] Instead of decomposing the crude hydrochloride with base it was crystallized from acetone–hexane to give a 74% yield of pure white needles, m. p. 157–158°.

Anal. Calcd. for $C_{16}H_{26}N_3O_2Cl$: C, 58.63; H, 7.99. Found: C, 59.07; H, 8.12.

To a stirred solution of 20.0 g. of ethyl γ-diethylamino-α-(phenylhydrazono)-butyrate hydrochloride in 80 ml. of glacial acetic acid there was added dropwise over a period of fifteen minutes 20 ml. of concentrated sulfuric acid. The solution was then heated on a steam-bath for two hours, cooled, and poured onto a mixture of ice and excess sodium hydroxide solution. The solid, which separated, was washed with water, dried, and crystallized. There was obtained 10.5 g. (63%) of white needles, m. p. 114–115°, softened at 104° (reported m. p. 104°[10]).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.10. Found: C, 70.38; H, 8.17.

1-(2′-Carbethoxy-3′-indolyl)-methyl-1-cyano-2-benzoyl-1,2-dihydroisoquinoline.—A small piece of sodium was added to a stirred solution of 2.7 g. (0.01 mole) of 2-carbethoxy-3-diethylaminomethylindole and 2.6 g. (0.01 mole) of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline in 25 ml. of xylene. The mixture was boiled under reflux in a nitrogen atmosphere for one hour. The mixture was then filtered to remove a small amount of precipitate, diluted with 25 ml. of benzene, and washed successively with dilute hydrochloric acid and water. After removal of the solvent *in vacuo*, the residue was crystallized from an ethanol–water mixture to yield 3.2 g. (69%) of an amorphous white powder, m. p. 114–116°.

Anal. Calcd. for $C_{29}H_{23}N_3O_3$: C, 75.47; H, 5.02. Found: C, 75.20; H, 4.98.

The small amount of precipitate obtained by filtering the reaction mixture was crystallized from acetic acid to give 0.5 g. of a white powder, m. p. 260°. The behavior

of this material toward alkali indicated it to be an ester. On the basis of its composition it is assumed to be bis-(2-carbethoxy-3-indolyl)-methane.

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68. Found: C, 70.96; H, 5.78.

1-(2′-Carbethoxy-3′-indolyl)-methylisoquinoline, VI.—To a solution of 1.0 g. of 1-(2′-carbethoxy-3′-indolyl)-methyl-1-cyano-2-benzoyl-1,2-dihydroisoquinoline in 20 ml. of methanol there was added 2 ml. of a 10% aqueous sodium hydroxide solution. The resulting solution was boiled under reflux for two minutes, cooled, and diluted with 100 ml. of water. This was then extracted with ether and the ether layer was extracted in turn with dilute hydrochloric acid. The aqueous layer was made basic and the precipitate, which formed, was collected. After crystallization from ethanol, there was obtained 100 mg. of white crystals, m. p. 185–186°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49. Found: C, 76.43; H, 5.42.

The **picrate** of VI was obtained from alcohol as yellow crystals, m. p. 230–231°.

Anal. Calcd. for $C_{27}H_{21}N_5O_9$: C, 57.96; H, 3.78. Found: C, 57.61; H, 3.95.

1-(2′-Carboxy-3′-indolyl)-methylisoquinoline Hydrochloride.—A solution of 4.6 g. of 1-(2′-carbethoxy-3′-indolyl)-methyl-1-cyano-2-benzoyl-1,2-dihydroisoquinoline in 100 ml. of methanol containing 6 ml. of 10% aqueous sodium hydroxide was boiled under reflux for two hours. The solution was then concentrated to one-fourth its original volume and diluted with 100 ml. of water. Dilute hydrochloric acid was then added until a *p*H of 2.0 was attained. The benzoic acid, which separated, was removed by ether extraction. The hot aqueous solution was then treated with charcoal, filtered, made basic to a *p*H of 3.4, and allowed to cool. The aqueous solution was then extracted several times with ether and dry hydrogen chloride was passed into the dried ether extract. The resulting solid was collected and, after crystallization from an alcohol–ether mixture, there was obtained 2.4 g. of a white amorphous powder, m. p. 195–196°.

Anal. Calcd. for $C_{19}H_{15}N_2O_2Cl$: C, 67.36; H, 4.46. Found: C, 67.44; H, 4.69.

The amino acid hydrochloride was readily esterified by allowing it to stand for two days with alcoholic hydrogen chloride. After removal of the alcohol *in vacuo*, the residue was taken up in water and the solution was made basic. The resulting solid was crystallized from alcohol and gave a 50% yield of white crystals, m. p. 185–186°. A mixture of these crystals and VI showed no depression of melting point.

1-(2′-Carbethoxy-3′-indolyl)-methyl-1,2,3,4-tetrahydroisoquinoline, IX.—A solution of 0.50 g. of VI and 0.10 g. of prereduced Adams catalyst in 20 ml. of glacial acetic acid was shaken at room temperature under an atmospheric pressure of hydrogen until two molar equivalents of hydrogen had been adsorbed. The catalyst was removed and the cooled solution was made basic with aqueous sodium hydroxide solution. The solid, which separated, was crystallized from a benzene–hexane mixture to give 0.44 g. (86%) of white crystals, m. p. 190–194°. Further recrystallization from benzene gave white prisms, m. p. 199–200°. IX gave a positive test with Ehrlich reagent.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.48; H, 6.51; N, 8.26.

The **picrate** of IX was obtained from alcohol as yellow needles, m. p. 206–207°.

Anal. Calcd. for $C_{27}H_{25}N_5O_9$: C, 57.55; H, 4.47. Found: C, 57.87; H, 4.68.

1-(2′-Hydroxymethyl-3′-indolyl)-methyl-1,2,3,4-tetraisoquinoline, X.—To a warm solution of 334 mg. of IX in 125 ml. of dry ether there was added dropwise 5 ml. of a 0.5 *M* lithium aluminum hydride solution. The mixture was boiled under reflux for twenty hours and then decomposed with moist ether. After removal of the precipitated alumina, the ether solution was concentrated. The residue was crystallized from alcohol and then from benzene to yield 140 mg. (54%) of white needles, m. p. 205–207°. This material also gave a positive test with Ehrlich reagent.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89. Found: C, 77.95; H, 6.81.

Cyclization of IX in Boiling Tetralin.—A solution of 0.87 g. of IX in 30 ml. of tetralin was boiled under reflux for twenty hours and then allowed to cool. The solid, which separated, was collected and recrystallized from dioxane to give 0.55 g. (73%) of yellow crystals, m. p. 310–312°. This material was quite insoluble in almost all organic solvents and also dilute acid and base.

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.69; H, 4.93. Found: C, 79.67, 79.22; H, 5.34, 5.22.

An attempted reduction of XII with lithium aluminum hydride gave back starting material. When XII was treated with sodium and butanol, a reaction occurred but no definite product was established.

Summary

The alkylation of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline followed by alkaline hydrolysis has been found to be a useful method for preparing some 1-skatylisoquinoline derivatives. Attempts have been made to convert several of these derivatives to 1,2-benzo-7,8-(2′,3′-indolo)-hexahydroquinolizine.

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