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.

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[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]

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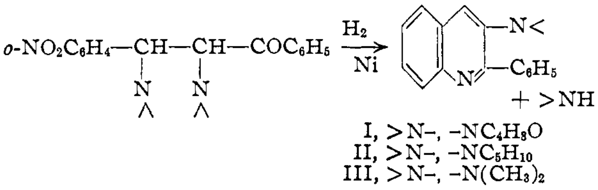
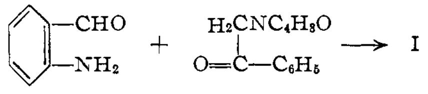
Catalytic hydrogenation of α,β-di-(*sec*-amino)-β-(2-nitrophenyl)-propiophenones gives good yields of 3-*sec*-amino-2-phenylquinolines, heretofore not readily available. The corresponding 4-amino-2-phenylquinolines were synthesized from 4-chloro-2-phenylquinoline by a known method. The hydrogenation 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]

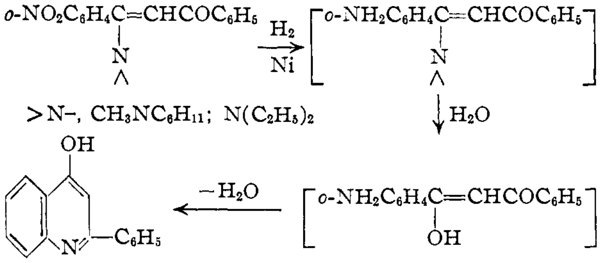
Using W-2 Raney nickel catalyst and a pressure of three atmospheres of hydrogen, the corresponding α,β-diaminoketones were converted in good yields to 3-morpholino- (I), 3-piperidino- (II) and 3-dimethylamino-2-phenylquinoline (III). The structure of the 3-morpholino-2-phenylquinoline (I) was established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





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.



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).

viously prepared by Rupe[6] from the same starting material using stannous chloride and hydrochloric acid as the reducing agent.

In contrast with the behavior of the α,β-diamino-β-(2-nitrophenyl)-propiophenones on catalytic hydrogenation, an example of the 4-nitrophenyl series, α,β-dipiperidino-β-(4-nitrophenyl)-propiophenone produced α,β-dipiperidino-β-(4-aminophenyl)-propiophenone (IX), which was stable enough to isolate. However, gentle warming of IX resulted in the loss of piperidine and the production of a very high melting, insoluble polymeric material. The nature of this polymer has not been investigated as yet. It was established, however, that it must be formed simultaneously with the loss of piperidine rather than from the polymerization of preformed α-piperidino-4-aminochalcone (X). This latter material (X) was prepared by the catalytic hydrogenation of α-piperidino-4-nitrochalcone and found to show no tendency for polymerization under these conditions.

The fact that IX does readily lose piperidine supports the thought that a β-amino group might be expected to be lost readily from the intermediate α,β-diamino-β-(2-aminophenyl)-propiophenones during the synthesis of the 3-amino-2-phenylquinolines (I–III). Since IX produces a polymeric material during the loss of piperidine, while the unsaturated amino ketone X is quite stable, it may be that α-*sec*-amino-2-aminochalcones are not necessarily intermediates in the formation of the 3-*sec*-amino-2-phenylquinolines. The β-*sec*-amino group may be lost from the α,β-diamino-β-(2-aminophenyl)-propiophenone in a process concerted with or subsequent to the ring closing condensation of the *o*-amino group with the carbonyl grouping.

The mechanisms suggested for the formation of 3-hydroxy[7] and 3-cyclohexylamino-2-phenylquinoline[3] from *cis*- and *trans*-*o*-nitrobenzalacetophenone oxide and *cis*- and *trans*-1-cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimine, respectively, indicate that the β-carbon to oxygen and β-carbon to nitrogen bonds in the three-rings are cleaved prior to closure of the six-ring. This seems to be required since the *cis* isomers give the same reactions as the *trans* compounds.

Absorption Spectra.—A summary of the ultraviolet and infrared spectra of these compounds is given in Table I. A general discussion of the spectra of the 2-phenylquinolines based partly on these results has been given in a previous publication.[3] α-Piperidino-4-aminochalcone (X) has an ultraviolet spectrum more related to that of an α-aminochalcone[8a] than to a 4-aminochalcone.[8a] On the other hand, the infrared spectra of X resembled that of the 4-aminochalcone rather than that of an α-aminochalcone,[8b] indicating that *p*-aminocinnammoyl resonance makes an important contribution to the ground state.

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Table I

Summary of Absorption Spectra

Compound	No.	Ultraviolet max.[a]		Band	Infrared bands[b]	
		λ, mμ	$\epsilon \times 10^{-3}$		Wave no. cm.$^{-1}$	Approx. % abs.
2-Phenylquinoline		256	46.7		1620	15
		322	9.0		1600	30
					1555	15
					1512	15
					1497	22
3-Morpholino	I	228	32.3		1600	16
		258	23.9		1490	16
		350	5.9			
3-Piperidino	II	228	33.4		1588	21
		258	22.9		1485	20
		355	6.0			
3-Dimethylamino hydrochloride	III	227	34.2			
		258	25.2			
		360	6.0			
4-Chloro		222	29.2		1602	21
		260	44.5		1590	21
		325	7.6		1555	10
					1515	10
					1501	20
4-Morpholino	IV	258	38.2		1593	36
		318	11.4		1555	13
					1513	12
					1500	20
4-Piperidino	V	260	32.9		1593	58
		323	11.0		1560	20
					1505	31
					1480	20
4-Dimethylamino hydrochloride	VI	221	21.8			
		265	26.8			
		345	10.1			
4-(N-Methylcyclohexylamino)	VII	220	29.2		1598	60
		262	28.6		1560	55
		338	15.9		1540	54
		350	16.4		1485	14
4-Diethylamino hydrochloride	VIIIa	225	24.2			
		263	34.2			
		330	7.2			
4-Aminochalcone		260	13.5	N—H	3370	10[c]
		400	31.4	C=O	1642	30
				C=C	1615	20
				C_6H_5	1600	25
					1588	35
α-Piperidino	X	254	16.5	N—H	3420	6[c]
		291	16.9	C=O	1645	35
		410	2.5	C=C	1612	35
				C_6H_5	1596	34
					1512	30

[a] The ultraviolet spectra were determined in the range of 220–450 mμ in 95% ethanol using 0.5 × 10^{-4} molar solutions and 10-mm. matched quartz cells with a Cary model 11 spectrophotometer. [b] The infrared spectra were determined over the range of 4000–600 cm.$^{-1}$ at 25° using 0.1-mm. matched NaCl cells with a Perkin–Elmer model 21 instrument; the test solutions were 20 mg./ml. CCl_4. [c] See ref. 3.

Experimental

3-Amino-2-phenylquinolines. Hydrogenation of α,β-Di-(*sec*-amino)-β-(2-nitrophenyl)propiophenones.—A 0.01-mole sample of the α,β-diaminoketone[1] was suspended in 50–75

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(6) H. Rupe and A. Porai-Koschitz, *Chem. Zentr.*, **77**, **II**, 1761 (1906).

(7) N. H. Cromwell and R. A. Setterquist, This Journal, **76**, 5752 (1954).

(8) (a) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949); (b) N. H. Cromwell, *et al.*, This Journal, **71**, 3337 (1949).

ml. of reagent grade ethyl acetate and approximately 0.50 g. of W-2 Raney nickel catalyst was added and the mixture shaken at room temperature for 3 hr. under 45 lb./in.[2] pressure of hydrogen. The catalyst was removed by filtration and the solvent distilled under reduced pressure. The residues were crystallized from 95% ethanol after decolorizing with charcoal.

3-Morpholino-2-phenylquinoline (I), m.p. 174–175°, was obtained as pale yellow crystals in 97% yield from α,β-dimorpholino-β-(2-nitrophenyl)-propiophenone.[1]

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.28; H, 6.51; N, 9.78.

Reduction of this diaminoketone using stannous chloride and aqueous hydrochloric acid[9] gave the same product, I, in a 35% yield.

3-Piperidino-2-phenylquinoline (II), m.p. 96–97°, yellow crystals, resulted in 80% yield from α,β-dipiperidino-β-(2-nitro)-propiophenone.[1]

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.72. Found: C, 83.50; H, 6.93; N, 9.86.

3-Dimethylamino-2-phenylquinoline Hydrochloride (III), m.p. 95–97°, was obtained in a 59% yield from α,β-bis-dimethylamino-β-(2-nitrophenyl)-propiophenone.[1] A residual oil from the original reaction mixture, which could not be crystallized, was converted to the hydrochloride III with dry hydrogen chloride gas in ether solution. This crude amine hydrochloride was decolorized and crystallized from hot isopropyl alcohol.

Anal. Calcd. for $C_{17}H_{17}N_2Cl$: C, 71.69; H, 6.02; Cl, 12.45. Found: C, 71.33; H, 6.41; Cl, 12.35.

Friedlander Synthesis of 3-Morpholino-2-phenylquinoline (I).—An adaptation of a known method was used.[4] A 2.5-g. (0.02 mole) sample of 2-aminobenzaldehyde[10] was added to a solution of 4.83 g. (0.02 mole) of phenacylmorpholine hydrochloride[11] in 100 ml. of 75% ethanol. To this solution 20 ml. of a 30% aqueous solution of sodium hydroxide was added and the reaction mixture allowed to stand at room temperature for two days. This was then concentrated to about 50 ml. by distillation of the solvent and the residue cooled to precipitate an oily solid product. This crude material was decolorized with charcoal and crystallized from 95% ethanol to produce a 45% yield of material, m.p. 173–175°, identical with I as described above.

4-Amino-2-phenylquinolines.—Following the method of John,[5] four 4-amino-2-phenylquinolines were prepared by heating 4-chloro-2-phenylquinoline[5] with an excess of the corresponding amine in a sealed glass tube at 216° for 12–14 hr.

4-Morpholino-2-phenylquinoline (IV), m.p. 132–133°, yield 93%, recrystallized from 95% ethanol.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.24; H, 6.13; N, 9.42.

4-Piperidino-2-phenylquinoline (V), m.p. 87–88°, yield 83.5%, recrystallized from 95% ethanol.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.72. Found: C, 83.40; H, 6.98; N, 9.78.

A 0.5-g. sample of V was dissolved in 50 ml. of 95% ethanol and shaken under a pressure of 45 lb./in.[2] of hydrogen for 2 hr. in the presence of 0.5 g. of W-2 Raney nickel and four drops of piperidine. The starting material, 0.42 g., was isolated unchanged after this treatment.

4-Dimethylamino-2-phenylquinoline hydrochloride (VI), m.p. 269–270°, yield 82%, recrystallized from abs. ethanol, was prepared from the oily, free base in dry ether with hydrogen chloride gas.

Anal. Calcd. for $C_{17}H_{17}N_2Cl$: C, 71.69; H, 6.02; Cl, 12.45. Found: C, 71.56; H, 6.22; Cl, 12.25.

4-(N-Methylcyclohexylamino)-2-phenylquinoline (VII), m.p. 133–134°, yield 82.5%, was recrystallized from petroleum ether and ether.

Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.65; N, 8.85. Found: C, 83.52; H, 7.36; N, 8.74.

The hydrochloride of VII was prepared in dry ether with dry hydrogen chloride gas, m.p. 184–185°, recrystallized from abs. ethanol.

Anal. Calcd. for $C_{22}H_{25}N_2Cl$: Cl, 10.05. Found: Cl, 10.37.

The monopicrate of VII was formed in ethanol by treating VII with one equivalent of picric acid, m.p. 207–208°.

Anal. Calcd. for $C_{28}H_{27}N_5O_7$: C, 61.64; H, 4.99. Found: C, 61.39; H, 5.01.

4-Diethylamino-2-phenylquinoline (VIII), was obtained as an oil and converted to the **hydrochloride VIIIa**, m.p. 158–161°, yield 75%, using dry hydrogen chloride gas in dry ether.

Anal. Calcd. for $C_{19}H_{21}N_2Cl$: C, 72.95; H, 6.76; Cl, 11.33. Found: C, 72.63; H, 6.84; Cl, 11.54.

The monopicrate of VIII was prepared from VIII in ethanol using one equiv. of picric acid; m.p. 177–180°.

Anal. Calcd. for $C_{25}H_{23}N_5O_7$: C, 59.40; H, 4.59. Found: C, 59.57; H, 4.72.

Hydrogenation of β-Amino-2-nitrochalcones.[1]—A 0.10-mole sample of β-diethylamino-2-nitrochalcone[1] was dissolved in 50 ml. of abs. ethanol and shaken for 2 hr. under 45 lb./in.[2] pressure of hydrogen in the presence of 0.5 g. of W-2 Raney nickel. The catalyst was removed by filtration, the solution decolorized with charcoal and concentrated to give a 74% yield of a product, m.p. 240–250°. Recrystallization from ethanol produced 4-hydroxy-2-phenylquinoline, m.p. 257–259°, identical with an authentic sample.[7]

This reaction was repeated using ethyl acetate as the solvent to give a 73% yield of the same product.

Similar hydrogenations of β-(N-methylcyclohexylamino)-2-nitrochalcone[1] produced 4-hydroxy-2-phenylquinoline in 81% yield when the solvent was abs. ethanol and in 88% yield in ethyl acetate.

Hydrogenation of 4-Nitrochalcone.—A 5.06-g. (0.02 mole) sample of 4-nitrochalcone[6] was suspended in 50 ml. of ethyl acetate and shaken under 45 lb./in.[2] pressure of hydrogen for 5 hr. in the presence of 0.5 g. of W-2 Raney nickel. The 4-aminochalcone was isolated and recrystallized from 95% ethanol, wt. 3.2 g. (72% yield), m.p. 151–152°.[6]

α,β-Dipiperidino-β-(4-aminophenyl)-propiophenone (IX).—A 2.1-g. (0.005 mole) sample of α,β-dipiperidino-β-(4-nitrophenyl)-propiophenone[1] was suspended in 50 ml. of ethyl acetate and shaken for 5 hr. under 45 lb./in.[2] pressure of hydrogen in the presence of 0.5 g. of W-2 Raney nickel. The catalyst was removed by filtration and the solution decolorized with charcoal. Careful evaporation of the solvent at room temperature under vacuum gave 1.94 g. (99% yield) of IX, m.p. 165–166°.

Anal. Calcd. for $C_{25}H_{33}O$: C, 76.68; H, 8.50; N, 10.73. Found: C, 76.79; H, 8.91; N, 11.14.

Attempts at recrystallization of IX from hot ethanol caused the release of piperidine in the solution and the precipitation of a polymeric substance, yellow in color and melting above 340°. This material was insoluble in most common organic solvents and was not attacked by cold chromic acid.

A 0.25-g. sample of IX was mixed with toluene and the solvent slowly distilled. Treatment of the distillate with dry hydrogen chloride gas gave 0.035 g. (50% yield of one equiv.) of piperidine hydrochloride, m.p. 245–247°.[12] The residue from the toluene distillate was a yellow-colored, high melting solid, insoluble in hot organic solvents.

α-Piperidino-4-aminochalcone (X).—Hydrogenation under the above-described conditions converted 1.68 g. (0.005 mole of α-piperidino-4-nitrochalcone[1] into 1.1 g. (72%) yield of X, red colored crystals, m.p. 139–140°, from ethyl acetate.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.17; H, 7.06; N, 8.96.

A 0.35-g. sample of X was heated for 3 hr. on the steambath in 50 ml. of 95% ethanol to which a few drops of piperidine was added. The starting material, wt. 0.30 g., m.p. 139–140°, was isolated unchanged after this treatment.

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[9] M. Kotake, T. Sakan and S. Senoh, THIS JOURNAL, **73**, 1832 (1951).

[10] L. I. Smith and J.W. Opie, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 56.

[11] N. Rubin and A. R. Day, *J. Org. Chem.*, **5**, 54 (1940).

[12] I. Heilbron, "Dictionary of Organic Compounds," Vol. IV Oxford University Press, New York, N. Y., 1953, p. 217.