[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Action of Metal Hydrides on β-(3-Indolyl)ethyl-1-pyridinium Salts*[1,2]

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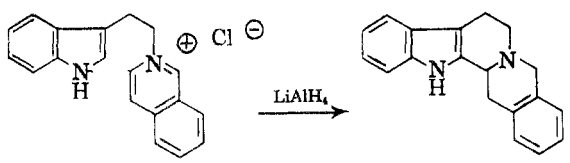
Received June 26, 1957

β-(3-Indolyl)ethyl-1-pyridinium bromides are reduced with lithium aluminum hydride or sodium borohydride to give tetrahydropyridine derivatives in good yield. No cyclization to tetracyclic β-carbolines occurred. Stepwise reduction of 4-styrylquinoline has been studied. An improved preparation of tryptophol is described.

In recent years the group of pentacyclic β-carbolines derived from the basic yohimbane skeleton or its stereoisomers has attracted considerable attention largely as a result of the interest in reserpine. In contrast, the chemistry and pharmacology of the analogous tetracyclic β-carbolines has been the subject of comparatively few investigations. In this paper and succeeding ones we wish to present the results of work looking to the synthesis of representative tetracyclic and pentacyclic β-carbolines.

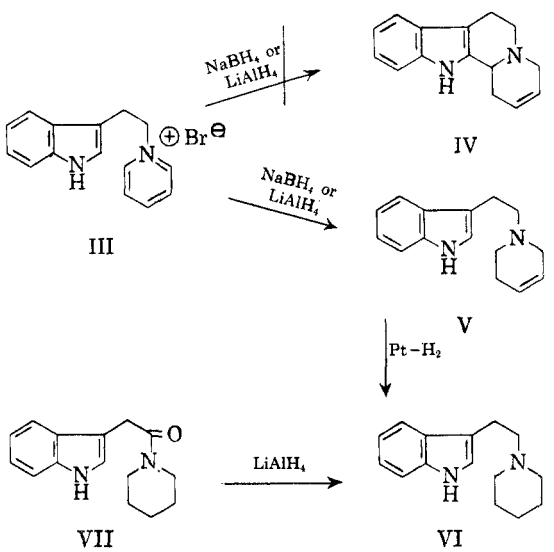
Belleau[3] and Potts and Robinson[4] have shown that reduction of the condensation product of 3-(β-chloroethyl)indole and isoquinoline (I) with lithium aluminum hydride leads to 5,6,7,8,13*a*,13*b*-hexahydrobenz[g]indolo[2.3-*a*]quinolizine (II).



I II

McCurdy[5] suggested that the cyclization might also occur with sodium borohydride as the reagent. Use of sodium borohydride presents obvious advantages, *e.g.* retention of ester groups without reduction by virtue of its reported selectivity of action. Accordingly the action of both hydrides on various condensation products of 3-(β-bromoethyl)indole and selected pyridine derivatives has been investigated as a possible route to tetracyclic β-carbolines.

At the outset, β-(3-indolyl)ethyl-1-pyridinium bromide (III) was reduced with either lithium aluminum hydride or sodium borohydride. The product was the same regardless of the reagent.



III IV V VII VI

It gave analytical data which agreed with $C_{15}H_{18}N_2$ rather than with the hexahydroindolo[2.3-*a*]-quinolizine (IV).[6] On further reduction with hydrogen over platinum oxide, the reduction product absorbed one equivalent of hydrogen to give a substance which was not identical with 1,2,3,4,6,7,12,12*b*-octahydroindolo[2.3-*a*]-quinolizine.[7]

It thus appeared that reduction of two double bonds of the pyridine ring of III without cyclization to yield V might have occurred under the influence of the metal hydrides. This was, indeed, shown to be the case. The structure of the product of catalytic reduction of V was shown to be VI by the preparation of VI by reduction of 1-(3-indoleacetyl)piperidine (VII) with lithium aluminum hydride.

The mechanism of this reductive ring closure is unknown. In view of the fact that it is successful with isoquinolinium compounds but fails with pyridinium compounds, electronic effects associated with the double bonds in the benzene ring of isoquinoline must play a role in the ring closure reaction. Therefore the action of the two metal

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) This investigation was supported in part by a research grant, H-1733, from the National Heart Institute, Public Health Service.

(2) Portions of this work are taken from a dissertation submitted by Jeanne M. Lagowski in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Michigan.

(3) B. Belleau, *Chemistry and Industry*, 229 (1955).

(4) K. T. Potts and Sir Robert Robinson, *J. Chem. Soc.*, 2675 (1955).

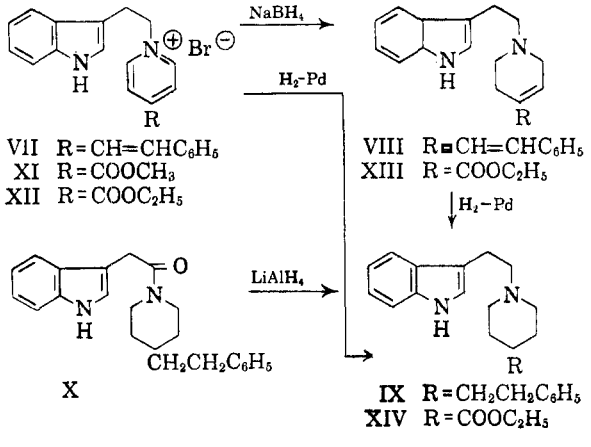
(5) O. L. McCurdy, Ph.D. Dissertation, University of Michigan, 1956.

(6) The position of the double bond in IV and V is assigned on a purely arbitrary basis. No evidence is at hand for placing it in any particular position. See J. J. Panouse [*Bull. soc. chim. France*, D 60 (1953)] for a discussion of the reduction of pyridinium methiodides with metal hydrides.

(7) We are indebted to Dr. D. S. Tarbell of the University of Rochester for an authentic sample of the quinolizine.

hydrides on pyridinium compounds carrying substituents which might be expected to exert a stabilizing effect on the Δ^3 double bond of the pyridine ring was investigated. The two β-(3-indolyl)-ethyl-1-pyridinium salts derived from 4-stilbazole and methyl isonicotinate were selected for this purpose.

The condensation product (VII) of 3-(β-bromoethyl)indole and 4-stilbazole on reduction with sodium borohydride gave excellent yields of a product which absorbed two equivalents of hydrogen on catalytic reduction over palladium in acetic acid to give a substance (IX) which was identical with that formed by the action of lithium aluminum hydride on 1-(3-indoleacetyl)octahydro-4-stilbazole (X). The structure of the product of the reduction of VII is therefore represented by VIII and cyclization to a β-carboline has not occurred in this instance. With lithium aluminum hydride VII gave an unstable base which has resisted all attempts at crystallization, hydrogenation and salt formation. IX also was formed when VII was reduced catalytically over palladium.



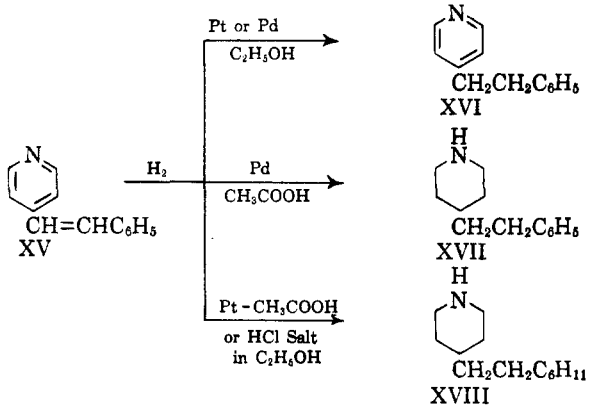
Condensation of 3-(β-bromoethyl)indole with methyl or ethyl isonicotinate readily gave the corresponding pyridinium compounds (XI and XII). Reduction of XI with sodium borohydride in methanol solution gave a waxy product which could not be crystallized and which failed to yield crystalline salts. The infrared spectrum showed a bond at 1715 cm.$^{-1}$ which indicates that the ester had not been reduced. On the other hand, reduction of XII with sodium borohydride in ethanol also gave a waxy base (XIII) from which a picrate could be prepared. The infrared spectrum showed a bond at 1705 cm.$^{-1}$ characteristic of α,β-unsaturated esters. Further reduction of XIII over platinum resulted in the uptake of one equivalent of hydrogen and the formation of a crystalline base (XIV). XIV was also obtained when XII was reduced over palladium.

With lithium aluminum hydride XII gave an unstable base which has resisted all attempts at crystallization, hydrogenation or salt formation.

In order to complete the study, the condensation products of 3-(β-bromoethyl)indole and methyl nicotinate and 6-methylnicotinate were prepared. Reduction of both substances with sodium borohydride gave intractable tars or waxes from which no crystalline product could be isolated.

It therefore appears that the exact limitations of this interesting reductive ring closure remain to be determined. As indicated above, the mechanism of the reaction is obscure. Further work is in progress which it is hoped will clarify the factors governing the course of the reaction. It appears from this work that ring closure to a β-carboline does not occur when β-(3-indolyl)ethyl-1-pyridinium salts are reduced with either lithium aluminum hydride or sodium borohydride.

During this investigation the hydrogenation of 4-stilbazole (XV) was studied. When the free base is reduced in ethanol solution over either platinum or palladium, the ethylenic double bond only was attacked with the formation of dihydro-4-stilbazole [4-(β-phenethyl)pyridine] (XVI). Hydrogenation over palladium in acetic acid solution produced octahydrostilbazole [4-(β-phenethyl)piperidine] (XVII). Complete reduction resulted when platinum was the catalyst in acetic acid solution yielding 4-(β-cyclohexylethyl)piperidine.



Finally, the yield of tryptophol is considerably increased over that previously reported when ethyl indole-3-acetate rather than indole-3-acetic acid is reduced with lithium aluminum hydride.

EXPERIMENTAL[8,9]

Ethyl 3-indoleacetate. To a hot solution of 87 g. of indole-3-acetic acid in 200 ml. of absolute ethanol in which 25 g. of anhydrous sodium sulfate was suspended was added 5 ml. of a saturated solution of anhydrous hydrogen chloride in absolute ethanol. After standing 24 hr. at room temperature, the ethanol was removed under reduced pressure, excess sodium bicarbonate solution was added and the mixture was extracted with ether. Evaporation of the ether left a

(8) All melting points are corrected for stem exposure except as noted. All boiling points are uncorrected.

(9) Microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by Mrs. Anna Griffin, of the University of Michigan.

pale yellow oil, b.p. 164–166° (1 mm.). Reported b.p. 180° (2 mm.).[10] The yield was 95 g. (95%).

Tryptophol. To a slurry of 2 g. of lithium aluminum hydride in 100 ml. of absolute ether a solution of 4 g. of ethyl indole-3-acetate in 50 ml. of absolute ether was added dropwise with stirring. The mixture was stirred under reflux for 1.5 hr. After decomposition of excess hydride by cautious addition of a little water, the mixture was filtered through a layer of Celite. After drying the filtrate over anhydrous sodium sulfate, removal of the solvent under reduced pressure left an oil which slowly crystallized, m.p. 57–58°. Reported m.p., 58°.[10] The yield was 2.95 g. (92%).

β-(3-Indolyl)ethyl-1-pyridinium bromide (III). A solution of 1.7 ml. of anhydrous pyridine and 4.06 g. of β-(3-indolyl)-ethyl bromide, prepared by the action of phosphorus tribromide on tryptophol,[11] in 75 ml. of absolute ethanol was allowed to stand at room temperature for 5 days. The red solution was concentrated under reduced pressure on the steam bath. On cooling pale yellow crystals separated which were filtered in a moisture-free atmosphere and recrystallized from absolute ethanol–absolute ether. The yield of broad straw-colored needles, m.p. 235–237° (dec.), was 2.66 g. (48%). The ultraviolet spectrum showed maxima at 261–262 (log ε 3.94), 281 (log ε 3.85) and 290 (log ε 3.77) mμ and minima at 240 (log ε 3.46), 277 (log ε 3.84), and 287 (log ε 3.75) mμ.

Anal. Calcd. for $C_{15}H_{15}BrN$: C, 59.41; H, 4.99; N, 9.24. Found: C, 59.43; H, 4.98; N, 9.51.

Reduction of β-(3-indolyl)ethyl-1-pyridinium bromide. A. With Lithium aluminum hydride. III (3.5 g.) was added in small portions over 40 min. to a suspension of 1.75 g. of lithium aluminum hydride in 350 ml. of anhydrous ether. After stirring at room temperature for 3.5 hr., the excess hydride was decomposed by careful addition of a few drops of water followed by 100 ml. of 10% sodium bicarbonate solution. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the ether left a red brown oil which became semisolid on cooling and rubbing. The semisolid was extracted with *n*-hexane in a Soxhlet apparatus for 24 hr. Concentration and cooling of the hexane extract gave a yellow, crystalline solid, m.p., 140–149° (uncorr.). Repeated recrystallization from hexane gave 1.3 g. (48%) of stout, white needles, m.p. 152–153°.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.37. Found: C, 79.54; H, 8.00; N, 12.19.

The ultraviolet spectrum, taken in ethanol, showed maxima at 283 (log ε 3.74), 291 (log ε 3.68) and a shoulder at 275 (log ε 3.71) mμ. Minima occurred at 244 (log ε 2.95) and 288 (log ε 3.65) mμ.

The compound depressed the melting point of 1,2,3,4,-6,7,12,12*b*-octahydroindolo[2.3-*a*] quinolizine 27° on admixture with the latter. The Ehrlich color test[12] for an indole unsubstituted in the α position, and the modified Adamkiewicz color test[13] for a β-carboline nucleus were inconclusive.

B. With sodium borohydride. To a solution of 1.5 g. of III in 50 ml. of absolute methanol was added slowly with stirring a solution of 4.5 g. of sodium borohydride in 75 ml. of absolute methanol. The yellow color of III was discharged immediately on addition of the borohydride. After stirring at room temperature for 2 hr., the mixture was diluted with 25 ml. of water and the methanol was removed under reduced pressure. The remaining aqueous solution was acidified (litmus) with hydrobromic acid and then made basic with potassium carbonate. The basic solution was extracted with ether. After drying the ether extracts with anhydrous magnesium sulfate, removal of the solvent left 0.24 g. (22%) of V, m.p. and mixture m.p. with the substance obtained by lithium aluminum hydride reduction, 152–153°. The infrared and ultraviolet spectra of V prepared by the two methods were identical.

Hydrogenation of V (VI). Three drops of concentrated ammonium hydroxide solution were added to a solution of 0.2 g. of V in 50 ml. of absolute methanol. *p*-Hydrion paper indicated a *p*H of 7. Adams' platinum oxide catalyst (99 mg.) was suspended in the solution which was then shaken with hydrogen at room temperature and atmospheric pressure. One equivalent of hydrogen was absorbed in about 15 min. and no appreciable additional hydrogen absorption was apparent after 4 hr. After filtration from the catalyst, the filtrate was taken to dryness under reduced pressure. The residual pale green oil crystallized on cooling and was recrystallized from absolute ether-hexane with decolorization with Norite yielding 105 mg. (52%) of white, feathery needles, m.p. 151–152°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.37. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.82; H, 8.76; N, 11.90.

The ultraviolet spectrum taken in ethanol solution showed maxima at 283 (log ε 3.74), 291 (log ε 3.68), and a shoulder at 275 (log ε 3.71) mμ. Minima occurred at 244 (log ε 2.95) and 288 (log ε 3.65) mμ.

p-Toluenesulfonic acid salt of VI. To a solution of 0.10 g. of VI in 15 ml. of anhydrous ether was added a solution of 0.10 g. of *p*-toluenesulfonic acid monohydrate in 25 ml. of anhydrous ether. After standing overnight at room temperature the precipitate was filtered off. Recrystallization from absolute ethanol-absolute ether gave lustrous, white plates, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{26}N_2O_3S$: C, 66.30; H, 6.58; N, 7.03. Calcd. for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.97; H, 7.16; N, 7.07.

1-(β-[3-Indolyl]ethyl)piperidine. To a solution of 3-indolylacetyl chloride, prepared from 2.0 g. of indole-3-acetic acid[14] in 50 ml. of anhydrous ethyl acetate was added slowly and with cooling a solution of 4 ml. of piperidine in 25 ml. of anhydrous ethyl acetate. After standing for 4 hr. at room temperature the crystalline precipitate was collected. The filtrate was washed successively with three 50 ml. portions of 1*N* hydrochloric acid and three 50 ml. portions of 10% sodium carbonate solution. After drying over anhydrous magnesium sulfate, removal of the solvent left a viscous, red-brown oil which could not be crystallized and which was reduced directly without purification.

To a solution of the crude piperidide in 200 ml. of anhydrous ether a slurry of 1.3 g. of finely powdered lithium aluminum hydride in 200 ml. of anhydrous ether was slowly added. The mixture was stirred at room temperature for 5 hr. after addition of the hydride was complete. Excess hydride was destroyed by careful addition of a few drops of water and 50 ml. of 10% sodium hydroxide solution was then added. The ether layer was separated and the aqueous layer was filtered and extracted exhaustively with ether. After drying the combined ether extracts over anhydrous magnesium sulfate, removal of the solvent left 1.25 g. (39% based on indole-3-acetic acid) of light tan crystals. Recrystallization from *n*-hexane-ether (Norite) gave white, feathery needles, m.p. 151–152°. The melting point was not depressed on admixture with VI obtained as described above and the infrared spectra of the compound obtained by the two routes were superimposible.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.83; H, 8.60; N, 12.21.

The *p*-toluenesulfonic acid salt of VI prepared by reduction of the piperidide melted at 181–182°. The melting

(10) R. W. Jackson, *J. Biol. Chem.*, **88**, 659 (1930).

(11) T. Hoskins and K. Shimodaira, *Ann.*, **520**, 19 (1935).

(12) F. C. Happold and L. Hoyle, *Biochem. J.*, **28**, 1171 (1934).

(13) N. J. Leonard and R. C. Elderfield, *J. Org. Chem.*, **7**, 556 (1942).

(14) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

point was not depressed on admixture with the salt obtained as above and the infrared spectra of the salts obtained by the two routes were identical.

Anal. Calcd. for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.83; H, 6.95; N, 7.06.

Condensation of 4-stilbazole with 3-(β-bromoethyl)indole (VII). A solution of 2.2 g. of 3-(β-bromoethyl)indole and 1.8 g. of 4-stilbazole[15] in 30 ml. of absolute methanol was refluxed for 15 min. After addition of ether to the hot solution a first crop of orange clumps was filtered off. Additional material was obtained from the mother liquor. The total yield was 2.5 g. (63%). Recrystallization from ethanol gave material, m.p. 231° (dec.). The infrared spectrum taken in a Nujol mull showed peaks at 765, 1170, 1615, 2350, 3700, and 3800 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{21}BrN_2$: C, 68.13; H, 5.23; N, 6.91. Found: C, 68.29; H, 5.23; N, 6.94.

Reduction of VII with sodium borohydride (VIII). To a suspension of 2 g. of VII in 200 ml. of absolute ethanol 6 g. of sodium borohydride was added gradually. The mixture was stirred at room temperature for 2 hr. after addition of the hydride was complete. After addition of 50 ml. of 5% hydrochloric acid the ethanol was removed under reduced pressure. The aqueous solution was made basic to litmus with 0.1*N* sodium hydroxide solution and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left a residue which was recrystallized from acetone to give 1.3 g. (80%) of material, m.p. 193°. The Ehrlich color test indicated that the α position of the indole nucleus was unsubstituted. The infrared spectrum taken in a Nujol mull showed peaks at 680, 735, 955, 1105, 1230, 1490, and 1590 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.52; H, 6.87; N, 8.68. Calcd. for $C_{23}H_{24}N_2$: C, 84.01; H, 7.37; N, 8.53. Found: C, 83.97; H, 7.33; N, 8.71.

Hydrogenation of VIII. *1-[β-(3-indolyl)ethyl]-4-(β-phenethyl) piperidine* (IX). A solution of 325 mg. of VIII in 50 ml. of glacial acetic acid was shaken with 10 mg. of 5% palladium on charcoal catalyst under hydrogen at room temperature and atmospheric pressure. Two equivalents (50 ml.) of hydrogen (calcd. 51 ml.) were absorbed in 12 min. and no further hydrogen uptake was noted. After filtering from the catalyst, removal of the solvent left an oil. This was taken up in water, and, after making the solution alkaline with potassium carbonate, it was extracted with ether. After drying over anhydrous magnesium sulfate, removal of the ether gave 320 mg. (97%) of fine white needles, m.p. 119° (uncorr.), after recrystallization from benzene-ligroin. The Ehrlich test indicated a free α position in the indole nucleus.

Anal. Calcd. for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Calcd. for $C_{23}H_{28}N_2$: C, 83.08; H, 8.49; N, 8.43. Found: C, 83.40; H, 8.44; N, 8.14.

The hydrobromide of IX was prepared in and recrystallized from absolute ethanol. It formed irregular white prisms, m.p. 219–221° (dec.) (uncorr.).

Anal. Calcd. for $C_{23}H_{27}BrN_2$: C, 66.90; H, 6.67; N, 6.86. Calcd. for $C_{23}H_{29}BrN_2$: C, 66.81; N, 7.07; N, 6.78. Found: C, 66.61; H, 6.92; N, 6.78.

1-[β-(3-Indolyl)ethyl]-4-phenethylpiperidine (IX). A solution of 1.5 ml. of 4-phenethylpiperidine and 2 ml. of *N*-ethylmorpholine in 25 ml. of anhydrous ethyl acetate was added slowly with cooling to a solution of 3-indolylacetyl chloride (prepared from 2.0 g. of indole-3-acetic acid) in 25 ml. of anhydrous ethyl acetate. After standing for 4 hr. at room temperature, the orange liquid was decanted and washed successively with dilute aqueous solutions of potassium carbonate, hydrochloric acid, and sodium bicarbonate. After drying over anhydrous sodium sulfate, removal of the ether left the amide as a foamy mass which could not be crystallized and was reduced directly.

(15) C. E. Kaslow and R. D. Stayner, *J. Am. Chem. Soc.*, 67, 1717 (1945).

To a solution of the crude amide in 20 ml. of anhydrous tetrahydrofuran was added slowly a slurry of 1.1 g. of finely powdered lithium aluminum hydride in 200 ml. of anhydrous ether. The mixture was stirred for 3 hr. after addition of the hydride was complete. After careful addition of a few drops of water the mixture was filtered through Celite. Evaporation of the solvent under reduced pressure gave a white solid which was dried by repeated evaporation with benzene. Recrystallization from ether-petroleum ether gave fine white needles, m.p. and mixture m.p. with the substance obtained by hydrogenation of VIII, 119° (uncorr.). The infrared spectra of the compounds obtained by the two routes were identical.

The hydrobromide of IX prepared by reduction of the amide melted at 219–221° (dec.) (uncorr.) and the infrared spectra of the two hydrobromides were identical.

4-Carbomethoxy-1-(β-[3-indolyl]ethyl)pyridinium bromide. (XI). To a solution of 2.24 g. of β-(3-indolyl)ethyl bromide in 125 ml. of anhydrous ether was added dropwise 1.5 g. of methyl isonicotinate. After standing at room temperature for 4 days the solution was concentrated at reduced pressure. The red-orange residual oil solidified on rubbing with cold anhydrous ether. Recrystallization from absolute methanol-anhydrous ether gave 2.4 g. (67%) of fine orange needles which darkened at 290° and decomposed at 300–301° (uncorr., copper block).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.75; N, 7.76. Found: C, 56.58; H, 4.77; N, 7.76.

4-Carboethoxy-1-(β-[3-indolyl]ethyl)pyridinium bromide. (XII). A hot solution of 2.2 g. of 3-(β-bromoethyl)indole and 1.5 g. of ethyl isonicotinate in 40 ml. of absolute methanol was allowed to cool and stand at room temperature for 48 hr. Removal of the methanol on the steam bath left an oil which furnished long needles from ether after 48 hr. Recrystallization from ethanol gave 2.3 g. (61%) of orange prisms, m.p. 202–203° (dec.) (uncorr.).

Anal. Calcd. for $C_{18}H_{19}BrN_2O_2$: C, 57.60; H, 5.11; N, 7.47. Found: C, 57.65; H, 5.23; N, 7.52.

Reduction of XII *with sodium borohydride* (XIII). To a suspension of 800 mg. of XII in 70 ml. of ethanol 2 g. of sodium borohydride was added in portions during 10 min. The mixture was stirred for 20 hr. during which the color of the solution changed to pale green. After addition of 50 ml. of water, the ethanol was removed under reduced pressure and the excess hydride was decomposed with 10% hydrochloric acid. The aqueous solution was made basic with 0.1*N* sodium hydroxide solution and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left a gum which did not crystallize. A picrate, m.p. 168–171° was prepared in ethanol. The yield was 600 mg. The infrared spectrum showed a band at 1705 cm.$^{-1}$ (α,β-unsaturated ester).

Anal. Calcd. for $C_{24}H_{25}N_5O_9$: C, 54.64; H, 4.78; N, 13.28. Found: C, 54.59; H, 4.78; N, 13.22.

Hydrogenation of XIII. A solution of 350 mg. of the crude base, XIII, in 70 ml. of ethanol was shaken with 20 mg. of platinum oxide under hydrogen at room temperature and atmospheric pressure. After 3 hr., 19 ml. of hydrogen was absorbed. Calcd. for one equivalent: 22 ml. After filtering from the catalyst, removal of the solvent left an oil. A picrate, m.p. 185–187°, was prepared in and recrystallized from ethanol. The yield was 130 mg. The infrared spectrum showed a band at 1725 cm.$^{-1}$ characteristic of an ester.

Anal. Calcd. for $C_{24}H_{27}N_5O_9$: C, 54.44; H, 5.14; N, 13.23. Found: C, 54.60; H, 5.13; N, 13.21.

A hydrobromide, m.p. 155–157°, after recrystallization from acetone-ether, was prepared from the picrate in 25% yield. It darkened on exposure to air.

Anal. Calcd. for $C_{18}H_{25}BrN_2O_2$: C, 56.68; H, 6.61; N, 7.35. Found: C, 56.66; H, 6.61; N, 7.31.

Hydrogenation of 4-carbethoxy-1-[β-(3-indolyl)ethyl]pyridinium bromide (XIV). A solution of 376 mg. of XII in 80 ml. of ethanol was shaken with 20 mg. of platinum oxide at room temperature and atmospheric pressure. In 2 hr.

64 ml. of hydrogen were absorbed. Calcd. for 3 equivalents: 66 ml. After filtering from the catalyst, removal of the solvent left the free base which could not be crystallized. The picrate, m.p. 184–186°, and the hydrobromide, m.p. 154–155°, did not depress the melting points of the salts prepared above. The infrared spectra of the salts prepared by the two routes were identical.

3-Carbomethoxy-1-[β-(3-indolyl)ethyl]pyridinium bromide. To a solution of 10.6 g. of 3-(β-bromoethyl)indole in 100 ml. of absolute methanol and 75 ml. of anhydrous ether was added 7.1 g. of methyl nicotinate. After standing at room temperature for 3 days, the mixture was concentrated. On cooling it crystallized. The crystalline material was recrystallized from absolute methanol yielding 2.3 g. (21%) of stout yellow needles which darkened at 207° and decomposed at 218–220° (m.p. block) (uncorr.).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.76. Found: C, 56.48; H, 4.81; N, 7.84.

3-Carboxy-1-[β-(3-indolyl)ethyl]pyridinium bromide. To a solution of 4.85 g. of 3-(β-bromoethyl)indole in 125 ml. of absolute ethanol was added 2.60 g. of nicotinic acid. After warming to effect solution, the mixture was allowed to stand 4 days at room temperature. The yellow solid which deposited after concentration at reduced pressure was recrystallized from 95% ethanol giving 3.16 g. (42%) of yellow needles, m.p. 269–270° (dec.). The ultraviolet spectrum of an ethanolic solution showed absorption maxima at 289 (log ε 3.82) and 270 (log ε 4.00) mμ and a shoulder at 280 mμ (log ε 3.92). Minima occurred at 241 (log ε 3.54) and 287 (log ε 3.80) mμ.

Anal. Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.34; H, 4.35; N, 8.07. Found: C, 55.55; H, 4.30; N, 8.09.

5-Carboxy-1-[β-(3-indolyl)ethyl]-2-methylpyridinium bromide. This was prepared from 5.25 g. of 3-(β-bromoethyl)-indole and 3 g. of 6-methylnicotinic acid by the same procedure as was used for the preceding compound. The yield of pale yellow feathery needles from 95% ethanol was 4.84 g. (61%). The substance darkens at about 263° and decomposes at 274–275°. The ultraviolet spectrum of an ethanolic solution showed a maximum at 272 mμ (log ε 3.94), a shoulder at 289 mμ (log ε 3.70), and a minimum at 240–242 mμ (log ε 3.33).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.76. Found: C, 56.56; H, 4.94; N, 7.69.

Dihydrostilbazole [4-(β-phenethyl)pyridine] (XVI). A solution of 1.83 g. of 4-stilbazole (XV) in 100 ml. of ethanol was shaken under hydrogen at room temperature and atmospheric pressure with 100 mg. of 5% palladium on charcoal catalyst. During 12 hr. 273 ml. of hydrogen was absorbed. Calcd. for 1 equivalent: 255 ml. The resultant dihydrostilbazole crystallized in quantitative yield from benzene-ligroin. It melted at 69–70°. Reported m.p. 69–71°[16] and 65°.[17] The picrate melted at 162–163°. Reported m.p., 162–163°.[16]

The same base was obtained when the reduction was done in ethanol over platinum oxide.

Octahydrostilbazole (4-phenethylpiperidine) (XVII). A solution of 1.83 g. of 4-stilbazole in 100 ml. of glacial acetic acid was shaken under hydrogen at room temperature and atmospheric pressure with 200 mg of 5% palladium on charcoal. After 6 hr., 4 equivalents of hydrogen (1,121 ml.) had been absorbed. Removal of the solvent from the filtered solution left an oil which was dissolved in water. After making the solution basic with sodium hydroxide solution, it was extracted with ether. The oil remaining after concentration of the dried ether solution was converted directly to the benzenesulfonamide, m.p. 130° (uncorr.), from ethanol. Reported m.p. 130°.[18]

4-(β-Cyclohexylethyl)piperidine (XVIII). A solution of 1.83 g. of 4-stilbazole in 100 ml. of ethanol containing an excess of anhydrous hydrogen chloride was shaken with 350 mg. of Adams' platinum oxide catalyst under hydrogen at room temperature and atmospheric pressure. During the course of 9 hr., 7 equivalents of hydrogen were absorbed. The free base, m.p. 33–35° showed no absorption in the ultraviolet.

For characterization, the base was converted to the 3,5-dinitrobenzamide by treatment with 3,5-dinitrobenzoyl chloride in pyridine for 1 hr. On dilution the amide crystallized. After recrystallization from ethanol, it melted at 154°.

Anal. Calcd. for $C_{20}H_{27}N_3O_5$: C, 61.68; H, 6.99; N, 10.79. Found: C, 61.63; H, 6.97; N, 10.95.

The benzenesulfonamide, prepared as in the preceeding case, melted at 120° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{29}NO_2S$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.76; H, 8.49; N, 4.14.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Cholesterol and Companions. X.[1] The Diol Fraction

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Received June 28, 1957

A technique of inverse chromatography facilitated isolation from various cholesterol samples of 25-hydroxycholesterol, cerebrostenediol (24-OH isomer), 7-ketocholesterol, and an alkane-1,2-diol mixture. 25-Hydroxycholesterol appears not to be a product of animal origin but to result from air-oxidation of crystalline cholesterol.

Oxidation of cholesterol with a variety of reagents has afforded no less than twenty oxidation products in which the original 27 carbon atoms are retained. The structure, and indeed the origin, of one of these products still awaits elucidation. This substance, designated ketone 104,[3] is a somewhat hindered ketone of the formula $C_{27}H_{44}O_3$[3,4] which is formed in 0.5–0.9% yield on oxidation of either commercial cholesterol or

(1) Paper IX: L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954).

(2) A friendship with the late Lyndon F. Small which began when we were fellow graduate students was later enlivened by his outstanding work on morphine and on general phenanthrene chemistry. Reviewing his work in books has been a pleasure, both because the experimentation is always meticulously done, and because I have known and admired this keen experimentalist. L.F.F.

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