A New Synthetic Method for Condensed Heterocycles, Carbazoles, Indoles, and Benzothiophenes, Based on Acid-Catalyzed Cyclization of β-Keto Sulfoxides[1]

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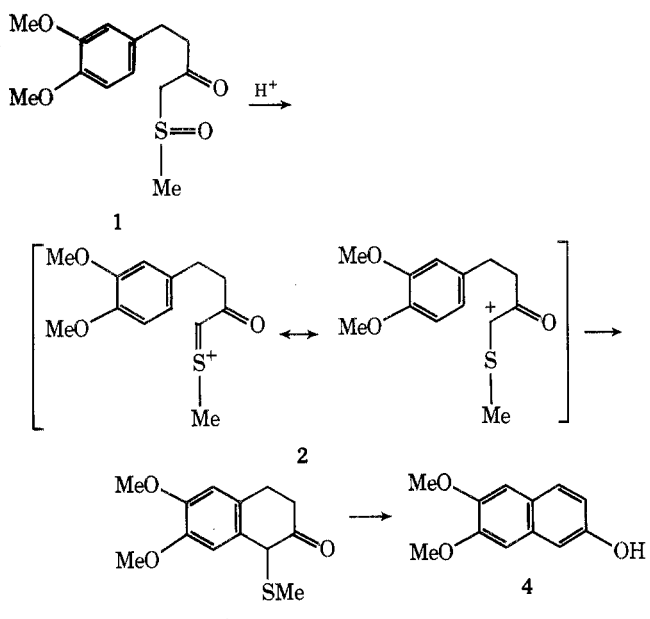
Received June 24, 1975

On heating with trichloroacetic acid or trifluoroacetic acid, β-keto sulfoxides (**5–11**) derived from indolepropionic acid, indolebutyric acids, and tryptophan cyclized to 1-methyl-2-oxotetrahydrocarbazoles (**12–18**). This cyclization proceeded more smoothly upon treatment with toluenesulfonic acid in tetrahydrofuran. Treatment with this acid in acetonitrile gave aromatized 2-hydroxycarbazoles (**20, 21, 26**). In the presence of methanol and ethanol, methoxy (**24, 27**) and ethoxy compounds (**25**) were isolated. The tryptophan derivative (**8**) gave an oxazolocarbazole (**28**). β-Keto sulfoxides (**31, 32**) with carboxamides introduced before the cyclization gave tetracyclic compounds (**35, 36**), as well as the expected products. The isolation of **35** and **36** clearly indicates the presence of intermediary indolenines (**38, 39**). Similarly, pyrrole derivatives (**40, 41**) gave unaromatized and aromatized indole derivatives (**42–45**). Thiophene derivatives (**46–48, 56**) also gave benzothiophenes (**49–53, 55, 57**), though somewhat inefficiently.

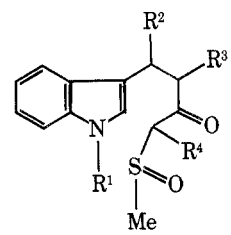
Recently we described an extended application of the Pummerer reaction for a new synthesis of condensed aromatics such as naphthalene and phenanthrene derivatives through the acid-catalyzed cyclization of β-keto sulfoxides (e.g., **1** → **3, 4**).[2] A common and key step in this cyclization is the intramolecular nucleophilic attack of aromatic ring on the carbocations (**2**) derived from β-keto sulfoxides (**1**) in the presence of acids. Accordingly, the use of electron-rich heterocycles instead of aromatics as intramolecular nucleophiles may give condensed heterocycles.



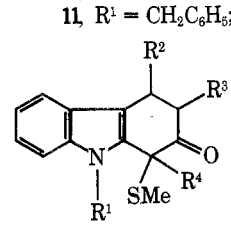
There are many useful synthetic methods for the preparation of condensed heterocycles, the majority of which naturally involves the procedures of the construction of heterocyclic rings.[3] In the present paper we report a new synthetic method for condensed heterocycles constructing the benzene ring from β-keto sulfoxides.

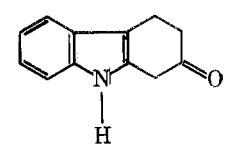
Carbazoles. Since indole is the most typical electron-rich heterocycle, synthesis of carbazoles through the cyclization of β-keto sulfoxides having an indole ring as nucleophiles was first examined (Table I).

Treatment of **5**, prepared from methyl indolepropionate and sodium methylsulfinylmethide,[4] with a half-molar quantity of trichloroacetic acid in boiling dichloroethane for 1 h resulted in its ready conversion to 1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (**12**) in a fair yield. Cyclization with trichloroacetic acid also proceeded smoothly in benzene, but not in tetrahydrofuran. The composition of **12** was determined by mass spectrometry and elemental analysis as $C_{13}H_{13}NOS$. In its ir spectrum, NH and CO groups appear at 3280 and 1690 cm^{-1}, respectively, and its NMR spectrum has distinct signals at 2.20 (SCH_3) and 4.36 ppm (COCHSMe), and no signal assignable to the proton at the C-2 position in the indole ring.



5, $R^1 = R^2 = R^3 = R^4 = H$
6, R^1 = Me; $R^2 = R^3 = R^4 = H$
7, $R^1 = CH_2C_6H_5$; $R^2 = R^3 = R^4 = H$
8, R^1 = Me; $R^2 = R^4 = H$; R^3 = NHAc
9, $R^1 = R^2 = R^3 = H$; R^4 = Me
10, $R^1 = R^2 = R^4 = H$; R^3 = Me
11, $R^1 = CH_2C_6H_5$; R^2 = Me; $R^3 = R^4 = H$





12, $R^1 = R^2 = R^3 = R^4 = H$
13, R^1 = Me; $R^2 = R^3 = R^4 = H$
14, $R^1 = CH_2C_6H_5$; $R^2 = R^3 = R^4 = H$
15, R^1 = Me; $R^2 = R^4 = H$; R^3 = NHAc
16, $R^1 = R^2 = R^3 = H$; R^4 = Me
17, $R^1 = R^2 = R^4 = H$; R^3 = Me
18, $R^1 = CH_2C_6H_5$; R^2 = Me; $R^3 = R^4 = H$

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N-Methyl (**6**) and *N*-benzyl compounds (**7**) also gave the corresponding cyclization products, **13** and **14**, by treatment with either trichloroacetic acid or trifluoroacetic acid. The cyclization of **6** and **7** proceeded more smoothly in boiling tetrahydrofuran in the presence of a stronger acid, *p*-toluenesulfonic acid (2 equiv), though the acid usually facilitates the formation of aromatized products (vide infra). Compound **8** drived from tryptophan easily gave **15**.

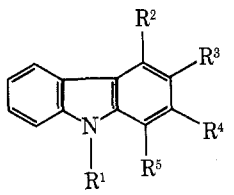
Table I. Cyclization of β-Keto Sulfoxides to 1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazoles

Compd	Acid	Solvent	Temp	Product	Yield, %
5	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	12	68
6	CCl_3CO_2H	Benzene	Reflux	13	60
6	CF_3CO_2H	Benzene	Reflux	13	74
6	TsOH	THF	Reflux	13	82
7	TsOH	THF	Reflux	14	75
8	CF_3CO_2H	Benzene	Reflux	15	66
9	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	16	10.7
10	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	17	45
11	TsOH	THF	Reflux	18	42

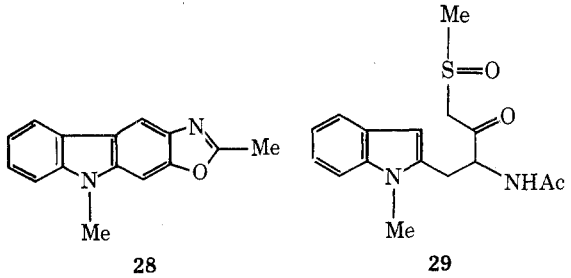
Similarly, **10** and **11** derived from indolebutyrates gave **17** and **18**, respectively.

1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazoles were easily converted to 2-oxo-1,2,3,4-tetrahydrocarbazoles by reductive desulfurization. As a typical example, **12** was reduced with aluminum amalgam to give **19** in a high yield.[5] This may provide a general and practical method for the preparation of 2-tetralone-type compounds.[6]

On treatment with toluenesulfonic acid in boiling acetonitrile, **5** gave 2-hydroxycarbazole (**20**) (Table II). Under these conditions, **12** also aromatized to **20** with concomitant elimination of methanethiol. Similarly **6** gave **21**, but at 50 °C a 2-methylthio compound (**22**) as well as **21** was isolated. Compound **22** was easily converted to *N*-methylcarbazole (**23**) by treatment with Raney Ni. The yields of **20** and **21** were somewhat improved by the use of dioxane instead of acetonitrile. In the presence of methanol and ethanol, **6** gave methoxy (**24**) and ethoxy compounds (**25**), respectively. Compound **10** in acetonitrile gave 2-hydroxy-3-methylcarbazole (**26**).[8] In the presence of methanol, **11** gave **27**. Compound **8** in the absence of alcohol gave recyclized oxazolocarbazole (**28**), and not a phenolic compound. Acid-catalyzed cyclization of 2-acylaminophenols is known to be the most common way for the synthesis of benzoxazoles.[9] Compound **28** has a characteristic uv spectrum, and no signal assignable to an amide group in its ir spectrum. Compound **29** derived from isotryptophan similarly gave an isomeric oxazolocarbazole (**30**), determined by mass spectrometry, though in a very poor yield because of instability of **29** to acids.



20, $R^1 = R^2 = R^3 = R^5 = H$; $R^4 = OH$
21, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OH$
22, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = SMe$
23, $R^1 = Me$; $R^2 = R^3 = R^4 = R^5 = H$
24, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OMe$
25, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OEt$
26, $R^1 = R^2 = R^5 = H$; $R^3 = Me$; $R^4 = OH$
27, $R^1 = CH_2C_6H_5$; $R^2 = Me$; $R^3 = R^5 = H$; $R^4 = OMe$



28 **29**

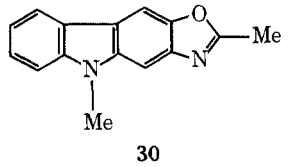


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Table II. Carbazoles from β-Keto Sulfoxides

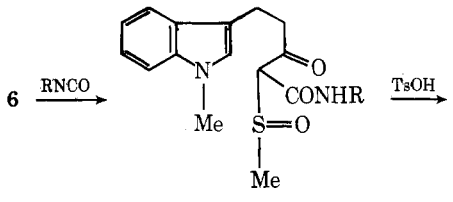
Compd	Acid	Solvent	Temp	Product	Yield, %
5	TsOH	MeCN	Reflux	20	40
5	TsOH	Dioxane	Reflux	20	55
6	TsOH	MeCN	50 °C	21	34
				22	22
6	TsOH	Dioxane	Reflux	21	54
6	TsOH	Me_2CO–MeOH	Reflux	24	47
6	TsOH	Me_2CO–EtOH	Reflux	25	40
8	TsOH	Benzene	Reflux	28	60
8	TsOH	MeCN	Reflux	28	80
10	TsOH	MeCN	Reflux	26	50
11	TsOH	Me_2CO–MeOH	Reflux	27	23
29	TsOH	MeCN	Reflux	30	3

As previously described,[2a] the formation of aromatized products consists of a series of two acid-catalyzed reactions, the cyclization of β-keto sulfoxides and the aromatization with loss of methanethiol. The latter usually requires a stronger acid and/or a higher temperature. In the case of **6**, the reaction with toluenesulfonic acid in tetrahydrofuran (bp 66 °C) gave the cyclization product (**13**) in a high yield, while in dioxane (bp 101 °C) only aromatized product (**21**) was formed. Thus the two types of products are arbitrarily available. This is one of the principal advantages of the synthetic method presented here, though the selection of the proper acid and solvent, especially the latter, is quite important.

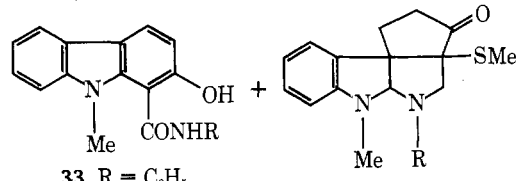
A substituent can be introduced before the acid-catalyzed cyclization at the methylene group between the carbonyl and sulfoxide groups of β-keto sulfoxides because of the high reactivity for electrophiles. The potassium salt prepared from **5** with potassium hydride in tetrahydrofuran was allowed to react with methyl iodide, and a methylated compound (**9**) was isolated in 78% yield. On treatment with trichloroacetic acid, **9** gave a cyclization product (**16**), though in a poor yield.

The sodium salt of **6** in tetrahydrofuran reacted with phenyl isocyanate and ethyl isocyanate to give **31** (94%) and **32** (97%), respectively. On treatment with toluenesulfonic acid in acetonitrile, **31** interestingly gave mainly a tetracyclic compound (**35**, 45%) as well as an expected product (**33**, 30%). The structure assignment of **35** rests on its spectral data. In its ir spectrum, **35** has two carbonyl groups assignable to a five-membered ketone (1745 cm^{-1}) and a five-membered lactam (1690 cm^{-1}). Distinct signals in its NMR spectrum appear at 2.28 (SCH_3), 2.60 (NCH_3), and 5.40 ppm (NCHN), and its uv spectrum is characteristic of indoline derivatives. Similarly, **32** gave **34** and **36** in 41 and 33% yield, respectively. Under milder conditions, viz., on treatment with toluenesulfonic acid at 50 °C in dioxane, **32** gave **36** (40%) and **37** (44%). In analogy with **35**, the structure of **36** was determined from spectral data, and, especially in the NMR spectrum, three singlet signals at 2.04 (3 H), 3.06 (3 H), and 4.88 ppm (1 H) are clearly assigned.

It is well known that the formation of 2,3-disubstituted indoles from 3-substituted indoles by electrophilic alkylation usually involves the initial formation of 3,3-disubstituted indolenines, followed by the rearrangement of one

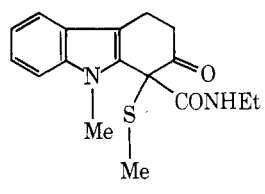


31, R = C_6H_5
32, R = Et



33, R = C_6H_5
34, R = Et

35, R = C_6H_5
36, R = Et



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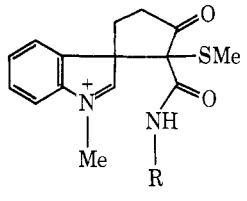
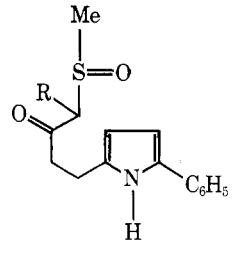


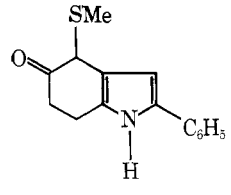
38, R = C_6H_5
39, R = Et

substituent from C-3 to C-2, rather than the direct alkylation at C-2.[10] This mechanism also acts in the cyclization of β-keto sulfoxides, because **35** and **36** can be formed through indolenines **38** and **39**, respectively. The isolation of **35** and **36** may provide an additional example proving the presence of intermediary indolenines in the electrophilic substitution of 3-substituted indoles by the direct trapping.

Indoles. The cyclization of pyrrole derivatives to indoles was examined next. The easily synthesized ethyl 5-phenylpyrrole-2-propionate[11] was converted to a β-keto sulfoxide (**40**), which was heated under reflux in tetrahydrofuran in the presence of 0.4 molar equiv of toluenesulfonic acid to give a cyclization product (**42**) (Table III). The structure was easily determined from its spectral data, especially by the characteristic signals in its NMR spectrum of an *S*-methyl and a methine groups appearing at 2.05 and 4.04 ppm, respectively.



40, R = H
41, R = $CONHC_6H_5$



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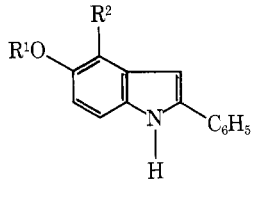


43, R^1 = Me; R^2 = H
44, R^1 = Et; R^2 = H
45, R^1 = H; R^2 = $CONHC_6H_5$

When **40** was heated in methanol with an equimolar amount of toluenesulfonic acid, 5-methoxy-2-phenylindole (**43**) was isolated in 80% yield. Similarly in ethanol, **40** gave an ethoxy compound (**44**). Compound **41** derived from **40** with phenyl isocyanate was heated with toluenesulfonic acid in 2-propanol to give 4-substituted indole derivative (**45**) in 91% yield. The reaction also proceeded, though inefficiently, either in acetonitrile or in benzene.

Table III. Cyclization of β-Keto Sulfoxides to Indole Derivatives

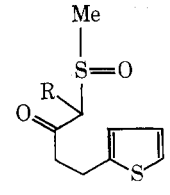
Compd	Acid	Solvent	Temp	Product	Yield, %
40	TsOH	THF	Reflux	**42**	63
40	TsOH	MeOH	Reflux	**43**	80
40	TsOH	EtOH	Reflux	**44**	72
41	TsOH	*i*-PrOH	Reflux	**45**	91

Table IV. Cyclization of β-Keto Sulfoxides to Benzothiophenes

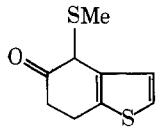
Compd	Acid	Solvent	Temp	Product	Yield, %
46	CF_3CO_2H	Benzene	Reflux	**49**	50
46	TsOH	MeCN	Reflux	**50**	56
				51	14
				54	7
46	TsOH	MeOH	Reflux	**52**	14
				54	5
46	CCl_3-CO_2H	MeCN–MeOH	Reflux	**52**	22
47	TsOH	Benzene	Reflux	**53**	55
48	TsOH	Benzene	Reflux	**55**	25
56	TsOH	MeCN	Reflux	**57**	53

Benzothiophenes. β-Keto sulfoxides having a thiophene ring were also subjected to the acid-catalyzed reaction and formed benzothiophene derivatives (Table IV). Thiophene is known to be somewhat less reactive than pyrrole and indole toward the usual electrophilic reagents, and this was also found to be the case in the cyclization of β-keto sulfoxides.

Compound **46** prepared from methyl thiophene-2-propionate was heated with trifluoroacetic acid in benzene to give a cyclization product (**49**), which has distinct signals of *m/e* 198 (M^+), and 2.05 (SCH_3) and 4.02 ppm ($COCHSCH_3$) in the mass and NMR spectra. In aromatization conditions with toluenesulfonic acid in acetonitrile, **46** gave 5-hydroxybenzothiophene (**50**) with unavoidable concomitant formation of 5-methylthiobenzothiophene (**51**) and a thioacetal (**54**).[12] In methanol, **46** gave a methoxy compound (**52**) also accompanied with **51**, but the treatment with a large excess of trichloroacetic acid in a mixture



46, R = H
47, R = $CONHC_6H_5$
48, R = CH_2CO_2Me



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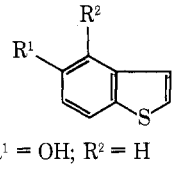
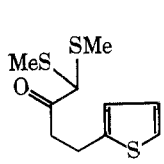


50, R^1 = OH; R^2 = H
51, R^1 = SMe; R^2 = H
52, R^1 = OMe; R^2 = H
53, R^1 = OH; R^2 = $CONHC_6H_5$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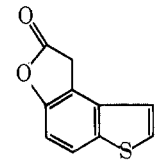
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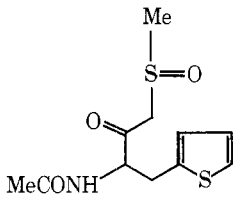
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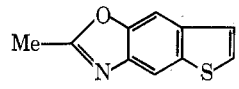
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of methanol and acetonitrile gave only **52** though in a poor yield. On treatment with toluenesulfonic acid, **47** prepared from **46** and phenyl isocyanate gave a 4-substituted benzothiophene (**53**), and similarly **48** prepared from **46** and methyl bromoacetate gave a lactone (**55**). In analogy with **8** and **29**, compound **56** derived from thiophene-2-alanine gave an oxazolobenzothiophene (**57**), which has the composition of $C_{10}H_7NOS$ as determined by the mass spectrum and elemental analysis, and neither a phenol nor amide in its ir spectrum.

Concluding Remarks. Although many useful methods are available for the synthesis of condensed heteroaromatics, the potential utility of the acid-catalyzed cyclization of β-keto sulfoxides in the area of heterocyclic chemistry can be emphasized because of the following advantages and characteristics. (1) The majority of usual synthetic methods for condensed heteroaromatics such as indole and benzothiophene involves the preparation of a heterocyclic ring moiety through ring closure, while the method described in this paper is characterized by the construction of a benzene ring. (2) The starting materials, β-keto sulfoxides, are easily prepared by the well-known reaction of methylsulfinyl carbanion[4] with the corresponding esters. (3) Two types of compounds, unaromatized cyclic β-keto sulfides and aromatized compounds, are arbitrarily obtained by the selection of reaction conditions. (4) Some substituents can be introduced in a benzene ring by the prior introduction of substituents at the methylene group between sulfinyl and carbonyl groups of β-keto sulfoxides.

Experimental Section

2-(3-Indolyl)ethyl Methylsulfinylmethyl Ketone (5). The anion of Me_2SO was prepared according to the procedure by Corey[4] from 1.08 g of NaH, 25 ml of Me_2SO, and 20 ml of THF. To this solution 3.0 g of methyl indole-3-propionate[13] dissolved in 10 ml of THF was added dropwise at 0–5 °C. After being stirred for an additional 1 h at room temperature, the mixture was poured into ice–water, acidified with HCl to pH 4–5, and then extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent left an oil, which was crystallized from EtOAc to give a colorless powder in 75% yield: mp 97–99° (from EtOAc); ν (Nujol) 3350, 1710 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 6.17; N, 5.55.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (6). Compound 6 was synthesized from methyl (1-methyl-3-indolyl)propionate[14] and Me_2SO in 77% yield: mp 82–83 °C; ν (Nujol) 1695 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.17. Found: C, 64.03; H, 6.48; N, 5.10; S, 11.94.

2-(1-Benzyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (7). To a stirring suspension of 2.4 g of NaH in 75 ml of Me_2SO was added dropwise 20.3 g of methyl indole-3-propionate[13] in 25 ml of THF keeping the temperature below 20 °C by occasional cooling. After the evolution of hydrogen ceased, the mixture was cooled in an ice bath and 12.7 g of benzyl chloride in 10 ml of THF was added dropwise. The stirring was continued for 2 h at room temperature. The reaction mixture was poured into 300 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was distilled under reduced pressure to give 23 g (80%) of methyl 3-(1-benzyl-3-indolyl)propionate: bp 205–207 °C (2 mm); *m/e* 293 (M^+), 220, 91 (base peak).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.78; H, 6.48; N, 4.87.

This ester was converted to compound **7** in 88% yield: mp 90–93° (from EtOAc); ν (Nujol) 1710 cm^{-1}.

Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 70.78; H, 6.24; N, 4.13; S, 9.43. Found: C, 70.61; H, 6.09; N, 4.25; S, 9.18.

1-Acetamido-2-(1-methyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (8). *N*-Acetyl-*dl*-tryptophan methyl ester[15] was methylated with methyl iodide in a manner similar to the benzylation described above to give methyl 2-acetamido-3-(1-methyl-3-indolyl)propionate in 97% yield as an oil: ν (neat) 3280, 1735, 1650 cm^{-1}; *m/e* 274 (M^+), 144 (base peak).

This ester was converted to compound **8** in 79% yield: mp 128–131 °C (from EtOAc); ν (Nujol) 3350, 1705, 1638 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.99; H, 6.29; N, 8.75; S, 9.98. Found: C, 59.85; H, 6.33; N, 8.65; S, 9.97.

2-(3-Indolyl)ethyl 1-Methylsulfinylethyl Ketone (9). To an ice-cooled solution of the K salt of **5**, prepared from 0.249 g of **5** and 40 mg of KH in 11 ml of THF, 0.150 g of methyl iodide was added in one portion with stirring. The stirring was continued for 3 h at room temperature, and then the mixture was poured into 30 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to leave an oil, which was purified by passing in CH_2Cl_2–EtOAc (1:1) through silica gel to give 0.205 g (78%) of **9** (oil) as a diastereomeric mixture: ν (neat) 3400, 3250, 1700, 1030 cm^{-1}; *m/e* 263 (M^+), 200, 144, 130 (base peak); δ ($CDCl_3$) 1.26 (d, 2 H, J = 8 Hz), 1.34 (d, 1 H, J = 8 Hz), 2.36 (s, 3 H), 2.84–3.14 (m, 4 H), 3.72 (broad q, 1 H), 6.7–7.6 (m, 5 H), 8.44 (broad s, 1 H).

1-(3-Indolylmethyl)ethyl Methylsulfinylmethyl Ketone (10). Compound **10** was synthesized from ethyl 3-(3-indolyl)-2-methylpropionate[16] and Me_2SO in 97% yield as an oil (1:1.3 diastereomeric mixture): ν (neat) 3325, 1710, 1040 cm^{-1}; *m/e* 247 (M^+), 130 (base peak); δ ($CDCl_3$) 1.20 (broad d, 3 H, J = 6 Hz), 2.40 (s, 1.3 H), 2.50 (s, 1.7 H), 2.70–3.30 (m, 3 H), 3.62 (0.9 H), 3.67 (1.1 H), 6.9–7.7 (m, 5 H), 8.50 (broad s, 1 H).

Ethyl 3-(1-Benzyl-3-indolyl)butyrate. A solution of 85 g of *N*-(3-indolyl-1-ethyl)-*N*-isopropylamine[17a] and 89.9 g of diethyl malonate in 450 ml of DMF was heated under reflux for 7.5 h. After evaporation of the solvent, the residue was dissolved in ether. The solution was washed with H_2O, 5% HCl, and H_2O, dried and then concentrated to leave crude diethyl 1-(3-indolyl)ethylmalonate. The crude ester was dissolved in a solution of 40 g of NaOH in 200 ml of EtOH and 84 ml of H_2O, and heated under reflux for 2 h. The reaction mixture was concentrated to remove the EtOH, diluted with H_2O, acidified with HCl, and then extracted with ether. The extract was washed with H_2O, dried, and evaporated to leave 1-(3-indolyl)ethylmalonic acid as an oil. The acid was dissolved in 100 ml of pyridine and heated under reflux for 5.5 h. After evaporation of the pyridine, to the residue was added H_2O, and the mixture was acidified with HCl to pH 3 and extracted with EtOAc. The extract was dried and evaporated to leave 3-(3-indolyl)butyric acid,[17b] which was esterified in the usual manner to yield 25.7 g (overall yield 26.5%) of ethyl 3-(3-indolyl)butyrate. The ester was benzylated as described above to give 27.5 g (73%) of ethyl 3-(1-benzyl-3-indolyl)butyrate: bp 197–200° (1 mm); *m/e* 321 (M^+), 234, 91 (base peak).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.62; H, 7.27; N, 4.45.

2-(1-Benzyl-3-indolyl)propyl Methylsulfinylmethyl Ketone (11). Compound **11** was synthesized from ethyl 3-(1-benzyl-3-indolyl)butyrate in 97% yield as an oil (1:1.3 diastereomeric mixture): ν (neat) 1710, 1041 cm^{-1}; δ ($CDCl_3$) 1.40 (d, 1.3 H, J = 6 Hz), 1.42 (d, 1.7 H, J = 6 Hz), 2.43 (s, 1.3 H), 2.50 (s, 1.7 H), 2.55–3.10 (m, 3 H), 3.62 (2 H), 6.9–7.4 (m, 9 H), 7.5–7.8 (m, 1 H).

1-Acetamido-2-(1-methyl-2-indolyl)ethyl Methylsulfinylmethyl Ketone (29). Ethyl 2-acetamido-3-(2-indolyl)propionate[18] was methylated as described above to yield ethyl 2-acetamido-3-(1-methyl-2-indolyl)propionate in 87% yield as an oil: ν (neat) 3350, 3300, 1740, 1660 cm^{-1}.

This ester was converted to **29** in 55% yield as a hard oil of a diastereomeric mixture: ν 3250, 1720, 1660, 1020 cm^{-1}; δ ($CDCl_3$) 1.96 (s, 3 H), 2.62 (s, 1.5 H), 2.65 (s, 1.5 H), 3.65 (s, 3 H), 3.3–3.8 (m, 5 H), 6.32 (s, 1 H), 7.17–7.30 (4 H).

1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (12). A solution of 0.63 g of **5** and 0.126 g of CCl_3CO_2H in 30 ml of $(CH_2Cl)_2$ was heated under reflux for 2.5 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated to leave a solid, which was recrystallized from EtOH to give 0.397 g (68%) of **12:** mp 149–151°; ν (Nujol) 3280, 1690 cm^{-1}; *m/e* 231 (M^+), 184 (base peak), 156; δ ($CDCl_3$) 2.20 (s, 3 H), 2.6–3.4 (m, 4 H), 4.36 (s, 1 H), 7.1–7.6 (m, 4 H), 8.13 (broad s, 1 H).

Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.52; H, 5.67; N, 6.06; S, 13.84. Found: C, 67.33; H, 5.68; N, 5.99; S, 13.71.

9-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (13). A. A solution of 0.132 g of **6** and 0.19 g of $TsOH-H_2O$ in 6 ml of THF was heated under reflux for 2 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove THF, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **13,** which was purified by passing in $CHCl_3$ solution through a silica gel column to give 0.101 g (82%) of **13.** Recrystallization from EtOH gave colorless scales: mp 147–148 °C; ν (Nujol) 1705 cm^{-1}; λ (EtOH) 288 nm; δ ($CDCl_3$) 2.19 (s, 3 H), 2.5–3.5 (4 H), 3.73 (s, 3 H), 4.15 (s, 1 H), 7.0–7.52 (4 H); *m/e* 245 (M^+), 198 (base peak).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.55; H, 6.16; N, 5.71; S, 13.04. Found: C, 68.39; H, 6.09; N, 5.59; S, 13.02.

B. The above neutralized reaction mixture was concentrated to remove the THF and allowed to stand at room temperature. The precipitated crystals were collected by filtration and recrystallized from EtOH to give **13** as colorless scales.

9-Benzyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (14). A solution of **7** (0.339 g) and 0.38 g of $TsOH-H_2O$ in 10 ml of THF was heated under reflux for 3 h. Work-up as described above gave crude **14,** which was purified by passing its CH_2Cl_2–hexane (1:1) solution through silica gel to give 0.24 g (75%) of **14** as an oil. The oil crystallized when its EtOH solution was scratched. Recrystallization from EtOH gave colorless needles: mp 132–133 °C; ν (Nujol) 1700 cm^{-1}; *m/e* 321 (M^+); δ ($CDCl_3$) 2.10 (s, 3 H), 2.4–3.6 (m, 4 H), 3.96 (s, 1 H), 5.46 (2 H), 6.95–7.6 (9 H).

Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.74; H, 5.96; N, 4.36; S, 9.96. Found: C, 74.61; H, 5.93; N, 4.18; S, 9.79.

3-Acetamido-9-methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (15). A solution of 0.16 g of **8** and 0.114 g of CF_3CO_2H in 8 ml of benzene was heated under reflux for 1 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (6:1) gave 0.1 g (66%) of **15** as a solid. Recrystallization from EtOH gave colorless needles: mp 162 °C (sintered from 150 °C); ν (Nujol) 3280, 3080, 1720, 1670, 1650 cm^{-1}; *m/e* 302 (M^+); δ ($CDCl_3$) 2.10 (s, 3 H), 2.16 (s, 3 H), 2.44–2.7 (1 H), 3.70 (s, 3 H), 3.75–4.02 (1 H), 4.32 (s, 1 H), 5.4–5.65 (1 H), 6.60 (broad s, 1 H).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.56; H, 6.00; N, 9.27; S, 10.58. Found: C, 63.50; H, 5.98; N, 9.32; S, 10.32.

1-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (16). A solution of 0.15 g of **9** and 30 mg of CCl_3CO_2H in 7 ml of $(CH_2Cl)_2$ was heated under reflux for 2 h. The solution was cooled, washed with $NaHCO_3$ solution, and dried. After evaporation of the solvent, the residual oil was chromatographed on a silica gel column. Elution with hexane–CH_2Cl_2 (1:1) gave 15 mg (10.7%) of **16** as an colorless oil: ν (neat) 3350, 1700 cm^{-1}; δ ($CDCl_3$) 1.76 (s, 3 H), 2.00 (s, 3 H), 2.6–3.4 (m, 4 H), 7.1–7.5 (m, 4 H), 8.08 (broad s, 1 H); *m/e* 245 (M^+), 198 (base peak).

3-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (17). A solution of 0.263 g of **10** and 0.05 g of CCl_3CO_2H in 12 ml of $(CH_2Cl)_2$ was heated under reflux for 2 h. Work-up as described above gave 0.112 g (45%) of **17:** mp 121–124 °C (from EtOH); ν (Nujol) 3350, 1685 cm^{-1}; *m/e* 245 (M^+), 198 (base peak), 170; δ ($CDCl_3$) 1.29 (d, 3 H, J = 6 Hz), 2.16 (s, 3 H), 2.44–2.74 (m, 1 H), 3.14–3.54 (m, 2 H), 4.28 (d, 1 H, J = 2 Hz).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.55; H, 6.16; N, 5.71; S, 13.05. Found: C, 68.49; H, 6.14; N, 5.57; S, 13.04.

9-Benzyl-4-methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (18). A solution of 0.353 g of **11** and 0.13 g of $TsOH-H_2O$ in 8 ml of THF was heated under reflux for 3 h. Work-up as described above gave 0.14 g (42%) of an oil of **18** as a diastereomeric mixture (1:1.5): ν (neat) 1710 cm^{-1}; δ ($CDCl_3$) 1.30 (d, 1.8 H, J = 6 Hz), 1.48 (d, 1.2 H, J = 6 Hz), 2.12 (s, 3 H), 2.2–3.7 (m, 3 H), 3.92 (s, 1 H), 5.44 (2 H), 6.9–7.7 (m, 9 H); *m/e* 335 (M^+), 288, 91 (base peak).

2-Oxo-1,2,3,4-tetrahydrocarbazole (19). To a solution of 0.2 g of **12** in 14 ml of THF and 13 ml of H_2O was added Al amalgam freshly prepared from 0.25 g of Al.[4] The mixture was stirred at 5 °C for 10 min and at room temperature for 30 min, and then filtered to remove the Al amalgam. The filtrate was concentrated and extracted with Et_2O. The extract was dried and evaporated to leave an oil, which was solidified to 0.135 g (95%) of **19:**[5] mp 128–130 °C (from 33% EtOH); ν (Nujol) 3380, 1720 cm^{-1}; *m/e* 185 (M^+), 156, 143 (base peak); δ ($CDCl_3$) 2.6–3.1 (4 H), 3.58 (s, 2 H), 7.0–7.55 (m, 4 H), 7.8 (broad s, 1 H).

2-Hydroxycarbazole (20). A. Compound **5** (0.25 g) was heated under reflux for 1 h with 0.17 g of $TsOH-H_2O$ in 12 ml of MeCN. The solvent was removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with $NaHCO_3$ solution and then extracted with 10% NaOH. After acidification of the NaOH extract, the solution was extracted with EtOAc. The extract was dried and concentrated to give crude **20.** Sublimation (2 Torr) or recrystallization from 40% EtOH gave 0.072 g (40%) of **20** as a pale yellow powder:[5,19] mp 259–262 °C; ν (Nujol) 3400, 3200 cm^{-1}; λ (EtOH) 253 (infl), 259, 303, 309 (infl), 316 (infl), 328 nm (infl); λ (pH 11) 246, 335 nm; δ ($CDCl_3$ + Me_2SO-d_6) 6.7–6.9 (m, 2 H), 7.1–7.4 (m, 3 H), 7.7–8.0 (m, 2 H).

Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.41; H, 4.70; N, 7.28.

B. Compound **5** (0.215 g) and 0.16 g of $TsOH-H_2O$ in 9 ml of dioxane was heated under reflux for 2 h. Work-up as described above gave 0.087 g (55%) of **20.**

2-Hydroxy-9-methylcarbazole (21). A solution of 0.264 g of **6** and 0.2 g of $TsOH-H_2O$ in 12 ml of dioxane was heated under reflux for 3 h. Work-up as described above gave 0.106 g (54%) of **21** as a colorless solid:[5] mp 164–165° (from 40% EtOH); ν (Nujol) 3320 cm^{-1}; λ (EtOH) 239, 256 (infl), 262, 265 (infl), 304, 320, 335 nm; λ (pH 11) 249, 336 nm; *m/e* 197 (M^+), 168; δ ($CDCl_3$) 3.72 (s, 3 H), 6.5–6.8 (m, 2 H), 7.2–7.4 (m, 3 H), 7.8–8.1 (m, 2 H).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.70; H, 5.63; N, 7.07.

Treatment of 6 with TsOH in MeCN at 50 °C. A solution of 0.132 g of **6** and 0.19 g of $TsOH-H_2O$ in 2 ml of MeCN was heated at 50 °C for 1.5 h. After the addition of $NaHCO_3$ solution, the mixture was evaporated to remove the MeCN and extracted with CH_2Cl_2. The extract was shaken with 10% NaOH. From the NaOH layer 34 mg (34%) of **21** was isolated. The CH_2Cl_2 layer was washed with H_2O and evaporated, and the residue was chromatographed on a silica gel column. Elution with CCl_4–$CHCl_3$ (5:1) gave 25 mg (22%) of **9-methyl-2-methylthiocarbazole (22):** mp 118–120° (from 90% EtOH); λ (EtOH) 240.5, 253, 260.5, 302 (infl), 313, 334 (infl), 344 nm (infl); *m/e* 227 (M^+), 212, 194; δ (CCl_4) 2.50 (s, 3 H), 3.70 (s, 3 H), 6.9–7.3 (5 H), 7.7–8.0 (2 H).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.99; H, 5.77; N, 6.16; S, 14.08. Found: C, 74.17; H, 5.62; N, 6.03; S, 13.87.

9-Methylcarbazole (23). A mixture of 50 mg of **22** and ca. 1 ml of Raney Ni in 8 ml of EtOH was heated under reflux for 3 h. After removal of Ni by filtration, the filtrate was evaporated to leave a solid, which was recrystallized form EtOH to give 21 mg of **23,**[20] mp 81–83 °C.

2-Methoxy-9-methylcarbazole (24). A solution of 0.264 g of **6** and 0.38 g of $TsOH-H_2O$ in 12 ml of Me_2CO and 1.2 ml of MeOH was heated under reflux for 5 h. The solution was cooled, neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove the organic solvents, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **24.** Purification by passing in CCl_4–$CHCl_3$ (5:1) through silica gel gave 0.1 g (47%) of **24** as a solid.[5] Recrystallization from 90% EtOH gave colorless needles: mp 97–98 °C; λ (EtOH) 255 (infl), 261, 264 (infl), 302, 320, 333 nm; *m/e* 211 (M^+), 196, 168; δ ($CDCl_3$) 3.72 (s, 3 H), 3.90 (s, 3 H), 6.7–6.9 (m, 2 H), 7.0–7.4 (m, 3 H), 7.8–8.1 (m, 2 H).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.56; H, 6.20; N, 6.63. Found: C, 79.76; H, 6.24; N, 6.37.

2-Ethoxy-9-methylcarbazole (25). When EtOH was used in the place of MeOH in the foregoing experiment, 0.09 g (40%) of **25** was isolated. Recrystallization from 90% EtOH gave colorless needles: mp 76–78 °C; *m/e* 225 (M^+), 197, 168; δ ($CDCl_3$) 1.50 (t, 3 H), 3.77 (s, 3 H), 4.18 (q, 2 H), 6.7–6.9 (m, 2 H), 7.1–7.5 (m, 3 H), 7.9–8.1 (m, 2 H).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.00; H, 6.72; N, 6.26.

2,9-Dimethyloxazolo[5,4-*b*]carbazole (28). A solution of 0.16 g of **8** and 0.19 g of $TsOH-H_2O$ in 6 ml of MeCN was heated under reflux for 3.5 h. The solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove MeCN, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **28,** which was chromatographed on a silica gel column. Elution with benzene–$CHCl_3$ (1:1) gave 0.095 g (80%) of a solid, which was re-

crystallized from EtOH: mp 180–181 °C; *m/e* 236 (M^+); λ (EtOH) 232, 239, 248, 278, 308, 338, 353 nm; δ ($CDCl_3$) 2.70 (s, 3 H), 3.90 (s, 3 H), 7.1–7.6 (4 H), 8.1 (d, 1 H, J = 7 Hz), 8.23 (s, 1 H).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.15; H, 4.93; N, 11.68.

2-Hydroxy-3-methylcarbazole (26). A solution of 0.526 g of **10** and 0.16 g of TsOH–H_2O in 10 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in Et_2O, washed with $NaHCO_3$ solution, and extracted with 10% NaOH solution. The aqueous layer was acidified with HCl and extracted with Et_2O, dried, and evaporated to give 0.197 g (50%) of **26**:[8] mp 237–240 °C (from cyclohexane–EtOH); ν (Nujol) 3500, 3375, 1630, 1605 cm^{-1}; *m/e* 197 (M^+); δ (Me_2SO-d_6) 2.28 (s, 3 H), 6.88 (s, 1 H), 7.00–7.40 (m, 3 H), 7.70 (s, 1 H), 7.86 (1 H).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.63; N, 6.98.

9-Benzyl-2-methoxy-4-methylcarbazole (27). A solution of 0.353 g of **11** and 0.38 g of TsOH–H_2O in 12 ml of Me_2CO containing 1.2 ml of MeOH was heated under reflux for 6 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove the solvent, and extracted with CH_2Cl_2. The extract was dried and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with hexane–CH_2Cl_2 (2:1) gave 0.065 g (23%) of **27**. Recrystallization from EtOH gave colorless needles: mp 164.5–166.5 °C; *m/e* 301 (M^+); δ ($CDCl_3$) 2.85 (s, 3 H), 3.82 (s, 3 H), 5.45 (s, 2 H), 6.65 (s, 2 H), 7.1–7.4 (m, 8 H), 8.0–8.25 (m, 1 H).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52; H, 6.36; N, 4.60.

2,5-Dimethyloxazolo[4,5-*b*]carbazole (30). A solution of 0.12 g of **29** and 0.083 g of TsOH–H_2O in 3 ml of MeCN was heated under reflux for 1 h. Work-up as described above gave 3 mg (3.4%) of **30** as a solid, which was recrystallized from EtOH: mp 200–202 °C; *m/e* 236 (M^+); λ (EtOH) 244, 251, 260 (infl), 272, 300, 306 (infl), 312 nm.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (31). To an ice-cooled solution of the Na salt of **6**, prepared from 0.526 g of **6** and 57 mg of NaH in 15 ml of THF, 0.24 g of phenyl isocyanate was added dropwise with stirring. The stirring was continued for 70 min at room temperature, and then the mixture was poured into 50 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to leave 0.718 g (94%) of **31**, which was recrystallized from EtOH: mp 136–139°; ν (Nujol) 1715, 1665 cm^{-1}.

Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.33; S, 8.37. Found: C, 66.10; H, 5.81; N, 7.22; S, 8.52.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinyl(ethylcarbamoyl)methyl Ketone (32). Compound **32** was synthesized from 0.526 g of **6** and 0.142 g of ethyl isocyanate in 97% yield (0.65 g) as described above: mp 116–117° (from EtOAc); ν (Nujol) 3250, 1717, 1655 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.06; H, 6.63; N, 8.38; S, 9.57. Found: C, 60.91; H, 6.61; N, 8.34; S, 9.52.

Treatment of 31 with TsOH in MeCN. A solution of 0.382 g (1 mmol) of **31** and 0.76 g (4 mmol) of TsOH–H_2O in 10 ml of MeCN was heated under reflux for 1 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2. The solution was washed with $NaHCO_3$ solution and H_2O, dried, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (15:1) gave 95 mg (30%) of **2-hydroxy-9-methylcarbazole-1-carboxanilide (33):** mp 247–249 °C (from EtOH); ν (Nujol) 3360, 3240, 1640 cm^{-1}; *m/e* 316 (M^+), 223 (base peak); δ (Me_2SO-d_6) 3.70 (s, 3 H), 6.7–8.0 (12 H), 9.75 (s, 1 H).

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.71; H, 5.14; N, 9.02.

The elution was continued to isolate 0.163 g (45%) of **3,4-dioxo-6-methyl-3a-methylthio-5-phenyl-1,2,3,3a,4,5,5a,6-octahydrocyclopent[*c*]pyrrolo[2,3-*b*]indole (35):** mp 185–187° (from MeOH); ν (Nujol) 1745, 1690 cm^{-1}; *m/e* 364 (M^+); δ ($CDCl_3$) 2.28 (s, 3 H), 2.35–2.9 (4 H), 2.60 (s, 3 H), 5.40 (s, 1 H), 6.4–7.4 (9 H).

Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69; S, 8.78. Found: C, 69.06; H, 5.51; N, 7.73; S, 8.77.

Treatment of 32 with TsOH. A. A solution of 67 mg of **32** and 57 mg of TsOH–H_2O in 6 ml of MeCN was heated under reflux for 2 h. After the addition of $NaHCO_3$ solution, MeCN was evaporated, and the residue was extracted with CH_2Cl_2. The extract was dried and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (6:1) gave 22 mg (41%) of ***N*-ethyl-2-hydroxy-9-methylcarbazole-1-carboxamide (34):** mp 224–226° (from EtOH); ν (Nujol) 3255, 1639 cm^{-1}; *m/e* 268 (M^+), 223 (base peak), 195, 167.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.48. Found: C, 71.66; H, 6.00; N, 10.41.

The elution was continued to isolate 21 mg (33%) of **3,4-dioxo-5-ethyl-6-methyl-3a-methylthio-1,2,3,3a,4,5,5a,6-octahydrocyclopent[*c*]pyrrolo[2,3-*b*]indole (36):** mp 160–161° (from MeOH); ν (Nujol) 1745, 1685 cm^{-1}; δ ($CDCl_3$) 1.20 (t, 3 H, J = 7 Hz), 2.04 (s, 3 H), 2.15–2.8 (4 H), 3.06 (s, 3 H), 3.3–3.7 (2 H), 4.88 (s, 1 H), 6.5–7.5 (4 H).

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.54; H, 6.37; N, 8.86; S, 10.11. Found: C, 64.25; H, 6.40; N, 8.77, S, 10.08.

B. A solution of 0.165 g (0.5 mmol) of **32** and 15 mg of TsOH–H_2O in 10 ml of dioxane was heated at 50 °C for 5 h. Work-up as described above gave two fractions. The first fraction was 70 mg (44%) of ***N*-ethyl-2-oxo-9-methyl-1-methylthio-1,2,3,4-tetrahydrocarbazole-1-carboxamide (37):** mp 139–141 °C (from EtOH); ν (Nujol) 3300, 1700, 1660 cm^{-1}; δ ($CDCl_3$) 1.10 (t, 3 H), 2.00 (s, 3 H), 2.7–3.1 (m, 6 H), 3.75 (s, 3 H), 7.1–7.7 (m, 4 H).

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.54; H, 6.37; N, 8.86; S, 10.11. Found: C, 64.46; H, 6.41; N, 8.83; S, 10.15.

The second fraction was 63 mg (40%) of **36.**

2-(5-Phenyl-2-pyrrolyl)ethyl Methylsulfinylmethyl Ketone (40). Compound **40** was prepared from 2.4 g of ethyl 5-phenylpyrrole-2-propionate[11] and Me_2SO: yield 2.1 g; mp 134–136 °C (from EtOAc); ν (Nujol) 3250, 1715 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.44; H, 6.22; N, 5.09; S, 11.62. Found: C, 65.54; H, 6.32; N, 5.22; S, 11.36.

2-(5-Phenyl-2-pyrrolyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (41). Compound **41** was prepared from 0.275 g of **40** and 0.12 g of phenyl isocyanate as described above: yield 0.19 g; mp 117 °C (from Et_2O); ν (Nujol) 3400, 3240, 1710, 1670, 1040 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.99; H, 5.62; N, 7.10; S, 8.11. Found: C, 67.03; H, 5.63; N, 7.07; S, 8.33.

4-Methylthio-5-oxo-2-phenyl-4,5,6,7-tetrahydroindole (42). A solution of 0.138 g of **40** and 0.038 g of TsOH–H_2O in 10 ml of THF was heated under reflux for 1 h. The solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove THF, and extracted with CH_2Cl_2. The extract was dried and evaporated to leave crude **42**, which was purified on a silica gel column eluting with $CHCl_3$ to give 0.081 g (63%) of a solid. Recrystallization from EtOH gave colorless needles: mp 139–141 °C; ν (Nujol) 3320, 1690 cm^{-1}; *m/e* 257 (M^+); δ ($CDCl_3$) 2.12 (s, 3 H), 2.35–2.56 (m, 1 H), 2.92–3.08 (m, 2 H), 3.24–3.50 (m, 1 H), 4.08 (s, 1 H), 6.40 (d, 1 H, J = 2 Hz), 7.18–7.5 (5 H), 8.35 (broad s, 1 H).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.02; H, 5.88; N, 5.44; S, 12.44. Found: C, 70.12; H, 5.73; N, 5.42; S, 12.57.

5-Methoxy-2-phenylindole (43). A solution of 0.137 g of **40** and 0.095 g of TsOH–H_2O in 15 ml of MeOH was heated under reflux for 40 min. To this solution, $NaHCO_3$ solution was added, and the neutralized solution was concentrated to remove MeOH and then extracted with CH_2Cl_2. The extract was dried and evaporated to leave crude **43**, which was decolorized by passing in benzene through a column of Al_2O_3 to give 0.088 g (80%) of **43.** Recrystallization from 60% EtOH gave colorless needles, mp 164–166 °C.[21]

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.66; H, 5.82; N, 6.02.

5-Ethoxy-2-phenylindole (44). A solution of 0.137 g of **40** and 0.095 g of TsOH–H_2O in 15 ml of EtOH was heated under reflux for 40 min. Work-up as described for **43** gave 0.085 g (72%) of **44,** mp 136–137 °C.[21]

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.07; H, 6.32; N, 5.69.

5-Hydroxy-2-phenylindole-4-carboxanilide (45). A solution of 0.198 g of **41** and 0.1 g of TsOH–H_2O in 10 ml of *i*-PrOH was heated under reflux for 1 h. To this solution was added $NaHCO_3$ solution, and the neutralized solution was concentrated and then extracted with CH_2Cl_2. The extract was dried and evaporated to give crude **45**, which was purified on a column of silica gel eluting with $CHCl_3$ to give 0.15 g (91%) of a solid. Recrystallization from benzene gave needles: mp 206–208 °C; *m/e* 328 (M^+); ν (Nujol) 3450, 1635 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.98; H, 4.71; N, 8.70.

2-(2-Thienyl)ethyl Methylsulfinylmethyl Ketone (46). Compound **46** was synthesized from methyl 2-thiophenepropionate[22] and Me_2SO in 70% yield as a pale yellow oil: ν (neat) 1700, 1030 cm^{-1}; δ ($CDCl_3$) 2.60 (s, 3 H), 3.00 (q, 4 H, J = 4 Hz), 3.72 (s, 2 H), 6.75–7.15 (3 H).

2-(2-Thienyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (47). Compound **47** was synthesized from the Na salt of 0.432 g of **46** and 0.24 g of phenyl isocyanate in THF. Work-up as described for **41** gave 0.6 g of **47**, which was recrystallized from EtOAc: mp 127–129 °C; ν (Nujol) 1715, 1670 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.31; H, 5.11; N, 4.18; S, 19.08. Found: C, 56.74; H, 5.01; N, 4.09; S, 18.68.

2-(2-Thienyl)ethyl 1-Methylsulfinyl-2-methoxycarbonylethyl Ketone (48). To an ice-cooled solution of the Na salt of **46**, prepared from 0.432 g of **46** and 0.06 g of NaH in 10 ml of THF, 0.32 g of methyl bromoacetate in 3 ml of THF was added with stirring. After being stirred for 1 h at room temperature, the mixture was concentrated in vacuo and then diluted with H_2O. The solution was acidified with HCl to pH 5 and extracted with $CHCl_3$. The extract was dried and concentrated to leave crude **48**, which was purified on a silica gel column eluting with $CHCl_3$–EtOAc (1:1) to give 0.28 g of **48** as an oil: ν (neat) 1730, 1700, 1050 cm^{-1}.

4-Methylthio-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (49). A solution of 0.23 g of **46** and 0.228 g of CF_3CO_2H in 6 ml of benzene was heated under reflux for 2 h. The solution was cooled, washed with $NaHCO_3$ solution, dried, and evaporated to leave crude **49**, which was purified on a silica gel column eluting with benzene to give 0.1 g (50%) of **49** as an oil: *m/e* 198 (M^+), 151, 150, 123; ν (neat) 1700 cm^{-1}; δ ($CDCl_3$) 2.05 (s, 3 H), 3.0–3.3 (4 H), 4.02 (s, 1 H), 6.87 (d, 1 H, J = 5 Hz), 7.08 (d, 1 H, J = 5 Hz).

Treatment of 46 with TsOH in MeCN. A solution of 0.27 g of **46** and 0.44 g of TsOH–H_2O in 8 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and the solution was washed with $NaHCO_3$ solution and then extracted with 10% NaOH. From the CH_2Cl_2 layer **51** and **54** were isolated (see below).

The aqueous layer was acidified with 10% HCl and extracted with CH_2Cl_2. The extract was dried and concentrated to give 0.101 g (56%) of **5-hydroxybenzo[*b*]thiophene (50),**[23] which was recrystallized from hexane to afford colorless plates: mp 103–105 °C; *m/e* 150 (M^+), 122, 121.

Anal. Calcd for C_8H_6OS: C, 64.00; H, 4.03; S, 21.31. Found: C, 63.71; H, 3.92; S, 21.15.

The initial CH_2Cl_2 layer was dried and concentrated to leave an oil (0.043 g), which was a mixture of 14% of **5-methylthiobenzo[*b*]thiophene (51),** *m/e* 180 (M^+), 165, 121, δ ($CDCl_3$) 2.47 (s, 3 H), and 7% of **2-(2-thienyl)ethyl (bismethylthio)methyl ketone (54),** *m/e* 107 [$CH(SMe)_2$], δ ($CDCl_3$) 1.95 (s, 6 H), 4.25 (s, 1 H).

5-Methoxybenzo[*b*]thiophene (52). A solution of 0.216 g of **46** and 0.978 g of CCl_3CO_2H in 12 ml of MeCN containing 0.4 ml of MeOH was heated under reflux for 4 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo, and extracted with CH_2Cl_2. The extract was dried and chromatographed on a column of silica gel eluting with CCl_4 to give 36 mg (22%) of **52** as a colorless solid:[24] mp 38–40 °C; *m/e* 164 (M^+), 149, 121.

5-Hydroxybenzo[*b*]thiophene-4-carboxanilide (53). A solution of 0.224 g of **47** and 0.126 g of TsOH–H_2O in 12 ml of benzene was heated under reflux for 1 h. The solution was cooled, washed with $NaHCO_3$ solution, dried, and evaporated to leave crude **53**, which was purified on a silica gel column eluting with $CHCl_3$ to give 0.1 g (55%) of **53.** Recrystallization from EtOH afforded colorless scales: mp 190–192°; ν (Nujol) 3320, 3120, 1630 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.12; N, 5.20. Found: C, 67.08; H, 4.00; N, 5.11.

2,3-Dihydro-2-oxobenzo[*b*]thieno[5,4-*b*]furan (55). A solution of 0.288 g of **48** and 0.19 g of TsOH–H_2O in 12 ml of benzene was heated under reflux for 1 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated. The residue was purified on a silica gel column eluting with benzene to give 0.048 g (25%) of **55,** which was recrystallized from benzene–hexane: mp 121–123 °C; ν (Nujol) 1790 cm^{-1}; *m/e* 190 (M^+), 162, 134.

Anal. Calcd for $C_{10}H_6O_2S$: C, 63.16; H, 3.18; S, 16.83. Found: C, 63.28; H, 3.18; S, 16.60.

1-Acetamido-2-(2-thienyl)ethyl Methylsulfinylmethyl Ketone (56). Compound **56** (3.57 g) was synthesized from 5.76 g of *N*-acetylthiophene-2-alanine methyl ester[25] and 1.86 g of NaH in 40 ml of Me_2SO: mp 132 °C (from EtOAc); ν (Nujol) 3250, 3070, 1715, 1650 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_3S_2$: S, 23.40. Found: S, 22.69.

2-Methyloxazolo[5,4-*f*]benzo[*b*]thiophene (57). A solution of 0.25 g of **56** and 0.39 g of TsOH–H_2O in 9 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, and the solution was washed with $NaHCO_3$ solution, dried, and concentrated to give **57,** which was purified by passing in benzene through an Al_2O_3 column to give 0.09 g (53%) of **57:** mp 76–77 °C (from hexane); ν (Nujol) 1618, 1600, 1565 cm^{-1}; *m/e* 189 (M^+), 120; δ ($CDCl_3$) 2.67 (s, 3 H), 7.45 (q, 2 H), 7.86 (s, 1 H), 8.15 (s, 1 H).

Anal. Calcd for $C_{10}H_7NOS$: S, 16.92. Found: S, 16.63.

Registry No.—**5,** 38499-75-1; **5** K salt, 57900-77-3; **6,** 57900-78-4; **6** Na salt, 57900-79-5; **7,** 57900-80-8; **8,** 38499-79-5; **9** isomer 1, 57900-81-9; **9** isomer 2, 57900-82-0; **10** isomer 1, 57900-83-1; **10** isomer 2, 57951-58-3; **11** isomer 1, 57900-84-2; **11** isomer 2, 57900-85-3; **12,** 38499-77-3; **13,** 38499-78-4; **14,** 51894-58-7; **15,** 38499-80-8; **16,** 57900-86-4; **17,** 57900-87-5; **18** isomer 1, 57900-88-6; **18** isomer 2, 57900-89-7; **19,** 40429-00-3; **20,** 86-79-3; **21,** 51846-67-4; **22,** 57900-90-0; **23,** 1484-12-4; **24,** 39027-93-5; **25,** 51846-68-5; **26,** 24224-30-4; **27,** 57900-91-1; **28,** 51846-69-6; **29** isomer 1, 57900-92-2; **29** isomer 2, 57900-93-3; **30,** 51846-71-0; **31,** 57900-94-4; **32,** 57900-95-5; **33,** 57900-96-6; **34,** 57900-97-7; **35,** 57900-98-8; **36,** 57900-99-9; **37,** 57901-00-5; **40,** 57901-01-6; **41,** 57901-02-7; **42,** 51846-54-9; **43,** 5883-96-5; **44,** 23746-83-0; **45,** 51846-55-0; **46,** 57901-03-8; **46** Na salt, 57901-04-9; **47,** 57901-05-0; **48,** 57901-06-1; **49,** 51846-59-4; **50,** 19301-35-0; **51,** 51846-60-7; **52,** 20532-30-3; **53,** 51846-61-8; **54,** 51846-62-9; **55,** 51846-63-0; **56,** 57901-07-2; **57,** 51846-65-2; Me_2SO, 67-68-5; methyl indole-3-propionate, 5548-09-4; methyl (1-methyl-3-indolyl)propionate, 57901-08-3; benzyl chloride, 100-44-7; methyl 3-(1-benzyl-3-indolyl)propionate, 57901-09-4; *N*-acetyl-*dl*-tryptophan methyl ester, 16108-06-8; methyl 2-acetamido-3-(1-methyl-3-indolyl)propionate, 57901-10-7; ethyl 3-(3-indolyl)-2-methylpropionate, 57901-11-8; *N*-(3-indolyl-1-ethyl)-*N*-isopropylamine, 14121-10-9; ethyl 3-(1-benzyl-3-indolyl)butyrate, 57901-12-9; diethyl malonate, 105-53-3; ethyl 2-acetamido-3-(1-methyl-2-indolyl)propionate, 57901-13-0; ethyl 2-acetamido-3-(2-indolyl)propionate, 27442-71-3; CCl_3CO_2H, 76-03-9; TsOH, 104-15-4; MeOH, 67-56-1; EtOH, 64-17-5; phenyl isocyanate, 103-71-9; ethyl isocyanate, 109-90-0; ethyl 5-phenylpyrrole-2-propionate, 57901-14-1; methyl 2-thiophenepropionate, 16862-05-8; CF_3CO_2H, 76-05-1; *N*-acetylthiophene-2-alanine methyl ester, 57901-15-2.

References and Notes

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