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Structure Determination of the Anorexic Agent Mazindol

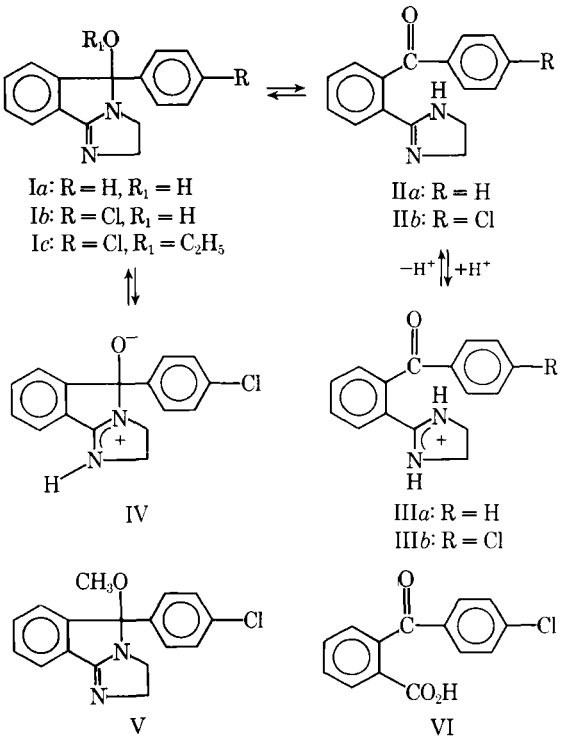
SANDOR BARCZA and WILLIAM J. HOULIHAN [x]

Abstract □ The anorexic agent mazindol was shown to exist as the carbinolamine tautomer 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol in solution and in the solid state. The latter was established by diffuse UV reflectance spectroscopy.

Keyphrases □ Mazindol—structure determination, diffuse UV reflectance spectroscopy □ Structure determination—mazindol in solution and solid state, diffuse UV reflectance spectroscopy □ UV spectroscopy, diffuse reflectance—structure determination, mazindol

It was reported (1) that condensation of 2-benzoylbenzaldehyde with ethylenediamine, followed by oxidation, gave a $C_{16}H_{14}N_2O$ product that can be formulated either as 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (I*a*) or the tautomeric form 2-(2-imidazolin-2-yl)benzophenone (II*a*). Near IR spectral measurement in chloroform gave OH and NH absorption in nearly equal amounts, indicating the presence of about a 1:1 mixture of I*a* and II*a* for the base form. UV study at varying pH in alcohol demonstrated that the protonated form exists as the benzophenone tautomer III. The X-ray single-crystal structure analysis (2) of the hydrobromide salt confirmed that III is also the preferred tautomeric form in the solid state (Scheme I).

In these laboratories the 4-chloro analog (mazindol) of III was prepared (3); and because of the commercial application[1] of the base form of this substance, it was of interest to determine the tautomeric form (I*b* or II*b*) in solution and the solid form.



Scheme I

DISCUSSION

As reference compounds, 5-chlorophenyl-5-methoxy-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindole[2] (V) was selected as a model for tautomeric form I*b* and 2-*p*-chlorobenzoylbenzoic acid (VI) was

[1] Mazindol is the active ingredient in the anorexic agent Sanorex.

[2] The structure of the deschloro analog of V, 5-methoxy-5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindole, was established by Metlesics *et al.* (1).

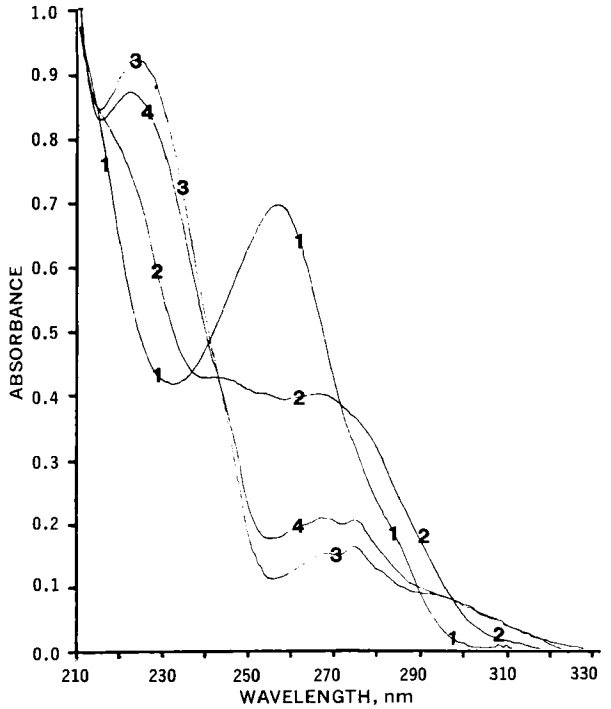


Figure 1—*UV spectra in 95% ethanol at 4.0 × 10^{-5} M of: 1, VI; 2, III*b; *3, V; and 4, I*b.

selected for tautomer II.

Figure 1 contains the UV spectra of mazindol (curve 4), its hydrochloride (curve 2), and the reference compounds V and VI at equimolar concentration in ethanol. Comparison of mazindol with V (curve 3) reveals that the spectra of both substances are nearly identical while the hydrochloride of mazindol exhibits a curve more similar to VI (curve 1). These data are in agreement with assignment of the base form of mazindol as the cyclic tautomer 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo-[2,1-*a*]isoindol-5-ol (I*b*).

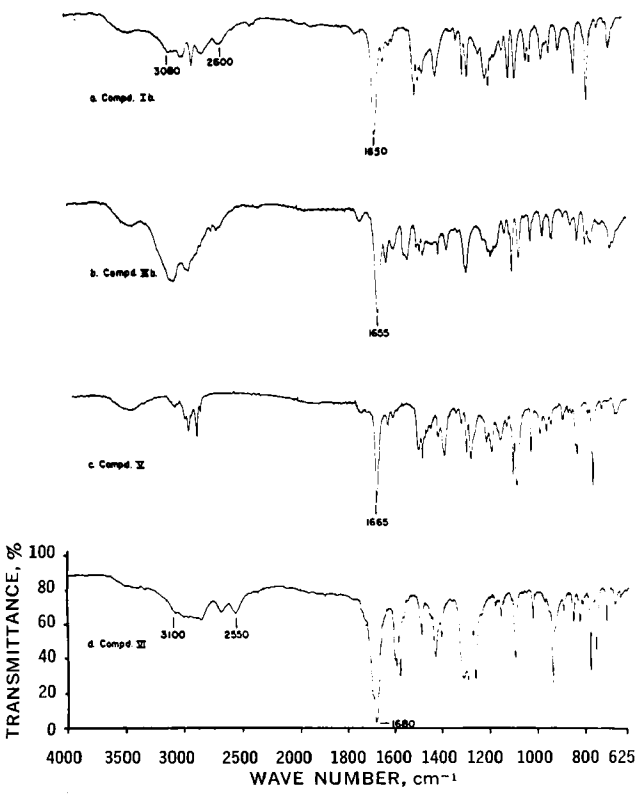


Figure 2—*IR spectra in potassium bromide.*

Table I—^{13}C-NMR Chemical Shifts

Carbon	Assignment[a], ppm[b]	
	I*b*[c]	V[d]
2	41.0*	42.2*
3	59.8*	61.0*
5	87.5	93.1
5a	154.0	150.5
6	121.9	123.2
7	131.2	131.8
8	128.6	129.8
9	123.6	124.4
9a	129.7	129.3
9b	166.3**	167.8
1′	140.0	138.2
2′,6′	127.8	128.2
3′,5′	128.1	128.9
4′	132.4	135.5**
OCH_3	—	50.6

[a] The assignments that are interchangeable are marked (*) while those that are uncertain are marked (**). All assignments are based on model compounds, ^{13}C-NMR shift theory, and intensity considerations. [b] Shifts are in parts per million downfield from tetramethylsilane and are accurate to ±0.1 relative and ±0.5 absolute. [c] Measured in dimethyl sulfoxide-d_6 at 17 mg/ml and 50%. The shifts are calculated from that of the central solvent peak, taken as 39.6 ppm. [d] Measured in $CDCl_3$ at 400 mg/ml and about 45°. The shifts are calculated from hexamethyldisiloxane internal standard, taken as 2.0 ppm.

The hydrochloride of mazindol appears to exist mainly as the benzophenone tautomer III*b*. The possible contribution by some protonated I*b* or the presence of some of the 5-ethoxy analog Ic cannot be excluded because of the relatively weak absorption in the "benzophenone" portion (about 260 nm) of the spectrum.

Additional evidence that the base form of mazindol exists in solution as the tautomer I*b* was obtained by comparing the ^{13}C-NMR spectra of mazindol with V. In $CDCl_3$ the C-5 signal of V was found at 93.1 ppm downfield from tetramethylsilane. Mazindol in dimethyl sulfoxide-d_6 gave a signal at 87.5 ppm that can be assigned to the C-5 atom of I*b*. No signals were found in the 160–200-ppm range of the spectrum, indicating the absence of the benzophenone[3,4] tautomer II*b* (Table I).

To obtain information on the tautomeric form in the solid state, the IR spectra of mazindol, III*b*, V, and VI in potassium bromide were obtained (Fig. 2). Inspection of the mazindol (I*b*) curve reveals an intense band at 1650 cm^{-1}, which could be due either to a C=O or a C=N stretching vibration (4). Unfortunately, no clear-cut distinction could be made between these possibilities since the hydrochloride II*b*[5], a substance containing a C=O group and a C=N group, absorbed at 1655 cm^{-1}, and V, a substance containing only the C=N group, absorbed at 1665 cm^{-1}.

The cluster of bands located at 3080–2600 cm^{-1} in the mazindol spectrum is similar in shape and position to the hydrogen-bonded OH bands at 3100–2550 cm^{-1} found in VI. These bands can be attributed to OH or NH hydrogen-bonded stretching vibrations (4) that could be present in either tautomer I*b* or II*b*, respectively. It is also possible that the zwitterionic form IV may be contributing to this cluster of bands since the overall shape is somewhat similar to the hydrochloride III*b*.

Since IR could not be used to determine the tautomeric form of mazindol in the solid form, diffuse UV reflectance was utilized[6]. The spectra of powdered mazindol, III*b*, and V from 400 to 270 nm are given in Fig. 3. For mazindol and V (curves 1 and 2), reflectance remained high from 400 to 355 nm where a smooth and steep drop occurred to about 0% reflectance at 325 nm. The hydrochloride (curve 3) gave a steep drop in reflectance at 380 nm with plateaus at 365, 355, and 335 nm and 0% reflectance at 310 nm. The

[3] The uncertainties of the values obtained by ^{13}C-NMR spectra are probably ±5%.

[4] The C=O atom of benzophenone is found at 194.8 ppm downfield from tetramethylsilane; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley–Interscience, New York, N.Y., 1972, p. 114.

[5] The free base I*a* and the hydrochloride of III*a* are reported to give an IR band in KBr at 1660 and 1665 cm^{-1}, respectively (1).

[6] Numerous unsuccessful attempts were made in this laboratory to obtain mazindol in a crystal form suitable for X-ray single-crystal analysis.

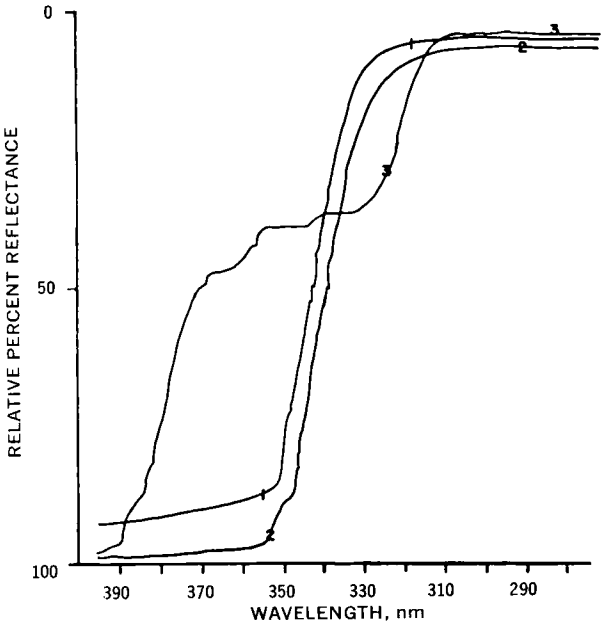


Figure 3—*Diffuse UV reflectance spectra of: 1, V; 2, Ib; and 3, IIIb.*

nearly superimposable spectrum of mazindol and V suggest that the former substance exists in the solid form solely as the imidazo[2,1-*a*]isoindole tautomer I*b*. The absence of any absorption in the 380-nm region rules out contribution by the benzophenone tautomer II*b*[7].

EXPERIMENTAL[8]

Apparatus—The diffuse reflectance spectra were measured on a recording spectrometer[9] equipped with a No. 1411 reflectance attachment that included an integrating sphere. The powdered samples were compressed at room temperature into the 2.54-cm (1-in.) diameter × 0.3-cm (0.125-in.) deep circular cavity of the aluminum reflectance attachment. Prior to running the samples, a new light source was installed and the baseline (100% reflectance) was established between 400 and 270 nm using magnesium oxide as a reference standard.

The solution UV spectra were determined with a recording spectrometer[10] between 210 and 400 nm at a scan speed of 5 Å/sec.

The ^{13}C-NMR spectrum of I*b* was taken on a spectrometer[11] equipped with a pulse-Fourier transform package[12]. The frequency was set at 25.2 MHz with broad band ^{1}H decoupling at δ 7 and a sweep width of 5000 Hz with 12-μsec pulse width. The internal D-lock on dimethyl sulfoxide-d_6 was at 15.4 MHz, and the spectrum was obtained from 32K scan over 10 hr.

The ^{13}C-NMR spectrum of V was taken on a spectrometer (Bruker) equipped with a pulse-Fourier transform accessory that included a signal averager and a computer providing 4K data points in the time domain. The frequency was set at 22.63 MHz with broad band ^{1}H decoupling at 90 MHz and a typical sweep width of 5000 Hz with 15-μsec pulse width. Hexafluorobenzene was added for locking, and hexamethyldisiloxane was used as the internal standard taken as 2 ppm downfield of tetramethylsilane.

5 - *p* - Chlorophenyl - 5 - methoxy - 2,3 - dihydro - 5*H* - imidazo[2,1-*a*]isoindole (V)—A stirred mixture of 56.0 g (0.20 mole) of I*b* and 1.0 liter of dry methanol was treated at room temperature with a stream of anhydrous hydrogen chloride gas until the solution was saturated. The solution was then refluxed for about 18 hr and concentrated *in vacuo* to about 500 ml. The concentrated solution was then slowly poured into 500 ml of a saturated sodium bicarbonate solution cooled in an ice bath. The mixture was extracted with four 200-ml portions of ether. The ether layer was dried with anhydrous potassium carbonate, filtered, and concentrated *in vacuo*. Crystallization from ether–pentane (1:1) gave 32.3 g (55%) of V, mp 104–105°; NMR[13] ($CDCl_3$): δ 3.15 (3H, s, OCH_3), 2.65–3.50 (2H, m, CH_2N), and 4.18–4.46 (2H, m, $=NCH_2$).

Anal.—Calc. for $C_{17}H_{15}ClN_2O$: C, 68.3; H, 5.1; Cl, 11.9; N, 9.1. Found: C, 68.5; H, 5.3; Cl, 12.0; N, 9.3.

4'-Chloro-2-(2-imidazolin-2-yl)benzophenone Hydrochloride (III*b*)—A solution of 5.0 g of I*b* in 100 ml of anhydrous methanol–tetrahydrofuran (1:1) was cooled in an ice bath and treated with a stream of anhydrous hydrogen chloride gas until it was saturated. The solution was then concentrated *in vacuo*, and the crystalline residue was filtered and washed with anhydrous ether. The solid was dried *in vacuo* at room temperature to give 5.2 g (92%) of III*b*, mp 175–177°.

Anal.—Calc. for $C_{16}H_{14}Cl_2N_2O$: C, 60.0; H, 4.4; Cl, 22.1; N, 8.8. Found: C, 60.1; H, 4.5; Cl, 22.2; N, 8.7.

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[7] A search of the chemical literature failed to uncover any examples where diffuse UV spectroscopy was used to distinguish tautomeric forms in organic solids. The relative ease of determining these spectra on solids, particularly those unsuitable for X-ray crystal analysis, warrants further application of this technique to tautomeric problems.

[8] Melting points were determined in a Thomas-Hoover capillary melting-point apparatus and are uncorrected.

[9] Cary model 14M.

[10] Cary model 15.

[11] Varian XL-100-15.

[12] Transform Technology Inc.

[13] The ^{1}H-NMR spectrum was obtained on a Varian Associates A-60 spectrometer.