TABLE I

N-Aralkylethylenediamines and their Dihydrochloride Salts

	Diamines	Dihydrochlorides	N		Cl	
	B.P., °C.	M.P., °C.	Calcd.	Found	Calcd.	Found
Benzyl-	111–113 (5 mm.)[7]	260 (dec.)	12.6	12.3	31.8	31.8
β-Phenethyl-	136–140 (12 mm.)[8]	240–260 (dec.)	11.8	11.6	30.0	29.7
p-Methylbenzyl-	107–110 (1 mm.)	>250 (dec.)	11.8	11.2	30.0	29.1

sodium to remove the final traces of water. Fractional distillation over sodium gave the products as colorless oils.

The dihydrochloride salts were prepared in the conventional manner and purified by recrystallization from aqueous ethanol.

Apparatus and Procedure. The titration assembly and procedure were essentially the same as that described by Chaberek and Martell.[9] The diamine dihydrochlorides were used at a concentration of about 1×10^{-3} mole of ligand per run. For the determination of copper complex stability constants a two to one molar ratio of ligand to copper(II) was used.

Acid Dissociation Constants. The consecutive dissociation constants of the acids conjugate to the diamines were calculated from potentiometric titration data of the free ligands by the algebraic method.[9]

Stability of the Copper-Diamine Complexes. The stability constants of the copper-diamine complexes (1–2) were calculated from the 1–2 titration curves by the method of Bjerrum.[10] From the plot of $\bar{n}$ (the degree of formation of the complex) versus pB (the negative logarithm of the ligand concentration), the values of log K_1 and log K_2 were read at $\bar{n}$ values of 1.5 and 0.5 respectively. In the titration of *N*-(*p*-methylbenzyl)ethylenediamine with copper(II), precipitation of a deep violet crystalline solid occurred at pH 5.9 even at ligand concentrations of 5×10^{-4} (2.5×10^{-4} mole copper(II)). However, a sufficient number of points was obtained to permit calculation of log K_1 and log K_2. The plots of $\bar{n}$ versus pB exhibited a definite inflection indicative of a greater tendency for complex formation with the first ligand molecule than with the second.

The marked base weakening effect of the aralkyl substituents on the acid dissociation constants of ethylenediamine compared to the base strengthening effect of alkyl substituents[3,4] is evident from a comparison of the data in Table II.

TABLE II

Acid Dissociation Constants and Copper Complex Stability Constants of *N*-Substituted Ethylenediamines $RNHCH_2CH_2NH_2$

R	$pK_{H_2B}{}^{+2}$	$pK_{HB}{}^{+}$	ΔpK	Log K_1	Log K_2	Log K_1/K_2
Benzyl-	6.48	9.41	2.93	9.12	7.56	1.56
p-Methylbenzyl-	6.51	9.41	2.90	9.23	7.57	1.66
β-Phenethyl-	6.59	9.44	2.85	9.11	7.38	1.73
H—[6]	7.47	10.18	2.71	10.76	9.37	1.43
CH_3—[3,6]	7.56	10.40	2.84	10.55	8.56	1.99
C_2H_5—[3,6]	7.63	10.56	2.93	10.19	8.38	1.81
i-C_3H_7—[3,5]	7.70	10.62	2.92	9.07	7.45	1.62

The inductive effect of the phenyl group, previously pointed out by Wepster,[11] appears to be responsible for the considerable increase in acid strength observed, as resonance interactions between the phenyl groups and nitrogen are prohibited by the intervening alkylene bridges.

Although the pK_{H_2B} values increase slightly in the expected order, the increase on going from the benzyl- to the phenethyl derivative is not as great as anticipated in view of the known marked attenuation of the inductive effect with increasing distance from the reaction center. This effect is prominent in the monoamines wherein pK_{HB} increases approximately 0.5 pK unit in going from benzylamine (pK_{HB} 9.37) to phenethylamine (pK_{HB} 9.83).[12] The strong inductive effect of the aralkyl group on the pK_{HB} values of the alkylamines is also evident.

The lower basicity of the donor nitrogens is reflected in the lower log K_1 and log K_2 values of the copper complexes. In addition, steric effects at least with respect to log K_2, undoubtedly contribute to the lower stability values observed. The steric effect on log K_2 can be attributed to the interference of the donor groups of the two ligands. The nature of the steric effects, if such are operative on log K_1, are not known. The overall effect of the *N*-aralkyl groups appears to be approximately equal to that of the bulky *N*-isopropyl substituent.[6]

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Anomalous Optical Rotatory Dispersion in the Morphine Series

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The study of the optical rotatory dispersion of organic compounds is an old idea[2,3] which has been extensively developed in recent years by Djerassi

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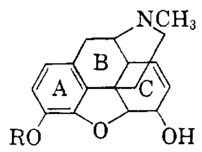
and his co-workers.[4] Investigation of the anomalous[5] dispersion of the optical rotatory power due to the ultraviolet absorption of a carbonyl group located in the vicinity of an asymmetric center has been particularly fruitful.

The application of dispersion techniques to the alkaloids and their derivatives has so far been limited to a relatively small number of compounds. Dispersion curves have been published for garryfoline, cuauchichicine, and their F-dihydroderivatives[6]; yohimbone,[6,7] alloyohimbone,[7] 3-epi-alloyohimbone[7] and yohimbane[6]; jervine[8]; seredone (from seredine)[7]; and 18-dehydrotetramethylholarrhimine.[9] In addition, the rotatory dispersions of two antipodal bases derived from haemanthamine and buphanisine,[10] of emetine and isoemetine,[11] morphinone,[12a] and a number of alkaloids from amaryllidaceous plants[12b] have been measured, although complete curves are not recorded. Of the compounds for which detailed data are available, only the ketonic bases (cuauchichicine, its F-dihydroderivative, yohimbone, alloyohimbone, 3-epialloyohimbone, seredone, jervine, and morphinone) have shown a pronounced anomalous dispersion. Two nonketonic bases (yohimbane and isoemetine) show a slightly anomalous curve while the others exhibit normal dispersion.

We would like to record evidence (Fig. 1) that pronouncedly anomalous optical rotatory dispersion curves are given by three bases, morphine (I), codeine (II), and dihydrocodeine (III), which contain no carbonyl group. In fact, dihydrocodeine has no ultraviolet chromophore other than the benzene ring. All three dispersion curves were measured down to 298 mμ and show distinct troughs at 304–305 mμ. Thus, by definition,[2,4] they are anomalous. Below 298 mμ the strong absorption band (λmax. 282–284, log ϵ *ca.*, 3.2)[13] produced by the aromatic ring prevented the passage of light at the concentrations investigated (0.209–0.358%). At much lower concentrations (0.01%), the solutions were transparent to 268 mμ, and it appeared that curves with two troughs were obtained. These latter data are not reported since the accuracy of the measurement of such low rotations ($\alpha = 0.008$–$0.03°$) is questionable[14] and because, as might be expected (ref. (2), p. 107), the wave length of the trough varies with the concentration.



I. R = H
II. R = CH_3
III. R = CH_3, no double bond in ring C

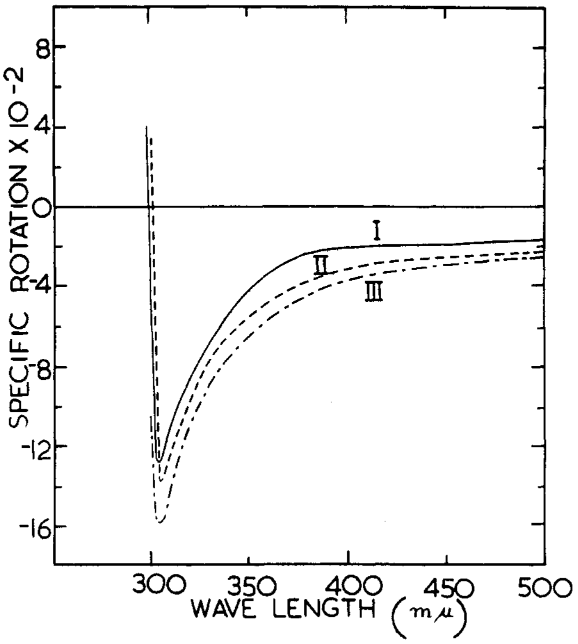


Fig. 1. Rotatory dispersion curves (dioxane solution) of: morphine (I), codeine (II), and dihydrocodeine (III)

The optical rotatory dispersion curves of morphine, codeine, and dihydrocodeine appear to constitute the first published evidence of *pronounced* anomalous behavior in non-ketonic bases[15] (note however the indistinct trough of yohimbane[6] and peak of isoemetine[11]). Interpretation of the observed anomalous dispersion effects is greatly complicated by the fact that they could arise from two sources: The superposition of the partial rotations produced by two asymmetric carbon atoms in the same molecule[16] and the presence of a chro-

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(15) Since the completion of the present work, we have been informed by Dr. Gloria Lyle (National Heart Institute) that some, although not all, nonketonic aromatic bases studied by her show strongly anomalous optical rotatory dispersion. Among the bases giving pronounced anomalies are the alkaloids ephedrine and tetrahydropalmatine. We are indebted to Dr. Lyle for permission to mention these results, which support and extend our findings.

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mophore in the vicinity of an asymmetric carbon atom[4] (ref. (2), p. 146). The latter possibility is apparently more important with Djerassi's ketonic compounds,[4,6,8] but the former might play an important role in nonketonic substances [*cf.* emetine, ref. (11)]. Three other nonketonic aromatic compounds for which data are available: estradiol,[17] 6-dehydroestradiol,[17] and *cis*-13-methyl-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene,[6] show normal behavior; however, their dispersion curves were followed only down to 315, 335, and 337.5 mμ, respectively. The present findings, together with those mentioned in ref. (15), suggest that the investigation of other aromatic nonketonic substances might be of great interest.

EXPERIMENTAL

The codeine and morphine samples were commercial samples manufactured by the New York Quinine and Chemical Works and Merck and Co., respectively; they were obtained through the Pharmacy School of the University of Connecticut. The dihydrocodeine was obtained from the L. F. Small Collection through the kind cooperation of Dr. L. J. Sargent of the National Institutes of Health. The measurements were made with a Model No. 200S Rudolph Photoelectric Spectropolarimeter[18] at the Ohio State University. A 0.1 decimeter tube with quartz ends was used.

Morphine (I), R. D. in dioxane (c 0.209): $[\alpha]^{19}$ ($\underline{500}$ mμ), −160°; ($\underline{340}$), −1280°; ($\underline{298}$), 420°.

Codeine (II), R. D. in dioxane (c 0.358): $[\alpha]^{21-21.7}$ ($\underline{650}$ mμ), −130°; ($\underline{589}$), −200°; ($\underline{305}$), −1360°; ($\underline{300}$), 360°.

Dihydrocodeine (III), R. D. in dioxane (c 0.246): $[\alpha]^{20.7-21}$ ($\underline{600}$ mμ), −210°; ($\underline{589}$), −220°; ($\underline{305}$), −1580°; ($\underline{300}$), −1050°.

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Characterization of Cupressaceae Tropolones as Dicyclohexylamine Salts

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Although a number of reactions can be used to characterize tropolones through the preparation of derivatives, only a few reagents appear to be generally satisfactory. For instance, transition metal chelates tend to have rather high melting points[1,2]; the nuclear substitution often yields several isomers, and the parent tropolone cannot be readily recovered from the derivative.[1] Similarly, several isomers usually result from esterification or etherification of the tropolonic hydroxyl;[1] hydrochloride salts do not appear to be very convenient for handling, and melting points often seem insufficiently sharp.[3,4] Picrates and ethylenediamine salts have been used with success in the case of a number of synthetically prepared tropolones.[3,5,6]

In our work on the natural tropolones from the heartwood of *Cupressaceae* species, (*i.e.*, tropolones of relatively weak acidity, carrying alkyl, methoxy, or hydroxy substituents), a question of identification of the isolated compounds often arose. The formation of amine salts appeared rather promising, and as it was felt to be generally desirable to have several convenient reagents available,[7] the whole area was reinvestigated using a number of amines in combination with several tropolones.

No derivatives could be obtained by using aromatic amines. This is understandable in view of their weaker basicity. Assuming pK values of 9.42 and 3.02[10] for aniline and diethylamine, respectively, and a pK of 7.21 for β-thujaplicin,[1] a rough calculation indicated that the corresponding salts should be hydrolyzed to 96% in the first case, and to only 1.4% in the second. Experimentally, using aniline and cyclohexylamine with nootkatin in 0.05 N ethanol solution, and utilizing change in absorbance at 490 m. as the measure of the degree of ionization, it was found that, with aniline, the hydrolysis of the salt was 96% complete, whereas with cyclohexylamine, hydrolysis could not be detected by the method used.

The lower boiling amines and ammonia were unsuitable for preparation of derivatives, the adducts being unstable to recrystallization, drying, or heating because of the gradual volatilization of the amine from the salt. Thus, the ammonia salts of a number of tropolones tested transformed into

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