[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XVII. SOME 5-SUBSTITUTED DERIVATIVES

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Substitution of a group such as chloro or methyl on the 5-position of the 4-quinazolone moiety of the Hydrangea alkaloid has been found to have a favorable effect on the activity and the chemotherapeutic index (1, 2). In order to exploit this lead the fluoro, iodo, ethyl, propyl, trifluoromethyl, nitro, acetamino, methylthio, and methylsulfonyl groups were introduced into the 5-position.

The fluoro derivative had an index and activity[1] about the same as the 5-Cl, whereas the iodo had a very low activity and index. When the methyl group was replaced by the larger ethyl or propyl groups the activity decreased in that order. These data indicate that a large group has an unfavorable action. However, trifluoromethyl had the highest index, 15, yet observed in analogs of the alkaloid, although the quinine coefficient was decreased to 35.

These compounds were all prepared by condensation of the appropriately substituted 4-quinazolone with the blocked side chain, 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine, followed by two-stage hydrolysis of the blocking groups as previously described (3).

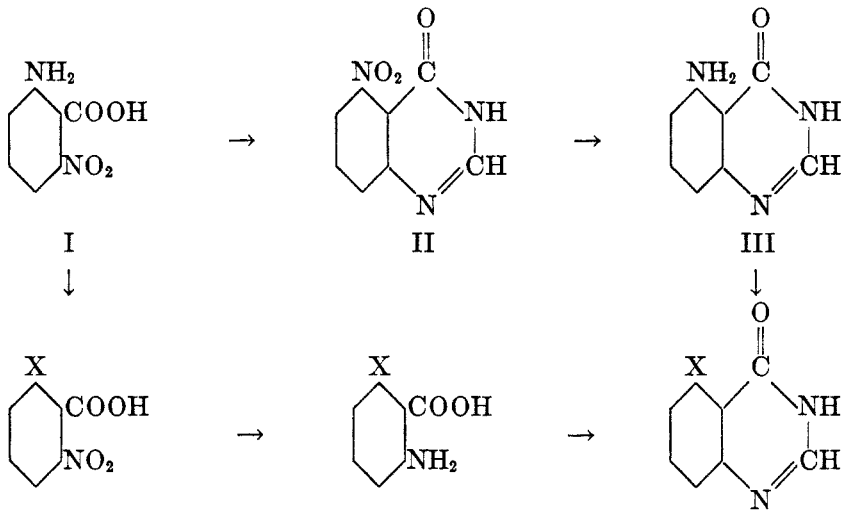
Six of the requisite 4-quinazolones were synthesized from the known 5-nitro-4-quinazolone (4) *via* the readily available 6-nitroanthranilic acid (I) (5). 6-Iodo-2-nitrobenzoic acid (IV) was obtained in good yield from I, but all attempts to reduce this compound chemically or catalytically to 6-iodoanthranilic acid (VII) were unsuccessful. The steps were then reversed by reduction of 6-nitro-2-formylaminobenzoic acid (VI) to VIII. Attempted replacements of the amino group with iodo through the diazonium salt were unsuccessful. The diazonium salt from I when treated with potassium ethyl xanthate gave 2-nitro-6-methylthiobenzoic acid (V) in low yield after methylation.

All of the above difficulties were surmounted by the use of the diazonium salt from 5-amino-4-quinazolone (III). The 5-iodo derivative, IX, was obtained in 59% yield by treatment with potassium iodide. The 5-methylthio derivative (XI) was obtained with sodium methyl mercaptide in 71% yield and was oxidized to the sulfone, XII, with permanganate in dilute acetic acid. The use of sodium thiophenoxide gave XIII, but the procedure could not always be duplicated. The 5-fluoro derivative offered some difficulty since the diazonium fluoroborate was water-soluble. However, the diazonium fluoroborate could be isolated when the diazotization was carried out in 42% fluoroboric acid (6) to give an over-all yield of 56% of IX after pyrolysis in xylene.

3-Nitrophthalic acid appeared attractive as a starting material for 5-ethyl- (XXIII) and 5-propyl-4-quinazolone (XXXIII). α-Methyl hydrogen 3-nitro-

[1] The biological data will be reported elsewhere by Dr. R. Hewitt and co-workers (1).

phthalate (5) was converted to the acid chloride and condensed with magnesio malonic ester to give the keto malonate, XV. Presumably, higher alkyl groups could be obtained by use of alkylmalonic esters. Dilute hydrochloric acid hydrolysis gave a mixture of 2-nitro-6-acetobenzoic acid (XVI) and its methyl ester, XVII. Catalytic reduction of the acid afforded 6-acetoanthranilic acid (XX). Attempts to reduce the carbonyl to 6-ethylanthranilic acid (XXIV) by Raney alloy and alkali (7) or the Clemmenson method were unsuccessful, decarboxylation taking place in both cases. Wolf-Kishner reduction (9) led to a high-melting by-product as the only product isolatable.



I, II, III

IV, X = I
V, X = CH_3S—
VI, X = HCONH—

VII, X = I
VIII, X = HCONH—

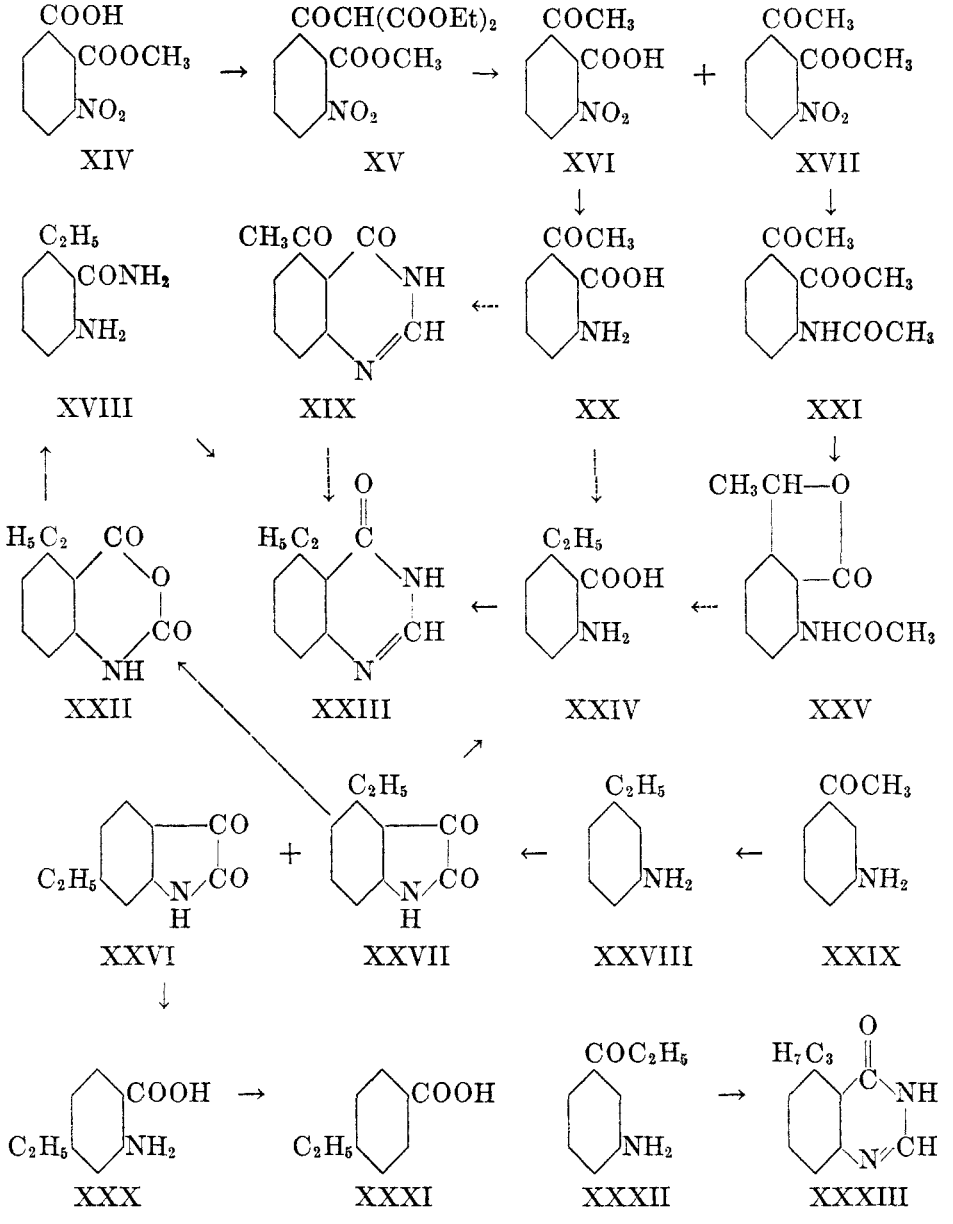
IX, X = F
X, X = I
XI, X = CH_3S—
XII, X = CH_3SO_2—
XIII, X = C_6H_5S—

Attempted conversion of XX to 5-aceto-4-quinazolone by fusion with formamide under the usual conditions (8) failed to give a solid product. This, perhaps, may have been due to the keto acid existing in the pseudo form.

Catalytic reduction of the ester, XVII, followed by acetylation gave XXI. High pressure hydrogenation of the latter with a copper chromite catalyst at 150–200° stopped with the uptake one mole of hydrogen. The product was the lactone, XXV, instead of the expected methyl N-acetyl-6-ethylanthranilate. This lactone was resistant to hydrogenolysis with a platinum or palladium catalyst in neutral or acid solution.

The isatin synthesis (2) was then investigated. Reduction of *m*-aminoacetophenone by the Huang-Minlon modification of the Wolf-Kishner method (9) proceeded smoothly to *m*-ethylaniline (XXVIII) in 80% yield. The amine was converted to *m*-ethyl-α-isonitrosoacetanilide and cyclized to a mixture of the isatins, XXVI and XXVII. These isatins were readily separated by acidifying

an alkaline solution of the mixture with acetic acid (10), the 4-ethylisatin (XXVII) precipitating as expected. Strong acidification with hydrochloric acid gave 6-ethylisatin (XXVI). The structure of the latter was proven unequivocally



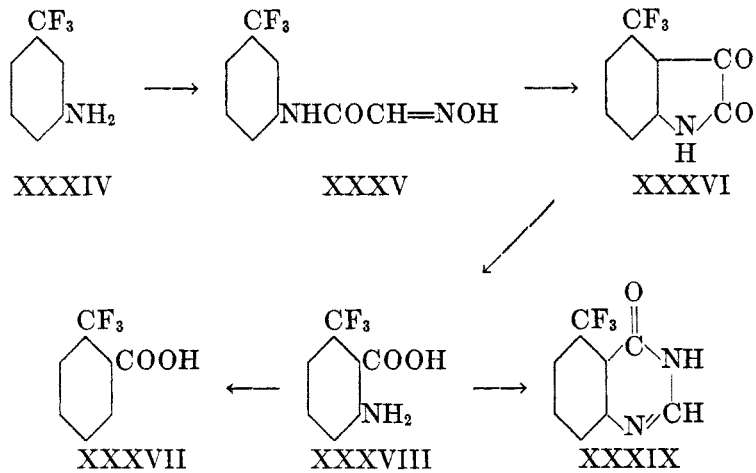
by oxidation to 4-ethylanthranilic acid (XXX) and deamination to the known *p*-ethylbenzoic acid (XXXI).

Peroxide oxidation of 4-ethylisatin (XXVII) gave 6-ethylanthranilic acid

(XXIV) in good yield, m.p. 97–99° with decarboxylation. This compound was not readily purified. It failed to give 5-ethyl-4-quinazolone on fusion with formamide (8) probably due to the fact that the initial fusion temperature is 30° higher than the decarboxylation temperature. This difficulty was circumvented by chromic acid oxidation of the isatin, XXVII, to the stable 4-ethylisatoic anhydride (XXII). The latter on treatment with ammonia in aqueous acetone formed the amide, XVIII, which was converted to the desired 5-ethyl-4-quinazolone (XXIII) by heating in formic acid.

m-Aminopropiophenone (XXXII), obtained readily from propiophenone in two steps, afforded 5-propyl-4-quinazolone (XXXIII) in the same fashion as 5-ethyl-4-quinazolone (XXIII) was obtained.

m-Trifluoromethylaniline (XXXIV) was converted to the isonitrosoacetanilide (XXXV) and cyclized to the isatin, XXXVI, with 96% sulfuric acid. Surprisingly, only one isatin was formed in this ring closure, in contrast to all the other un-



symmetrical isonitroso compounds which have always given both isomers, though in varying ratios (2, 10, 17, 18). Fortunately, the one isatin obtained[2] was the desired 4-trifluoromethyl derivative, XXXVI, as shown by oxidation to the anthranilic acid, XXXVIII, and deamination to the known *o*-trifluorobenzoic acid (XXXVII) (19). The anthranilic acid, XXXVIII, was converted to 5-trifluoromethyl-4-quinazolone by formamide fusion (8).

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EXPERIMENTAL

2-Nitro-6-iodobenzoic acid. To a solution of 1.8 g. of 6-nitroanthranilic acid (5) and 0.53 g. of anhydrous sodium carbonate in 10 cc. of water was added 0.76 g. of sodium nitrite.

[2] After this work was complete Maginnity and Gaulin (20) ran this same sequence and also obtained only 4-trifluoromethylisatin, but proved the structure in a different manner.

The solution was cooled to 3°, then poured on a mixture of 8.4 cc. of concentrated hydrochloric acid and 12 g. of ice with stirring. The solution was allowed to stand in an ice-bath for 90 minutes. After the excess nitrous acid was destroyed with urea, the solution was poured into a solution of 6.6 g. of potassium iodide in 12 cc. of water. Nitrogen was evolved and an oil separated. The mixture was heated on the steam-bath for a few minutes when the oil solidified. The red color was removed by the addition of sodium bisulfite. The mixture was kept at 3° overnight, then the product was collected; yield, 2.3 g. (80%), m.p. 181–183°. If the amount of hydrochloric acid was $\frac{1}{2}$ or $\frac{1}{4}$ of the above amount, the yields dropped to 68% and 24%, respectively.

Rule and Smith (11) record m.p. 188–189° and a 77% yield when the diazotization was carried out in fuming nitric acid by the addition of sodium metabisulfite.

Attempts to reduce the nitro group to form 6-iodoanthranilic acid were unsuccessful. Catalytic hydrogenation in alcohol with a platinum oxide catalyst was incomplete and dark tars resulted. The standard iron-water reduction with a trace of acid eliminated the iodo group. Reduction with ammoniacal ferrous sulfate, the procedure used by Wheeler and Johns (12) for 2-nitro-4(and 5)-iodobenzoic acid, gave tars.

2-Nitro-6-methylmercaptobenzoic acid (V). The diazonium solution from 1.8 g. of 6-nitroanthranilic acid prepared as in the preceding experiment using 4.2 cc. of concentrated hydrochloric acid was added dropwise with stirring over a period of five minutes to a solution of 1.8 g. of potassium ethyl xanthate and 5.3 g. of anhydrous sodium carbonate in 20 cc. of water at 70°. To the solution was added 10 cc. of 10% sodium hydroxide. After being refluxed three hours, the solution was cooled and stirred with 1.3 cc. of methyl sulfate for 30 minutes. Acidification gave a semi-solid which was crystallized from ethyl acetate-heptane to give 0.6 g. (28%) of crude product, m.p. 142–145°. Several recrystallizations from toluene gave white crystals of constant m.p. 176–177°.

Anal. Calc'd for $C_8H_7NO_4S$: N, 6.57. Found: N, 6.42.

2-Formylamino-6-nitrobenzoic acid (VI). To 2 g. of 6-nitroanthranilic acid was added 20 cc. of 90% formic acid and 6.6 cc. of acetic anhydride. The solution was heated on the steam-bath for one hour, then evaporated to dryness *in vacuo* leaving a quantitative yield of yellow crystals, m.p. 173–175° dec. Recrystallization from ethyl acetate-heptane raised the m.p. to 184–185° dec.

Anal. Calc'd for $C_8H_6N_2O_5$: C, 45.8; H, 2.88; N, 13.3.
Found: C, 45.9; H, 3.14; N, 13.6.

6-Formylaminoanthranilic acid (VIII) *hydrochloride*. A solution of 5.4 g. of 2-formylamino-6-nitrobenzoic acid (VI) in 100 cc. of alcohol was added to a suspension of 0.5 g. of 10% palladium-charcoal in 5 cc. of Methyl Cellosolve. The mixture was shaken with hydrogen at 2–3 atm. and reduction was complete in five minutes. To the filtered solution was added 5 cc. of 12 *N* hydrochloric acid. Evaporation to dryness *in vacuo* gave a quantitative yield of nearly white crystals which decomposed at 210–230° without melting. For analysis a sample was recrystallized several times from methanol-ether.

Anal. Calc'd for $C_8H_8N_2O_3 \cdot HCl \cdot 2H_2O$: C, 38.0; H, 5.18.
Found: C, 37.8, 37.8; H, 5.17, 5.08.

If the hydrochloric acid was omitted before evaporation, deep coloration took place and the yield was considerably decreased.

Attempted diazotization of this compound in dilute hydrochloric acid by the addition of sodium nitrite and the sodium salt in water to dilute hydrochloric acid or with butyl nitrite and hydrogen chloride on the acid in methanol failed to take place. Deep red solutions were formed which evolved no nitrogen when added to aqueous potassium iodide.

5-Nitro-4-quinazolone (II). A mixture of 75 g. of 6-nitroanthranilic acid and 64 cc. of formamide was heated in a bath at 130–135° for 45 minutes, then at 160° for seven hours. The cooled residue was ground in a mortar with methanol; yield, 53.5 g. (68%) of orange-brown crystals, m.p. 244–246°. In a 15-g. run it only was necessary to run the reaction at 160–165° for four hours when it was complete; yield, 11.7 g. (75%), m.p. 248–252°.

This is a modification of the method of Bogert (4), who recorded m.p. 255–256° dec.

5-Amino-4-quinazolone (III). A mixture of 25 g. of II, 250 cc. of Methyl Cellosolve, and 2 g. of 10% palladium-charcoal was shaken with hydrogen at 2–3 atm. until reduction was complete (one hour). The filtered solution was evaporated to dryness *in vacuo* leaving 19.6 g. (99%) of nearly white crystals, m.p. 225–227°.

Bogert (13) employed the less convenient stannous chloride and recorded m.p. 235–236°.

5-Acetamino-4-quinazolone. A mixture of 3.0 g. of 5-amino-4-quinazolone and 60 cc. of acetic anhydride was refluxed 25 minutes, solution being complete in ten minutes. The solution was evaporated to dryness *in vacuo*. The residual acetate salt was heated on the steam-bath with 15 cc. of water, then cooled to give 3.0 g. (79%) of white needles, m.p. 286–287°.

Bogert (13) recorded m.p. 285–286°, but gave no yield or experimental details.

5-Iodo-4-quinazolone (IX). A warm solution of 3.0 g. of III in 60 cc. of water and 6.8 cc. of 12 *N* hydrochloric acid was cooled in an ice-salt bath which caused the hydrochloride salt to separate. After the slow addition of 1.43 g. of sodium nitrite with shaking, the red solution was allowed to stand in the ice-bath for one hour. The excess nitrous acid was destroyed with urea. The diazonium solution was poured in a thin stream into a solution of 12.5 g. of potassium iodide in 24 cc. of water, then the solution was heated on the steam-bath for a few minutes until nitrogen evolution was complete. The cooled solution deposited 5 g. of the red hydriodide salt (m.p. 298–301° dec.) which was collected and washed with a little ice-water. The solid was dissolved in excess 5% sodium hydroxide and the solution acidified to *p*H 4 with acetic acid; yield, 3.0 g. (59%), m.p. 265–267°. Recrystallization from Methyl Cellosolve and water with the aid of Norit gave white crystals, m.p. 268–270°.

Anal. Calc'd for $C_8H_5IN_2O$: N, 10.3. Found: N, 10.3.

An attempt to prepare this compound from 5-chloro-4-quinazolone by refluxing in Cellosolve with sodium iodide and copper-bronze for three hours resulted in no reaction.

5-Methylthio-4-quinazolone (XI). The cold diazonium solution from 10 g. of 5-amino-4-quinazolone, prepared as described in the previous experiment, was added in a thin stream to a stirred solution of 4 cc. of methanethiol in 150 cc. of water containing 35 g. of potassium hydroxide. The temperature was maintained at 40–50° during the addition and for one hour more, then it was raised to 70° for ten minutes. The warm solution was acidified with acetic acid and allowed to stand overnight to complete crystallization; yield, 8.4 g., (71%), m.p. 256–258°. Several recrystallizations from 25% alcohol gave white crystals, m.p. 271–272°.

Anal. Calc'd for $C_9H_8N_2OS$: C, 56.3; H, 4.20; N, 14.6.
Found: C, 56.7; H, 4.46; N, 14.2.

Replacement of the methanethiol with 0.72 cc. of benzenethiol for a run employing 1 g. of III gave a crude solid which was thoroughly washed with benzene; yield, 0.45 g. (28%) of *5-phenylmercapto-4-quinazolone* (XIII), m.p. 243–245°. Recrystallization from 30% alcohol with the aid of Norit gave white crystals, m.p. 250–252°.

Anal. Calc'd for $C_{14}H_{10}N_2OS$: C, 66.2; H, 3.97; N, 11.1.
Found: C, 66.1; H, 4.18; N, 11.0.

Two attempts to duplicate this reaction on a 10-g. scale gave amorphous red products from which the desired product could not be isolated.

5-Methylsulfonyl-4-quinazolone (XII). To a stirred mixture of 3 g. of XI and 90 cc. of acetic acid at 40–45° was added a solution of 6.8 g. of potassium permanganate in 60 cc. of water over a period of 70 minutes. The mixture was stirred 30 minutes longer without application of heat, then it was treated with sufficient solid sodium bisulfite to dissolve the manganese dioxide. The yellow solution was evaporated to dryness *in vacuo* and cooled. The solid was washed three times with ice-water to remove inorganic salts; yield, 1.9 g. (54%), m.p. 274–277°. Recrystallization of a sample from absolute alcohol gave white crystals, m.p. 275–276°.

Anal. Calc'd for $C_9H_8N_2O_3S$: C, 48.2; H, 3.58; N, 12.5.
Found: C, 48.2; H, 3.85; N, 12.3.

5-Fluoro-4-quinazolone (IX). To a stirred solution of 6 g. of III in 71 cc. of 42% fluoroboric acid cooled in an ice-bath was added 2.8 g. of sodium nitrite in 4.5 cc. of water in

portions maintaining the temperature at 0–5°. The solution was stirred 30 minutes longer in the ice-bath, then it was diluted with 71 cc. of cold absolute alcohol and 50 cc. of cold ether. The diazonium fluoroborate contaminated with inorganic salts was collected and washed with 1:1 absolute alcohol-ether; wt., 11.4 g., m.p. 130–135° dec.

A mixture of 10 g. of the diazonium fluoroborate and 200 cc. of xylene was refluxed with stirring on a heating mantle for ten minutes. The solid melted with gas evolution to an insoluble brown tarry mass which solidified on cooling. The solid was collected and dried, then shaken with 100 cc. of water and sufficient hydrochloric acid was added to give a 1 *N* acid solution. Some insoluble material was removed by filtration. The filtrate was brought to *p*H 5 with sodium bicarbonate, then extracted with five 15-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate, and clarified with Norit, were evaporated to dryness *in vacuo* leaving 3.0 g. (56%) of product, m.p. 213–215° dec. Several recrystallizations from ethyl acetate gave white crystals, m.p. 225–227°.

Anal. Calc'd for $C_8H_5FN_2O$: C, 58.5; H, 3.08; N, 17.1.

Found: C, 58.5; H, 3.38; N, 17.1.

2-Carbomethoxy-3-nitrobenzoic acid (XIV). 3-Nitrophthalic acid (100 g.) was heated in a bath at 230–235° until water was no longer evolved (75 minutes). The cooled anhydride was refluxed with 240 cc. of methanol for three hours, then evaporated to dryness *in vacuo*. The residue was dissolved in hot ethyl acetate and crystallized by the addition of heptane; yield, 68.7 g. (65%), m.p. 151–152° and 144–147° in two crops.

The filtrate was evaporated to dryness *in vacuo* and the residue was heated on the steam-bath for two hours with 150 cc. of 10% sodium hydroxide. Acidification gave 35 g. (35%) of recovered diacid, m.p. 216–218° (sealed tube).

This procedure is a simplification of that described by Kahn (5) who recorded a crude yield of 83% from the anhydride; m.p. 150°.

The *anilide ester*, prepared *via* the acid chloride in 67% yield, formed white crystals from absolute alcohol, m.p. 147–148°.

Anal. Calc'd for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.00; N, 9.34.

Found: C, 59.7; H, 4.23; N, 9.45.

Ethyl 2-carbomethoxy-3-nitrobenzoylmalonate (XV). A mixture of 48.4 g. of XIV and 96 cc. of thionyl chloride was refluxed on the steam-bath for 30 minutes when gas evolution was complete, then it was evaporated to dryness *in vacuo* (bath 55°). The residue was dissolved in 110 cc. of toluene and the evaporation repeated. The residual acid chloride (m.p. 67–69°), dissolved in 145 cc. of toluene, was added dropwise over 25 minutes to the vortex of a stirred solution of 102 cc. of ethyl malonate and 48.4 g. of magnesium methoxide in 200 cc. of toluene cooled by a 20°-bath. The mixture was stirred 45 minutes more, then it was acidified with 50 cc. of acetic acid and stirred with 175 cc. of 3 *N* hydrochloric acid for a few minutes until the color changed from orange to white. The separated organic layer was washed twice with water, and evaporated to dryness *in vacuo*. The residue, dissolved in 290 cc. of ethyl acetate, was shaken a few minutes with 430 cc. of 10% cupric acetate, then cooled in an ice-bath. The *green copper salt*, m.p. 169–171° dec., was collected and washed with ethyl acetate. The wet salt was shaken with 250 cc. of chloroform and 170 cc. of 6 *N* hydrochloric acid until the organic layer was no longer green. The separated chloroform layer, dried with magnesium sulfate, was evaporated *in vacuo* leaving a viscous oil which gradually solidified to a low-melting solid; yield, 55.2 g. (70%).

A sample of the *copper derivative*, recrystallized from alcohol, formed green crystals, m.p. 182–184° dec.

Anal. Calc'd for $C_{32}H_{32}CuN_2O_{18}$: C, 48.3; H, 4.02; N, 3.52; Cu, 8.05.

Found: C, 47.5; H, 4.50; N, 3.43; Cu, 7.20.

2-Nitro-6-acetobenzoic acid (XVI) *and its methyl ester* (XVII). A mixture of 7.1 g. of XV, 35 cc. of alcohol, and 35 cc. of 6 *N* hydrochloric acid was refluxed for 2.5 hours when carbon dioxide evolution was essentially complete. The solution was concentrated to turbidity *in vacuo*, diluted with an equal volume of water, and extracted twice with ethyl acetate. The combined extracts were back extracted with excess aqueous sodium bicarbonate. Acidi

fication gave 1.2 g. (30%) of acid, m.p. 187–189°. Recrystallization from ethyl acetate-heptane afforded white crystals, m.p. 196–197°.

Anal. Calc'd for $C_9H_7NO_5$: C, 51.7; H, 3.35; N, 6.70.
Found: C, 52.0; H, 3.65; N, 6.54.

The ethyl acetate solution of neutral material was washed with water and evaporated *in vacuo* leaving 2.3 g. (52%) of ester, m.p. 73–75°. Recrystallization of a sample from heptane gave white crystals, m.p. 78–79°.

Anal. Calc'd for $C_{10}H_9NO_5$: N, 6.28. Found: N, 5.92.

In two more runs the yields of acid were 29 and 40% and of the ester 57% each. If 3 *N* hydrochloric acid was employed instead of 6 *N*, the reaction required 3.5 hours and gave a 57% yield of acid and a 43% yield of ester.

6-Acetoanthranilic acid (XX). A solution of 1.00 g. of 2-nitro-6-acetobenzoic acid in 50 cc. of 2*N* ammonium hydroxide was shaken with hydrogen at 1 atm. in the presence of 100 mg. of palladium-charcoal catalyst, reduction being complete in 20 minutes. The filtered solution was acidified to *p*H 2 with hydrochloric acid, saturated with salt, and extracted with two 50-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated *in vacuo*; yield, 620 mg. (73%), m.p. 152–153°. Recrystallization from toluene gave pale yellow crystals, m.p. 155–156°.

Anal. Calc'd for $C_9H_9NO_3$: C, 60.4; H, 5.03; N, 7.83.
Found: C, 60.1; H, 5.34; N, 7.90.

When the hydrogenation was run on the free acid in alcohol, the yield was 18% and gummy by-products were formed.

Attempts to reduce the carbonyl group to form 6-ethylanthranilic acid (XXIV) by Raney alloy (7) or the Clemmenson method led to decarboxylation. The Huang-Minlon modification of the Wolf-Kishner reduction (9) gave an alkali-insoluble product, m.p. 276–278°, in 70% weight-yield which appeared to be 4-methyl-8-amino-1-phthalazone.

An attempt to prepare 5-aceto-4-quinazolone (XIX) by fusion of XX with formamide at 130–150° (8) gave only a dark tar. Similar results were obtained by fusion of the ammonium salt of the formyl derivative of XX at 170°.

Methyl 2-acetamino-6-acetobenzoate (XXI). A solution of 7 g. of XVII in 100 cc. of alcohol was added to a suspension of 1 g. of 10% palladium-charcoal in 10 cc. of Methyl Cellosolve. The mixture was shaken with hydrogen at 2–3 atm. and reduction was complete in 95 minutes. Evaporation of the filtered solution *in vacuo* left 5.3 g. (88%) of yellow crystals of methyl 6-acetoanthranilate, m.p. 62–64°, which were not readily purified. To a solution of 5.2 g. of this ester in 5.7 cc. of acetic acid was added 3.2 cc. of acetic anhydride. After ten minutes the solution was diluted with 40 cc. of water, concentrated to about 15 cc. *in vacuo*, and chilled; yield, 3.3 g. (52%), m.p. 86–87°. Recrystallization of a sample from heptane gave white crystals, m.p. 87–88°.

Anal. Calc'd for $C_{12}H_{13}NO_4$: N, 5.96. Found: N, 5.84.

α-Methyl 6-acetaminophthalide (XXV). A mixture of 3.2 g. of XXI, 1 g. of copper chromite catalyst, and 10 cc. of methanol was shaken with hydrogen at 1800 p.s.i. and 150° for 15 minutes when one mole-equivalent of hydrogen was absorbed. No further hydrogen uptake was observed up to 200°. The cooled, filtered, solution was evaporated to dryness *in vacuo*. Addition of heptane to the residue gave 1.9 g. (68%) of product, m.p. 102–105°. Recrystallization from heptane afforded white crystals, m.p. 106–107°.

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.37; N, 6.83.
Found: C, 64.8; H, 5.71; N, 6.67.

No hydrogen was taken up with a nickel (Universal Oil Products) catalyst up to 210°. A mixture of copper chromite and the nickel catalyst again gave lactone up to 200°. This lactone failed to undergo hydrogenolysis with palladium-charcoal or platinum oxide catalysts in alcohol or acetic acid at 1 atm. of hydrogen.

m-Ethylaniline. To a suspension of 0.5 g. of 10% palladium-charcoal in 10 cc. of Methyl Cellosolve was added 25 g. of *m*-nitroacetophenone and 150 cc. of alcohol. The mixture was shaken with hydrogen at 2–3 atm. for 30 minutes when reduction was complete (shaking

intermittent due to heat of reaction). The filtered solution was evaporated *in vacuo* leaving a slightly solvent-wet solid of *m*-aminoacetophenone, m.p. 93–95°, in quantitative yield. This was mixed with 29 g. of potassium hydroxide, 21 cc. of 85% hydrazine hydrate, and 180 cc. of diethylene glycol, then refluxed for 30 minutes. The flask was equipped for downward distillation and with a gas evolution indicator and was heated in a bath at 150°. The temperature was raised to 180° as fast as foaming would permit which required 90 minutes. After 30 minutes more at 180° nitrogen evolution was complete. The cooled reaction mixture was diluted with three volumes of water, combined with the distillate, and extracted with 250 cc. of benzene. The extract, washed twice with water, was concentrated *in vacuo* (bath 50°) and the residue distilled; yield, 14.6 g. (80%) of nearly colorless oil, b.p. 101–102° (15 mm.).

m-Propylaniline. The crude *m*-aminopropiophenone from 105 g. of *m*-nitropropiophenone (14) prepared as described in the previous experiment was dissolved in 400 cc. of diethylene glycol and added to 110 g. of potassium hydroxide in 275 cc. of diethylene glycol and 78 cc. of 85% hydrazine hydrate. The solution was refluxed eight hours without distillation when nitrogen evolution became slow. Work-up as described for *m*-ethylaniline gave 59.7 g. (75%) of a light yellow oil, b.p. 114–116° (15 mm.). The acetyl derivative melted at 52–53°.

Baddeley and Kenner (15) have prepared this compound by a complicated multi-step synthesis. They recorded b.p. 112° (20 mm.) for the amine and m.p. 53° for the acetyl derivative.

m-Ethyl-α-isonitrosoacetanilide. Treatment of 49.3 g. of *m*-ethylaniline with chloral and hydroxylamine in the usual manner (16) by the Sandmeyer method, except that a five-minute boil period was employed gave, after reprecipitation from an alkaline solution, 64.3 g. (82%) of product, m.p. 133–135°. Several recrystallizations from aqueous methanol with the aid of Norit gave white crystals, m.p. 145–145.5°.

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.25; N, 14.6.
Found: C, 62.9; H, 6.63; N, 14.9.

Similarly, 53.7 g. of *m*-propylaniline gave 65.5 g. (80%) of *m-propyl-α-isonitrosoacetanilide*, m.p. 110–113°. Several recrystallizations from dilute methanol with the aid of Norit gave white crystals, m.p. 132–133°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.80; N, 13.6.
Found: C, 64.3; H, 7.18; N, 14.1.

In the same manner 75 g. of *m*-trifluoromethylaniline gave 103 g. (96%) of *m-trifluoromethyl-α-isonitrosoacetanilide* (XXXV), m.p. 125–130°. Recrystallization from toluene afforded white crystals m.p. 141–142°. (lit. m.p. 143° corr.[2])

Anal. Calc'd for $C_9H_7F_3N_2O_2$: C, 46.6; H, 3.04; N, 12.1.
Found: C, 46.8; H, 3.38; N, 12.2.

4- (and 6)-Ethylisatin (XXVII and XXVI). The crude isatin obtained by 86% sulfuric acid cyclization of 64.3 g. of *m*-ethyl-α-isonitrosoacetanilide in the usual manner (17) was dissolved in 500 cc. of water and 200 cc. of 10% sodium hydroxide by heating on the steam-bath. The solution was clarified with Norit by filtration through Celite. The cooled solution was acidified to *p*H 4 with acetic acid (10). The 4-ethylisatin was collected and washed with water; yield, 13.8 g. (24%), m.p. 134–135° with softening at 125°. Several recrystallizations from 50% methanol gave orange crystals, m.p. 139–140°.

Anal. Calc'd for $C_{10}H_9NO_2$: C, 68.6; H, 5.14; N, 8.00.
Found: C, 68.2; H, 5.41; N, 8.17.

The filtrate from XXVII was strongly acidified with hydrochloric acid and stirred 30 minutes more; yield, 18.4 g. (31%) of 6-ethylisatin, m.p. 172–174°. Recrystallization from 50% methanol gave yellow-orange crystals, m.p. 177–178°.

Anal. Calc'd for $C_{10}H_9NO_2$: N, 8.00. Found: N, 7.97.

Similarly, 65.5 g. of *m*-propyl-α-isonitrosoacetanilide gave 8.8 g. (15%) of once recrystallized *4-propylisatin*, m.p. 121–123°, in the first fraction and 18.2 g. (30%) of *6-propylisatin*, m.p. 152–154°, in the second fraction. Recrystallization of both compounds from 50% methanol gave orange crystals, m.p. 127–128°, and yellow-orange crystals, m.p. 157–158°, respectively.

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.9; H, 5.82; N, 7.41.
Found (*4*): C, 69.7; H, 5.99; N, 7.66.
Found (*6*): C, 69.7; H, 6.07; N, 7.54.

4-Ethylanthranilic acid (XXX). Oxidation of 1.6 g. of 6-ethylisatin with alkaline peroxide in the usual manner (2) gave 1.3 g. (86%) of product, m.p. 118–120°. Recrystallization of a sample from heptane afforded nearly white crystals, m.p. 119–120°.

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.5; H, 6.67; N, 8.49.
Found: C, 65.2; H, 6.80; N, 8.95.

Deamination of a sample in hypophosphorous acid with sodium nitrite (21) gave *p*-ethylbenzoic acid (XXXI), m.p. 105–107°. A m.p. of 112° has been recorded for *p*-ethylbenzoic acid and a m.p. of 68° for *o*-ethylbenzoic acid (22). The latter would be formed from the isomeric 4-ethylisatin by this sequence.

6-Ethylanthranilic acid (XXIV). Oxidation of 900 mg. of 4-ethylisatin with alkaline peroxide in the usual manner (2) gave 600 mg. (71%) of product, m.p. 97–99° dec., isolated by ethyl acetate extraction. This compound was not readily purified due to its ease of decarboxylation.

4-Propylanthranilic acid. Oxidation of 1.8 g. of 6-propylisatin with alkaline peroxide (2) gave 1.35 g. (84%) of product, m.p. 129–131°. Recrystallization from heptane afforded nearly white crystals, m.p. 133–134°.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.1; H, 7.26; N, 7.82.
Found: C, 67.4; H, 7.60; N, 7.98.

This structure was proven unequivocally by deamination (21) to *p*-propylbenzoic acid, m.p. 134–137°, in 83% yield. Recrystallization from heptane with the aid of Norit gave white crystals, m.p. 139–140°.

Körner (23) has recorded m.p. 140° for *p*-propylbenzoic acid. In contrast Gabriel (24) recorded m.p. 58° for *o*-propylbenzoic acid, the product which would be obtained from the isomeric 4-propylisatin by this sequence.

4-Ethylisatoic anhydride (XXII). To a stirred solution of 11.2 g. of 4-ethylisatin in 110 cc. of acetic acid warmed to 60° was added 37 g. of chromic anhydride in portions over a period of 15 minutes maintaining the temperature at 70–75° by occasional cooling. The solution was maintained at this temperature for one hour more, then poured into 410 cc. of water. The product was collected and washed well with water; yield, 5.1 g. (42%), m.p. 196–198°. Recrystallization of a sample from toluene gave nearly white crystals, m.p. 197–198°.

Anal. Calc'd for $C_{10}H_9NO_3$: C, 62.9; H, 4.71; N, 7.34.
Found: C, 62.9; H, 5.00; N, 7.51.

When the oxidation was carried out at a lower temperature as described for 5-bromoisatin (25), the yield was only 19%.

Similarly, oxidation of 8.8 g. of 4-propylisatin at 70° gave 3.6 g. (38%) of *4-propylisatoic anhydride*, m.p. 170–172°. Recrystallization of a sample from toluene afforded white crystals, m.p. 171–172°.

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.36; N, 6.84.
Found: C, 64.1; H, 5.59; N, 6.92.

5-Ethyl-4-quinazolone (XXIII). A mixture of 4.8 g. of 4-ethylisatoic anhydride (XXII), 24 cc. of acetone, and 2.7 cc. of 28% ammonia water was refluxed gently for 40 minutes during which solution took place and another solid separated. After the addition of 2.7 cc. more of ammonia water, the mixture was stirred and refluxed for 30 minutes more when solution was again complete. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in 24 cc. of 87% formic acid and heated on the steam-bath for one hour. Evaporation of the solution to dryness *in vacuo* left a gum which was dissolved in 24 cc. of warm water by the addition of sufficient 10% sodium hydroxide to give *p*H > 10. The solution was clarified with Norit by filtration through Celite, acidified to *p*H 4 with acetic acid, and cooled to 0° to give 2.7 g. (62%) of product, m.p. 205–207°. Recrystallization of a sample from dilute methanol gave white crystals, m.p. 215–216°.

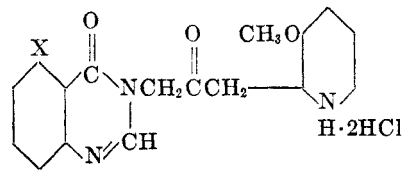
Anal. Calc'd for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.75; N, 16.1.
Found: C, 68.7; H, 5.95; N, 16.2.

Similarly, 3.6 g. of 4-propylisatoic anhydride gave 2.0 g. (62%) of *5-propyl-4-quinazolone* (XXXIII), m.p. 196–199°. Recrystallization from dilute methanol with the aid of Norit gave white crystals, m.p. 198–199°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: N, 14.9. Found: N, 14.6.

4-Trifluoromethylisatin (XXXVI). The crude product obtained by cyclization of 50 g. of *m*-trifluoromethyl-α-isonitrosoacetanilide (XXXV) by essentially the same procedure recently described by Maginnity and Gaulin[2] was dissolved in 375 cc. of warm water by the addition of 105 cc. of 10% sodium hydroxide. The solution was clarified with Norit and acidified to *p*H 5. After some purple by-product was removed by filtration, strong acidificaiton gave 11.5 g. (25%) of product, m.p. 208–213° dec. That only one isatin isomer was

TABLE I



X[a]	YIELD, %	M.P., °C. dec.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
NO_2	6.8	212–213	none	47.1	5.08	12.9	47.1	5.12	13.8
NH_2[b]	14.5	115–120	none	50.6	5.96	13.9	50.4	6.35	13.1
F	12	206	none	50.3	5.42	10.3	50.4	5.76	10.1
I	7.7	253	sesqui	37.7	4.61		37.6	3.73	
MeS	7.6	218–219	mono	47.8	6.03	9.31	47.3	5.27	9.86
$MeSO_2$	8.6	217–219	none	46.4	5.36	9.00	47.7	5.47	9.05
C_2H_5	2.0	210	mono	52.5	6.75	9.68	52.7	6.50	10.0
C_3H_7	6.4	202	none	55.8	6.75	9.77	55.3	6.92	9.73
CF_3	9.2	215	none	47.4	4.82	9.21	47.6	5.22	9.24

[a] These compounds were prepared by condensation of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine with the appropriate 4-quinazolone followed by 6 *N* hydrochloric acid hydrolysis of the crude product (2, 3). [b] 5-Acetamino-4-quinazolone employed as starting material.

present was shown by the identity of all fractions obtained by fractional acidification of an alkaline solution. Recrystallization of a sample from xylene gave orange crystals, m.p. 224–225° dec.

Anal. Calc'd for $C_9H_4F_3NO_2$: C, 50.4; H, 1.87; N, 6.52.
Found: C, 50.8; H, 2.17; N, 6.48.

Magginnity and Gaulin[2] recorded m.p. 212° and a yield of 47%.

6-Trifluoromethylanthranilic acid (XXXVIII). Oxidation of XXXVI with alkaline peroxide in the usual manner (2) gave a 51% yield of product, m.p. 121–123°. Recrystallization from toluene-heptane gave white crystals, m.p. 131–132°.

Anal. Calc'd for $C_8H_6F_3NO_2$: C, 46.8; H, 2.96; N, 6.83.
Found: C, 46.8; H, 3.21; N, 6.85.

Deamination (21) gave *o*-trifluoromethylbenzoic acid (XXXVII), m.p. 106–108°, thus proving its structure. Jones (19) has recorded m.p. 107° for *o*-trifluoromethylbenzoic acid and 212–213° for the *p*-isomer.

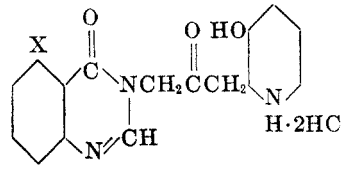
5-Trifluoromethyl-4-quinazolone (XXXIX). Fusion of XXXVIII with formamide in the usual manner (2) gave an 80% yield of product, m.p. 228–229°. Recrystallization from water afforded white crystals, m.p. 236–237°.

Anal. Calc'd for $C_9H_5F_3N_2O$: C, 50.4; H, 2.35; N, 13.1.

Found: C, 51.0; H, 2.85; N, 13.2.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-5-acetamino-4-quinazolone. A solution of 655 mg. of 3-[β-keto-γ-(3-methoxy-2-piperidyl)propyl]-5-amino-4-quinazolone dihydrochloride (Table I) in 7 cc. of 48% hydrobromic acid was refluxed ten minutes, then evaporated to dryness *in vacuo*. The residue, dissolved in 6 cc. of water, was stirred with 3 cc. of acetic anhydride for ten minutes. Evaporation to dryness *in vacuo* left a solid which was dissolved in 10 cc. of absolute alcohol and the evaporation repeated. The residue was heated to boiling with 10 cc. of absolute alcoholic hydrogen chloride, then cooled in an ice-bath. The

TABLE II



X[a]	YIELD, %	M.P., °C. dec.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
NO_2	55	209–210	hemi	44.8	4.91	13.1	44.5	5.01	12.8
AcNH[b]	54	>275	mono	48.1	5.79	12.5	48.2	5.99	12.8
F	54	216	hemi	47.9	5.24	10.5	48.0	5.53	10.4
I	81	252[c]	none	41.4	4.11	9.07	41.5	4.07	9.16
MeS	65	229	di	44.7	5.53	9.22	44.8	5.23	9.19
$MeSO_2$	77	246–248	mono	43.4	4.90	8.94	43.2	4.98	8.53
C_2H_5	67	217–218	mono	51.4	6.48	10.0	51.3	6.20	10.4
C_3H_7	70	213	sesqui	51.2	6.74	9.43	51.5	6.43	9.70
CF_3	50	211	none	46.2	4.53	9.50	45.9	4.75	9.81

[a] All compounds prepared by 48% hydrobromic acid hydrolysis of the methyl ethers of Table I as previously described (3). [b] Crude hydrolysis product was acetylated, see experimental. Calc'd: N-Ac, 9.59. Found: N-Ac, 7.88. [c] Monohydrochloride.

solid was removed and washed with 1:3 absolute alcohol-acetone. Additional data are listed in Table II.

The success of the selective acetylation of the 5-amino group is dependent on the following factors. In water solution the rate of reaction with acetic anhydride is $RNH_2 > H_2O > ROH$. Secondly, the acetylation of the piperidine nucleus was avoided by use of the dihydrobromide salt in water solution. The strong piperidine base remains as a salt whereas the weakly basic 5-amino group exists mostly as the free base under these conditions and is selectively acetylated.

SUMMARY

The syntheses of nine derivatives of the *dl*-form of the Hydrangea alkaloid containing a substituent on the favorable five position are described, almost all of which are active antimalarials with favorable chemotherapeutic indices.

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