Trifluoroacetyl-DL-γ-hydroxyglutamic acid B was prepared in the same manner as the corresponding A-form from 5.4 g. of amino acid and 5 g. of sodium bicarbonate; yield 3 g., m.p. 190° (softens at 138°).

Anal. Calcd. for $C_7H_8O_6NF_3$: C, 32.4; H, 3.1; N, 5.4. Found: C, 32.7; H, 3.1; N, 5.5.

Resolution of Chloroacetyl-DL-γ-hydroxyglutamic Acid A and B.—Five and one-half grams of chloroacetyl-DL-γ-hydroxyglutamic acid lactone (A- or B-form) was suspended in 200 ml. of water and brought into solution by the addition of lithium hydroxide until the *p*H remained constant at 8.5–9. Addition of 375 mg. of cobalt acetate and 500 mg. of purified acylase I powder[13] (300 mg. in the case of diastereomer B) lowered the *p*H to about 7.5. The reaction mixture was diluted to 1500 ml. (0.017 *M* substrate, 10^{-3} *M* cobalt) and incubated at 38°, with the *p*H of the medium being readjusted up to 7.5 whenever required during the first few hours of digestion. After 24 hr., analysis on an aliquot by the usual manometric ninhydrin–CO_2 procedure revealed that the hydrolysis had proceeded to 50%.[18] An additional 100 mg. of enzyme was added and the incubation allowed to proceed another 12 hr. The solution was then deproteinized by adjusting the *p*H to 5 and filtering with the aid of charcoal. The filtrate was concentrated to about 100 ml. and placed on a 2.5 × 35 cm. column of Dowex 50 (100–200 mesh) which was in the acid form and previously had been washed with water; 400 ml. of water was allowed to flow through the column, followed by *N* HCl. The emergence of the chloroacetyl-D-amino acid in the first 200 ml. of aqueous eluate was indicated by the low *p*H of the solution. The appearance of the L-amino acid in the hydrochloric acid eluate was revealed by spot test employing a basic ninhydrin solution. The fractions containing the chloroacetyl-D-component were combined, concentrated hydrochloric acid added to a final concentration of 2.5 *N* and the solution refluxed for 3 hr. to liberate the D-amino acid.

The two solutions containing the free enantiomorphs were evaporated to dryness in order to remove excess hydrochloric acid, the residues were dissolved in water and the solutions made alkaline with sodium hydroxide and subsequently desalted by passage through a 2.5 × 35 cm. column of Dowex 1 (50–100 mesh) in the acetate form (previously washed with water). The cations, including some cobalt in the case of L-enantiomorph, were washed through with water and the amino acid then eluted with 0.5 *N* acetic acid. Complete removal of the acetic acid from the appropriate eluate by repeated evaporation yielded crystalline material in the case of both A-antipodes and an oil in the case of the B-antipodes. These residues were dissolved in hot water, the solutions decolorized with charcoal and ethanol added. After cooling, the products were recovered by filtration and recrystallized from hot water by the addition of a small volume of ethanol. The final products were washed first with ethanol, then acetone and finally dried over phosphorus pentoxide *in vacuo*.

The optically active enantiomorphs of the A-form crystallized as large transparent prisms, whilst those of the B-form were secured as small, irregular, crystalline needles. Two resolutions were effected with each racemate. The yields varied from 40 to 60%; optical rotation data appear in Table I.

Anal. Calcd. for $C_5H_9O_5N$: C, 36.8; H, 5.6; N, 8.6. Found (L-A): C, 36.7; H, 5.7; N, 8.6. Found (D-A): C, 36.8; H, 5.8; N, 8.5. Calcd. for $C_5H_9O_5N\cdot H_2O$: C, 33.2; H, 6.1; N, 7.7. Found (L-B): C, 33.4; H, 6.1; N, 7.8. Found (D-B): C, 33.5; H, 6.2; N, 7.8.

Nitrous Acid Deamination of γ-Hydroxyglutamic Acid to α,α′-Dihydroxyglutaric Acid.—Two hundred and fifty mg. of each of the four optically active isomers of γ-hydroxyglutamic acid was dissolved in a mixture of 1.5 ml. of *N* HCl, 3 ml. of acetic acid and 6 ml. of water. To the cooled solution was added, in small portions with shaking, a solution of 1.2 g. of sodium nitrite in 2 ml. of water.[27] The mixture was stored at 5° for 1 hr. and then at room temperature overnight. Three ml. of concentrated hydrochloric acid was added, the solution evaporated to dryness and the evaporation repeated several times after the addition of water. The residue was extracted three times with boiling acetone, the sodium sulfate-dried extract concentrated to an oil and the latter taken up in water and shaken in the presence of a few grams of Dowex 50 (20-50 mesh) to remove any residual amino acid or sodium ions. The aqueous solution was treated with barium hydroxide solution to a *p*H of 9 (to hydrolyze any possible lactone) and the *p*H subsequently readjusted to 5 by the addition of a few beads of Dowex 50. To the final solution (75 ml.) was added three volumes of acetone with vigorous shaking. The barium salt was filtered, triturated with acetone, collected by centrifugation and dried at 137° *in vacuo* over phosphorus pentoxide to remove final traces of water; yield 250 mg.; $[M]^{26}_{\text{D}}$ values, as 1% solutions in water, were: L-A, −30.9°; D-A, +31.4°; L-B, 0°; D-B, 0°. *Anal.* Calcd. for $C_5H_6O_6Ba$: Ba, 45.8. Found: L-A, Ba, 45.6; D-A, 45.5; L-B, Ba, 45.6; D-B, 45.7.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE ANNEX C LABORATORY, DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

The Reaction of N-Benzylpyrrole with Acetylenedicarboxylic Acid. A Diels–Alder Addition to a Pyrrole[1]

BY LEON MANDELL AND WESLEY A. BLANCHARD[2]

RECEIVED JUNE 3, 1957

The reaction of N-benzylpyrrole and acetylenedicarboxylic acid has been shown to lead to the formation of three products, I, II and III. Compound I represents the first case of a pyrrole partaking in a normal Diels-Alder addition. The proof of structure of these products is discussed.

Although a great number of different types of dienes have been shown to be capable of participating in the Diels–Alder reaction,[3] including the diene system of heterocycles such as furans[4] and thiophenes,[5,6] the dienic moiety of pyrroles has in general resisted normal Diels–Alder addition[7] and undergoes instead substitutive processes leading to α-substituted pyrroles[8] and dihydroindoles.[9] As part of a synthetic scheme designed to utilize this known mode of reaction of pyrroles with dienophiles, the reaction of N-benzylpyrrole and acetylenedicarboxylic acid was investigated.

Reaction between N-benzylpyrrole and acetylenedicarboxylic acid was effected readily by allowing an ether solution of the two to reflux for 24

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(1) For a preliminary account of this work, see L. Mandell and W. A. Blanchard, THIS JOURNAL, **79**, 2343 (1957).

(2) Taken in part from a dissertation submitted by W. A. Blanchard in partial fulfillment of the requirements for the Ph.D. degree at Emory University.

(3) For a review of the Diels–Alder reaction see M. C. Kloetzel and H. L. Holmes, in R. Adams, Ed., "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948.

(4) O. Diels and K. Alder, *Ber.*, **62**, 554 (1929).

(5) D. B. Clapp, THIS JOURNAL, **61**, 2733 (1939).

(6) C. F. H. Allen and J. W. Gates, *ibid.*, **65**, 1283 (1943).

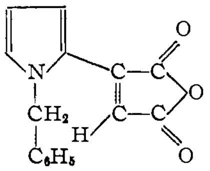
(7) An interesting exception to this is the recent report of G. Wittig, *Angew. Chem.*, **69**, 245 (1957).

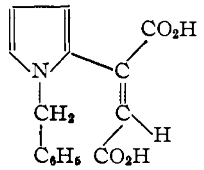
(8) O. Diels and K. Alder, *Ann.*, **498**, 1 (1932).

(9) O. Diels and K. Alder, *ibid.*, **490**, 267 (1931).

hr. From this reaction three materials were isolated. The first, white in color, I, which started precipitating out of the reaction mixture shortly after initiation of the reaction, was isolated by direct filtration. Cooling the filtrate to 0° afforded needles of the second, bright yellow in color, II. Concentration of the mother liquors from II yielded the third, yellow-orange in color, III.

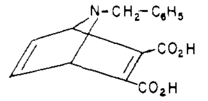
The structures of II and III were quickly elucidated from the evidence outlined below and were assigned the structures of N-benzylpyrrole-α-maleic anhydride and N-benzylpyrrole-α-fumaric acid, respectively.


II


III

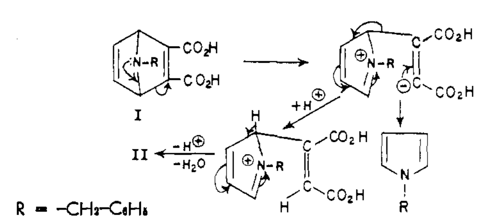
The infrared spectrum of II exhibited a typical anhydride absorption, whereas that of III showed a carboxyl absorption.[10] The elemental analysis and neutral equivalent of II and III indicated a one-to-one (N-benzylpyrrole to acetylenedicarboxylic acid) substitution product. Careful acidification in the cold of the titration solution of II yielded a diacid shown to be different from III by mixture melting point and comparison of infrared spectra. Upon hydrogenation at atmospheric pressure both II and III took up four equivalents of hydrogen, affording, after both reduction products were converted to their methyl esters, a common product as evidenced by comparison of infrared spectra, dimethyl α-pyrrolidinesuccinate. This evidence and mode of reaction follows exactly the findings of Diels and Alder on simpler pyrroles.[8]

With the proof of structure of compounds II and III, the major portion of the reaction product, attention was directed toward the white material isolated first, I. This substance was isomeric with II and III. It was amphoteric, being soluble in both dilute sodium bicarbonate and dilute hydrochloric acid. This latter fact is indicative that the nitrogen is no longer part of a pyrrole nucleus and immediately suggested that compound I had resulted by a normal Diels–Alder addition of the pyrrole to the dienophile giving


I

Confirmation of this postulation was obtained from the spectral analysis of I which showed in the infrared absorptions associated with zwitterion formation and the lack of absorption in the ultraviolet indicating the absence of any conjugated diene. Further, hydrogenation at atmospheric pressure proceeded smoothly with the uptake of three equivalents of hydrogen (two double bonds and hydrogenolysis of the benzyl grouping) thus indicating the presence of a bicyclic ring system.

Direct chemical degradative evidence to firmly establish the structure of I was obtained from the treatment of I and the partial hydrogenation product of I with aqueous sodium carbonate. Although I is stable in hot water and even may be recrystallized with excellent recovery from water, a solution of I in 10% sodium carbonate when heated gives evidence (by appearance of an insoluble phase) of facile reaction. From this reaction may be isolated two products; the first, obtained by extraction of the basic carbonate solution, was shown by infrared comparison to be N-benzylpyrrole; the second, isolated by acidification of the extracted basic solution followed by extraction, was shown by mixture melting point and infrared comparison to be II. These facts, as is seen from the following scheme, are in accord with the postulated structure I.



The necessity of base to initiate these transformations follows from the fact that I exists as a zwitterion. Thus, it is not until the "lone pair" electrons on the nitrogen are released from their binding proton by the base that reaction may ensue.

Additional confirmation of the structure of I was obtained by the basic degradation of the dihydro adduct which could be prepared by hydrogenation of I over 5% palladium-on-charcoal in 10% sodium carbonate solution at atmospheric pressure and stopping the reduction after the uptake of one equivalent of hydrogen. This point was indicated by a lessening of the rate of hydrogenation. The dihydro-compound thus prepared was refluxed for 24 hr. in 10% sodium carbonate solution and upon acidification a new crystalline product, IV, was isolated. Structural assignment to IV proved to be interesting owing to its misleading behavior on titration. The compound had an elemental analysis indicating the formula $C_{13}H_{11}O_4N$ and a neutral equivalent of 240 which thus indicated the substance to be a monocarboxylic acid. That this conclusion is wrong was shown by the following: 1. Compound IV is soluble in dilute sodium bicarbonate but is insoluble in even concentrated hydrochloric acid; thus, the *neutral* nitrogen must be incorporated as an amide or a pyrrole grouping. 2. The infrared spectrum of IV shows two strong absorptions in the carbonyl region, one at 5.89 μ and the second at 6.10 μ, which upon esterification with diazomethane shift to lower wave lengths, 5.75 and 5.85 μ. These lower wave lengths are consistent with ester groupings. 3. If the nitrogen of IV were incorporated as an amide, the shift of both absorptions would not be expected as the amide should have remained unaffected by the diazomethane treatment. Thus, the nitrogen must be a pyrrolic nitrogen. 4. From the empirical formula,

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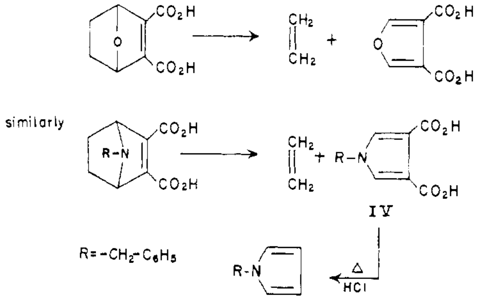
(10) The infrared absorptions are given in the Experimental.

accepting the above argument that a pyrrole grouping is present (which is further confirmed below), the assignment of a dicarboxylic acid structure becomes mandatory.

Further evidence as to the existence of a pyrrole grouping in IV was obtained by refluxing IV in 10% hydrochloric acid which effected decarboxylation yielding N-benzylpyrrole. Having established that IV is a N-benzylpyrroledicarboxylic acid, its structure was assigned by analogy with a similar reaction that occurs for the dihydro adduct of furan and acetylenedicarboxylic acid,[11] *i.e.*



The explanation for the anomalous titration rests in the fact that one of the carboxyls in IV is an extremely weak acid and thus the end-point is indicated, with phenolphthalein, at the monosodium salt stage.[12]

With both the physical and degradative evidence thus confirming the structure of I, we have established the occurrence of a Diels–Alder addition to a pyrrole. This addition must reflect a greater "dienic" character of N-benzylpyrrole as compared to simple N-methyl or unsubstituted pyrroles which do not undergo this type of addition. This point finds explanation in a consideration of what is involved in the aromatic nature of pyrrole. From a study of the microwave spectrum of pyrrole,[13] it has been shown that the nitrogen-hydrogen grouping is coplanar with the ring system and that the thus incurred strain of flattening the nitrogen tetrahedron is offset by the gained aromaticity of the planar system. With a bulkier group, as for example benzyl, in place of the hydrogen, one would expect the energy needed for coplanarization of the system to be accordingly greater, this increase being reflected in a lessening of the aromatic nature of the pyrrole or an increase of the "dienic" character as indicated by the system now partaking of a normal Diels–Alder addition.

Experimental[14]

Reaction of N-Benzylpyrrole with Acetylenedicarboxylic Acid.—N-Benzylpyrrole[15] (15.7 g., 0.1 mole), acetylenedicarboxylic acid (11.4 g., 0.1 mole) and 65 ml. of dry ether were refluxed for 24 hr. during which time a quantity of crystalline material separated from the reaction mixture. The hot ether solution was filtered and the yellow residue recrystallized and charcoaled from water to give 2.3 g. of I as colorless plates, m.p. 210–212°. The infrared spectrum run as a potassium bromide pressing showed, among other absorptions, bands at 2.92 μ and a strong unresolved band between 6.25 and 6.60 μ indicative of zwitterion formation.[16] The substance was soluble in 5% hydrochloric acid and 5% sodium bicarbonate.

Anal. Calcd. for $C_{15}H_{13}O_4N$ (I): C, 66.4; H, 4.8; N, 5.2; neut. equiv., 135.5. Found: C, 66.0; H, 4.9; N, 5.1; neut. equiv., 133.

The filtrate from above was cooled to 0° and the precipitated crystals filtered giving, after recrystallization from benzene–ligroin, 2.4 g. of yellow needles, II, m.p. 117.5–119.5°. The infrared spectrum exhibited characteristic anhydride absorptions at 5.44 and 5.69 μ.

Anal. Calcd. for $C_{15}H_{11}O_3N$ (II): C, 71.2; H, 4.4; N, 5.5; neut. equiv., 126.5. Found: C, 71.3; H, 4.2; N, 5.2; neut. equiv., 127.

The filtrate from above was concentrated on a hot water-bath to about 60 ml. and the solvent replaced with benzene by repeated addition and concentration. Upon cooling 13 g. of a bright orange solid was obtained, III, which upon recrystallization from methanol–benzene afforded 10.5 g. of III, as orange prisms, m.p. 162–164° dec. The infrared spectrum determined as the potassium bromide pressing contained a carbonyl absorption at 5.85 μ, typical of a carboxyl carbonyl.

Anal. Calcd. for $C_{15}H_{13}O_4N$ (III): C, 66.4; H, 4.8; N, 5.2; neut. equiv., 135.5. Found: C, 65.8; H, 4.8; N, 5.1; neut. equiv., 135.

N-Benzylpyrrole-α-maleic acid was isolated by ether extraction of the acidified solution in which the neutral equivalent of II had been determined. Removal of the ether, recrystallization of the residue from ligroin–ethyl acetate afforded yellow crystals, m.p. 123.5–125°. An infrared spectrum showed a characteristic carboxyl carbonyl absorption at 5.84 μ. *Anal.* Calcd. for $C_{15}H_{13}O_4N$: C, 66.4; H, 4.8; N, 5.2. Found: C, 65.9; H, 4.7; N, 5.0.

Hydrogenation of II and III.—Both II and III were reduced at atmospheric pressure and at room temperature using prereduced platinum oxide as the catalyst. A typical reduction would use 0.1 g. of platinum oxide in 50 ml. of methanol and 0.6 ml. of concentrated hydrochloric acid. After the catalyst was reduced 0.1 g. of II or III was added and the uptake of hydrogen followed. In both cases, after between 4 to 4.3 equivalents of hydrogen had been absorbed the reaction ceased. The reductions took between 5–6 hr.

The catalyst was filtered and the filtrate concentrated by boiling. The residues were converted to their dimethyl esters by treatment with diazomethane. The infrared spectra of the products thus obtained from both II and III were identical.

Treatment of I with Sodium Carbonate.—A solution of 0.5 g. of I in 25 ml. of 10% sodium carbonate was refluxed 15 hr. The solution was cooled and extracted with ether. The ether extract after drying over sodium sulfate and concentration *in vacuo* afforded 0.21 g. of N-benzylpyrrole as shown by infrared comparison. The aqueous extract was acidified with hydrochloric acid and extracted with ether. Evaporation of the ether *in vacuo* gave 0.05 g. of II as shown by infrared comparison and mixture melting point.

Conversion of I to IV.—One-half gram of I was reduced at atmospheric pressure and room temperature in 25 ml. of 10% sodium carbonate over 0.1 g. of 5% palladium-on-char-

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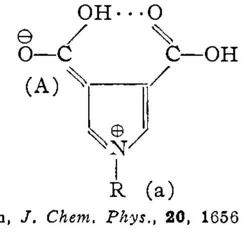
[11] K. Alder and H. F. Rickert, *Ber.*, **70**, 1354 (1937).

[12] The difference in acidity of the two carboxyls in IV and the infrared absorption spectrum of IV, which exhibits an extremely strong hydroxyl stretch at 2.95 μ, suggest that IV exists to a considerable extent as shown in structure (a). This form would cause a shift of the absorption of the carbonyl of one of the carboxyls to high wave lengths (A) and also, coupled with the depicted hydrogen bonding, would decrease the acidity of this carboxyl.



(a)

[13] W. S. Wilcox and J. H. Goldstein, *J. Chem. Phys.*, **20**, 1656 (1952).

[14] Melting points are uncorrected. Analyses are by Mr. W. Manser, Analytical Laboratory, E. T. A., Zurich, Switzerland. Infrared spectra were recorded on a Perkin–Elmer model 21 double beam spectrophotometer and the samples run as 5% solutions in chloroform unless otherwise indicated.

[15] Prepared by the procedure of N. Clauson-Kaas and N. Elming, *Acta Chem. Scand.*, **6**, 867 (1952).

[16] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y. 1954, pp.. 109–111.

coal. The hydrogenation was stopped after the uptake of one equivalent of hydrogen, the catalyst filtered and the filtrate allowed to reflux overnight. Acidification yielded a white crystalline precipitate which upon recrystallization from a methanol–water mixture afforded 0.32 g. of colorless needles, m.p. 216–218° with slight decomposition. The infrared spectrum, run as a potassium bromide pressing, showed absorptions at 2.97(s), 5.89(s) and 6.10(s) μ.

Anal. Calcd. for $C_{13}H_{11}O_4N$ (IV): C, 63.7; H, 4.5; N, 5.7; neut. equiv., 122.5. Found: C, 63.6; H, 4.5; N, 5.7; neut. equiv., 240.

A sample of IV (50 mg.) was esterified with diazomethane and the infrared spectrum of its dimethyl ester run. The spectrum showed the complete absence of hydroxyl and showed a strong absorption at 5.75 μ with a shoulder at 5.85 μ.

Decarboxylation of IV.—Fifty mg. of IV was refluxed 5 hr. in 20 ml. of 10% hydrochloric acid and 2 ml. of ethanol. The reaction mixture was cooled, extracted with ether and the ether extract washed successively with 10% sodium carbonate and water. After drying the ether solution over sodium sulfate, the ether was removed *in vacuo* yielding 22 mg. of N-benzylpyrrole as shown by infrared comparison.

Hydrogenation of I.—A sample of I was hydrogenated as described in the conversion of I to IV and the reduction allowed to proceed until uptake of hydrogen ceased. At this point three equivalents of hydrogen had been absorbed.

Acknowledgment.—We gratefully wish to acknowledge the support of this work by a Frederick Gardner Cottrell grant from Research Corporation. The authors are also indebted to Drs. J. H. Goldstein and A. L. Underwood for many helpful discussions.

EMORY UNIVERSITY, GEORGIA

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Amino Derivatives of Nitrochalcones. II.[1] A New Synthetic Method for 3-Aminoquinolines

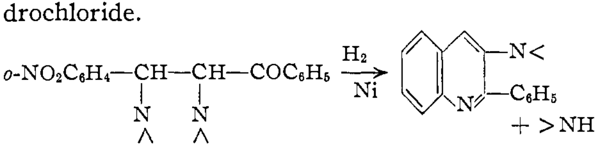
BY NORMAN H. CROMWELL AND GERALD D. MERCER[2]

RECEIVED JUNE 27, 1957

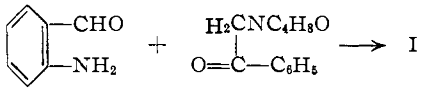
Catalytic hydrogenation of α,β-di-(*sec*-amino)-β-(2-nitrophenyl)-propiophenones gives good yields of 3-*sec*-amino-2-phenylquinolines, heretofore not readily available. The corresponding 4-amino-2-phenylquinolines were synthesized from 4-chloro-2-phenylquinoline by a known method. The hydrogenation of β-amino-2-nitrochalcones resulted in the unexpected production of 4-hydroxy-2-phenylquinoline. The nature of these reactions is discussed.

In a previous[3] investigation it was found that the catalytic hydrogenation of *cis*- and *trans*-1-cyclohexyl-2-(*o*-nitrophenyl)-3-benzoyl-ethylenimine led to the opening of the three-ring and closure of a six-ring to produce 3-cyclohexylamino-2-phenylquinoline. A related reaction has now been found for the production of various 3-*sec*-amino-2-phenylquinolines from α,β-di-(*sec*-amino)-β-(2-nitrophenyl)-propiophenones.[1]

Using W-2 Raney nickel catalyst and a pressure of three atmospheres of hydrogen, the corresponding α,β-diaminoketones were converted in good yields to 3-morpholino- (I), 3-piperidino- (II) and 3-dimethylamino-2-phenylquinoline (III). The structure of the 3-morpholino-2-phenylquinoline (I) was established by comparison with the product resulting from a Friedlander synthesis,[4] employing 2-aminobenzaldehyde and phenacylmorpholine hydrochloride.

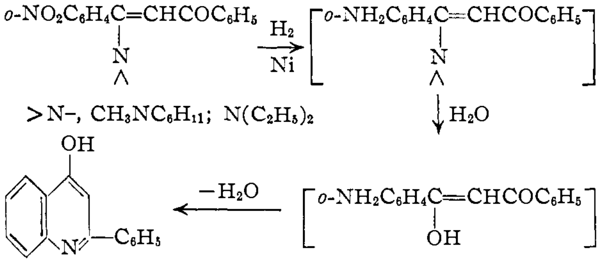


I, >N–, $-NC_4H_8O$
II, >N–, $-NC_5H_{10}$
III, >N–, $-N(CH_3)_2$



The corresponding 4-amino-2-phenylquinolines were synthesized from 4-chloro-2-phenylquinoline[5] for spectral and biological activity comparison with the 3-amino isomers. In this way 4-morpholino- (IV), 4-piperidino- (V), 4-dimethylamino- (VI), 4-(N-methylcyclohexylamino)- (VII) and 4-diethylamino-2-phenylquinoline (VIII) were obtained in good yields.

It was somewhat surprising to find that the hydrogenation of the β-amino-2-nitrochalcones[1] produced 4-hydroxy-2-phenylquinoline rather than the expected 4-amino-2-phenylquinolines. The fact that 4-amino-2-phenylquinolines were not found to hydrolyze under these reaction conditions indicates that the amino group probably was replaced by the hydroxy group before ring closure. Although the β-amino-2-nitrochalcones are known to be very difficult to hydrolyze,[1] the expected intermediate β-amino-2-aminochalcones appear to give a facile replacement of the β-amino group by hydroxyl.



>N–, $CH_3NC_6H_{11}$; $N(C_2H_5)_2$

Catalytic hydrogenation of 4-nitrochalcone gave a good yield of the known 4-aminochalcone, pre-

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[1] For paper I in this same series see, N. H. Cromwell and G. D. Mercer, THIS JOURNAL, **79**, 3819 (1957).

[2] Standard Oil Co. of Indiana Fellow, 1955–1956.

[3] N. H. Cromwell and G. D. Mercer, THIS JOURNAL, **79**, 3815 (1957).

[4] S. Bargellini and S. Berlingozzi, *Gazz. chim. ital.*, **53**, 3 (1923).

[5] H. John, *J. prakt. Chem.*, **118**, 303 (1927); **133**, 350 (1932).