[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

THE ERGOT ALKALOIDS. XX. THE SYNTHESIS OF DIHYDRO-*dl*-LYSERGIC ACID. A NEW SYNTHESIS OF 3-SUBSTITUTED QUINOLINES

FREDERICK C. UHLE AND WALTER A. JACOBS

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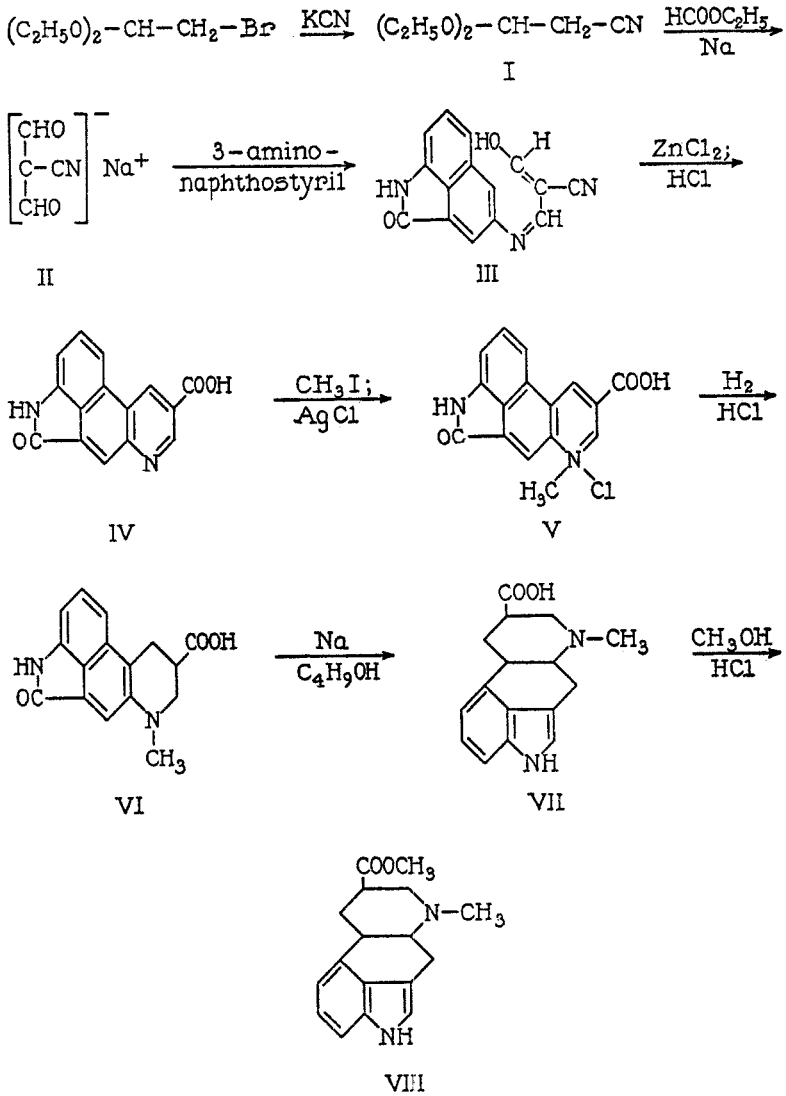
On the basis of degradation studies, lysergic acid was shown to be an unsaturated 6-methyl-8-ergolinecarboxylic acid (1). This structure appeared to be confirmed by the transformation of lysergic acid to 6,8-dimethylergoline, a substance which could be obtained by synthesis (2). More rigid confirmation of the structure has now been obtained by the synthesis of a closer derivative of lysergic acid itself, dihydro-*dl*-lysergic acid. In the course of this work, a new synthesis of the difficultly accessible 3-substituted quinolines has been developed. By this procedure, it is possible to synthesize directly quinolines substituted in the hetero-ring in only the 3-position. 3-Nitroquinolines and 3-quinolinecarboxylic acids are obtained directly, while other substituents are introduced into the 3-position through these groups. Dihydro-*dl*-lysergic acid was synthesized by the series of reactions shown in Formulas I–VIII.

Cyanoacetal (I) was prepared from bromoacetal with potassium cyanide. The bromine atom in bromoacetal was found to be quite inert in metathetical reactions with metallic cyanides. No appreciable reaction was apparent when bromoacetal was refluxed with cuprous cyanide. With potassium cyanide in aqueous ethanol solution, 67% of the bromo compound was recovered unchanged, and the higher-boiling cyanoacetal was obtained in only 14% yield. By refluxing for a longer period, the yield was decreased. The cyanoacetal was allowed to react with ethyl formate and sodium in ether solution. The resulting sodium derivative of cyanomalonic dialdehyde (II), when dissolved in water, reacted at once with aniline hydrochloride in acid solution to give 2-cyano-2-formylethylidenaniline (IX). The monoanil was converted to the dianil (X) with aniline in ethanol solution, and the dianil, in turn, could be readily hydrolyzed to the monoanil by dilute acids. The dianil was obtained directly in neutral or alkaline solution. 2-Cyano-2-formylethylidenaniline (IX) was cyclized by fusion with zinc chloride. The basic fraction isolated from the reaction mixture consisted, apparently, of both the nitrile and the amide, for 3-quinolinecarboxamide (XI) was isolated by fractional crystallization from benzene. In further experiments, the basic fraction from the condensation reaction was hydrolyzed directly to 3-quinolinecarboxylic acid (XII), which was also characterized as the methyl ester.

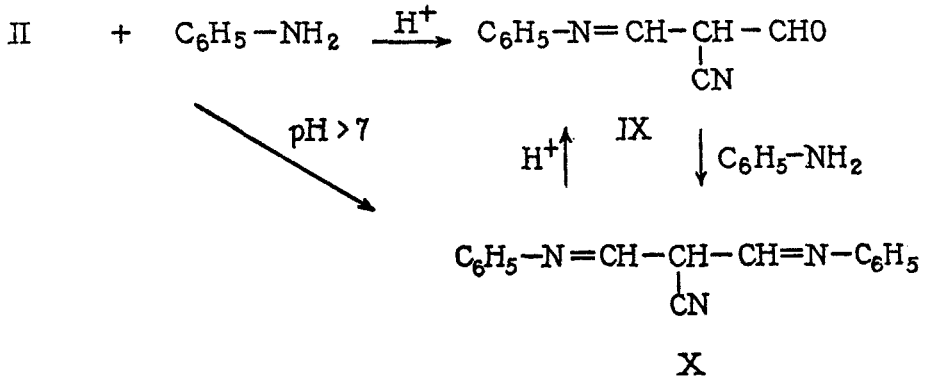
In application of the above reactions to the synthesis of dihydrolysergic acid, 3-aminonaphthostyril was allowed to react with sodio-cyanomalonic dialdehyde in acid solution. The slightly soluble, bright yellow 2-cyano-2-formylethyliden-3-aminonaphthostyril (III) was converted to 3′-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (IV) by fusion with zinc chloride and hydrolysis of the

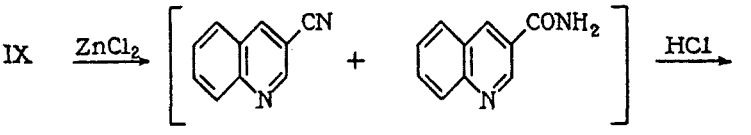
mixture of basic products with hydrochloric acid. The benzoquinolinecarboxylic acid was converted to the methiodide, which was, in turn, transformed to the methochloride (V).



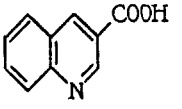
When attempts were made to hydrogenate the methochloride (V) to the tetrahydro stage, an unexpected difficulty was encountered. Although two moles of hydrogen were readily absorbed, the major portion of the reaction product consisted of material in which the carboxyl function had somehow been eliminated. The purified product, although nicely crystalline, appeared to consist of more than one substance. A wide variety of experimental conditions was investi-

gated, but always the methochloride was converted to alkali-insoluble products. A study of the hydrogenation of the simple 3-quinolinecarboxylic acid methiodide as a model was then made. The product, under most conditions, proved to be N-methyl-1,2,3,4-tetrahydroquinoline hydriodide. Finally, it was discovered that, if the hydrogenation was conducted in 18% hydrochloric acid, the carboxyl group was retained, and the product was the salt of N-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid. However, the low solubility of the methochloride (V) in hydrochloric acid seemed to preclude the application of these conditions to the more complex compound. When a suspension of the methochloride





XI



XII

in 18% hydrochloric acid was submitted to hydrogenation, the small amount of material in solution was reduced beyond the tetrahydro stage before additional methochloride dissolved and, eventually, as much as eight moles of hydrogen were absorbed, leading to a colorless perhydro compound. These difficulties were, however, finally surmounted in the following manner. A very dilute solution of the methochloride in boiling water was added to an equal volume of concentrated hydrochloric acid and the hot "supersaturated" solution was at once shaken with hydrogen and freshly prepared platinum black. The brilliant red color of the solution gave way to a bright yellow in a few minutes and the hydro-

genation was interrupted. The product was isolated through the copper salt, and the beautifully crystalline 3′-amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (VI) was obtained in 30% yield.

This tetrahydro derivative was reduced to the indole stage with sodium and butanol. The ampholyte fraction crystallized, and recrystallization was accomplished from dilute ammonium hydroxide. The yield was 8.5% and, after sublimation at 10^{-4} mm. at 200–230°, the substance gave analytical data for dihydrolysergic acid. It darkened at 280°, but did not melt below 360°. The synthetic material paralleled the dihydro-*dl*-lysergic acid obtained from lysergic acid in all such properties as solubility, melting point, conditions of sublimation, and crystalline form. The accompanying drawings from microphotographs

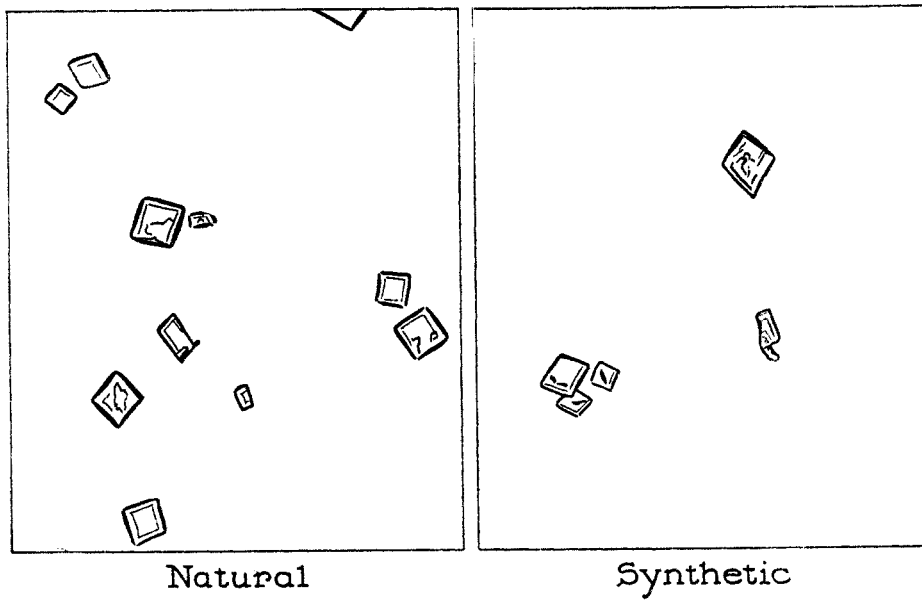
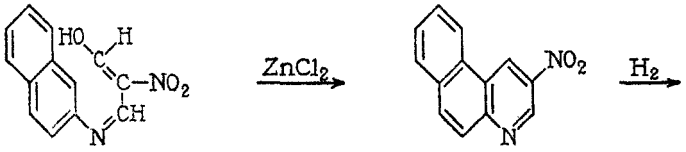


FIG. 1

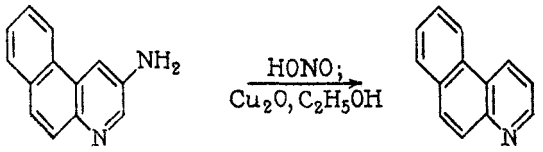
(Fig. 1) clearly show this. The synthetic dihydrolysergic acid (VII) was converted to the methyl ester (VIII) with methanolic hydrogen chloride, and the ester was sublimed at 0.1 mm. at 200°. The sublimate crystallized in characteristic broad leaves from benzene. After one recrystallization, the first crystals to melt began rather sharply at 145°, but the last crystal did not disappear until about 175°, and this melting range was not appreciably changed after four recrystallizations. This was not unexpected, since the substance could still be a mixture of two or more of the four possible pairs of diastereoisomers. With the small amount of material available it has not as yet been feasible to attempt a systematic separation of such isomers. A sample of dihydro-*dl*-lysergic acid prepared from lysergic acid yielded a methyl ester which exhibited the same properties as the synthetic material and showed no depression of melting points when mixed. The dihydro acids and their methyl esters from both sources gave indistinguishable colors in the Keller and van Urk tests.

The new quinoline synthesis applied above in the preparation of dihydrolysergic acid was first studied with the 3-nitro derivatives. 2-Nitro-2-formylethylidenaniline, when fused with zinc chloride, yielded 3-nitroquinoline. Zinc chloride was the only condensing agent found which appeared to effect ring closure to the quinoline compound. Acetic anhydride, concentrated sulfuric acid, potassium acid sulfate, sodium ethoxide in absolute ethanol, hot mineral oil, among other reagents, when allowed to react with the anil, led to no basic products.

β-Naphthylamine was condensed with sodio-nitromalonic dialdehyde, and the resulting 2-nitro-2-formylethylidene-β-naphthylamine (XIII) was similarly converted to 3-nitro-5,6-benzoquinoline (XIV) with zinc chloride. The nitro compound was reduced to 3-amino-5,6-benzoquinoline (XV) by hydrogenation. The 3-amino compound, when diazotized and treated with cuprous oxide in absolute ethanol, yielded 5,6-benzoquinoline (XVI) in 48% yield, as shown by com-



XIII XIV



XV XVI

parison with an authentic sample. This proved that the zinc chloride condensation with the β-naphthylamine derivatives led to the angular isomer. 3-Aminonaphthostyril was, accordingly, allowed to react with sodio-nitromalonic dialdehyde. The slightly soluble 2-nitro-2-formylethyliden-3-aminonaphthostyril was cyclized with zinc chloride to 3′-amino-3-nitro-5,6-benzoquinoline-7-carboxylic acid lactam. The lactam, after saponification with alkali, was reduced with ferrous sulfate. The expected 3,3′-diamino-5,6-benzoquinoline-7-carboxylic acid lactam was isolated in 30% yield. Attempts were then made to replace the 3-amino group by the cyano group by the Sandmeyer procedure. Diazotization could be accomplished in strong acid solution, but when the mixture was brought toward the neutral point, preparatory to adding the cuprous cyanide, decomposition and subsequent precipitation occurred. Because of the difficult solubility relationships and the rather low yield in the reduction of the nitro compound, this procedure was abandoned in favor of attempts which eventually led to the introduction of the 3-carboxyl group directly, as discussed above.

Among a number of other projected sequences for the preparation of 3-substituted quinolines which were investigated, the following may be mentioned briefly. Although 3-quinolinecarboxylic acid can be prepared by conversion at elevated temperature of quinoline hydrobromide-perbromide to 3-bromoquinoline with subsequent replacement of the bromine atom by the cyano group, and hydrolysis of the latter to the acid (3), this procedure could not be applied successfully to the more complex 5,6-benzoquinoline derivatives. When attempts were made to brominate the hydrobromides of 5,6-benzoquinoline-7-carboxylic acid or its methyl ester, and of 3′-nitro-5,6-benzoquinoline-7-carboxylic acid and its methyl ester, no simple monobromoquinoline derivatives could be isolated. Small amounts of dibromo derivatives in the case of the 3′,7-substituted 5,6-benzoquinolines, and of tribromo derivatives in the case of the 7-substituted 5,6-benzoquinolines were isolated. They were difficult to purify. Some decarboxylation occurred with the free acids, and dealkylation of the ester grouping was observed in bromination experiments with the esters.

In another attempt to prepare a 3-bromoquinoline, α-bromoacrolein was allowed to react with β-naphthylamine in the presence of 40% hydrobromic acid. The only product which could be isolated was 5,6-benzoquinoline, since aromatization apparently occurred by the elimination of hydrogen bromide. Attempts to convert α-bromoacrolein to α-cyanoacrolein were not successful. An attempted condensation of aniline, methylal, and carbethoxydiethylacetal did not yield 3-quinolinecarboxylic acid.

EXPERIMENTAL

Cyanoacetal. A mixture of 536 g. (2.7 moles) of bromoacetal, 175 g. (2.7 moles) of potassium cyanide, 50 g. (0.33 mole) of sodium iodide, 350 ml. of ethanol, and 150 ml. of water was heated on the steam-bath under reflux for 40 hours. A modified Hershberg mechanical stirrer was used to maintain vigorous stirring. The ethanol was distilled off, and the dark residue was extracted with a large volume of ether. The extract was washed with water and dried over potassium carbonate. After removal of solvent, the resultant oil was fractionated under diminished pressure through a 30 cm. Vigreux column. Three hundred sixty grams of unchanged bromoacetal, which boiled at 70–72° at 14 mm., or 67% of the starting material, was recovered. The residue in the distilling flask was fractionated *in vacuo* through a shorter column and the distillate was then redistilled. The yield of cyanoacetal was 54 g. (14%); b.p.$_{14}$ 99°; d_{20}^{20} 0.9496; n_D^{20} 1.4155; M_D calc'd: 37.57; M_D found: 37.77.

Anal. Calc'd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78.
Found: C, 58.41; H, 9.21; N, 9.55.

2-Cyano-2-formylethylidenaniline. To a solution of 7.15 g. (0.05 mole) of cyanoacetal and 5 g. (0.067 mole) of ethyl formate in 25 ml. of absolute ether was added 1.15 g. (0.05 mole) of sodium. The reaction began at once and, after the mixture had been allowed to stand overnight at room temperature, a tan colored precipitate had formed. Fifty milliliters of water was added, and the aqueous and ether layers were separated. The water solution, which contained the sodium derivative of cyanomalonic dialdehyde, was added to a solution of 5 g. (0.054 mole) of aniline in 120 ml. of 3% hydrochloric acid. The crystalline precipitate, which separated at once, was collected and then recrystallized from ethanol. The yield was 5.3 g. (61%, based on the cyanoacetal); m.p. 189–190°.

Anal. Calc'd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27.
Found: C, 69.76; H, 4.82; N, 16.42.

Cyanomalonic dialdehyde dianil. The dianil was prepared by warming the monoanil with aniline in alcoholic solution for a short time. The yellow crystalline product was obtained in almost quantitative yield, and was recrystallized from ethanol; m.p. 132–133°.

Anal. Calc'd for $C_{16}H_{13}N_3$: C, 77.72; H, 5.30; N, 17.00.
Found: C, 77.58; H, 4.94; N, 17.20.

Preparation of 3-quinolinecarboxamide. A mixture of 0.4 g. (0.0023 mole) of 2-cyano-2-formylethylidenaniline and 2 g. of anhydrous zinc chloride was heated to 300°. The cooled mass was extracted with water and the solid was collected. This material was extracted with hot 10% hydrochloric acid. The filtrate from a black insoluble residue was concentrated to dryness *in vacuo*. After addition of water to the residue, the bases were liberated with ammonia and extracted with ether. The extract yielded a residue which was recrystallized from benzene. The product appeared to consist of a mixture of the amide and the more soluble nitrile. After three recrystallizations from benzene, hexagonal plates were obtained, which melted at 198–199°, the melting point reported for 3-quinolinecarboxamide (4).

Anal. Calc'd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68.
Found: C, 69.46; H, 4.45.

Preparation of 3-quinolinecarboxylic acid. One gram (0.0058 mole) of 2-cyano-2-formylethylidenaniline and 3 g. of zinc chloride were heated to 260°. The cooled brittle mass was treated with water to remove the zinc chloride, and the solid was collected. It was refluxed with 50 ml. of 18% hydrochloric acid for 1 hour. The hot mixture was filtered from insoluble by-products, and the filtrate was concentrated to dryness *in vacuo*. The residue was extracted with sufficient dilute sodium carbonate solution. The filtered extract was concentrated *in vacuo* to approximately 5 ml., and a solution of cupric acetate was added as long as precipitation occurred. The green precipitate was collected and washed by centrifugation and, after suspension in water, was decomposed with hydrogen sulfide. The copper sulfide was filtered off and then washed repeatedly with hot ethanol. The filtrate on concentration to dryness *in vacuo* gave a residue which was crystallized from dilute ethanol. The yield was 50 mg.; m.p. 273–275°. When mixed with authentic material, no depression of melting point was observed.

Anal. Calc'd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09.
Found: C, 69.45; H, 4.15; N, 8.22.

3-Quinolinecarboxylic acid methyl ester. The ester was prepared by refluxing the acid with methanol and sulfuric acid. It crystallized in broad leaves and melted at 73–74°, and agreed in all properties with the ester prepared from an authentic sample of 3-quinolinecarboxylic acid.

Anal. Calc'd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85.
Found: C, 70.81; H, 5.11.

3-Quinolinecarboxylic acid methiodide. One gram (0.0058 mole) of quinoline 3-carboxylic acid, when heated at 100° in a sealed tube for 16 hours with 20 ml. of methyl iodide, yielded a dark red solid, which was collected with methanol and recrystallized from a mixture of methanol and anhydrous ether. The yield was 1.75 g. (96%); m.p. 247°.

Anal. Calc'd for $C_{11}H_{10}INO_2$: C, 41.92; H, 3.20; N, 4.44.
Found: C, 41.88; H, 3.23; N, 4.30.

Conversion to N-methyltetrahydroquinoline hydriodide. Two hundred milligrams (0.00063 mole) of the methiodide of 3-quinolinecarboxylic acid was hydrogenated in 35 ml. of methanol at ordinary temperature and pressure, with 200 mg. of platinum oxide. Hydrogenation ceased after absorption of 69 ml. during 3 hours (calculated: 74 ml.). The product crystallized from methanol-ether mixture in a yield of 60 mg. and melted at 167–168°, as recorded for N-methyltetrahydroquinoline hydriodide (5).

Anal. Calc'd for $C_{10}H_{14}IN$: C, 43.65; H, 5.13; N, 5.09; (N)—CH_3, 5.45.
Found: C, 43.54; H, 4.93; N, 4.89; (N)—CH_3, 5.14.

2-Cyano-2-formylethyliden-3-aminonaphthostyril. To a mixture of 14.3 g. (0.1 mole) of cyanoacetal and 8.2 g. (0.11 mole) of ethyl formate in 25 ml. of absolute ether was added

2.3 g. (0.1 mole) of sodium. After the mixture had been allowed to stand overnight, 25 ml. of water was added, and the aqueous layer was separated. This solution was added to a solution of 13 g. of 3-aminonaphthostyril (0.07 mole) in 500 ml. of 2% hydrochloric acid. The yellow precipitate which separated at once was collected and recrystallized from ethanol. The yield was 17 g. (65% based on cyanoacetal); m.p. 290–292°.

Anal. Calc'd for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.45; N, 15.96.
Found: C, 68.10; H, 3.33; N, 15.85.

3'-Amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam. A mixture of 2 g. (0.0076 mole) of 2-cyano-2-formylethyliden-3-aminonaphthostyril and 1 g. of anhydrous zinc chloride was heated to 250°. At this temperature the mixture fused to a black, viscous liquid. It was then cooled and the brittle solid was extracted with several portions of water and collected. It was then heated under reflux with 100 ml. of 18% hydrochloric acid for 1 hour. The hot solution was filtered to remove a black, insoluble by-product, and the dark red filtrate was concentrated to dryness under diminished pressure. Fifty milliliters of water was added, and the solution was made alkaline with ammonium hydroxide. A small amount of undissolved brown material was filtered off and hydrochloric acid was then cautiously added to the filtrate to precipitate the acid. The yellow solid was collected and recrystallized from ethanol. The yield was 0.76 g. (38%). The substance did not melt below 360°.

Anal. Calc'd for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05.
Found: C, 68.14; H, 3.05.

Methyl ester of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam. Seven hundred seventy milligrams of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam was refluxed in a mixture of 25 ml. of methanol and 5 ml. of concentrated sulfuric acid for 10 hours. After dilution with water, the mixture was made alkaline with sodium carbonate. The yellow precipitate was extracted with ethyl acetate and the extract was washed and dried. After concentration to dryness under diminished pressure, the resultant solid was recrystallized from methanol. The ester crystallized in beautiful golden-yellow needles. The yield was 350 mg. (44%); m.p. 300–301°.

Anal. Calc'd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07.
Found: C, 69.22; H, 3.69; N, 10.32.

3'-Amino-5,6-benzoquinoline-3,7-dicarboxylic acid methochloride. Two and seventy-five hundredths grams (0.0104 mole) of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid and 15 ml. of methyl iodide were heated at 100° for 40 hours in a sealed tube. The brick-red reaction product was added to a hot suspension of freshly precipitated silver chloride in water, and the silver salts were removed by filtration. When hydrochloric acid was added to the dark red solution, beautiful red needles of the methochloride separated. The compound was recrystallized by addition of hydrochloric acid to a hot aqueous solution. The yield was 1.5 g. (46%). The substance did not melt below 360°.

Anal. Calc'd for $C_{16}H_{11}ClN_2O_3$: C, 61.05; H, 3.53; N, 8.84.
Found: C, 60.50; H, 3.57; N, 8.75.

3'-Amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic lactam. Eighty milligrams (0.00025 mole) of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam methochloride was dissolved in 100 ml. of hot water, and the solution was added to 100 ml. of concentrated hydrochloric acid. This solution while hot was poured into a hydrogenation tube containing platinum black prepared from 150 mg. of platinum oxide and at once shaken with hydrogen. The brilliant red color of the solution changed to bright yellow after a few minutes. The hydrogenation was then interrupted, and the platinum was removed by filtration. The filtrates from four runs were combined and evaporated to dryness *in vacuo*. Ten milliliters of water was added and potassium carbonate was introduced in small amounts until the tetrahydro derivative dissolved as the potassium salt. A small amount of insoluble material was removed by centrifugation, and cupric acetate solution was added as long as precipitation occurred. The precipitated copper salt was collected and washed with water by centrifugation. After suspension in 40 ml. of water, it was decomposed with hydrogen sulfide. The copper sulfide, after filtration, was washed

repeatedly with hot methanol. The bright yellow solution on concentration *in vacuo* gave a residue which was recrystallized from dilute methanol. The product formed fine golden-yellow needles. The yield was 85 mg. (30%); m.p. 230–235° with decomposition.

Anal. Calc'd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.99; (N)—CH_3, 5.32.
Found: C, 67.88; H, 5.30; N, 9.89; (N)—CH_3, 4.70.

Dihydro-dl-lysergic acid. Two hundred fifty milligrams (0.00089 mole) of 3′-amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam was dissolved in 400 ml. of boiling butanol. Ten grams of sodium was added and the mixture was shaken vigorously until the sodium had dissolved. One liter of water was added and the butanol was removed *in vacuo*. Carbon dioxide was passed into the alkaline solution until all the alkali had been converted to sodium bicarbonate. The solution was then concentrated to dryness *in vacuo*, and the residue was repeatedly extracted with hot ethanol. The extract was concentrated to dryness *in vacuo* and the residue was redissolved in 50 ml. of water and extracted with chloroform. The aqueous phase was then acidified with acetic acid. A small, black, amorphous precipitate was removed by filtration and the filtrate was extracted with chloroform. The aqueous phase was then concentrated *in vacuo* to about 5 ml. and made alkaline with ammonia. The mixture was boiled down to expel the ammonia and liberate the free ampholyte. It was then allowed to crystallize in the cold for several days. The crystalline fraction weighed 20 mg. (8.4%). It was recrystallized as above from dilute ammonia. The crystalline material was finally sublimed at 10^{-4} mm. and 200–230°. It darkened at 280°, but did not melt below 360°. This behavior parallelled that of the dihydrolysergic acid prepared from racemized lysergic acid. The purified material, which crystallized on concentration of its solution in dilute ammonia, formed microscopic, thin, rhombic leaflets, which were indistinguishable from the crystals obtained with the dihydro acid from *dl*-lysergic acid. The Keller color tests in each case were indistinguishable.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: C, 71.08; H, 6.78.
Found: C, 70.90; H, 6.74.

Dihydro-dl-lysergic acid methyl ester. Fifteen milligrams of synthetic dihydrolysergic acid was added to 2 ml. of absolute methanol which had been saturated with hydrogen chloride. The solution was allowed to stand at room temperature for 1 hour and then evaporated to dryness *in vacuo*. A few milliliters of water was added and the solution was made alkaline with ammonium hydroxide and extracted with ether. The residue from the ether was sublimed at 0.1 mm. and 200°. The sublimate was recrystallized 4 times from a few drops of benzene. It crystallized in characteristic broad plates. It melted over a range of 145–175°.

Anal. Calc'd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09.
Found: C, 71.94; H, 6.74.

The dihydro ester similarly prepared from the dihydrolysergic acid obtained from *dl*-lysergic acid melted over the same range and showed no depression when mixed with the above ester.

Preparation of 3-nitroquinoline. A mixture of 2 g. (0.0104 mole) of 2-nitro-2-formylethylidenaniline (6) and 5 g. of anhydrous zinc chloride was heated to 200°. The cooled black mass was treated with 50 ml. of hot 18% hydrochloric acid. After filtration of insoluble material, the filtrate was concentrated *in vacuo*. The residue was dissolved in 25 ml. of water and the solution was made alkaline with dilute ammonium hydroxide. The collected precipitate was recrystallized from dilute ethanol. The product, which weighed 0.38 g. (21%), melted at 127–128°, as recorded for 3-nitroquinoline (7).

Anal. Calc'd for $C_9H_6N_2O_2$: C, 62.06; H, 3.47; N, 16.09.
Found: C, 62.32; H, 3.59; N, 15.91.

2-Nitro-2-formylethylidene-β-naphthylamine. To a solution of 2.6 g. (0.018 mole) of β-naphthylamine in 100 ml. of 2% hydrochloric acid was added a solution of 2.6 g. (0.0165 mole) of the sodium derivative of nitromalonic dialdehyde (6) in 25 ml. of water. The yellow precipitate which formed was collected and recrystallized from ethanol. The yield was 3.0 g. (75%); m.p. 195–196°.

Anal. Calc'd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57.
Found: C, 64.65; H, 4.45; N, 11.67.

3-Nitro-5,6-benzoquinoline. A mixture of 3.5 g. (0.0145 mole) of 2-nitro-2-formylethylidene-β-naphthylamine and 1.5 g. of anhydrous zinc chloride was heated to 220°. At this temperature the mass melted and was then allowed to cool. After extraction with water, the collected insoluble material was refluxed for 5 minutes with 100 ml. of 18% hydrochloric acid. The hot mixture was filtered from black tar and the filtrate was concentrated to dryness *in vacuo*. Water (25 ml.) was added and the solution was made alkaline with dilute ammonium hydroxide. The precipitated base was extracted with ether. The latter left a residue which was recrystallized from dilute ethanol. The yield was 2.5 g. (77%); m.p 155–156°.

Anal. Calc'd for $C_{13}H_8N_2O_2$: C, 69.63; H, 3.60; N, 12.50.
Found: C, 69.37; H, 3.60; N, 12.51.

3-Amino-5,6-benzoquinoline. Four hundred fifty milligrams (0.002 mole) of 3-nitro-5,6-benzoquinoline was dissolved in 150 ml. of ethanol and hydrogenated at ordinary temperature and pressure, using 100 mg. of platinum oxide. Absorption of hydrogen ceased after 182 ml. had been taken up during 30 minutes (theory, 175 ml.). The product was recrystallized from dilute ethanol. The yield was 270 mg. (70%); m.p. 135–136°.

Anal. Calc'd for $C_{13}H_{10}N_2$: C, 80.37; H, 5.19; N, 14.43.
Found: C, 80.58; H, 5.40; N, 14.33.

Conversion to 5,6-benzoquinoline. To a solution of 250 mg. (0.0013 mole) of 3-amino 5,6-benzoquinoline in 5 ml. of glacial acetic acid was added a cold solution of 120 mg. (0.0013 mole) of sodium nitrite in 2 ml. of concentrated sulfuric acid. The mixture was allowed to stand for 30 minutes and was then added dropwise to a suspension of 350 mg. of cuprous oxide in 15 ml. of absolute ethanol. Nitrogen was evolved, and the odor of acetaldehyde was apparent. After the reaction had ceased, the mixture was poured into 100 ml. of water, potassium carbonate was added until alkaline, and the liberated amine was extracted with ether. The washed and dried extract on concentration gave a residue which was sublimed *in vacuo* at 15 mm. The white crystalline sublimate on recrystallization from dilute ethanol yielded 110 mg. (48%); m.p. 89–91°. When mixed with an authentic sample of 5,6-benzoquinoline, the m.p. was 89–91°.

Anal. Calc'd for $C_{13}H_9N$: C, 87.12; H, 5.06.
Found: C, 86.60; H, 5.13.

2-Nitro-2-formylethyliden-3-aminonaphthostyril. To a solution of 1.84 g. (0.01 mole) of 3-aminonaphthostyril in 120 ml. of 3% hydrochloric acid was added a solution of 1.57 g. (0.01 mole) of the sodium derivative of nitromalonic dialdehyde in 120 ml. of water. The yellow precipitate was collected, dried, and recrystallized from acetic acid. The yield was 2.5 g. (89%). The substance did not melt below 360°.

Anal. Calc'd for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84.
Found: C, 59.02; H, 3.33; N, 14.65.

3'-Amino-3-nitro-5,6-benzoquinoline-7-carboxylic acid lactam. A mixture of 1.42 g. (0.005 mole) of 2-nitro-2-formylethyliden-3-aminonaphthostyril and 5 g. of anhydrous zinc chloride was heated to 280° and the melt was then allowed to cool slowly. The black mass was heated with 50 ml. of 18% hydrochloric acid, and black, insoluble material was filtered off. The filtrate was concentrated to dryness *in vacuo*. Fifty milliliters of water was added, the mixture was made alkaline with dilute ammonium hydroxide, and the orange precipitate was collected. After recrystallization from acetic acid, the yield was 0.75 g. (57%). The substance did not melt below 360°.

Anal. Calc'd for $C_{14}H_7N_3O_3$: C, 63.40; H, 2.66.
Found: C, 63.10; H, 3.16.

3,3'-Diamino-5,6-benzoquinoline-7-carboxylic acid lactam. One gram (0.0038 mole) of 3-nitro-3'-amino-5,6-benzoquinoline-7-carboxylic acid lactam was heated with 100 ml. of 10% sodium hydroxide solution until saponification of the lactam was complete. A solution of 6.3 g. (0.020 mole) of ferrous sulfate in 50 ml. of water was added, and the mixture was

boiled and then filtered. The filtrate on acidification with acetic acid yielded insoluble material, which was removed by filtration. The filtrate yielded the amino compound with dilute ammonium hydroxide. It was recrystallized from dilute ethanol. The yield was 0.30 g. (34%); m.p. 345–347° with decomposition.

Anal. Calc'd for $C_{14}H_9N_3O$: C, 71.48; H, 3.85.
Found: C, 71.00; H, 4.20.

All recorded melting points are micro melting points.

All analyses were made by Mr. D. Rigakos of this laboratory.

SUMMARY

A new synthesis of 3-substituted quinolines has been developed. This procedure has made possible the synthesis of dihydro-*dl*-lysergic acid.

NEW YORK, N. Y.

REFERENCES

(1) CRAIG, SHEDLOVSKY, GOULD, AND JACOBS, *J. Biol. Chem.*, **125**, 289 (1938); JACOBS AND CRAIG, *J. Am. Chem. Soc.*, **60**, 1701 (1938); and earlier papers.
(2) JACOBS AND GOULD, *J. Biol. Chem.*, **130**, 399 (1939); GOULD, CRAIG, AND JACOBS, *J. Biol. Chem.*, **145**, 487 (1942).
(3) CLAUS AND COLLISCHON, *Ber.*, **19**, 2763 (1886); GILMAN AND SPATZ, *J. Am. Chem. Soc.*, **63**, 1556 (1941).
(4) MILLS AND WATSON, *J. Chem. Soc.*, **94**, 745 (1910).
(5) WEDEKIND, *Ber.*, **36**, 3799 (1903).
(6) HILL AND TORRY, *Am. Chem. J.*, **22**, 95 (1899).
(7) Ger. Pat. No. 335,197, *Chem. Abstr.*, **17**, 1802 (1923).