Synthesis and Spectral Data for Cinchoninic Acids

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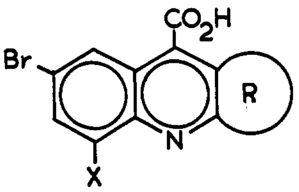
Twenty-two cinchoninic acids (quinoline-4-carboxylic acids) were synthesized by the Pfitzinger method from substituted isatin and a series of ketones. A detailed study of the ir, uv, and nmr spectra of these acids was carried out. These studies suggest the existence of cinchoninic acids in the zwitterionic form.

Twenty-two cinchoninic acids were synthesized by the Pfitzinger method (*7*) for use in biological activity studies, through the condensation of isatin, 5-bromoisatin, and 5,7-dibromoisatin with the following ketones: acetone, cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, α-, β-, and γ-acetylpyridines. The structure and physical properties of the synthesized cinchoninic acids are given in Table I.

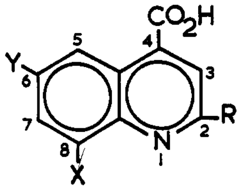
The ketones were allowed to react with isatin, 5-bromoisatin, and 5,7-dibromoisatin in strong alcoholic potassium hydroxide (33%). In most cases the reaction mixture was refluxed for 72 hr. In a few cases, the time of reflux was varied from 22–72 hr, but no significant change in the yield was observed. It has been mentioned by El-Abbady et al.(*3*), that α-tetralone condensed with 5-bromoisatin and 5,7-dibromoisatin under the normal Pfitzinger condition, and that the bromine atoms in both 5- and 7-positions were hydrolyzed giving the corresponding hydroxy- and dihydroxycinchoninic acids, respectively. In the present investigation, 5,7-dibromoisatin was allowed to react with cyclohexanone under the usual Pfitzinger condition of 33% potassium hydroxide for 96 hr. The product was 6,8-dibromo-2,3-cyclohexanocinchoninic acid (If), and no hydrolysis products were observed as indicated by its elemental analysis, ir and nmr spectra.

Nuclear Magnetic Resonance Spectra of Cinchoninic Acids. The chemical shifts and coupling constants for the cinchoninic acids studied are summarized in Table II. The assignments of the resonance lines were as follows: the aromatic protons appeared as an ABX pattern. The AB part of this system appeared as double-doublet at 1.44 τ and 1.1 τ (J_{78} = 2 Hz). The resonance line at 1.10 τ was assigned to H_8 adjacent to the tertiary nitrogen atom of the quinoline ring. The coupling constant between H_5 and H_7 was too small to be measured. The signal at 1.75 τ could not be resolved into a doublet, therefore a broad singlet was observed for H_5. The aliphatic part of the spectrum appeared as two groups of lines. An unsymmetrical triplet appeared

Table I. Physical Properties of Cinchoninic Acids[a]



I



II

	Molecular formula	*X*	*Y*	R	Mp, °C, decomp.	Yield	Reflux time
Ia	$C_{13}H_{10}BrNO_2$	H		Cyclopentane	286–8	57	22
Ib	$C_{14}H_{12}BrNO_2$	H		Cyclohexane	290–2	60	72
Ic	$C_{15}H_{14}BrNO_2$	H		Cycloheptane	301–3	70	72
Id	$C_{16}H_{16}BrNO_2$	H		Cyclooctane	316–18	65	72
Ie	$C_{13}H_9Br_2NO_2$	Br		Cyclopentane	314–16	55	22
If	$C_{14}H_{11}Br_2NO_2$	Br		Cyclohexane	310–12	65	24
Ig	$C_{15}H_{13}Br_2NO_2$	Br		Cycloheptane	256–8	60	24
Ih	$C_{16}H_{15}Br_2NO_2$	Br		Cyclooctane	265–7	60	72
IIa	$C_{11}H_9NO_2$	H	H	CH_3	246–8	70	72
IIb	$C_{11}H_8BrNO_2$	H	Br	CH_3	266–8	75	72
IIc	$C_{11}H_7Br_2NO_2$	Br	Br	CH_3	265–6	70	72
IId	$C_{15}H_{10}N_2O_2$	H	H	α-Pyridyl	296–8	55	72
IIe	$C_{15}H_{10}N_2O_2$	H	H	β-Pyridyl	316–18	65	72
IIf	$C_{15}H_{10}N_2O_2$	H	H	γ-Pyridyl	310–12	70	72
IIg	$C_{15}H_9BrN_2O_2$	H	Br	α-Pyridyl	324–6	61	22
IIh	$C_{15}H_9BrN_2O_2$	H	Br	β-Pyridyl	307–9	50	22
IIi	$C_{15}H_9BrN_2O_2$	H	Br	γ-Pyridyl	308–10	50	22
IIj	$C_{15}H_8Br_2N_2O_2$	Br	Br	α-Pyridyl	314–16	50	22
IIk	$C_{15}H_8Br_2N_2O_2$	Br	Br	β-Pyridyl	330–2	61	22
IIl	$C_{15}H_8Br_2N_2O_2$	Br	Br	γ-Pyridyl	324–6	60	22
IIm	$C_{11}H_6Br_3NO_2$	H	H	CBr_3	194–6		
IIn	$C_{11}H_7NO_4$	H	H	COOH	246–7		

[a] Elemental analyses (C, H, N) in agreement with theoretical values were obtained and submitted for review.

Table II. Nuclear Magnetic Resonance Data for Cinchoninic Acids

	Solvent	Aliphatic or pyridine-H	H-1	H-3	H-5	H-6	H-7	H-8	J_{78} Hz	J_{57} Hz	J_{56} Hz
Ia	TFA	6.24t, 7.27q			1.75s		1.44d	1.1d	2		
Ib	DMSO	5.6s, 7.1s, 8.1s			2.05s		2.0s	2.0s			
Ic	TFA	6.37s, 6.67bs, 7.92bs			1.74s		1.74s	1.5s			
Id	TFA	6.56bs, 7.9bs, 8.4bs	−4.35		1.75s		1.75s	1.56s			
Ie	DMSO	6.66bs, 7.86bs			1.67s		1.36s				
If	TFA	6.33bs, 6.67bs, 7.78bs			1.5d		1.35d			2	
Ig	TFA	6.22bs, 6.66bs, 7.9bs	1.66		1.48		1.35			2	
	DMSO	6.75bs, 7.1bs, 8.2bs	2.00		2.05d		1.57d			2	
Ih	TFA	6.26bs, 6.34bs, 7.86bs, 8.39bs.			1.48d		1.34d			2	
	DMSO	6.9bs, 8.22bs, 8.64bs			2.03d		1.55d			2	
IIa	TFA	6.67 CH_3	−4.55	1.34s	1.58dd	1.58	1.58	0.68	6	2	6
	DMSO	6.9 CH_3	−0.35	1.72	1.5dd	2.0m	1.75m	0.85dd	6	2	6
IIb	TFA	6.8 CH_3	0.10	1.37s	1.67s		1.67s	0.55s			
	DMSO	7.28 CH_3	0.20	2.0s	2.0s		0.85s	2.0			
IIc	TFA	6.33 CH_3	−0.85	1.25s	1.25d		0.55d			2	
	DMSO	7.20 CH_3	−0.82	1.90s	1.6d		0.92d			2	
IIg	TFA	0.83m(py)	−1.50	1.65s	1.6s		1.6s	1.85d	2		
IIh	TFA	−0.5, 0.3d, 1.45m(py)	−0.65	1.10s	0.9s		0.9s	1.65s	2		
IIi	TFA	1.0d, 0.5d,(py)	−2.0	0.85s	1.5s		1.5s	1.35s			
IIj	TFA	1.7dd, 0.75m(py)	−0.70	1.75s	1.5d		0.95d			2	
IIk	TFA	−0.1, 1.45m, 0.25dd(py)		1.0s	1.6d		0.84d				
	DMSO	0.3, 1.1m, 1.10dd(py)		1.47s	1.55d		0.60d			2	
IIl	TFA	1.4m(py)		0.83s	0.95s		0.55s				
IIm	DMSO		−0.50	1.15s	1.6dd	2.0m	2.0m	0.9dd	6	2	6
IIn	DMSO		−0.80	1.30s	1.6dd	2.0m	2.0m	1.0dd	6	2	6

s = singlet, bs = broad singlet, m = multiplet, d = doublet, dd = double doublet, q = quintet, t = triplet, TFA = trifluoroacetic acid, DMSO = deuterated dimethylsulfoxide, Py = pyridine.

Table III. Infrared Absorption Data for Cinchoninic Acids

	νOH	νC=NH^{+}	νCO$_2^-$,C=O	νCO$_2$H	ν=C—H,C=C,C=N	νC—H in-plane deformation	νC—H out-of-plane deformation
Ib	3448w 2469m	2469m 1818m	1639s 1369s	1449w 1422w 1282s	1675s, 1587s 1492m, 3096m	1234m, 1176m 1136m, 1063m 1010m	884m, 819s 826s, 735w
Ic	3472w 2500m	2500m 1960m	1666s 1369m 1282s	1418m 1396m	1666s, 1600s 1492m, 3096m	1227m, 1194m 1162m, 1123s	900s, 877m 862m, 840m 819s, 775m 746m, 724m
Id	3448w 2500m	2500m 2000m	1724s 1666s 1369s	1449m 1428w 1392m	1666s, 1587s 1492s, 3096m 2941m	1222m, 1204w 1176w, 1098m 1075s	980m, 884m 826s, 793m 757m, 717m
If	3448m 2564m	2564m 1923w	1724s	1428s 1388s 1333s 1265s	1626w, 1587s 1470s, 3096m	1242m, 1204s 1136w, 1087m 1020m, 980w 970m	862s, 826m 787m, 729m 704m, 680s
Ig	3448w 2564m	2564m 1923w	1724s	1428m 1388m 1265w 1250s	1585s, 1538w 1470m, 1449m 3096m	1204s, 1190s 1123w, 1098w 1075w, 1030m 1010m, 961s	884m, 869s 833m, 826m 806m, 787m 735m, 724m
Ih	3448w	2564m 1886w	1724s	1408m 1388m 1245s	1639w, 1587s 1538w, 1470s 3096m	1219s, 1190s 1162m, 1136m 1123m, 1098m 1042m, 990s	877m, 869s 819m, 787m 775m, 763w 735m, 724m
IIa	3508s 2439s	2439s 2000s	1680m	1388s 1369s 1282s	1612s, 1492m 3030m	1234m, 1212m 1187m, 1129m 1087s, 1030m	847s, 806s 781s, 769s 757m, 719s
IId	3448m 2500m	2500m 1886m	1709s	1408w 1360m 1282s	1587s, 1481s	1204m, 1149m 1098w, 1087m 1010s,	892m, 862m 826w, 793m 775m, 757m 740m, 724m
IIe	3448m 2500m	2500m 1923m	1715s	1438m 1408w 1360m 1282s	1605s, 1587s 1481s, 3125m	1250s, 1183s 1098m, 1087m 1063m, 1052m 1015s, 929m	892m, 869m 826s, 793s 757m, 746m 729m
IIi	3448m 2439s	2439s 1960s	1724s	1464w 1408s 1273s	1612s, 1587s 1515m, 3096m	1250s, 1219s 1204s, 1149s 1098w, 1063s	909m, 862m 840s, 800s 781s, 763m
IIj	3448m 2500w	2500w 1923w	1694m	1388s 1315m 1250m	1592s, 1574s 1479m, 3096m	1197m, 1183m 1123w, 1075m 1041m	892m, 869s 819m, 806m 781m, 775m 746w, 719s 704s.

at 6.24 τ, and was assigned for the four protons adjacent to the quinoline ring. A quintet centered at 7.27 τ was assigned for the two other protons of the cyclopentane ring. The spectrum of this compound was measured in TFA, and the NH$^+$ signal was not detected. It probably overlapped with the strong TFA signal. The nmr spectra of the remaining compounds were interpreted in the same manner.

An examination of the nmr spectra of cinchoninic acids shows that the NH$^+$ signal could be observed easily in those acids substituted with pyridyl groups at the 2-position of the quinoline ring. This may be explained by the fact that pyridyl groups are electron-withdrawing groups, therefore they decrease the electron density on the quinoline ring. This effect makes these acids stronger than those with saturated alicyclic rings attached to C$_2$ and C$_3$, thus increasing the amount of the zwitterionic form. Stephenson and Sponer (*9*) have noticed in a series of pyridylcarboxylic acids, that the basicity of the nitrogen atom is changed very little by the introduction of the carboxyl group, but the acidity of the carboxyl group itself is greatly enhanced by the presence of the nitrogen. When a methyl group is attached to the 2-position of the quinoline ring, the NH$^+$ proton peak was easily detected, and appeared at higher fields. This group increases the basicity of the nitrogen atom, thus increasing the zwitterionic form.

The position of the NH$^+$ signal in IIa, IIb, and IIc is subject to a great change. In IIa, this proton appeared at -4.55 τ while in IIc, it appeared at -0.85 τ, both measured in TFA. The two bromine atoms in IIc donate electrons by resonance to the ring, thus developing a large negative charge on the carbon attached to nitrogen. This negative charge will repel the pair of electrons on the nitrogen, making these electrons closer to the proton of the nitrogen. This will increase the shielding effect causing the large shift to higher fields.

Infrared Spectra of Cinchoninic Acids. Substituted cinchoninic acids listed in Table III showed the presence of a carboxylic OH group in the 3448 cm^{-1} and 2500–2469 cm^{-1} regions (*1*). The intensity of these bands varied greatly; it was weak and broad in most of these acids indicating extensive hydrogen bonding. A band in the high frequency region of 1724–1639 cm^{-1} range was attributed to C=O stretching vibration. The band in the low frequency region was assigned to the carboxylate ion (CO$_2^-$). The presence of two bands at about 2500 cm^{-1} and 2200–1818 cm^{-1} suggests the presence of an NH$^+$ group (*2*). The presence of these two bands, together with that of the carboxylate ion, suggests the existence of these acids at least, in part, in the solid state as the dipolar ion "zwitterion." This behavior has been noted in amino acids, as the ionized and unionized carboxyl groups are present together in the solid state (*1*). In the dipolar structure of these acids, the carboxyl group is ionized giving the CO$_2^-$ group, in which resonance is possible between the two C—O bonds. In consequence, the characteristic carboxyl absorption vanishes and is replaced by two bands between 1610 cm^{-1} and 1550 cm^{-1} and between 1400 cm^{-1} and 1300 cm^{-1}, which correspond to the symmetric and antisymmetric vibrations of the CO$_2^-$ structure. Table III shows that the cinchoninic acids studied have 3–4 bands in the region 1675–1470 cm^{-1} which were assigned for the C=C and C=N vibrations of the quinoline ring. Interaction between C=C and C=N vibrations appear to occur in a very similar way to

Table IV. Ultraviolet Absorption Data for Cinchoninic Acids

	Ethanol, $\lambda_{max(m\mu)(\log\epsilon)}$	Dioxan, $\lambda_{max(m\mu)(\log\epsilon)}$	0.1 *N* NaCH, $\lambda_{max(m\mu)(\log\epsilon)}$	Water, λ_{max}	0.1*N* HCl, $\lambda_{max(\log\epsilon)}$
Ia	203 (3.75), 237 (4.32) 295 (3.53), 328 (3.47)	252 (3.79), 295 (3.13) 337 (3.36)	225 (5.31), 238 (5.32) 330 (4.54)	222, 241 330	
Ib	232 (4.84), 302 (3.83) 314 (3.90),	239 (4.47), 306 (3.83) 317 (3.90)	232 (4.80), 303 (3.85) 315 (3.92)		
Ic	232 (4.82), 300 (3.74) 312 (3.80)	239 (4.48), 302 (3.80) 314 (3.91)	231 (4.72), 300 (3.71) 315 (3.80)		
Id	236, 312, 326	242 (4.08), 315 (3.34) 329 (3.44)	236, 312, 327	237, 313, 327	
Ie	220 (4.56), 241 (4.50) 317 (3.75), 331 (3.75)	250 (4.51), 321 (3.95) 334 (3.98)	223 (4.30), 239 (4.43) 318 (3.66)	220, 241 317, 331	
If	234 (4.72), 317 (3.71) 319 (3.68)	241 (4.51), 309 (3.68) 321 (3.71)	238 (4.69), 307 (3.77) 309 (3.74)		
Ig	233 (5.99), 270 (5.72) 316 (4.80)	217 (5.33), 306 (4.62) 318 (4.66)	236 (4.68), 305 (3.60) 317 (3.60)		
Ih	234 (4.54), 305 (3.49) 317 (3.45)	242 (4.59), 307 (3.71) 319 (3.76)	237 (4.79), 306 (3.80) 318 (3.77)		
IIa	210 (4.49), 228 (4.45) 285 (3.71), 317 (3.29)	209, 231	218, 230, 303, 317	203, 238 305, 317	203 (4.70) 237 (4.70) 267 (4.00)
IIb	217 (4.15), 234 (4.30) 286 (3.44), 326 (3.31)	249 (3.95), 292 (3.22) 335 (3.46)	224 (4.30), 233 (4.35) 280 (3.60), 325 (3.82)	215, 236 312, 326	
IIc	202 (4.00), 215 (4.23) 231 (4.41), 282 (3.35)	215 (4.24), 244 (4.12) 322 (3.42)	216 (4.50), 233 (4.62) 268 (4.01), 318 (3.60)	214; 233 287, 318	209, 245
IId	207 (5.43), 222 (5.52) 258 (5.28),	252 (5.33), 271 (5.19) 326 (4.88)	216 (5.12), 242 (5.57) 265 (5.32)	208, 250 325	
IIe	204 (4.23), 248 (4.38) 307 (3.68)	215 (5.53), 323 (5.92)	217 (4.36), 242 (4.62) 310 (3.94)	213, 255 333	
IIf	214 (3.61), 257 (3.84) 312 (3.37)	263 (4.13), 289 (3.59) 348 (3.67)	220 (3.85), 255 (4.07) 336 (3.43)	212, 258 328	
IIg	210 (4.15), 256 (4.20) 275 (4.03), 327 (3.71)	237 (4.06), 259 (4.33) 278 (4.21), 350 (3.93)	218 (4.06), 250 (4.24) 272 (4.06), 338 (3.72)	208, 250 273, 325	
IIh	212 (4.09), 258 (4.26) 330 (4.62)	263 (3.86), 348 (2.41)	220 (3.86), 255 (4.07) 325 (2.44)	214, 256 325	
IIi	205, 255, 310	220, 253, 312	217, 255, 314	202, 255 320	202, 270 330
IIj	210 (3.96), 257 (4.08) 277 (3.97), 330 (3.61)	262 (4.07), 287 (4.11) 350 (3.85)	218 (4.17), 254 (4.35) 275 (4.24), 325 (3.89)		
IIk	210, 262, 277, 330	237, 260, 282, 352	217, 253, 275, 338	253, 278 345	203 (3.66) 266 (3.68)

benzene giving rise to two bands in the range 1660–1590 cm^{-1} about 100 cm^{-1} apart which are at lower frequency than those of benzene.

Ultraviolet Absorption Spectra of Cinchoninic Acids. The ultraviolet absorption spectra for 19 cinchoninic acids shown in Table IV were examined in different solvents. In polar (neutral or alkaline) solvents, the absorption properties are similar, but the fine structure of the B-band is reduced. In acidic solutions, the fine structure is completely lost, a smooth absorption curve of greater intensity is observed. This change is due to the introduction of a formal positive charge on the nitrogen atom. From the comparison of the data in Table IV, it is clear that the spectra of cinchoninic acids in ethanol solutions are very similar to the spectra of the aqueous solution anion of these molecules. In consequence of these facts, it seems reasonable that cinchoninic acids would be dissociated to a small extent in ethanol solution and that the corresponding spectra accordingly represent the spectra of the neutral form of these acids. In water solution, the uv spectra for most of the compounds studied is similar to that in alcohol, indicating that in such compounds the zwitterion formation in water is not greatly increased. For some of the acids—e.g., IIe and IIc—the spectra are slightly different in alcohol and water indicating that the extent of zwitterion formation in water is slightly increased. This is consistent with the fact that cinchoninine acids are very weak acids.

EXPERIMENTAL

Melting points were taken using a Kofler Hot Bench, and are uncorrected. Elemental analyses were performed by Alfred Bernhadt's Laboratories, Ruhr, Germany. Ultraviolet spectra were obtained by a Unicam sp800B ultraviolet spectrophotometer. Infrared spectra were recorded on a Beckman IR 4 spectrophotometer at the Sadtler Research Laboratories, Philadelphia, PA. KBr wafer technique was used in obtaining the ir spectra. Nmr spectra were recorded on a Varian A60A spectrometer in deuterated dimethylsulfoxide (DMSO-d$_6$) and trifluoroacetic acid (TFA), with tetramethylsilane (TMS) as external reference. All τ-values are correct to 0.01 τ unit.

Materials. 5-Bromoisatin was prepared according to the method of Inagaki (*4*). 5,7-Dibromoisatin was prepared according to the procedure of Lindwall et al. (*6*).

General Procedure for Preparation of Cinchoninic Acids. The isatin (0.03 mole) was dissolved in a warm ethanolic solution of potassium hydroxide (100 ml, 33%). The ketone (0.34 mole) in ethanol (20 ml) was then added gradually. The mixture was kept under continuous stirring and heated as indicated in Table I. The contents of the flask were allowed to cool to room temperature, evaporated under reduced pressure, extracted twice with ether to remove excess ketone, and neutralized (pH 6–7) with dilute hydrochloric acid (10%). Recrystallization of the product from ethanol gave the pure cinchoninic acid.

Melting points, yields, and time of reflux are in Table I.

2-Methylcinchoninic Acid and 6,8-Dibromo-2-methylcinchoninic Acid. These two acids were prepared as described by Pfitzinger (*7*) and Lawson et al. (*5*), respectively.

2-Tribromomethylcinchoninic Acid and 2,4-Quinolinedicarboxylic Acid. These were prepared from 2-methylcinchoninic acid by bromination in glacial acetic acid and hydrolysis of the tribromomethylcinchoninic acid with dilute sulfuric acid as described by Sarkis and Al-Tai (*8*).

LITERATURE CITED

(1) Bellamy, L. J., "The infrared Spectra of Complex Molecules," pp 161, 234, Methuen and Co., Ltd, 1957.

(2) Cross, A. D., "Introduction to Practical Infrared Spectroscopy," p 65, Butterworths, 1960.

(3) El-Abbady, A. M., Al-Tai, F. A., Al-Tai, A. S., *J. Chem. U.A.R.*, **10**, 339 (1967).

(4) Inagaki, S. *J. Pharm. Soc.* (*Japan*) **58**, 96 (1938).

(5) Lawson, W., Perkin, W. H. Robinson, R., *J. Chem. Soc.*, **1924**, p 626

(6) Lindwall, E. G. Bandes, J., Weinberg, I., *J. Amer. Chem. Soc.*, **53**, 317 (1931).

(7) Pfitzinger, W., *J. Prakt. Chem* (*2*), **33**, 100 (1886).

(8) Sarkis, G. Y., Al-Tai, F. A., *Bull. Coll. Sci.* (*Baghdad*), **4**, 21 (1959).

(9) Stephenson, H. P., Sponer, H., *J. Amer. Chem. Soc.*, **79**, 2050 (1957).

RECEIVED for review July 29, 1971. Accepted March 18, 1972.