ride (0.93 g., 0.005 mole) and 5% sodium hydroxide (4 ml.) were added concomitantly in portions with cooling and shaking. An additional 6 ml. of 5% sodium hydroxide and ice were added and mixture was shaken occasionally for one hour; all of the solid dissolved by this time. The solution was washed with 15 ml. of chloroform, then chilled and acidified with dilute hydrochloric acid. The chilled mixture was filtered and the solid was washed with water. The air-dried solid weighed 1.6 g. and melted at 98–100° then resolidified and melted again at 187–188°. After drying *in vacuo* at 100° over phosphorus pentoxide the material melted at 188–189° without melting at the lower temperature. The melting point remained unchanged after recrystallization from ethyl acetate–pentane.

3-(*p*-Aminobenzamido)-3-carboxypropanesulfonamide.—A mixture of 662 mg. (0.002 mole) of 3-(*p*-nitrobenzamido)-3-carboxypropanesulfonamide, 215 mg. of 5% palladium–carbon catalyst and 5 ml. of absolute ethanol was shaken with hydrogen at atmospheric pressure and 25°. Reduction was complete when 147 cc. of hydrogen was absorbed (theory, 145 cc.). The mixture was filtered and solid was removed from the catalyst by washing first with warm ethanol (150 ml.) and then with warm ethyl acetate (50 ml.). The combined organic solutions were evaporated to dryness at *ca.* 55° under a current of dry nitrogen. The residue, a light tan solid, weighed 600 mg. and melted at 124–126° dec. It was recrystallized from aqueous ethanol (charcoal) in the presence of nitrogen to give 290 mg. of white solid, m.p. 133–134°.

Microbiology.—The amino acids in Table I were tested, as described by Czekalowski,[10] against T_2 bacteriophage and its host cell (*E. coli* strain at A.T.C.C. No. 11303) at *p*H 7 and 37°.

(10) J. W. Czekalowski, *Brit. J. Exptl. Path.*, **33**, 57 (1952).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Phenanthridine Syntheses via the Diels–Alder Reaction. A New Route to 6(5)-Phenanthridinone

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Starting from isoprene and *o*-nitrobenzenediazonium chloride, by 9-methyl-6(5)-phenanthridinone (IX) has been prepared *via* a seven-step reaction sequence. An alternate route to IX by Diels–Alder condensation of isoprene with *o*-nitrocinnamic acid, followed by reductive cyclization and catalytic dehydrogenation, gave in addition the isomeric 8-methyl-6(5)-phenanthridinone (XIII). The latter method was employed for a new, three-step synthesis of 6(5)-phenanthridinone (XVII) from butadiene and *o*-nitrocinnamic acid.

Although many synthetic methods for the preparation of phenanthridine derivatives have been developed,[3,4] the potentialities of utilizing the Diels–Alder reaction have received little attention.[5–9] The present paper describes several Diels–Alder phenanthridine syntheses which have made possible the preparation of two new methyl 6(5)-phenanthridinones, and a new route to 6(5)-phenanthridinone.

o-Nitrobenzenediazonium chloride (I) was treated with isoprene under Meerwein conditions according to the method described by Braude and Fawcett[9] for the analogous condensation with butadiene, and the intermediate chloro compound II was dehydrochlorinated with methanolic potassium hydroxide. That the product of this reaction sequence was 1-(*o*-nitrophenyl)-3-methyl-1,3-butadiene (IV) rather than the isomer 1-(*o*-nitrophenyl)-2-methyl-1,3-butadiene was shown by ozonolysis of the chloro adduct II, followed by hydrogen peroxide oxidation to give *o*-nitrophenylacetic acid (III) identical with an authentic sample. This structural assignment was subsequently confirmed by conversion of IV to 9-methyl-6(5)-phenanthridinone (IX) (*vide infra*).

It proved to be impossible to purify either II or IV sufficiently for correct, reproducible analyses. Both products were obtained crude as dark red oils. Attempts to distil II *in vacuo* gave small amounts of an impure red liquid with large amounts of a dark, tarry substance remaining in the pot. An attempt to obtain a solid ester derivative by the addition of potassium benzoate to the crude intermediate chloro compound was unsuccessful. Corresponding oils which could not be purified were obtained when iodine was substituted for chlorine. Similarly, the diene IV could not be purified completely by distillation or by chromatography. However, a comparison of the ultraviolet absorption spectrum of distilled IV with the spectrum of authentic 1-(*o*-nitrophenyl)-1,3-butadiene (see Table I) showed the product to be substantially

TABLE I

COMPARISON OF ULTRAVIOLET ABSORPTION SPECTRA (SOLVENT: 95% ETHANOL)

1-(*o*-Nitrophenyl)-1,3-butadiene[9]		Cmpd. IV (1-(*o*-nitrophenyl)-3-methyl-1,3-butadiene)	
λmax in Å.	log εmax	λmax in Å.	log εmax
2175	5.04	2180	5.19
2230	5.05	2230	5.21
2625	4.50	2640	4.47
3350	3.58	3350	3.30

pure, even though microanalytical values were unsatisfactory. Attempts to prepare a solid dibromo derivative of IV gave only tars. In contrast to the ease with which 1-(*o*-nitrophenyl)-1,3-butadiene undergoes the Diels–Alder reaction,[9] no product could be isolated from the reaction of IV with methyl acrylate, methyl vinyl ketone or N-(*p*-nitrophenyl)-maleimide. However, the

(1) Frick Chemical Laboratory, Princeton University, Princeton, N. J.

(2) Parke, Davis and Company Fellow, 1952–1954.

(3) R. S. Theoband and K. Schofield, *Chem. Revs.*, **46**, 171 (1950).

(4) L. P. Walls, in "Heterocyclic Compounds," ed. by H. Gilman, Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 564.

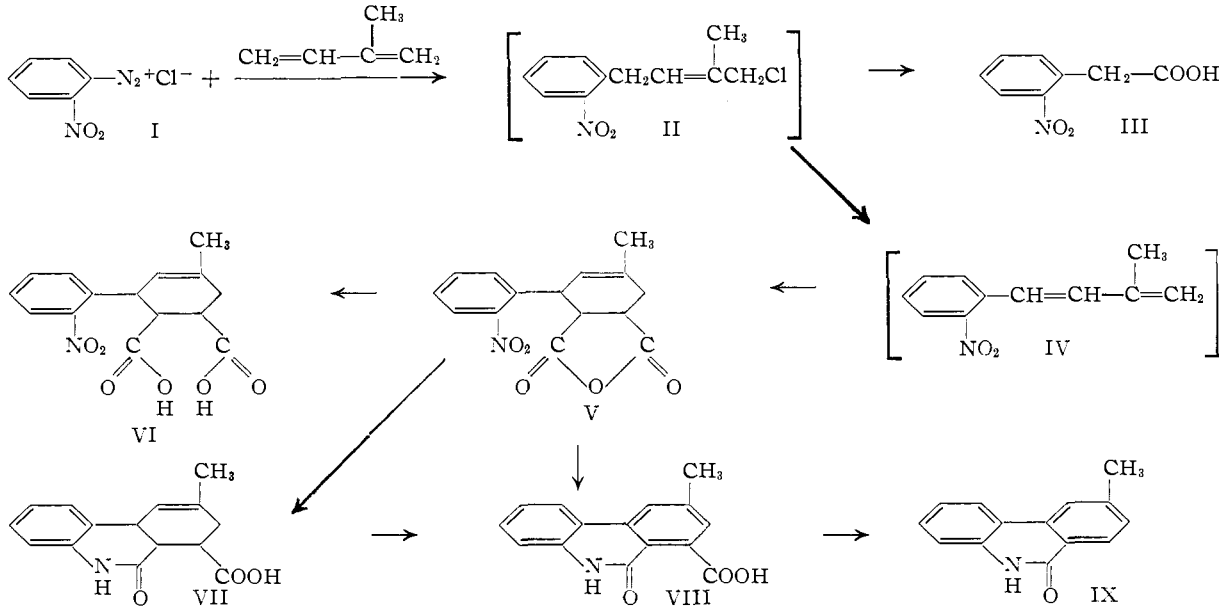
(5) S. Sugasawa, K. Kodama and S. Hara, *J. Pharm. Soc. Japan*, **60**, 138 (1940).

(6) S. Sugasawa and K. Kodama, *Ber.*, **72B**, 675 (1939).

(7) L. H. Mason and W. C. Wildman, THIS JOURNAL, **76**, 6194 (1954).

(8) W. C. Wildman and W. T. Norton, *ibid.*, **76**, 152 (1954).

(9) E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 3113 (1951).



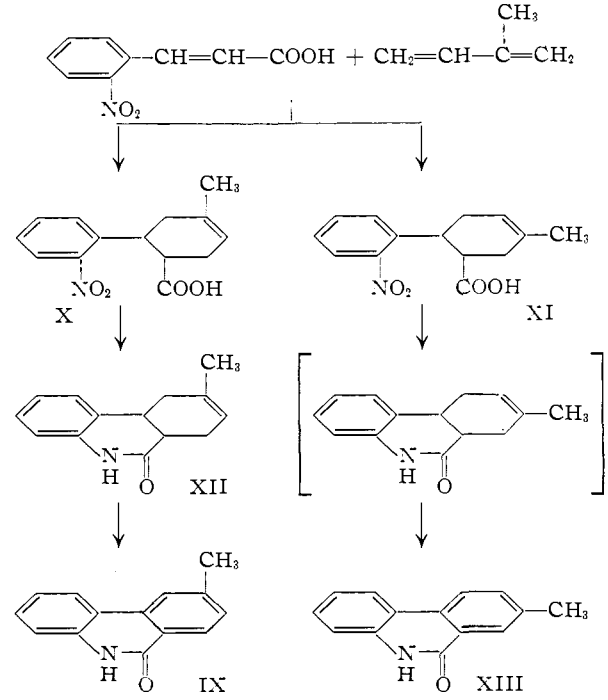
reaction of IV with maleic anhydride yielded 3-(*o*-nitrophenyl)-5-methyl-Δ^4-tetrahydrophthalic anhydride (V), although in very low yield (6%).

Conclusive confirmation for the structure IV assigned to the intermediate diene was obtained by conversion of V to 9-methyl-6(5)-phenanthridinone (IX). Hydrolysis of the anhydride V yielded the dibasic acid VI, which was then reduced with hydrogen and Raney nickel to give 7-carboxy-9-methyl-6a,7,8,10a-tetrahydro-6(5)-phenanthridinone (VII). That the 9,10-double bond in VII was still intact was shown not only by microanalysis but also by the ability of VII to discolor dilute potassium permanganate solution. VII could also be obtained by direct reduction of V under similar conditions, but the yield was poor (25%).

Dehydrogenation of VII with sulfur at 235–255° gave 7-carboxy-9-methyl-6(5)-phenanthridinone (VIII), which was converted in 75% yield to 9-methyl-6(5)-phenanthridinone (IX) by decarboxylation in freshly distilled quinoline in the presence of copper chromite catalyst.

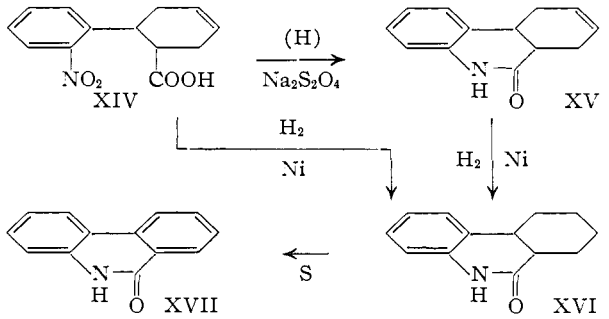
An alternative route to IX was then investigated. The reaction of *o*-nitrocinnamic acid with isoprene at 180–185° for six hours yielded two products, 2-(*o*-nitrophenyl)-4-methyl-Δ^4-tetrahydrobenzoic acid (X) and 2-(*o*-nitrophenyl)-5-methyl-Δ^4-tetrahydrobenzoic acid (XI). The higher melting isomer X, m.p. 183–185°, was readily obtained pure in 23% yield, but the lower melting isomer XI, m.p. 148–152°, was obtained in only 12% yield and its purification was difficult because of contamination with starting material X and decomposition products. Catalytic reduction of X gave 9-methyl-6a,7,10,10a-tetrahydro-6(5)-phenanthridinone (XII). Retention of the 8,9-double bond was confirmed by microanalysis and by the ability of XII to discolor dilute potassium permanganate solution. Dehydrogenation of XII with sulfur at 215–225° yielded 9-methyl-6(5)-phenanthridinone (IX), identical in all respects with the product obtained from II via the previously described reaction sequence. Similarly, catalytic reduction of XI followed by dehydrogenation with palladium-on-charcoal yielded 8-methyl-6(5)-phenanthridinone (XIII).

That the above structural assignments are indeed correct follows from the ensuing argument. The reaction sequence employing the Meerwein reaction between *o*-nitrobenzenediazonium chloride and isoprene could result in a methylphenanthridinone with the methyl group either in the 9- or 10-position. On the other hand, the reaction sequence starting from *o*-nitrocinnamic acid and isoprene led to two isomeric products which must have been 8-methyl-6(5)-phenanthridinone and 9-methyl-6(5)-phenanthridinone. The latter compound (IX) is the only isomer common to both reaction sequences. The identity of the products

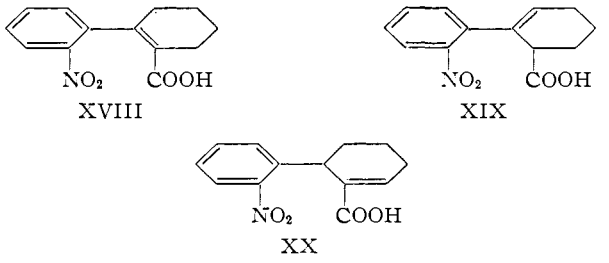


from the two syntheses thus establishes the structure of this product as IX, and at the same time confirms the structure of the second product from the *o*-nitrocinnamic acid—isoprene sequence as XIII.

The second reaction sequence was readily adapted to a new synthesis of 6(5)-phenanthridinone (XVII). Diels–Alder condensation of *o*-nitrocinnamic acid and butadiene yielded 2-(*o*-nitrophenyl)-Δ^4-tetrahydrobenzoic acid (XIV). The optimum yield of XIV obtained was 55%, and the reaction appeared to be sensitive to small variations in the reaction conditions (see Table II). Reduction of XIV with basic sodium hydrosulfite gave 6a,7,10,10a-tetrahydro-6(5)-phenanthridinone (XV) in 62% yield, while reduction of XIV with hydrogen in the presence of Raney nickel yielded the corresponding hexahydro derivative XVI. Catalytic reduction of XV under similar conditions also led to XVI. Dehydrogenation of XVI with sulfur then gave 6(5)-phenanthridinone (XVII) identical with an authentic sample, in an over-all yield of 24% from *o*-nitrocinnamic acid.



The possibility that the isolated double bond in the alicyclic ring in XIV had perhaps migrated to a conjugated position (structures XVIII, XIX or XX) during the Diels–Alder reaction had to be considered, since the condensation was carried out at a high temperature in the presence of an acid.



Structure XVIII can be immediately eliminated, since it was shown that chemical reduction of the adduct XIV yielded a tetrahydrophenanthridinone (XV), m.p. 236–238°, which was obviously not identical with 7,8,9,10-tetrahydro-6(5)-phenanthridinone, m.p. 267–268°,[10] which would have been obtained on reduction of XVIII. Structures XIX and XX (as well as XVIII), can be eliminated by the observation that the ultraviolet absorption spectra of 6a,7,10,10a-tetrahydrophenanthridinone (XV) and hexahydrophenanthridinone (XVI) are essentially identical[11].

(10) B. K. Blount, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 1975 (1929).

TABLE II

REACTION OF *o*-NITROCINNAMIC ACID WITH 1,3-BUTADIENE

Molar ratio of diene to dienophile	Temp., °C.	Time, hours	Yield pure adduct, %
1.25	135–140	20	0
1.52	175–180	19	30
1.92	180	1	0
2.12	170–175	32	50
2.12	190–195	40.5	27
2.70	205–210	4	50
2.70[a]	180	2.5	0
2.88	150	7	0
2.88	180–185	5	51.5
2.88	205	4	49
2.92	190	3	17
3.06	180–185	6	55
1.06[b]	170	0.5	0

[a] Solvent was acetic acid and trifluoroacetic acid; in all other cases, xylene was used as the solvent. [b] Six grams of trifluoroacetic acid was added to the xylene solution; only starting material was recovered.

TABLE III

Compound	λ_{max}	ϵ_{max}
XV	251	7,400
XVI	251	11,100

The *o*-nitrocinnamic acid employed in the above Diels–Adler reactions was prepared by hydrogen peroxide oxidation of *o*-nitrocinnamaldehyde, which was in turn prepared by nitration of cinnamaldehyde.[12] Although the over-all yield in this conversion is only 19%, the reagents are readily available and the final product is easily obtained in a high state of purity.

Experimental[13]

3-(*o*-Nitrophenyl)-5-methyl-Δ^4-tetrahydrophthalic Anhydride (V).—To a solution of 15 g. of cupric chloride dihydrate, 100 ml. of water, 52 g. of sodium acetate trihydrate, 1 l. of acetone and 88 g. of freshly distilled isoprene, cooled to 0°, was added slowly a filtered, ice-cold *o*-nitrobenzenediazonium chloride solution prepared from 133.6 g. of *o*-nitroaniline, 67 g. of sodium nitrite, 175 ml. of water and 175 ml. of concentrated hydrochloric acid. Rapid stirring was maintained during the addition and continued for several hours, while the temperature was maintained at 5°. Gas evolution occurred immediately upon addition of the diazonium solution, and the reaction mixture rapidly turned a deep wine-red color. Excess isoprene and acetone were removed by evaporation under reduced pressure, and the dark brown residue was extracted with 1 l. of ether, the ether extract washed four times with 500-ml. portions of water and then dried over magnesium sulfate. Removal of the ether gave an oil (160 g.) (compound II) which was dissolved in 200 ml. of methanol. With the temperature maintained below 30° and with constant stirring, a solution of 50 g. of potassium hydroxide in 160 ml. of methanol was slowly added. The resulting mixture was then heated for 50 minutes at 30–40°. Potassium chloride (32.5 g.) was removed by filtration and the filtrate was diluted with 600

(11) Since no migration of the isolated double bond in XIV occurred, it is assumed that no migration took place in the Diels–Alder adducts V, X and XI, and that the structures indicated are indeed correct. This assumption would appear justifiable, since the isolated double bond in XIV is stabilized through hyperconjugation by only four hydrogens, while the isolated double bond in V, X and XI is stabilized in each case by seven hydrogens.

(12) W. H. Mills and P. E. Evans, *J. Chem. Soc.*, **117**, 1035 (1920).

(13) All melting points are corrected. The microanalyses were carried out by Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth.

ml. of water and then extracted with two 300-ml. portions of ether. The dried extracts were evaporated to give 114 g. of a red oil (compound III) which was treated directly with 30 g. of maleic anhydride. The mixture was heated on a steam-bath for 15 minutes and then cooled at 0° overnight. On addition of the resulting oil to 300 ml. of ether, the adduct separated as well-formed needles. Recrystallization from a mixture of benzene and petroleum ether yielded 17.2 g. (6.2%, based on *o*-nitroaniline) of yellow needles, m.p. 131–132°.

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.79; H, 4.62; N, 4.79.

Ozonolysis of II to *o*-Nitrophenylacetic Acid.—Ten grams of the crude oil (compound II) obtained from the reaction of *o*-nitrobenzenediazonium chloride with isoprene (see above) was dissolved in 80 ml. of ethyl bromide, the solution cooled with Dry Ice, and a stream of 5% ozone in oxygen passed in. After five hours, the reaction was stopped and the ethyl bromide distilled off below 15° under reduced pressure. The ozonide obtained in this manner was a clear, light yellow, viscous oil. To it was added a cooled solution of 30 ml. of 30% hydrogen peroxide, 15 ml. of concentrated hydrochloric acid and 25 ml. of water, and the mixture was heated under reflux for 12 hours. The cooled reaction mixture was then extracted with ether, the ether extracts washed with saturated sodium bicarbonate solution, and the bicarbonate wash acidified with hydrochloric acid. Extraction of this solution with ether and removal of the ether yielded a small amount of a brown solid, m.p. 135–139°. Recrystallization from aqueous ethanol with the use of charcoal yielded pale yellow needles, m.p. 139–141°, which did not depress the melting point of an authentic sample of *o*-nitrophenylacetic acid, m.p. 139–141°.

3-(*o*-Nitrophenyl)-5-methyl-Δ^4-tetrahydrophthalic Acid (VI).—A solution of 17.75 g. of 3-(*o*-nitrophenyl)-5-methyl-Δ^4-tetrahydrophthalic anhydride (V) in 100 ml. of 6% sodium hydroxide was heated for one hour on a steam-bath, cooled and then acidified to *p*H 1 with 50% sulfuric acid. The solid which separated was collected by filtration and recrystallized from aqueous ethanol to give 16.96 g. (90%) of pale yellow crystals, m.p. 232.5–234.5° dec.

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.27; H, 4.84; N, 4.60.

7-Carboxy-9-methyl-6a,7,8,10a-tetrahydro-6(5)-phenanthridinone (VII).—A solution of 16.96 g. of 3-(*o*-nitrophenyl)-5-methyl-Δ^4-tetrahydrophthalic acid (VI) in 120 ml. of purified dioxane was hydrogenated for two hours under three atmospheres of hydrogen, using Raney nickel as catalyst. Removal of the catalyst, followed by dilution of the reaction mixture with 200 ml. of water and evaporation of the dioxane under diminished pressure, caused the separation of 12.1 g. (85%) of a colorless solid. Recrystallization from aqueous ethanol yielded the product in the form of glistening, colorless platelets, m.p. 274–275° dec.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 69.88; H, 5.68; N, 5.48.

Reduction of V under similar conditions yielded 7-carboxy-9-methyl-6a,7,8,10a-tetrahydro-6(5)-phenanthridinone directly, although only in 25% yield.

7-Carboxy-9-methyl-6(5)-phenanthridinone (VIII).—An intimate mixture of 7.93 g. of 7-carboxy-9-methyl-6a,7,8,-10a-tetrahydro-6(5)-phenanthridinone (VII) and 15 g. of sulfur was heated to 235–255° for 75 minutes. The cooled solid was ground to a powder in a mortar and extracted with 100 ml. of boiling carbon disulfide. Recrystallization of the residue from glacial acetic acid, with the use of charcoal, yielded 3.0 g. (38.5%) of a pale yellow solid, m.p. 322–325° dec.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.02; H, 4.34; N, 5.72.

9-Methyl-6(5)-phenanthridinone (IX). (Method A).—A mixture of 1 g. of 7-carboxy-9-methyl-6(5)-phenanthridinone (VIII), 0.46 g. of copper chromite catalyst and 10 ml. of freshly-distilled quinoline was heated at 230° until gas evolution ceased. The cooled reaction mixture was then diluted with 50% ethanol and the precipitated solids collected by filtration and extracted with hot dimethylformamide. Addition of water to the dimethylformamide extract yielded 0.25 g. of a gray-white solid, m.p. 268–270° dec. An additional 0.37 g. of product, m.p. 265–268° dec., was obtained by acidification of the quinoline filtrate above; total yield, 0.62 g. (75%). Recrystallization of the product from aqueous dimethylformamide yielded long, white needles, m.p. 272.5–273.5°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.40; H, 5.08; N, 6.65.

***o*-Nitrocinnamic Acid.**—A mixture of 11.0 g. of *o*-nitrocinnamaldehyde,[11] 20 ml. of 30% hydrogen peroxide and 75 ml. of glacial acetic acid was heated on a steam-bath for 50 minutes. The reaction mixture was then cooled and the solid collected by filtration and recrystallized from aqueous acetic acid; yield 7.0 g. (58%), m.p. 244–246°. *o*-Nitrocinnamic acid is reported to melt at 243–245°.[14]

2-(*o*-Nitrophenyl)-4-methyl-Δ^4-tetrahydrobenzoic Acid (X).—A mixture of 10 g. of *o*-nitrocinnamic acid, 7.0 g. of isoprene and 50 ml. of dry xylene was heated in a sealed Pyrex ampoule at 180–184° for eight hours. Filtration of the cooled bomb contents yielded 10.3 g. of a beige-colored solid, m.p. 158–165°. Extraction of the solid with acetone removed the isomeric 5-methyl compound (see below) and left 3.09 g. (23%) of light yellow crystals, m.p. 183–185°, which were recrystallized from hot acetone.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.70; N, 5.26. Found: C, 64.63; H, 5.92; N, 5.48.

2-(*o*-Nitrophenyl)-5-methyl-Δ^4-tetrahydrobenzoic Acid (XI).—Addition of petroleum ether to the acetone extract of the crude Diels–Alder product obtained above yielded a light tan solid which was purified by repeated recrystallization from acetone and petroleum ether to give 1.60 g. (12%) of tan crystals, m.p. 148–152°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.70; N, 5.26. Found: C, 64.61; H, 5.89; N, 5.54.

9-Methyl-6a,7,10,10a-tetrahydro-6(5)-phenanthridinone (XII).—A solution of 2.43 g. of 2-(*o*-nitrophenyl)-4-methyl-Δ^4-tetrahydrobenzoic acid (X) in 100 ml. of purified dioxane was shaken under four atmospheres pressure of hydrogen in the presence of 2 ml. of Raney nickel catalyst for a period of six hours. After removal of the catalyst by filtration, the solution was concentrated to 25 ml. under reduced pressure and 100 ml. of water added to give 1.77 g. (89%) of a pale pink, fluffy solid, m.p. 212–217°. Sublimation at 160° (0.05 mm.) raised the melting point to 220–223°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.96; H, 7.10; N, 6.72.

9-Methyl-6(5)-phenanthridinone (IX). (Method B).—An intimate mixture of 0.76 g. of 9-methyl-6a,7,10,10a-tetrahydro-6(5)-phenanthridinone (XII) and 1.50 g. of sulfur was heated at 215–225° for one hour. The cooled fusion mixture was ground to a powder and extracted overnight with carbon disulfide. Recrystallization of the insoluble residue (0.55 g. (74%), m.p. 260–270°) from aqueous dimethylformamide with the use of charcoal gave long, white needles, m.p. 272.5–273.5°. A mixture melting point determination and comparison of infrared spectra showed this product to be identical with 9-methyl-6(5)-phenanthridinone prepared as described above from *o*-nitrobenzenediazonium chloride and isoprene.

8-Methyl-6(5)-phenanthridinone (XIII).—A solution of 1.01 g. of 2-(*o*-nitrophenyl)-5-methyl-Δ^4-tetrahydrobenzoic acid (XI) in 20 ml. of purified dioxane was shaken with hydrogen in the presence of Raney nickel at three atmospheres pressure for two hours. After removal of the catalyst by filtration, the reaction mixture was diluted with water to give a white, crystalline solid which was purified by sublimation at 150° (0.05 mm.). The white sublimate (0.46 g., m.p. 215–220°) was mixed with 0.30 g. of 30% palladium-on-charcoal and heated at 210° for ten hours. The product was sublimed from the mixture at 210° (0.05 mm.), recrystallized once from 95% ethanol and sublimed again to give white needles, m.p. 218–219°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 79.84; H, 5.12; N, 6.77.

2-(*o*-Nitrophenyl)-Δ^4-tetrahydrobenzoic Acid (XIV).—A mixture of 14 g. of *o*-nitrocinnamic acid, 12.0 g. of 1,3-butadiene, 0.14 g. of hydroquinone and 55 ml. of xylene was heated in a sealed Pyrex ampoule at 180–185° for six hours. The dark brown crystals which separated from the cooled reaction mixture were collected, dissolved in 500 ml. of acetone containing 5 g. of charcoal and heated under reflux for 15 hours. Removal of the charcoal, concentration to

(14) Tanascescu, *Bull. soc. chim.*, [4] **41**, 1075 (1927).

about 100 ml. and cooling caused the separation of some unreacted *o*-nitrocinnamic acid. Further concentration yielded some additional *o*-nitrocinnamic acid (total recovery, 1.3 g.). Continued concentration then yielded the crystalline adduct XIV, which was collected by filtration, washed with 95% ethanol and recrystallized from acetone to give 8.9 g. (55% based on *o*-nitrocinnamic acid, corrected for recovered material). The product was purified readily by sublimation at 170° (0.3 mm.), m.p. 187–188°.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.42; H, 5.43; N, 5.64.

6a,7,10,10a-Tetrahydro-6(5)-phenanthridinone (XV).—A mixture of 5 g. of 2-(*o*-nitrophenyl)-Δ^4-tetrahydrobenzoic acid, 17.5 g. of sodium hydrosulfite and 100 ml. of 10% sodium hydroxide solution was heated under reflux for 70 minutes and then acidified with glacial acetic acid. The colorless product (2.3 g.) was collected and sublimed at 205° (0.08 mm.), m.p. 231–236°. The above filtrate was evaporated to dryness and the residue extracted with ether in a Soxhlet apparatus for eight hours. Evaporation of the ether yielded an additional 0.15 g. of product; total yield, 2.5 g. (62%). The product was purified by sublimation, m.p. 235.5–237.5°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.57; H, 6.47; N, 7.02.

6a,7,8,9,10,10a-Hexahydro-6(5)-phenanthridinone (XVI).—A solution of 2.47 g. of 2-(*o*-nitrophenyl)-Δ^4-tetrahydrobenzoic acid in 100 ml. of purified dioxane was shaken with four atmospheres of hydrogen in the presence of Raney nickel at room temperature for 13.5 hours. Removal of the catalyst by filtration and dilution of the filtrate with 200 ml. of water caused the separation of 1.64 g. of product, m.p. 226–227°. Concentration of the filtrate to about 100 ml. yielded an additional 0.11 g. of crude product. Sublimation of the combined material at 210° (0.5 mm.) then yielded 1.69 g. (84%) of white crystals, m.p. 226–228°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.96. Found: C, 77.75; H, 7.43; N, 7.09.

Reduction of 6a,7,10,10a-tetrahydro-6(5)-phenanthridinone (XV) under similar conditions yielded XVI in 90% yield.

6(5)-Phenanthridinone (XVII).—An intimate mixture of 1.44 g. of 6a,7,8,9,10,10a-hexahydro-6(5)-phenanthridinone and 3.0 g. of sulfur was heated for one hour at 170–180°, for another hour at 225–230°, and finally at 250° for 30 minutes. After cooling, the solid mass was powdered and extracted with 100 ml. of boiling carbon disulfide. The insoluble residue was purified by sublimation at 230° (0.5 mm.) to give 0.71 g. (51%) of pure 6(5)-phenanthridinone, m.p. 290–293°, identical in all respects with an authentic sample.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Synthesis of Pyrimido[4,5-*b*]quinolines[1-3]

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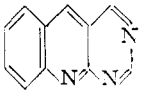
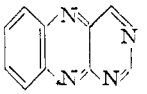
A number of pyrimido[4,5-*b*]quinolines (I) of interest because of structural similarity to the flavins have been prepared by four independent routes which are described in detail. Method I involves the cyclization of 2-aminoquinoline-3-carboxamide with reagents such as formamide, acetic anhydride, phenyl isocyanate, phenyl isothiocyanate and diethyl carbonate to give a variety of 4-hydroxypyrimido[4,5-*b*]quinolines. Method 2 involves the cyclization of 2-amino-3-cyanoquinoline with reagents such as ammonia, urea and formamide to give derivatives of 4-aminopyrimido[4,5-*b*]quinoline. Method 3 involves preliminary reduction of 2-amino-3-cyanoquinoline to 2-amino-3-aminomethylquinoline, followed by cyclization with a variety of reagents to a series of 3,4-dihydropyrimido[4,5-*b*]quinolines. Method 4 involves the synthesis and subsequent nucleophilic displacement reactions of 2,4-dichloropyrimido[4,5-*b*]quinoline.

Relatively little has been reported on the synthesis and properties of pyrimido[4,5-*b*]quinolines, although this system (I) is of interest because of its structural similarity to the pyrimido[4,5-*b*]quinoxaline ring system (II) of the naturally-occurring flavins. Most of the known pyrimido[4,5-*b*]quinolines were prepared by the condensation of barbi-

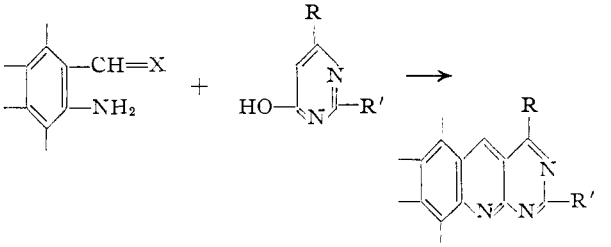


I



II

turic acid with *o*-aminobenzaldehydes[5-8] and with *o*-aminobenzilidinetoluidines,[9] and the reaction has been extended to include the condensation of *o*-aminobenzaldehyde with a number of pyrimidine derivatives related to barbituric acid.[8] An alternative route to these compounds involved the condensation of barbituric acid with isatin and N-



methylisatin to give 3,3-di-(5-barbituryl)-oxindole and its N-methyl derivative, followed by cyclization of these intermediates with acid to give 2,4-dihydroxypyrimido[4,5-*b*]quinoline-5-carboxylic acid and the 10-methyl derivative, respectively. Standard transformations operating on the 5-carboxylic acid group provided a number of additional derivatives.[10]

In all these synthetic procedures, the pyrimidine ring of the product was constructed from a pre-

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(2) Taken in part from the doctoral dissertation of N.W.K., University of Illinois, 1955.

(3) Presented before the Division of Medicinal Chemistry of the 128th National ACS Meeting, September, 1955, in Minneapolis, Minnesota.

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