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# Synthesis of Sparsomycin Analogs as Potential Antitumor Agents

**R. J. DUBOIS ˣ, C.-C. L. LIN, and B. L. MICHEL**

**Abstract** □ No information is available on the structural requirements for the antitumor activity of sparsomycin, an antibiotic obtained from the fermentation broth of *Streptomyces sparsogenes*. Its high *in vivo* and *in vitro* activity, novel structure, and uncommon mode of action have, therefore, suggested the synthesis of analogs. This report describes the preparation and screening of a series of *N*-substituted 3-aryl acrylamides which are closely related to sparsomycin. Three compounds exhibited some tumor inhibition but insufficient to warrant further testing.

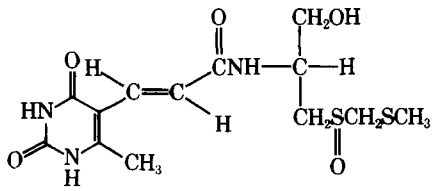
**Keyphrases** □ Antitumor agents, potential—synthesis and screening of sparsomycin analogs □ Cysteinol derivatives—synthesis and screening as possible anticancer agents □ 3-Aryl acrylamides, *N*-substituted—synthesis and pharmacological screening as possible anticancer agents □ Sparsomycin analogs—synthesis and screening as potential antitumor agents

The antibiotic sparsomycin (I) was first isolated in 1962 (1) from the fermentation broth of *Streptomyces sparsogenes*. Not until 1970, however, was the structure elucidation reported (2).

Following its isolation, sparsomycin was subjected to several preliminary biological tests where it displayed a broad spectrum of moderate *in vitro* activity against bacteria and moderate antifungal activity (3). Of greater interest was its very high activity against KB human epidermoid carcinoma cells (3). It also showed moderate to high inhibition in several *in vivo* tumor systems such as the Walker carcinosarcoma 256 and the sarcoma 180 solid tumor (3).

On the basis of this antitumor activity, sparsomycin was selected for Phase I clinical studies. It displayed severe eye toxicity, however, and the Phase I study was terminated (4).

Its biological activity appears to be primarily due to inhibition of protein synthesis, and this inhibition has been substantiated (5, 6). Further work (7) indicated that its mechanism of action in the *Escherichia coli* system is on the 50S ribosome subunit, where it prevents peptide transfer by interfering with the function of the enzyme peptidyl transferase.




I

**Table I**—NSC Numbers and Screening Data

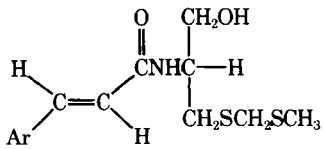
| Compound | NSC Number | Walker 256 Data, % T/C (Dose, mg/kg) |
|---|---|---|
| II | 173109 | 49 (120) |
| III | 177934 | 55 (40) |
| IV | 181493 | 85 (50) |
| V | 181494 | 64 (160) |
| VI | 184712 | 96 (80) |
| VII | 184714 | 107 (50) |
| VIII | 159934 | — |
| IX-HCl | 166004 | — |
| X | 169798 | — |
| XI | 169799 | — |
| XII | 173110 | — |
| XIII | 174260 | — |
| XIV | 177936 | — |
| XV | 179898 | — |

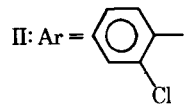
To date, no analogs of sparsomycin have been reported. Its high to moderate antitumor activity, novel structure, and somewhat uncommon mode of action have prompted the development of a structure–activity relationship by synthesis. This report describes some initial investigations.

## RESULTS AND DISCUSSION

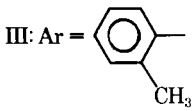
As an initial synthetic goal, the novel *N*-substituted 3-aryl acrylamides (II–VII) were chosen. These compounds represent analogs in which the uracil portion of sparsomycin has been replaced by other heterocyclic or aromatic moieties and the sulfoxide portion has been replaced by sulfur. It was believed that these compounds retained a sufficient portion of the sparsomycin structure to warrant their preparation and testing as potential antitumor agents.

Scheme I outlines the proposed synthetic approach. Condensation of the amino ester (IX) with the appropriate acrylic acid should yield esters (X–XV), which could then be selectively reduced to the desired compounds (II–VII). A synthetic pathway to the key intermediate (IX), involving the amino acid cystine, was developed (Scheme II). Since sparsomycin is optically active with a D-configuration at the asymmetric carbon atom, D-cystine would





II: Ar =



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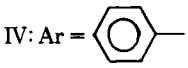
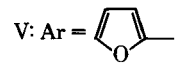
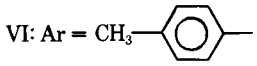


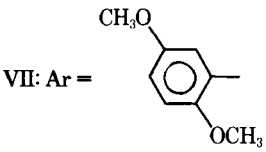
IV: Ar =



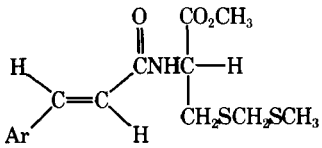
V: Ar =

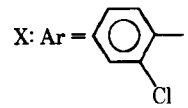


VI: Ar = $CH_3$—

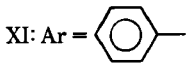


VII: Ar =

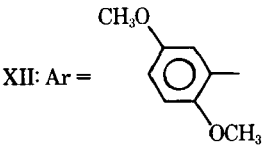




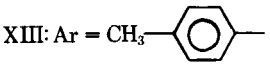
X: Ar =



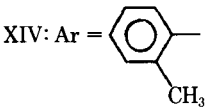
XI: Ar =



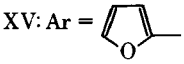
XII: Ar =



XIII: Ar = $CH_3$—



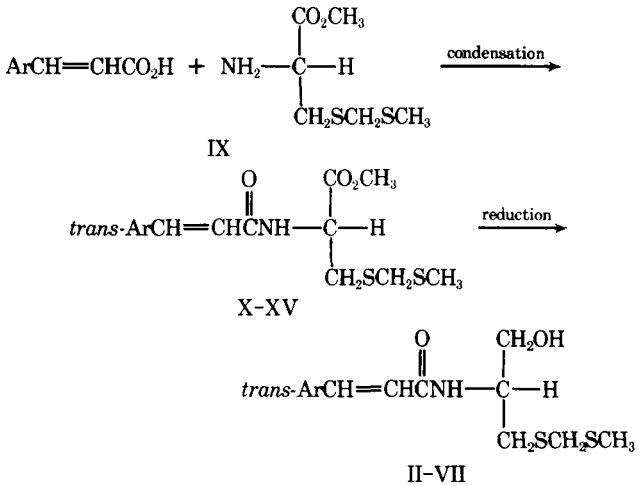
XIV: Ar =



XV: Ar =

be the most desirable starting material. Its extremely high cost precludes its use, however, in the initial trial-and-error procedures necessary in development of a synthetic pathway. The DL-mixture and *meso*-form, on the other hand, would give no information on potential racemization during synthetic elaboration. Consequently, L-cystine was chosen to begin the synthesis. With the synthetic scheme established, it would be possible to substitute the D-enantiomer; this substitution would be made if subsequent evidence indicated that the antitumor activity of sparsomycin was dependent on absolute configuration.

As shown in Scheme II, reduction of L-cystine with sodium and liquid ammonia followed by addition of chloromethyl methyl sulfide yielded the amino acid (VIII). Compound VIII was then converted to the desired amino ester as the free base by treatment



*Scheme I*

with methanol saturated with hydrogen chloride[1], followed by base treatment with sodium bicarbonate.

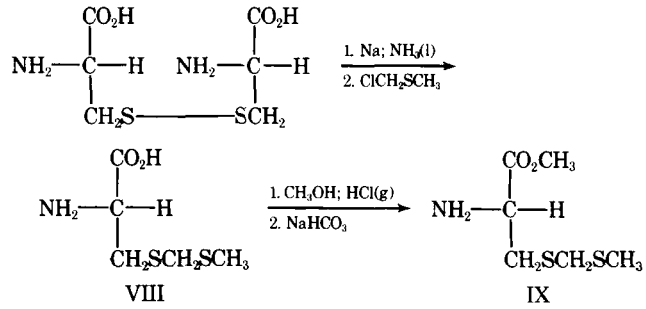
The desired intermediate was subsequently coupled with the appropriate acrylic acid (Scheme I) by means of the versatile reagent *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (8), allowing isolation of compounds (X–XV) in the *trans*-configuration. These compounds, in turn, were selectively reduced with lithium borohydride to the desired analogs (II–VII), also in the *trans*-configuration.

## PHARMACOLOGY

The intermediates (VIII–XV) (see Table I for NSC numbers) were tested in $BDF_1$ mice in the L-1210 lymphoid leukemia system and P-388 lymphocytic leukemia system according to the standard protocol of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health (9). These compounds were dissolved in saline or suspended in saline with polysorbate 80[2] and administered on Days 1, 5, and 9 or daily on Days 1–9. The compounds showed no significant activity as indicated by the ratio of the mean or median survival times of the test animals over those of the control animals expressed as a percentage (% T/C).

Since it had been shown (3) that the Walker carcinosarcoma 256 tumor system was sensitive to sparsomycin (I), Compounds II–VII (see Table I for NSC numbers) were evaluated in this system. The test was conducted according to the standard Walker 256 protocol (10), where an inoculum of tumor homogenate containing $10^6$ viable cells was implanted intramuscularly in random-bred albino rats. The compounds were dissolved in saline or suspended in hydroxypropyl cellulose[3] and administered daily on Days 3–6. Mean tumor weight was the evaluation parameter expressed as % T/C wherein a value ≤42 was the criterion for activity.

Sparsomycin displayed antitumor activity in this protocol at a



*Scheme II*

[1] It was later found that thionyl chloride in methanol gave superior yields and purer products.
[2] Tween 80, Sigma Chemical Co.
[3] Klucel, Ben Venue Laboratories.

**Table II—Experimental Data**

| Compound | Melting Point (Solvent) | Procedure | Yield, % | Optical Rotation $[\alpha]_D$ (Temperature, Concentration in g/100 ml, Solvent) | Formula | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|
| II | 96.5–103.5° (Benzene) | B | 44 | −78.79° (28.0°, 0.84, ethanol) | $C_{14}H_{18}ClNO_2S_2$ | C 50.67<br>H 5.46<br>N 4.22 | 51.02<br>5.14<br>4.15 |
| III | 73–77° (Benzene) | B | 39 | −95.54° (28.5°, 0.81, ethanol) | $C_{15}H_{21}NO_2S_2$ | C 57.84<br>H 6.80<br>N 4.50 | 57.35<br>6.91<br>4.56 |
| IV | 65–70° (Benzene) | B | 26 | −111.40° (21.5°, 0.91, ethanol) | $C_{14}H_{19}NO_2S_2$ | C 56.53<br>H 6.44<br>N 4.71 | 56.30<br>6.63<br>4.68 |
| V | 102–104.5° (Benzene) | B | 42 | −123.75° (20.8°, 0.75, ethanol) | $C_{12}H_{17}NO_3S_2$ | C 50.15<br>H 5.96<br>N 4.88 | 50.21<br>6.06<br>4.77 |
| VI | 72–84° (Toluene) | B | 49 | −64.40° (21.0°, 0.69, ethanol) | $C_{15}H_{21}NO_2S_2$ | C 57.84<br>H 6.80<br>N 4.50 | 57.76<br>6.72<br>4.47 |
| VII | 103–108° | B | 30 | −48.68° (22.3°, 0.66, dimethyl sulfoxide) | $C_{16}H_{23}NO_4S_2$ | C 53.76<br>H 6.48<br>N 3.92 | 53.66<br>6.53<br>3.87 |
| X | 110–115° (Ethanol) | A | 30 | −73.79° (29.0°, 0.77, ethanol) | $C_{15}H_{18}ClNO_3S_2$ | C 50.06<br>H 5.04<br>N 3.89 | 50.18<br>4.87<br>3.90 |
| XI | 75.5–78.5° (Isopropanol) | A | 36 | −95.17° (28.0°, 0.82, ethanol) | $C_{15}H_{19}NO_3S_2$ | C 55.36<br>H 5.88<br>N 4.30 | 55.32<br>5.54<br>4.24 |
| XII | 105–108.5° (Ethyl acetate) | A | 38 | +1.45° (27.0°, 0.97, chloroform) | $C_{17}H_{23}NO_5S_2$ | C 52.96<br>H 6.02<br>N 3.64 | 52.96<br>6.23<br>3.60 |
| XIII | 91–93° (*n*-Butanol) | A | 40 | −98.09° (22.5°, 0.68, ethanol) | $C_{16}H_{21}NO_3S_2$ | C 56.60<br>H 6.23<br>N 4.12 | 56.44<br>6.13<br>4.10 |
| XIV | 101–105° (*n*-Butanol) | A | 53 | −82.54° (29.0°, 0.83, ethanol) | $C_{16}H_{21}NO_3S_2$ | C 56.60<br>H 6.24<br>N 4.13 | 56.51<br>6.07<br>4.19 |
| XV | 80–82.5° (*n*-Butanol) | A | 33 | −125.61° (21.0°, 0.76, ethanol) | $C_{13}H_{17}NO_4S_2$ | C 49.50<br>H 5.44<br>N 4.44 | 49.57<br>5.54<br>4.39 |

dose level of 0.8 mg/kg with % T/C = 19[4]. Therefore, the analogs (II–VII) were tested at dose levels ranging from 1.6 to 0.2 mg/kg, but no activity was displayed. At higher dose levels ranging from 160 to 40 mg/kg, only Compounds II, III, and V exhibited tumor inhibition (Table I), but it was not sufficient to meet the criterion for antitumor activity in this protocol.

## EXPERIMENTAL[5]

Table II gives the experimental data for the individual compounds, and Tables III and IV give their NMR[6] and IR spectral characteristics. Chemical shifts are given in parts per million ($\delta$) downfield from tetramethylsilane, the internal standard. IR spectra[7] were recorded as paraffin oil mulls. For dry column chromatography, 50 g of silica gel (activity III)[8] was used per 1 g of compound.

***S*-(Methylthiomethyl)cysteine (VIII)**—L-Cystine (25.0 g, 0.1 mole) in 500 ml of liquid ammonia was treated with small pieces of sodium metal until a blue color was retained for several minutes. Then 19.3 g (0.2 mole) of chloromethyl methyl sulfide was added dropwise. The solution was allowed to evaporate overnight, and the residue was dissolved in water and extracted with chloroform. The aqueous phase was then cooled to 5° and acidified to pH 5 with 6 *N* HCl. The solid was filtered and dried overnight at 36° under vacuum to give 23.9 g (66% yield) of VIII, mp 220° dec.; $[\alpha]_D^{28.5}$ −29.91° (c 1.06 g/100 ml in 6 *N* HCl); IR: 2900 (broad, $NH_3$), 2120 ($NH_3$), and 1600 ($CO_2$) $cm^{-1}$.

*Anal.*—Calc. for $C_5H_{11}NO_2S_2$: C, 33.13; H, 6.18; N, 7.73. Found: C, 33.00; H, 6.10; N, 7.92.

***S*-(Methylthiomethyl)cysteine Methyl Ester Hydrochloride (IX-HCl)**—To 17.5 g (0.094 mole) of the amino acid (VIII) slurried in 125 ml of methanol was added hydrogen chloride gas until saturated. The mixture was refluxed for 20 min and then stirred at ambient temperature for 2 hr. The solvent was removed under vacuum, and the residue was triturated with ether to give 14.0 g (64% yield) of solid. The crude product was recrystallized from isopropanol and dried under high vacuum at 46° for 1 hr to give an analytical sample of IX-HCl, mp 128–131° dec.; $[\alpha]_D^{28}$ −15.2° (c 1.14 g/100 ml in ethanol); NMR[9]: $\delta$ 2.14 (s, 3H, $SCH_3$), 3.20 (d, 2H, $CH_2S$), 3.78 (s, 3H, $CO_2CH_3$), 3.85 (s, 2H, $SCH_2S$), 4.28 (t, 1H, *H*C—$CH_2$), and 8.76 (broad, 3H, $NH_3$); IR: 2900 (broad, $NH_3$), 2000 ($NH_3$), and 1735 (C=O ester) $cm^{-1}$.

*Anal.*—Calc. for $C_6H_{14}ClNO_2S_2$: C, 31.10; H, 6.09; N, 6.04. Found: C, 31.32; H, 6.05; N, 6.18.

**Alternative Procedure**—To 15 ml of methanol at −25° was added dropwise 3.95 ml (0.055 mole) of thionyl chloride. Then 9.06 g (0.05 mole) of the amino acid (VIII) was added in small portions, while the temperature was maintained below −5°. The mixture was allowed to warm to room temperature, then heated at 45° for 4 hr, and finally allowed to remain at room temperature overnight. It was filtered and the filtrate evaporated under vacuum. The residue was then treated with ether to give 9.75 g (84% yield) of solid. Recrystallization from isopropanol gave a material identical to that obtained in the original procedure.

**General Preparation of Compounds X–XV, Procedure A**—

[4] Determined at these laboratories in a control experiment.
[5] Optical rotations were obtained with a Perkin-Elmer 141 polarimeter, and melting points (uncorrected) were obtained with a Thomas-Hoover capillary apparatus. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn.
[6] Varian A-60A spectrometer.
[7] Perkin-Elmer 521 spectrophotometer.
[8] Woelm, Waters Associates, Framingham, Mass.
[9] In dimethyl sulfoxide-$d_6$.

**Table III**—NMR Data ($\delta$, Parts per Million) with Tetramethylsilane Reference and $CDCl_3$ as Solvent

| Compound | $SCH_3$ | $CH_2S$ | OH[a] | $SCH_2S$ | $CH_2O$ | *HC*—$CH_2$ | CH=CH | NH | $CO_2CH_3$ | Aromatic | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| II | 2.16 (s) | 2.95 (d) | 3.50 (Broad) | 3.72 (s) | 3.88 (d) | 4.24 (Broad) | 6.48 (d) 8.01 (d) $J$ = 16 Hz | 6.72 (d) | — | 7.32 (m) | — |
| III | 2.17 (s) | 2.95 (d)[b] | 3.38 (Broad) | 3.72 (s) | 3.85 (d) | 4.20 (Broad) | 6.38 (d) 7.96 (d) $J$ = 16 Hz | 6.63 (d) | — | 7.32 (m) | 2.41 (s) |
| IV | 2.13 (s) | 2.94 (d) | 4.0 (Broad) | 3.70 (s) | 3.83 (d) | 4.0 (Broad) | 6.50 (d) 7.62 (d) $J$ = 16 Hz | 6.98 (d) | — | 7.30 (m) | — |
| V | 2.18 (s) | 2.95 (d) | 3.75 (Broad) | 3.71 (s) | 3.84 (d) | 4.25 (Broad) | 6.40 (d) 7.42 (d) $J$ = 16 Hz | 6.81 (d) | — | 6.50 (m)$\beta$ 7.42 (s)$\alpha$ | — |
| VI | 2.15 (s) | 2.94 (d) | 4.09 (Broad) | 3.70 (s) | 3.85 (d) | 4.09 (Broad) | 6.47 (d) 7.62 (d) $J$ = 16 Hz | 6.92 (d) | — | *AA'BB'* (q) 7.23 $J$ = 8 Hz | 2.33 (s) |
| VII[c] | 2.15 (s) | 2.89 (d of d)[b] | 4.62 (t) | 3.75 (s) | 3.70 (m) | 4.13 (m) | 6.70 (d) 7.80 (d) $J$ = 16 Hz | 7.67 (d) | — | 6.90 (m) | 3.78 (s) 3.84 (s) |
| X | 2.18 (s) | 3.22 (d)[b] | — | 3.72 (s) | — | 5.08 (m) | 6.67 (d) 8.09 (d) $J$ = 16 Hz | 7.42[d] | 3.82 (s) | 7.42 (m) | — |
| XI | 2.18 (s) | 3.22 (d)[b] | — | 3.73 (s) | — | 5.08 (m) | 6.64 (d) 7.76 (d) $J$ = 16 Hz | 7.13 (d) | 3.82 (s) | 7.44 (m) | — |
| XII | 2.14 (s) | 3.16 (d)[b] | — | 3.67 (s) | — | 5.0 (m) | 6.67 (d) 7.90 (d) $J$ = 16 Hz | 6.92[d] | 3.78 (s) | 6.92 (m) | 3.78 (s) |
| XIII | 2.13 (s) | 3.19 (d)[b] | — | 3.69 (s) | — | 5.03 (m) | 6.57 (d) 7.68 (d) $J$ = 16 Hz | 7.19[d] | 3.77 (s) | *AA'BB'* (q) 7.26 $J$ = 8 Hz | 2.33 (s) |
| XIV | 2.15 (s) | 3.20 (d) | — | 3.68 (s) | — | 5.03 (m) | 6.42 (d) 7.99 (d) $J$ = 16 Hz | 6.72 (d) | 3.82 (s) | 7.38 (m) | 2.42 (s) |
| XV | 2.14 (s) | 3.18 (d) | — | 3.67 (s) | — | 5.0 (m) | 6.48 (d) 7.47 (d) $J$ = 16 Hz | 6.97 (d) | 3.78 (s) | 7.43 (s)$\alpha$ 6.50 (m)$\beta$ | — |

[a] Exchangeable with $D_2O$. [b] Extra splitting due to the presence of an asymmetric center. [c] In $CDCl_3$–dimethyl sulfoxide-$d_6$ (5:1). [d] Resonates at the same frequency as the aromatic protons.

Compound IX-HCl was dissolved in water and treated with sodium bicarbonate until the foaming ceased and the pH was 8. It was then extracted with chloroform, dried over magnesium sulfate, and evaporated under vacuum to give IX as an oil.

To a solution of 0.034 mole of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in 230 ml of tetrahydrofuran was added 0.031 mole of the appropriate acrylic acid and 0.031 mole of IX. The mixture was then stirred at 35° for 4 days, filtered if necessary, and evaporated under vacuum. The residue was triturated with petroleum ether to a solid, which was then purified by recrystallization. In the case of XV, dry column chromatography over silica gel with carbon tetrachloride–benzene (1:3) preceded recrystallization.

**General Preparation of Compounds II–VII, Procedure B**—To 0.04 mole of lithium borohydride in 75 ml of tetrahydrofuran at room temperature was slowly added 0.02 mole of the appropriate ester (X–XV) in 75 ml of tetrahydrofuran. Cooling was used to maintain the temperature below 30°. After addition, the mixture was stirred at room temperature for 22 hr. The solution was then cooled in a water bath, and 23 ml of 6 *N* HCl was added dropwise while the temperature was maintained below 30°. After addition, the mixture was stirred at ambient temperature for 1 hr; then the tetrahydrofuran was removed under vacuum. The residue was diluted to 100 ml with water, extracted with chloroform, dried over potassium carbonate, and evaporated under vacuum to an oil. This oil was triturated with petroleum ether, and the residue was purified by recrystallization in the case of II. Dry column chromatography with silica gel followed by recrystallization provided Compounds III–VII.

**Table IV**—IR Data (Centimeters$^{-1}$) from Paraffin Oil Mulls

| Compound | C=O Amide (Amide I Band) | Amide II Band | C=O (Ester) | NH | OH |
|---|---|---|---|---|---|
| II | 1610 | 1520 | — | 3200–3500 | 3200–3500 |
| III | 1625 | 1545 | — | 3110–3510 | 3110–3510 |
| IV | 1620 | 1530 | — | 3100–3500 | 3100–3500 |
| V | 1615 | 1520 | — | 3100–3400 | 3100–3400 |
| VI | 1625 | 1535 | — | 3110–3510 | 3110–3510 |
| VII | 1630 | 1550 | — | 3110–3410 | 3110–3410 |
| X | 1625 | 1545 | 1740 | 3310 | — |
| XI | 1615 | 1525 | 1735 | 3330 | — |
| XII | 1620 | 1535 | 1735 | 3270 | — |
| XIII | 1615 | 1520 | 1750 | 3335 | — |
| XIV | 1620 | 1535 | 1740 | 3330 | — |
| XV | 1610 | 1520 | 1738 | 3330 | — |

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# Structure Determination of the Anorexic Agent Mazindol


**SANDOR BARCZA and WILLIAM J. HOULIHAN** [x]



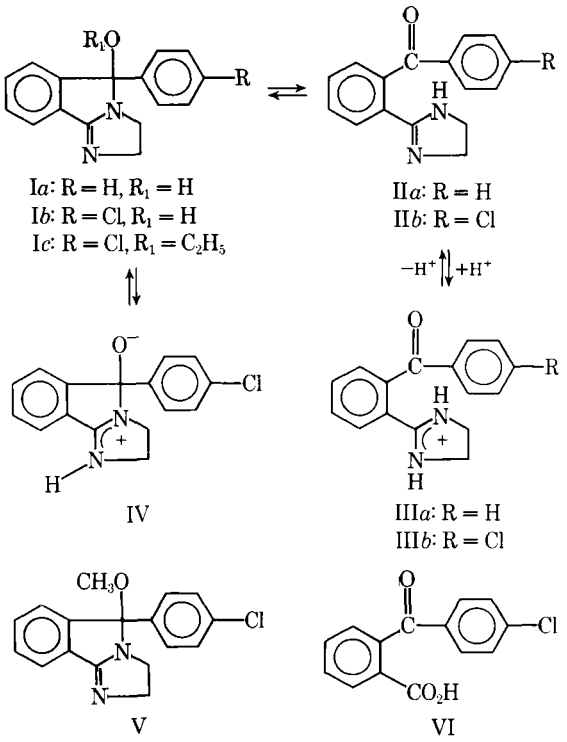
**Abstract** □ The anorexic agent mazindol was shown to exist as the carbinolamine tautomer 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol in solution and in the solid state. The latter was established by diffuse UV reflectance spectroscopy.



**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).