Chem. Soc., **80**, 6249(1958).
(17) Hielsher, R., *Ber.*, **31**, 277(1898).
(18) Gabriel, S., and Colman, J., *ibid.*, **41**, 513(1908).
(19) Cheng, S. S., Piantadosi, C., and Irvin, J. L., *J. Med. Chem.*, **9**, 945(1966).
(20) Cheng, S. S., "The Chemistry and Antimicrobial Activity of Amino Ketones," Ph.D. dissertation, University of North Carolina, Chapel Hill, N. C., 1961.
(21) Gabriel, S., *Ber.*, **42**, 1240(1909).
(22) Ciamician, G., *ibid.*, **37**, 4231(1904).
(23) Allen, C. F. H., Young, D. M., and Gilbert, M. R., *J. Org. Chem.*, **2**, 235(1937).
(24) Koller, W., and Schlack, P., Ger. pat. 1,111,188; through *Chem. Abstr.*, **56**, 2427c (1962).

Keyphrases

2-(4′-Substituted phenyl)-Δ^1-pyrrolines—synthesis
Friedel-Crafts acylation—synthesis method
NMR spectroscopy—structure
UV spectrophotometry—structure
IR spectrophotometry—structure

Model Catalysts Which Simulate Penicillinase III

Structure-Reactivity Relationship in Catalysis of Penicillin Hydrolysis by Morpholinomethyl Derivatives of Catechol and Pyrogallol

By RENAAT D. KINGET and MICHAEL A. SCHWARTZ*

Studies of catalysis of hydrolysis of benzylpenicillin by aminoalkylcatechols have been extended to a series of morpholinomethyl derivatives of catechol and pyrogallol. Catalytic rate constants for each of the active species are related to their basicity and presence or absence of electrophilic groups and a positively charged amine in proper position to assist nucleophilic attack by a phenolate ion. Ionization constants for these compounds determined spectrally were the same as those determined potentiometrically indicating that the catalytic species are hybrids between charged amine and phenolate ion. The structures of these species are correlated with their efficiency as catalysts on the basis of a mechanism involving participation by up to four functional groups on the catalyst.

PREVIOUS STUDIES in this laboratory (1, 2) have shown that 3,6-bis(dimethylaminomethyl)catechol (CDM) is an efficient catalyst for the hydrolysis of benzylpenicillin to benzylpenicilloic acid and that both metastable tetrahedral intermediates and a catechol monoester are probably involved in the reaction pathway. The nature of the reactive catalytic species (CDM^{+1}) was deduced on the basis of the pH-rate profile, which showed a maximum at pH 8, and the bathochromic shift in the UV absorption spectrum upon neutralization of one equivalent of the dihydrochloride.

In the present work the studies have been extended to include a series of morpholinomethyl derivatives of catechol and pyrogallol. Morpholine is much less basic than dimethylamine and, it was thought, this difference in basicity would affect the catalytic efficiency of the catecholamines. Additionally, spectrophotometric titrations were carried out in order to learn more about the nature of the various species produced in the stepwise ionization of both the morpholine and dimethylamine derivatives.

EXPERIMENTAL

Synthesis of Catalysts—The morpholinomethyl derivatives of catechol and pyrogallol were prepared by the method of Fields *et al.* (3). In the case of the pyrogallol derivative the reaction was carried out in a nitrogen atmosphere to minimize oxidation. The hydrochloride salts were prepared by admitting dry hydrogen chloride gas into a methanol solution of the base and crystallization was induced by addition of ethyl acetate or dry ether. Table I lists these

Received May 22, 1968, from the Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214
Accepted for publication July 19, 1968.
Presented to Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.
Supported by grant No. AI-06901 from the National Institute of Allergy and Infectious Disease, U. S. Public Health Service, Bethesda, Md.
* To whom correspondence should be addressed.

TABLE I—MORPHOLINOMETHYL DERIVATIVES

Compd.	Abbreviation	M.p., °C.	Anal.[a] Calcd.	Found
3-Morpholinomethylcatechol·HCl	CMo	161–163	C, 53.77 H, 6.56 N, 5.70 Cl, 14.43	C, 53.61 H, 6.63 N, 5.83 Cl, 14.40
3,6-Bis(morpholinomethyl)catechol·2HCl	CDMo	265 dec.	C, 50.40 H, 6.87 N, 7.35 Cl, 18.60	C, 50.50 H, 6.83 N, 7.39 Cl, 18.48
3,4,6-Tris(morpholinomethyl)catechol·3HCl	CTMo	170–176	C, 48.80 H, 7.00 N, 8.13 Cl, 20.58	C, 48.57 H, 7.20 N, 8.01 Cl, 20.30
4,6-Bis(morpholinomethyl)pyrogallol·2HCl	PDMo	209–210 dec.	C, 48.37 H, 6.60 N, 7.05 Cl, 17.85	C, 48.16 H, 6.49 N, 6.91 Cl, 17.67

[a] Analyses were done by Galbraith Laboratories, Knoxville, Tenn.

compounds. The preparation of the dimethylaminomethyl derivatives was previously described (1).

Reagents—Potassium benzylpenicillin was kindly supplied by Bristol Laboratories, Syracuse, N. Y. All other materials were Fisher certified reagents.

Potentiometric Titrations—The apparent acid dissociation constants (pKa′) were determined by potentiometric titration at 31.5°, ionic strength 0.20, using a Radiometer TTT-1 automatic titrator with PHA 630T scale expander. Catecholamine concentration was 0.008 *M* and 0.2 *M* NaOH was used as titrant. When successive pKa′ values were less than 3 units apart the method of Noyes (4) was used to calculate the result.

Spectrophotometric Titration—The change in absorption at a single wavelength in the UV region as a function of pH was measured as follows.

A solution of the compound, acidified to pH 2, was placed in a conical flask modified with exit and entry tubes and containing electrodes from a Radiometer M-26 pH meter, a titrant delivery tube, and tube for admission of nitrogen. The solution was circulated to a flow cell on a Hitachi-Perkin-Elmer model 139 spectrophotometer by means of a peristaltic pump at a rate of about 300 ml./min. Titrant (1.0 *M* NaOH) was added from an ultraburette model 200, the volume added during a titration being insignificant relative to the total volume of solution.

The wavelengths at which the titrations were conducted were selected after preliminary observation of the effect of pH on absorption spectrum of the compound. Generally, the wavelength chosen was that at which there was the greatest change in absorbance with pH. From the plots of absorbance *versus* pH, spectral pKa′ values were determined.

The spectral dissociation constants were determined at room temperature (about 27°). In addition to the morpholinomethyl compounds in Table I, two of the dimethylaminomethyl derivatives were also titrated. Table II lists all the compounds studied with the characteristics of their spectra and the wavelengths at which the titrations were conducted.

Hydrolysis Rates—Rate of hydrolysis of benzylpenicillin in presence of catalyst was carried out as previously described (1) by following the rate of acid production on a pH-stat. All rates were measured at 31.5° and ionic strength 0.20. First-order kinetics was observed at constant pH and the concentrations of materials used.

TABLE II—SPECTRAL CHARACTERISTICS OF COMPOUNDS STUDIED

Compd.	$\lambda_{max.}$ at pH 1.5(mμ)	Change with Increasing pH	Wavelength Titrated
CMo	285	Decrease at 285; shoulder at 298	285
CDMo	288	Decrease at 288; shoulder at 300	288
CTMo	295	Decrease at 295; shoulder at 312	295
PDMo	273	Increase at 273	273
CDM[a]	287	Shift of $\lambda_{max.}$ to 305	305
CTM[b]	293	Shift of $\lambda_{max.}$ to 307; new peak 253 mμ	253, 307

[a] 3,6-Bis(dimethylaminomethyl)catechol·2HCl. [b] 3,4,6-Tris(dimethylaminomethyl)catechol·3HCl.

RESULTS

Spectral Titrations—The effect of pH on the ultraviolet absorption spectra of CDMo and CTMo are shown in Figs. 1 and 2, respectively. In each case the change with increasing pH involves a decrease in absorbance at the maximum and the formation of a shoulder at a higher wavelength. The pattern for CMo is the same as that shown for CDMo and is not depicted. These curves may be contrasted with the pattern previously observed for CDM (1) which is typical of all the dimethylaminomethyl derivatives. The latter compounds show pronounced bathochromic shifts of the wavelength of maximum absorption with increasing pH.

Figure 3 shows the spectral titration curves for CDMo and CMo. The dissociation constants for the latter compound were determined from the pH at the midpoint of the descending and ascending arms of the curve. For CDMo the situation is more complex. There is an obvious curvature at about pH 6.5. Apparently two ionization constants are involved in this portion of the curve. These constants were taken as the pH values at the midpoints of each section.

In the curve for PDMo in Fig. 4 there are clearly three dissociation constants involved and these were

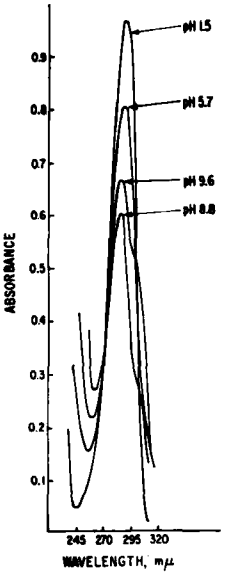


Fig. 1—UV absorption spectra of CDMo at various pH's.

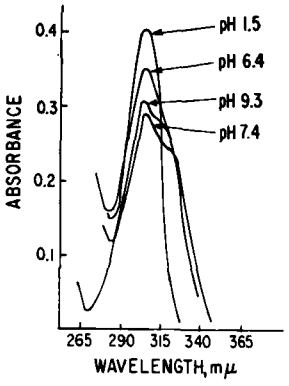


Fig. 2—UV absorption spectra of CTMo at various pH's.

estimated from the midpoints of the appropriate portions of the curve.

In Fig. 5 is shown the titration curve for CTMo in which are seen three distinct breaks in the downward portion corresponding to the three spectral pKa′ values taken as the midpoints of each section.

Figure 6 shows the titration curve for CDM with two unambiguous dissociations while in Fig. 7, showing the curve for CTM, there is a definite discontinuity in the ascending arm of the curve at both wavelengths studied. Again there are apparently two dissociations involved prior to the maximum at pH 9

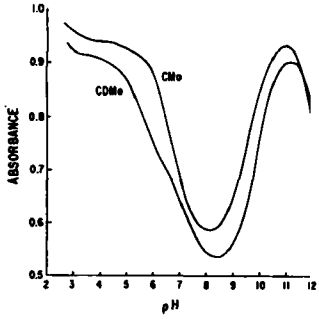


Fig. 3—Spectral titration curves for CDMo and CMo.

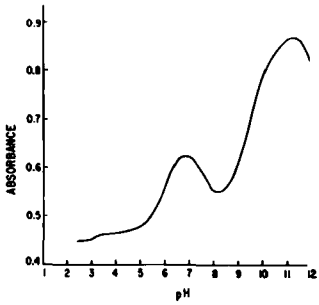


Fig. 4—Spectral titration curve for PDMo.

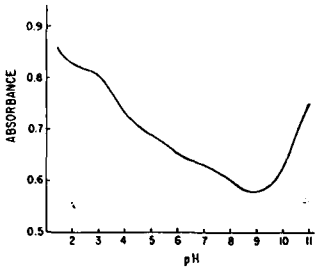


Fig. 5—Spectral titration curve for CTMo.

and the constants were determined as described above in the case of CDMo.

All of the pKa′ values determined both spectrally and potentiometrically are listed in Table III. It is apparent that in almost every case the values determined spectrally parallel those determined potentiometrically. The one apparent exception is pK_1' for PDMo where there is a difference of about 0.25 units between the two values. The value obtained by potentiometric titration is the more accurate of the two and the spectral pKa′ cannot be lower than the other on theoretical grounds. For this compound pK_1' and pK_2' are fairly close together and the overlap caused a change in direction of the spectral titration curve making it extremely difficult to separate pK_1' and pK_2' as was done in the potentiometric titration. The value for pK_1' used for purposes of this work was therefore 6.25.

Since the spectral and potentiometric ionization constants are the same, no microconstants are required and only one species is formed at each stage in the ionization scheme. This may be considered to be a hybrid between phenolate ion and free base of the amine.

Kinetic Studies—The observed first-order rate

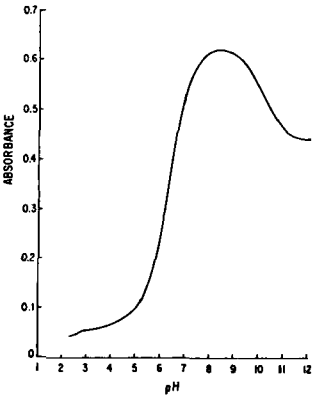


Fig. 6—Spectral titration curve for CDM.

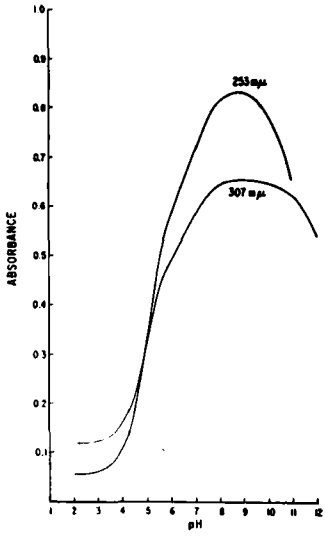


Fig. 7—Spectral titration curves for CTM at two wavelengths.

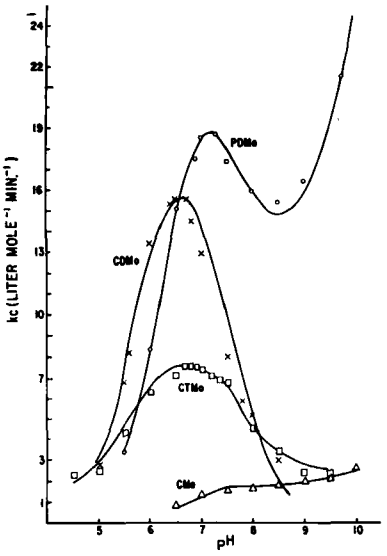


Fig. 8—pH-Rate profiles for morpholine derivatives. The curves were drawn from calculated constants while the points represent experimental data.

constants, after correction for alkaline hydrolysis where necessary, were divided by the molar concentration of catalyst to obtain the catalytic rate constants, k_c, at each pH. From the pH and pKa′ values the fraction of the total concentration of catalyst present in each ionic state was calculated. Specific rate constants for each species were calculated by assuming that the total rate constant, k_c, was the sum of the individual constants, *i.e.*,

$$k_c = k_{+2}f_{+2} + k_{+1}f_{+1} + k_0f_0 \ldots$$

where the subscripts represent the electrostatic charge on the particular species and the f's designate fraction. The curves shown in Fig. 8 were drawn from the calculated constants given in Table IV, while the points are the actual experimental data. Generally these follow a pattern similar to that of the corresponding dimethylamine derivatives (1) but the pH of maximum rate is different in each case. The species of CDMo with +1 charge has its maximum concentration at pH 6.5 where the maximum rate occurs, exactly as observed with CDM. The rate constant for $CDMo^{+1}$ is lower than that for CDM^{+1} (45 M^{-1} min.$^{-1}$) indicating the effect of basicity on catalytic efficiency. This effect is more explicitly depicted in the typical Brönsted plot of Fig. 9 which also includes data from the previous study (1). Statistical corrections of these data were made by the criteria of Benson (5). It can be seen that all of the species involved fall into three distinct groups. The lines drawn through two of the groups are essentially parallel while the right-hand line was drawn parallel to the other two through the points involved.

TABLE III—DISSOCIATION CONSTANTS

Compd.		pKa′ by Potentiometric Titration	pKa′ by Spectral Titration
CMo	pK_1'	6.75	6.7
	pK_2'	9.66	9.6
CDMo	pK_1'	5.65	5.6
	pK_2'	7.32	7.3
	pK_3'	9.86	9.8
CTMo	pK_1'	3.75	3.7
	pK_2'	5.80	5.7
	pK_3'	7.90	7.8
PDMo	pK_1'	6.25	6.0
	pK_2'	7.66	7.6
	pK_3'	9.65	9.6
CDM[a]	pK_1'	6.35	6.4
	pK_2'	9.65	9.7
CTM[a]	pK_1'	4.95	4.9
	pK_2'	7.10	7.2
	pK_2'	10.35	

[a] pKa′ by potentiometric titration was previously determined (1).

DISCUSSION

It is apparent from Fig. 9 that there is a consistent pattern in the relationship between the catalytic efficiency and structural features of the compounds studied. The most reactive group of species, taking into account basicity, is on the left-hand line and all have in common two electrophilic groups *ortho* and a positively charged amine *meta* to the nucleophilic phenolate. The next group (middle line in Fig. 9) lacks the charged amine in the *meta* position and as a result is 50-fold less reactive at the same pKa′ than the first group. The third group, consisting only of catecholate ion (C^{-1}), CMo^{-1}, and CMM^0, is 10-fold

TABLE IV—RATE CONSTANTS

Compd.	Net Charge on Species	Catalytic Rate Constant (M^{-1} min.$^{-1}$)
CMo	0	1.5
	−1	2.6
CDMo	+1	19.0
	0	2.0
	−1	—
CTMo	+2	1.5
	+1	8.5
	0	2.5
PDMo	+1	23.5
	0	10.0
	−1	30.0

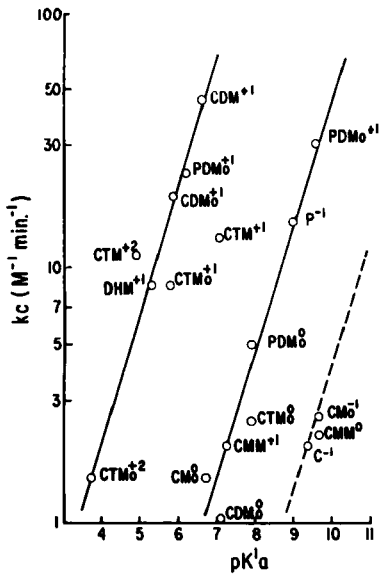


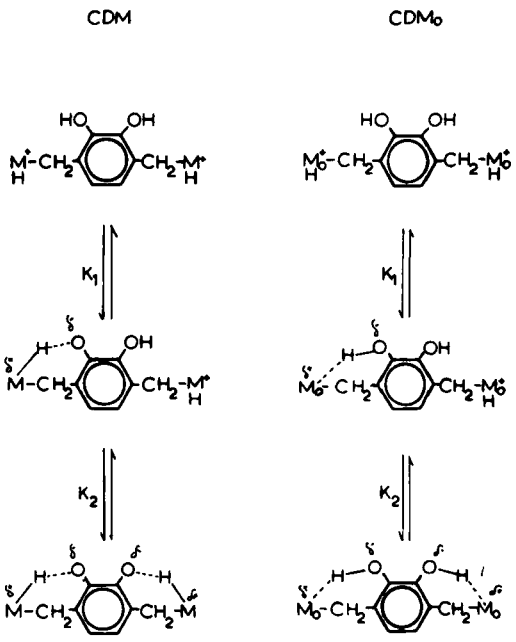
Fig. 9—Brönsted plot including data from the present study and Reference 1. *The symbols are all defined in the text.*

less reactive than the middle group and is missing one of the *ortho* electrophilic groups referred to above. These data provide a quantitative measure of the effect of each of the groups mentioned.

The results are in agreement with the previously proposed thesis that all four groups on species like CDM^{+1} are involved in the catalysis of penicillin hydrolysis. Study of rate of penicillin loss in addition to acid formation in the case of catechol (2) and CMo (6) has clearly demonstrated the presence of an intermediate, probably catechol monopenicilloate, in the reaction pathway. Thus the two electrophilic groups on the catalyst *ortho* to the phenolate may participate in either one or both steps, *i.e.*, ester formation and/or ester hydrolysis. Studies of hydrolysis of catechol monoesters (7, 8) have indicated participation by the phenolate ion and it seems likely that a positively charged amine on the other side of the ester would enhance the hydrolysis rate still further by general acid catalysis. The *ortho* phenolic hydroxyl group participates in the reaction of catecholate ion with isopropylmethylphosphonofluoridate (sarin) (9) and probably plays a similar role in formation of the ester intermediate in catechol-catalyzed penicillin hydrolysis. The role of the charged amine groups in the reaction with sarin is not clear. Epstein *et al.* (10) have referred to a "charge effect" by which these charged groups lower the basicity of the phenol without affecting its nucleophilicity toward the neutral substrate. This "charge effect" does not seem to be significant in the reaction of these compounds with penicillin. The species CMo^{0} falls on the same line as pyrogallol in Fig. 9, in one case a phenolic hydroxyl and in the other a protonated amine being involved. If the charge effect were significant, one would expect CMo^{0} to show a somewhat greater rate enhancement than pyrogallol. Also CMM^{+1} [3,5-bis(dimethylaminomethyl)catechol] falls on the line in the Brönsted plot with pyrogallol (P^{-}), the charged amine in the 5 position having no apparent effect on catalysis, as it should according to the charge effect hypothesis.

One species which does not fit with any group is CTM^{+1}. This species if formed by neutralization of the dimethylamine group in the 4 position would retain all of the structural features of the species on the left-hand line in Fig. 9. While its basicity is lower than that of CTM^{+2}, its reactivity is changed only very slightly. It seems that neutralization in the 4 position has little effect on the reactivity of the phenolate ion in CTM^{+1} while in $CTMo^{+1}$ there is a much larger effect. This result is consistent with the greater basicity of dimethylamine relative to morpholine.

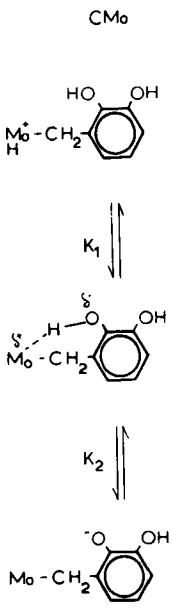
The kinetic data combined with the effects of pH change upon UV spectra provide a basis for consideration of the nature of each of the species of the catecholamines studied. In doing this, account must be taken of the fact that in each step some phenolic dissociation is involved and that only one species is produced. The spectral changes as a function of pH with the morpholine derivatives are much smaller than those observed with the dimethylamine compounds. This difference may be rationalized by the differences in basicity of the two amines. For comparison, pKb of *N*-methylmorpholine is 6.06 (11) and that of trimethylamine is 4.2 (12). The morpholine would therefore, have much less attraction for a proton than the dimethylamine and less influence on ionization of the phenol. Consider, for example, the comparison of CDM and CDMo in Scheme I. In each case neutralization of one acidic function leads to a hybrid species in which a proton is shared by the amine and phenolate ion. In CDM this proton is closer to the amine than in CDMo, consistent with the observed spectral behavior. While a rate constant for CDM° could not be determined accurately a value in the range 1–4 M^{-1} $min.^{-1}$ was estimated (1), placing this species in the



Scheme I

group with catecholate ion on the Brönsted plot. The similar species CDMo^0 however, fits better with the middle group containing pyrogallol anion. The rationale for this difference between the two species can be seen from the structures drawn in Scheme I. In CDMo^0 the protons are closer to the oxygens making them more available for the catalytic reaction than in CDM where they are closer to the amine groups.

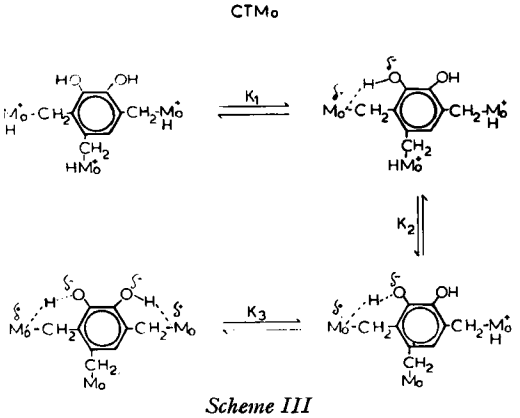
Scheme II depicts the proposed mode of ionization of CMo. It can be seen from Fig. 9 that the zero



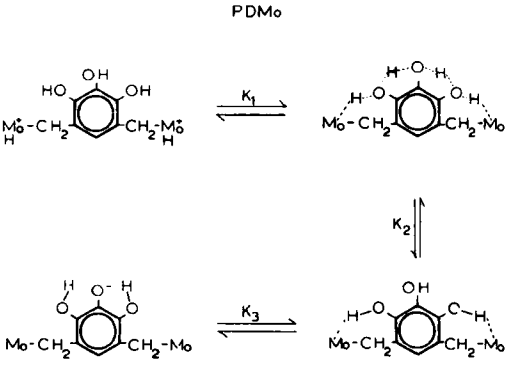
Scheme II

charged species behaves kinetically like pyrogallolate anion while CMo^{-1} resembles catechol in its catalytic activity. The structures drawn for these species reflect both the observed spectral changes and the rate data.

Of principal interest in Scheme III for CTMo is the fact that both CTMo^{+2} and CTMo^{+1} fall on the left-hand line of Fig. 9, and should resemble CDM^{+1} in arrangement of participating functional groups. Removal of a proton in the second step, from the



Scheme III



Scheme IV

morpholino in the 4 position leaves a structure with these features. Removal of the positive charge in the 4 position should enhance the attraction for the phenolic proton by the morpholine in the 3 position resulting in the observed further spectral shift. The structure shown for CTMo^0 is appropriate for a species resembling pyrogallolate ion in its catalytic activity.

In Scheme IV the dissociation process for PDMo is depicted. There are added complexities with this compound due to its symmetry and the fact that there are three hydroxyl groups which may influence spectral changes. Although there are probably other ways in which the kinetic and spectral data for this compound may be reconciled, that shown here does account for the observed results.

A point worthy of special note in this study is the effect of amino groups situated close to a phenol on the ionization of the latter. While phenols normally have pKa′ values in the range 9–10, the phenols in the present study have pKa′ values as low as 3.7. Even this weakly basic group shows a relatively high degree of nucleophilicity toward penicillin. Similar effects on phenolic groups in enzymes may occur if the environment surrounding the phenol is suitable. Therefore, tyrosine should not be excluded from consideration as a group in the active site of an enzyme on the basis of pKa′ measurements alone.

Perturbation of the pKa of a phenolic hydroxyl in a "reporter group" at the active site of chymotrypsin by a charged amine has been reported (13), further emphasizing the importance of local environment on the dissociation of an acidic group.

REFERENCES

(1) Schwartz, M. A., *J. Pharm. Sci.*, **54**, 1308(1965).
(2) Schwartz, M. A., and Pflug, G. R., *ibid.*, **56**, 1459 (1967).
(3) Fields, D. L., Miller, J. B., and Reynolds, D. D., *J. Org. Chem.*, **29**, 2640(1964).
(4) Noyes, A. A., *Z. Physik. Chem.* (Leipzig) **11**, 495 (1891).
(5) Benson, S. W., *J. Am. Chem. Soc.*, **80**, 5151(1958).
(6) Schwartz, M. A., and Pflug, G. R., unpublished data.
(7) Capon, B., and Ghosh, B. C., *J. Chem. Soc.*, **1966**, 492.
(8) Hansen, B., *Acta Chem. Scand.*, **17**, 1375(1963).
(9) Epstein, J., Rosenblatt, D. H., and Demek, M. M., *J. Am. Chem. Soc.*, **78**, 341(1956).
(10) Epstein, J., Michel, H. O., Rosenblatt, D. H., Plapinger, R. E., Stephani, R. A., and Cook, E., *ibid.*, **86**, 4959 (1964).
(11) Perrin, D. D., "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, England, 1965, p. 198.
(12) *Ibid.*, p. 15.
(13) Hille, M. B., and Koshland, D. E., Jr., *J. Am. Chem. Soc.*, **89**, 5945(1967).

Keyphrases

Catalysts, model—penicillinase simulation
Benzylpenicillin hydrolysis—catalyst structure-activity relationship
Catechol morpholinomethyl derivative—penicillin hydrolysis
Pyrogallol morpholinomethyl derivative—penicillin hydrolysis
Potentiometric titration—pKa determination
UV spectrophotometry—pKa determination

Synthesis of (±)-Norargemonine

By KUO-HSIUNG LEE and T. O. SOINE*

(±)-Norargemonine was synthesized in good yield by a multiple-step process. The procedure involved Bischler-Napieralski ring closure of *N*-4-benzyloxy-3-methoxy-phenethyl-2-(3,4-dimethoxyphenyl)acetamide, reduction of the ensuing 3,4-dihydro base to the tetrahydro form, and dehydrogenation of the latter to yield the isoquinoline which, however, had been debenzylated during dehydrogenation. Rebenzylation of the phenol, conversion to the methiodide, reduction to the corresponding *N*-methyl-1,2-dihydro base, and acid catalyzed cyclization accompanied by simultaneous debenzylation afforded (±)-norargemonine to complete the synthesis.

NORARGEMONINE WAS FIRST isolated by Soine and Gisvold (1) in 1944 from *Argemone hispida* (Gray). It was shown to be the monophenolic precursor of argemonine (I) by methylation with diazomethane (2–4) and argemonine, itself, has been shown to be (−)-*N*-methylpavine (2, 4, 5).

In a recent communication, the structure of norargemonine has been shown by Stermitz *et al.* (6) to be II by the reduction of protopapaverine methochloride with tin in hydrochloric acid according to the method of Späth and Epstein (7). An alternate reduction, not utilized but simply mentioned, would have been the catalytic method of Schöpf and Thierfelder (8). The Späth and Epstein method yielded the tetrahydro derivative [*i.e.*, (±)-codamine] together with a small amount of the objective compound (II). Since II is essentially a by-product of the above procedure and is obtained in poor yield it appeared that a more feasible synthetic route would be needed for other studies with II contemplated in these laboratories.

DISCUSSION

Benzyl vanillin (IV), prepared by benzylation of vanillin (III) according to Tomita *et al.* (9) was condensed with nitromethane, as described by Gairaud *et al.* (10) to furnish a good yield of 4-benzyloxy-3-methoxy-β-nitrostyrene (V). The latter was then subjected to lithium aluminum hydride reduction to give 4-benzyloxy-3-methoxyphenethylamine (VI), characterized as its formate salt. Condensation of VI and 3,4-dimethoxyphenylacetic acid (VII) was effected by application of the method reported by Shepard *et al.* (11) to yield the corresponding acid amide (VIII), *viz.*, *N*-(4-benzyloxy-3-methoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl)acetamide (Scheme I).

Cyclization of VIII by the Bischler-Napieralski procedure (12) led to the expected 3,4-dihydroisoquinoline which was isolated as its hydrochloride (IX). Sodium borohydride reduction of IX furnished a quantitative yield of the corresponding 1,2,3,4-tetrahydroisoquinoline (X) which showed 3,300 cm.$^{-1}$ (ν NH) in the IR spectrum in mineral oil and was very unstable, decomposing within 24 hr. at room temperature. Characterization of this compound was carried out by preparing its stable hydrochloride salt (XI) which exhibited a group of relatively sharp bands over 2,440–2,700 cm.$^{-1}$ (ν $\overset{+}{N}H_2$) in the IR spectrum. It also showed a typical benzyltetrahydroisoquinoline UV absorption and no bathochromic shift was observed upon the addition of sodium hydroxide. The NMR (τ, in $CDCl_3$) of this compound showed signals at 6.26 (3H, s, C_3'-$OC_3\underline{H}$),[1] 6.18 (6H, s., C_4'-$OC\underline{H}_3$ and C_6-$OC\underline{H}_3$),[1] 5.20 (2H, s, C_7-$OC\underline{H}_2C_6H_5$), 3.83 (1H, s, C_8-$\underline{H}$),[1] 2.75 (5H, s, C_7-$OCH_2C_6\underline{H}_5$), and the remaining aromatic protons appeared at 3.34–3.45 (4H).

Received June 3, 1968, from the Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455
Accepted for publication July 24, 1968.
* To whom all correspondence should be addressed.

[1] These assignments are based mainly on the suggestions of Tomita *et al.* (13) together with direct comparison with the series of closely related compounds prepared during the present studies.