Structure and Synthesis of 2-(4′-Substituted Phenyl)-Δ^1-pyrrolines from 4-Phthalimidobutyryl Chloride *via* Friedel-Crafts Acylation

By SHU-SING CHENG*, CLAUDE PIANTADOSI†, and J. LOGAN IRVIN

2-(4′-Substituted phenyl)-Δ^1-pyrrolines can be prepared conveniently from the hydrochlorides of 4′-substituted-4-aminobutyrophenones or their cyclization products, the corresponding Δ^1-pyrrolines hydrochlorides, by alkalinization. The hydrochlorides were prepared by the hydrolyses of 4′-substituted-4-phthalimidobutyrophenones, which were obtained from the Friedel-Crafts acylation reaction between the substituted benzenes and γ-phthalimidobutyryl chloride. Spectral evidence indicates that all the products obtained are Δ^1-pyrrolines rather than the Δ^2-isomers. This method should provide easy access to those 2-(4′-substituted phenyl)-Δ^1-pyrrolines unavailable by other routes due to the unavailability of the corresponding β-cyano and γ-nitro ketone intermediates or the corresponding Grignard reagents.

A GREAT NUMBER of 2-aryl-Δ^1-pyrrolidines have been prepared for a variety of pharmacological studies. For instance, 2-phenylpyrrolidine has been found to possess a weak antihypertensive effect against small doses of nicotine in the dog (1). These 2-arylpyrrolidines can be prepared from the low-pressure hydrogenation of the corresponding β-aroylpropionitrile or the intermediate 2-aryl-Δ^1-pyrrolines (2–5). Besides being employed as important intermediates for preparation of a variety of compounds, Δ^1-pyrroline has also been found to be a food flavor for fat or oil (6). However, the synthetic route mentioned above for the preparation of either aryl-Δ^1-pyrrolines or pyrrolidines is limited by the availability of the corresponding β-aroylpropionitriles and their precursors γ-amino ketones in the form of Mannich bases as indicated by Burckhalter and Short (1).

Other widely accepted methods for the synthesis of pyrrolines center on the reductive cyclization of γ-nitro ketones (7, 8) or the Grignard reaction between 4-chlorobutyronitrile and alkyl-, aryl-, or aralkylmagnesium halides (7, 9–16). All of the reductive cyclization reactions are based on the fact that the presumed intermediates, *N*-unsubstituted γ-amino ketones, are not stable and undergo dehydrative cyclization in the basic media. An early observation was made by Hielsher (17), who obtained 2-methyl-Δ^2-pyrroline from the reaction of 5-bromo-2-pentanone and alcoholic ammonia at 40–45°. Subsequently, Gabriel and Colman (18), reported the isolation of 2-phenyl-Δ^2-pyrroline hydrochloride from an attempted synthesis of 4-aminobutyrophenone hydrochloride, and that the corresponding pyrroline base was then obtained by alkalinization of the hydrochloride. Recent evidence has led to the concept that most of the Δ^2-pyrrolines reported in the earlier literature and those obtained from reaction between Grignard reagent and γ-chlorobutyronitrile are best represented by Δ^1-structures (7). In view of this fact and the observation made by Gabriel and Colman on the isolation of phenylpyrroline from the presumable cyclization of 4-aminobutyrophenone hydrochloride, it seemed feasible to prepare 2-(4′-substituted phenyl)-Δ^1-pyrrolines from substituted benzenes and γ-phthalimidobutyryl chloride *via* the Friedel-Crafts acylation reaction.

Since most of the substituted benzenes undergo Friedel-Crafts acylation with ease and give fair yields, this route should provide those 2-(4′-substituted phenyl)-Δ^1-pyrrolines which are difficult to obtain by other routes due to the unavailability of either the corresponding β-cyano and γ-nitro ketone intermediates, or the corresponding Grignard reagents.

In the work described herein, the condensations of γ-phthalimidobutyryl chloride with benzenes carrying *ortho* and *para* orienting groups afforded various substituted phenyl 4-phthalimidobutyrophenones. These can be alkyl, alk-

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oxyl, or halogens. However, iodobenzene failed to undergo the condensation under the influence of anhydrous aluminum chloride at elevated temperatures. Iodobenzene was decomposed with the liberation of iodine under these reaction conditions. The hydrolyses of these 4-phthalimidobutyrophenones in a mixture of glacial acetic acid and concentrated hydrochloric acid resulted in either the hydrochlorides of phenyl substituted 4-aminobutyrophenones or the 2-(4′-substituted phenyl)-Δ^1-pyrrolines. The latter are regarded as the cyclization products of the former and are readily obtainable by either raising the reaction temperature during the hydrolysis or by lengthening the period of acid treatment. The preparation of *para*-substituted 4-aminobutyrophenone hydrochlorides has recently been described in conjunction with the biological study of these compounds (19). By varying the reaction temperature and the length of acid treatment, both the open-chain *para*-substituted 4-aminobutyrophenone hydrochlorides and the corresponding 2-(4′-substituted phenyl)-Δ^1-pyrroline hydrochlorides can be obtained from the same reaction as will be described below. The open-chain *para*-substituted 4-aminobutyrophenone hydrochlorides are relatively unstable and tend to undergo dehydrative cyclization to form the corresponding 2-(4′-substituted phenyl)-Δ^1-pyrroline hydrochlorides, particularly during the melting process. For example, 4′-methyl-4-aminobutyrophenone hydrochloride first melted at 142–143° and solidified when the temperature reached approximately 160°, but after the material was cooled for several hours and reheated to determine the melting point, the melting did not occur until the temperature reached 201–202°, which corresponded to the melting point of the product of the dehydrative cyclization, 2-(4′-methylphenyl)-Δ^1-pyrroline hydrochloride. Thus, it is possible that the melting points that were reported for the other *para*-substituted 4-aminobutyrophenone hydrochlorides may represent the melting points of the corresponding 2-(4′-substituted phenyl)-Δ^1-pyrroline hydrochlorides, since the dehydration process occurs readily at elevated temperatures and the transition from one form to the other is not readily observable.

Since *N*-unsubstituted γ-amino ketones do not exist in the form of free base, but as pyrroline derivatives, it was conceivable that the 2-(4′-substituted phenyl)-pyrrolines could be obtained by the alkalinization of the corresponding 4′-substituted-4-aminobutyrophenone hydrochlorides. The experiments described below prove this is the case.

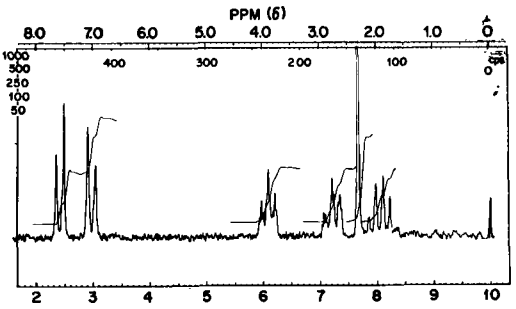


Fig. 1—The 60-Mc.p.s. proton NMR spectrum of 2-(4′-methylphenyl)-Δ^1-pyrroline in CCl_4 with tetramethylsilane internal standard (10τ).

All of the phthalimidobutyrophenones obtained from Friedel-Crafts condensations of 4-phthalimidobutyryl chloride with the monosubstituted benzenes are the *para*-substituted 4-phthalimidobutyrophenones as revealed by their IR spectra. The hydrolytic products are the corresponding *para*-disubstituted benzene derivatives (8.2–8.4 μ and 12.1–12.3 μ, *para*-disubstituted benzenes). The pyrroline bases obtained from the alkalinization of either the hydrochlorides of the γ-amino ketones or the corresponding pyrrolines are identical pairs, and are all Δ^1-pyrrolines, as can be shown by the lack of the chemical shift for olefinic proton in the 2.8–5.8 τ region of the 60 Mc. NMR spectra measured in carbon tetrachloride, using tetramethylsilane as internal standard (Figs. 1–3). In the spectrum of 2-(4′-methylphenyl)-Δ^1-pyrroline, the chemical shift of the methyl protons on the phenyl ring appears as a singlet at 7.68 τ, and the NMR pattern of the chemical shifts for phenyl protons agrees with that expected for *para*-disubstituted benzene with two different sets of protons. The two sharp bands at 2.35 and 2.5 τ may be assigned to the two phenyl protons at the *ortho* positions related to the carbon atom which is at the junction of the two rings and near the π-electron cloud of the —N=C<, whereas

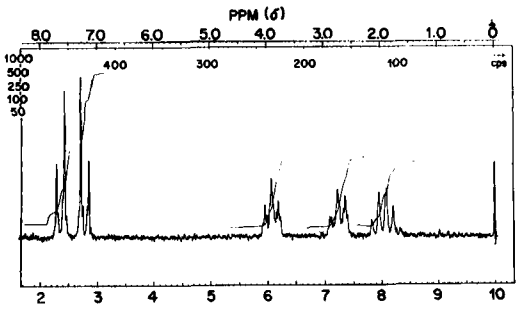


Fig. 2—The 60-Mc.p.s. proton NMR spectrum of 2-(4′-chlorophenyl)-Δ^1-pyrroline in CCl_4 with tetramethylsilane internal standard (10τ).

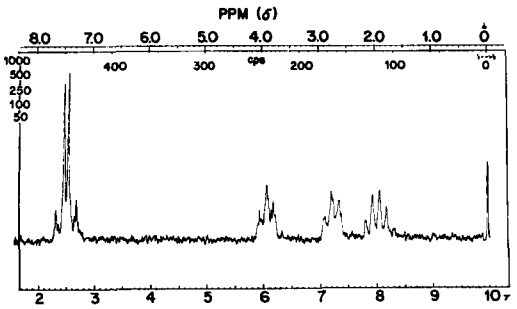


Fig. 3—The 60-Mc.p.s. proton NMR spectrum of 2-(4′-bromophenyl)-Δ¹-pyrroline in CCl_4 with tetramethylsilane internal standard (10τ).

the other two sharp bands at 2.9 and 3.05 τ might be the signals of the two other protons at the *meta* positions related to the carbon at the ring junction, and are far from the —N=C⟨.

All of the NMR spectra (Figs. 1–3) of the 2-(4′-substituted phenyl)-Δ¹-pyrroline bases studied herein display a quintet at 7.84, 7.95, 8.09, 8.20, 8.33 τ, and a triplet at 7.10, 7.23, 7.36 τ, and another low-field triplet at 5.95, 6.07, and 6.20 τ. The quintet may be due to the resonance of the two protons at C_4, split by two sets of two protons at C_3 and C_5. The high-field triplet may represent the chemical shift of two protons at C_3 split by the two protons at C_4, whereas the low-field triplet may be assigned to the two protons at C_5, which is in close proximity to the electron-rich nitrogen atom of the —N=C⟨. The spin-spin coupling constants are 7 c.p.s. for all the coupled protons mentioned above.

The UV spectra of 2-(4′-methylphenyl)-, 2-(4′-fluorophenyl)-, 2-(4′-chlorophenyl)-, and 2-(4′-bromophenyl)-Δ¹-pyrrolines in ethanol display an absorption maximum at 252 mμ. These absorption maxima were displaced to longer wavelengths when the ethanolic solutions were acidified with 0.1 *N* hydrochloric acid to a final concentration of approximately 0.001 *N*. The bathochromic shifts range from 13 to 23 mμ. The UV spectrum of 2-(4′-methoxyphenyl)-Δ¹-pyrroline has two absorption maxima, an intense end absorption occurs at 206 mμ with a molecular extinction coefficient 17,078, and a K-band maximum at 265 mμ (ε = 13,376), and on acidification, these maxima were displaced to 226 mμ (ε = 11,370) and 306 mμ (ε = 20,000), respectively (Fig. 4). The exceptionally long wavelength of these absorption maxima can be attributed to the auxochromic effect of the unshared electron pairs of the oxygen atom in the *para* methoxyl group. A similar effect also accounts for the longer wavelength of the absorption

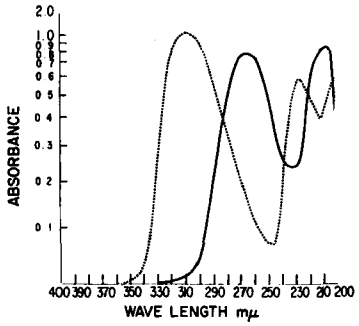


Fig. 4—Absorption spectrum of 2-(4′-methoxyphenyl)-Δ¹-pyrroline in ethanol (——) and in ethanol acidified with HCl (. . .).

maxima of the three *para*-halogeno-derivatives as compared with the absorption maximum of 2-phenyl-Δ¹-pyrroline ($\lambda_{max.}^{244 m\mu}$ $\epsilon_{max.}^{20,000}$). The relatively longer wavelength of the absorption maximum ($\lambda_{max.}^{255\ m\mu}$) in the spectrum of 2-(4′-methylphenyl)-Δ¹-pyrroline compared with that of 2-phenyl-Δ¹-pyrroline could be due to the effect of hyperconjugation. All of these UV spectral data are consistent with the observations made on the 2-aminoacetophenones and the 3-aminopropiophenones (20).

In the UV spectra, all of these Δ¹-pyrrolines display absorption maxima at the same wavelength in aqueous solution as in ethanol. Also, the same bathochromic shifts were observed for aqueous as for the alcoholic solutions. The absorption spectra of 2-(4′-chlorophenyl)-Δ¹-pyrroline in buffered aqueous solutions at various values of pH are presented in Fig. 5. From these data the apparent acid ionization exponent (pK′) of the 2-(4′-chlorophenyl)-pyrrolinium ion was calculated to be 6.46 at an ionic strength of 0.15 by use of the equation:

$$pH = pK' + \log \frac{\epsilon_{BH^+} - \epsilon}{\epsilon - \epsilon_B}$$

in which ε is the molar absorptivity at a certain pH value at which both the proton-donor species,

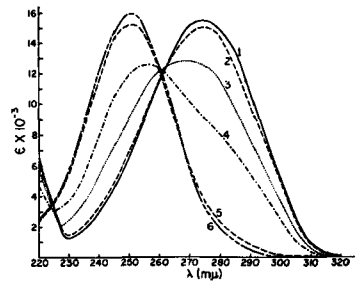


Fig. 5—Absorption spectra for aqueous solutions of 2-(4′-chlorophenyl)-Δ¹-pyrroline at several pH values. Key: 1, pH 1.0; 2, pH 4.58; 3, pH 5.9; 4, pH 6.53; 5, pH 7.99; 6, pH 12.2.

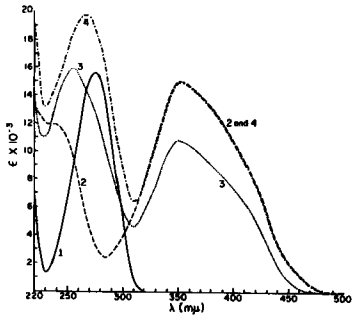


Fig. 6—Absorption spectra of aqueous solutions. Key: 1, 2-(4′-chlorophenyl)-Δ¹-pyrroline hydrochloride at pH 1; 2, picrate ion (picric acid in phosphate buffer at pH 7); 3, 2-(4′-chlorophenyl)-Δ¹-pyrroline picrate in distilled water; 4, the sum of Spectra 1 and 2.

BH^+ and the proton-acceptor species, B, are present in equilibrium; ϵ_{BH^+} is the molar absorptivity at a low pH at which the pyrroline is entirely in the form BH^+; ϵ_B is the molar absorptivity at a high pH at which the pyrroline is entirely in the form B. The average value of pK′ calculated from values of ϵ, ϵ_{BH^+}, and ϵ_B at $\lambda = 275$ mμ agreed closely with the average value calculated from absorptivity determined at 250 mμ.

In Fig. 6 are presented the absorption spectrum of the picrate of 2-(4′-chlorophenyl)-Δ¹-pyrroline (Spectrum 3) and for comparison, the spectra of the 2-(4′-chlorophenyl)-Δ¹-pyrrolinium ion (Spectrum 1), the picrate ion (Spectrum 2), and the sums of the latter two spectra (Spectrum 4). It can be seen that the absorption spectrum (Spectrum 3) of the picrate of 2-(4′-chlorophenyl)-Δ¹-pyrroline closely resembles that of the sum of the spectra of the picrate ion and the 2-(4′-chlorophenyl)-Δ¹-pyrrolinium ion, but the molar absorptivities are smaller at each wavelength than those of the combined spectrum (Spectrum 4). On the other hand, the absorption spectrum of the picrate complex also differs from that of the sum of the absorption spectra of free picric acid and the free base of 2-(4′-chlorophenyl)-Δ¹-pyrroline (Fig. 7). Consequently, it is concluded that the pyrroline in the picrate complex is incompletely protonated and exists as a mixture of the free base and the pyrrolinium ion.

The elemental analyses of the picrates of the various pyrrolines indicate a 1:1 ratio of picric acid to pyrroline. When an attempt (19) was made to prepare picrates of the 4′-substituted 4-aminobutyrophenones by addition of an excess of 4% picric acid in ethanol to an alcoholic solution of the hydrochlorides of the 4-aminobutyrophenones, the products isolated were identical in properties and analyses to the picrates of the corresponding 2-(4′-substituted phenyl)-Δ¹-pyrrolines, indicating that cyclization to the pyrrolines had occurred. A probable explanation may be that picric acid converted the water-soluble hydrochlorides into the difficultly soluble picrates, but did not completely protonate the *N*-unsubstituted γ-ketones; the latter underwent dehydrative cyclization to form the corresponding 5-membered ring Δ¹-pyrrolines, thus giving 2-(4′-substituted phenyl)-Δ¹-pyrroline picrates as products.

The IR absorption spectra of these 2-(4′-substituted phenyl)-Δ¹-pyrroline bases in mineral oil display a medium band in the region of 1613–1640 $cm.^{-1}$ (6.20–6.10 μ), characteristic of the —N=C< stretching. For the hydrochlorides, these bands shift to slightly higher frequencies.

All of the Δ¹-pyrroline bases studied herein gave 2,4-dinitrophenylhydrazones when dissolved in a saturated solution of 2,4-dinitrophenylhydrazine in 1 *N* hydrochloric acid. The onset of the precipitation started within 2–15 min., varying with the concentration of the base and the nature of the 2-substituent in the Δ¹-pyrroline ring. This illustrates the facility of the opening of the Δ¹-pyrroline ring, in the acidic medium when carbonyl reagent is present. The opening of the pyrroline ring under the influence of base and acyl halide to form the corresponding acylamido ketone derivatives of γ-amino ketones is documented in the literature (7, 21) and has also been observed in this laboratory. In view of the fact that these 2-(4′-substituted phenyl)-Δ¹-pyrrolines undergo ring opening with ease and behave chemically as open-chain γ-amino ketones, these pyrroline derivatives may be regarded as anhydro forms of γ-amino ketones and serve as a good source for the latter entities. Perhaps these two forms are in equilibrium in the solution, and any reagent capable of forming derivatives with either the amino or the carbonyl function will displace the equilibrium in favor of

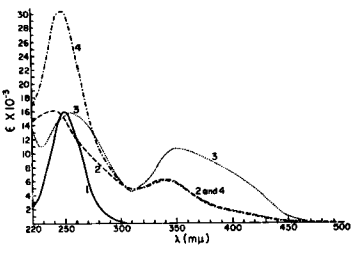
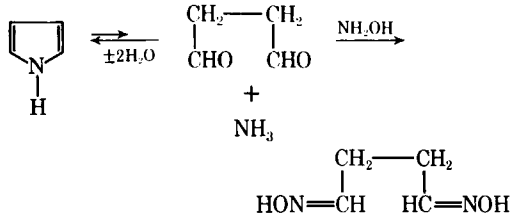


Fig. 7—Absorption spectra of aqueous solutions. Key: 1, 2-(4′-chlorophenyl)-Δ¹-pyrroline at pH 12; 2, picric acid in 2 N HCl; 3, 2-(4′-chlorophenyl)-Δ¹-pyrroline picrate in distilled water; 4, sum of Spectra 1 and 2.

the open-chain γ-amino ketone. Thus, with the reagent 2,4-dinitrophenylhydrazine in 1 *N* hydrochloric acid, the 2-(4′-chlorophenyl)-Δ¹-pyrroline base gave a 2,4-dinitrophenylhydrazone, m.p. 213–215°, in 2 min. This speculation seems analogous to the postulation made by Ciamician (22) on the reversible hydrolysis of pyrrole by bases (including the nearly neutral solution of hydroxylamine), in which the equilibrium, normally greatly in favor of the cyclic form, is displaced by fixing the succinaldehyde as the oxime:



The opening of the substituted pyrrole ring was also observed with hydrazines as the reagents (23), the products being the hydrazones of the diketones.

EXPERIMENTAL[1]

γ-Phthalimidobutyric Acid and γ-Phthalimidobutyryl Chloride—These compounds were prepared as described previously (19).

4′ - Methyl - 4 - phthalimidobutyrophenone—4-Phthalimidobutyryl chloride (40 g., 0.158 mole) was dissolved in 240 ml. of dry toluene. Forty grams (0.30 mole) of the anhydrous aluminum chloride (practical grade) was added in eight portions during a period of 40 min. while the solution was kept vigorously stirred and maintained at 90°. After 2 hr. of stirring, the mixture was poured with stirring into a mixture of 200 ml. of 1 *N* hydrochloric acid and 300 g. of crushed ice. The aqueous layer was extracted with four 30-ml. portions of toluene, and the extracts were combined with the toluene solution. The organic solution was washed with water, 5% sodium carbonate solution and dried over anhydrous sodium sulfate. The solid obtained from vacuum distillation of the solution was recrystallized from 95% alcohol. Twenty-nine grams of white crystals was obtained (60% yield), m.p. 115–116°.

4′-Methyl-4-aminobutyrophenone Hydrochloride and 2-(4′-Methylphenyl)-Δ¹-pyrroline Hydrochloride—The preparation of 4′-methyl-4-aminobutyrophenone hydrochloride has been reported (19). The procedure described below illustrates the isolation of both hydrochlorides of both 4′-methyl-4-amino-butyrophenone and 2-(4′-methylphenyl)-Δ¹-pyrroline from the same hydrolytic reaction by varying the reaction conditions as compared with those previously described (17).

4′-Methyl-4-phthalimidobutyrophenone (12 g., 0.052 mole) was dissolved in 36 ml. glacial acetic acid with the aid of heat. To this well stirred solution, 36 ml. of concentrated hydrochloric acid gradually was added, and the mixture was heated at the boiling point (*ca.* 107°) for 52 hr. A total of 60 ml. of concentrated hydrochloric acid was added during this period in order to compensate for the loss of hydrogen chloride due to refluxing. The mixture was allowed to cool to room temperature and filtered to remove the phthalic acid. The filtrate was evaporated under vacuum to remove hydrogen chloride and the resulting residue dissolved in water, extracted with diethyl ether to remove the remaining phthalic acid and the aqueous solution was then treated with decolorizing carbon.[2] The mixture was filtered and the filtrate evaporated *in vacuo* to a yield a syrupy liquid which was dissolved in ethanol, and upon the addition of ether, 6 g. of white crystals as the hydrochloride were obtained. Recrystallization from 20 ml. of ethanol gave 2.2 g. of crystals, m.p. 202–203°. The addition of acetone to the mother liquid gave a 2.6 g. yield of needle crystals, m.p. 142–143° after recrystallization from ethanol. From all the combined mother liquids, 0.5 g. of a mixture of these two hydrochlorides was obtained.

Both hydrochlorides gave a 2,4-dinitrophenylhydrazone when a saturated solution of 2,4-dinitrophenylhydrazine in 1 *N* hydrochloric acid was added to their aqueous solutions. Both of the 2,4-dinitrophenylhydrazones are identical and melt at 205–208° dec. The elemental analyses for the hydrochloride having a melting point of 142–143° correspond to the values calculated for 4′-methyl-4-aminobutyrophenone hydrochloride as previously described, whereas the elemental analyses of the hydrochloride having a m.p. of 202–203° agree with the structure for the dehydrated form, 2-(4′-methylphenyl)-Δ¹-pyrroline hydrochloride.

Anal.—Calcd. for $C_{11}H_{14}ClN$: C, 67.50; H, 7.21; Cl, 18.14; N, 7.17. Found: C, 66.84; H, 7.41; Cl, 18.05; N, 7.15. The UV spectra of both these hydrochlorides display an absorption maximum at 278 mμ. The $\epsilon_{max.}$ of 4′-methyl-4-aminobutyrophenone hydrochloride is 19,580, whereas that of 2-(4′-methylphenyl)-Δ¹-pyrroline hydrochloride is 16,904. When the solutions of these two compounds were buffered with sodium acetate, the maxima in both spectra were displaced to 252 mμ, the $\lambda_{max.}$ of the free 2-(4′-methylphenyl)-Δ¹-pyrroline.

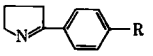
2-(4′-Methylphenyl)-Δ¹-pyrroline—4′-Methyl-4-aminobutyrophenone hydrochloride (1.65 g., 0.0077 mole) was dissolved in 15 ml. of water, and to this solution was added dropwise a solution of 5% sodium carbonate until the pH of the mixture was approximately equal to 8. The white precipitate was filtered and thoroughly washed with water to obtain 1 g. (81%) of white crystals, m.p. 58–58.5°.

Anal.—Calcd. for $C_{11}H_{13}N$: C, 82.96; H, 8.23; N, 8.80. Found: C, 83.08; H, 8.26; N, 8.80.

[1] All elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Ruhr, Germany. All melting points were taken in a Fisher-Johns melting point apparatus and have been corrected. The IR spectra were determined for mineral oil mulls, using the Perkin-Elmer Infracord spectrophotometer. The UV spectra for aqueous or ethanolic solutions were determined manually by using a Beckman DU spectrophotometer, and automatically by using a Beckman DB and DK-1 spectrophotometer with automatic recorders. NMR spectra were determined for carbon tetrachloride solutions, using the Varian A-60 high-resolution NMR spectrometer.

[2] Norit A, American Norit Co., Jacksonville, Fla.

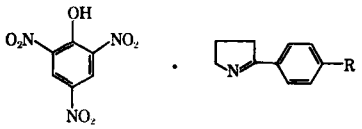
TABLE I—2-(4′-SUBSTITUTED PHENYL)-Δ¹-PYRROLINES



R	M.p., °C.	Yield, %	Molecular Formula	Anal., % Calcd.	Found
OCH_3	72–73[a]	90	$C_{11}H_{13}NO$	C, 75.38	C, 75.33
				H, 7.48	H, 7.62
				N, 7.80	N, 8.15
Br	87–88	80	$C_{10}H_{10}BrN$	C, 53.70	C, 53.60
				H, 4.52	H, 4.58
				N, 6.22	N, 6.23
				Br, 35.60	Br, 35.77
Cl	68–69	81	$C_{10}H_{10}ClN$	C, 66.83	C, 66.09
				H, 6.12	H, 5.68
				N, 7.09	N, 6.84
				Cl, 19.74	Cl, 19.80
F	42.5–43	84	$C_{10}H_{10}FN$	C, 73.57	C, 74.23
				H, 6.19	H, 6.02
				N, 8.58	N, 8.60
				F, 11.65	F, 11.57

[a] Lit. (24), m.p. 73–73.5°.

TABLE II—2-(4′-SUBSTITUTED PHENYL)-Δ¹-PYRROLINE PICRATES



R	M.p., °C	Yield, %	Molecular Formula	Anal., % Calcd.	Found
OCH_3	174–177	90	$C_{17}H_{16}N_4O_8$	C, 50.48	C, 50.77
				H, 3.98	H, 4.20
				N, 13.86	N, 13.84
Br	225–230 dec.	90	$C_{16}H_{13}BrN_4O_7$	C, 42.38	C, 43.08
				H, 2.89	H, 3.10
				N, 12.36	N, 12.11
				Br, 17.64	Br, 17.40
Cl	215–218 dec.	90	$C_{16}H_{13}ClN_4O_7$	C, 46.99	C, 47.11
				H, 3.21	H, 3.43
				N, 13.71	N, 13.55
				Cl, 8.68	Cl, 8.68
F	190 dec.	85	$C_{16}H_{13}FN_4O_7$	C, 48.97	C, 49.01
				H, 3.34	H, 3.50
				N, 14.28	N, 14.08
				F, 4.84	F, 4.73

This product was identical with that prepared from the hydrochloride of 2-(4′-methylphenyl)-Δ¹-pyrroline. The other 2-(4′-substituted phenyl)-Δ¹-pyrroline bases prepared by a similar procedure are recorded in Table I.

2-(4′-Methylphenyl)-Δ¹-pyrroline Picrate—2-(4′-Methylphenyl)-Δ¹-pyrroline (0.2148 g., 0.0013 mole) was dissolved in 3 ml. of 95% alcohol, an excess of 4% picric acid in 95% ethanol was added dropwise to this solution to obtain a precipitate. After the mixture was allowed to stand at room temperature for 15 min., the precipitate was filtered and washed with 95% alcohol. The crude product was then recrystallized from 30 ml. of 95% boiling alcohol. The yellow shining crystals (0.445 g., 88% yield) melted at 187–189° with decomposition.

Anal.—Calcd. for $C_{17}H_{16}N_4O_7$: C, 52.56; H, 4.15; N, 14.43. Found: C, 52.58; H, 4.55; N, 14.49. Data for other picrates of 2-(4′-substituted phenyl)-Δ¹-pyrroline prepared by a similar procedure are recorded in Table II.

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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

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