2-Benzazepines. 1.[1] Synthesis of 2-Benzazepin-4-ones and -5-ones via 2-Acetylenic Benzophenones

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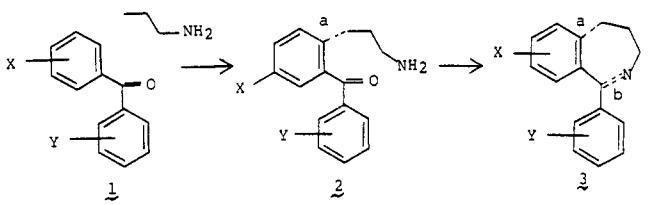
The preparation of 1-phenyl-2-benzazepin-4-ones and -5-ones is discussed. The palladium-catalyzed coupling of an iodobenzophenone to a monosubstituted acetylene assembles the necessary atoms required for the benzazepine ring. Transformation of the acetylene group into a ketone with concomitant cyclization of the resulting β-amino ketone completes the synthesis. The synthetic limitations and details are discussed.

As part of a program aimed at the discovery of novel anxiolytic agents, the synthesis and pharmacological evaluation of 1-carbon isosteres of 5-phenyl-1,4-benzodiazepines presented an attractive and logical extension of our work in the 1,4-benzodiazepine area.[2,3] In order to conduct a thorough investigation of the 1-phenyl-2-benzazepine ring system, we required a facile synthesis which would incorporate functionality into the 4- or 5-position of the azepine ring and would also accommodate halogen or other electron-withdrawing substituents on the aromatic rings.

During the course of our investigation Gschwend[4] reported a synthesis of 1-phenyl-2-benzazepin-5-ones which accommodated aromatic halogen substitution but was not suitable for large-scale preparations. The Bischler–Napieralski cyclization[5] and the Friedel–Crafts acylation,[4] the two most widely used methods for the synthesis of 2-benzazepines, also presented drawbacks in that these electrophilic reactions would be deactivated by aromatic halogens and electron-withdrawing substituents.

For our work, an alternate synthetic approach was clearly needed, and this paper describes a short and high-yield synthesis of substituted 1-phenyl-2-benzazepines, amenable to large-scale preparations.

Formally, a 1-phenyl-2-benzazepine can be constructed in two steps. First, bond a is formed (see structure **2**) by

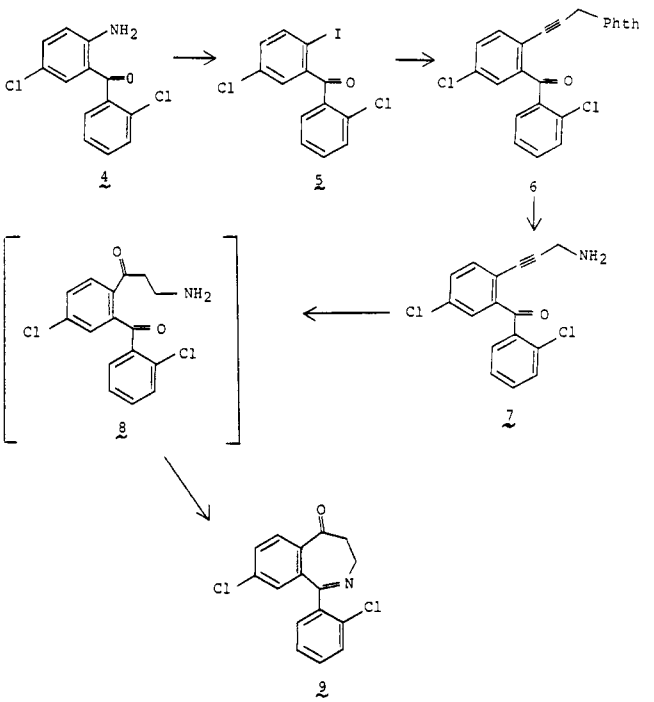


1 **2** **3**

the addition of a 3-carbon synthon having a terminal amino group to a substituted benzophenone **1**. Second, bond b is formed (see structure **3**) by cyclization of the amino group with the carbonyl group, followed by the loss of water.

The palladium-catalyzed coupling of an aromatic iodide with a monosubstituted acetylene[6] presented an attractive starting point for this approach. Propargylamine or a derivative of propargylamine could serve as the three-carbon synthon which could be coupled to an iodobenzophenone to form bond a (see structure **2**). The two carbons of the acetylenic group in the resulting coupled benzophenone correspond to the 4- and 5-positions of the 2-benzazepine ring system. Transformation of these two carbon atoms, which are sp hybridized and prevent intramolecular ring closure, into carbon atoms having sp^2 or sp^3 hybridization then allows the terminal amino group in structure **2** to condense intramolecularly with the benzophenone carbonyl to form bond b and thus give the 2-benzazepine ring system.

Scheme I



[a] Phth = phthalimido.

The iodobenzophenone **5** required for the coupling reaction was readily prepared by diazotization of the corresponding *o*-aminobenzophenone **4** with nitrosyl sulfate followed by treatment of the diazonium salt with aqueous potassium iodide (Scheme I). The coupling of **5** with propargylphthalimide in the presence of dichlorobis(triphenylphosphine)palladium(II) and cuprous iodide in a mixture of diethylamine and methylene chloride yielded the acetylenic benzophenone **6**. Removal of the phthaloyl protecting group from **6** with 40% aqueous methylamine in ethanol gave the amine **7** in quantitative yield which contained the atoms necessary for construction of the benzazepine ring. Hydration of the acetylene in **7** with

(1) Dedicated to the memory of Dr. Willy Leimgruber, died July 8, 1981.
(2) (a) Archer, A. G.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747. (b) Gschwend, H. "Industrial Pharmacology"; Fielding, S., Lab, H., Eds.; Futura: Mount Kisco, NY, 1979; Chapter 1.
(3) Fryer, R. I.; Leimgruber, W.; Trybulski, E. J. *J. Med. Chem.*, in press.
(4) Gschwend, H. U.S. Patent 3 947 585, Mar 30, 1976.
(5) Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45.
(6) Sanogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Edo, K.; Yamanka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271. (c) Yoshihito, A.; Ohsawa, A.; Heihachiro, A.; Igeta, H. *Ibid.* **1978**, *9*, 1397.

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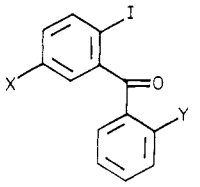
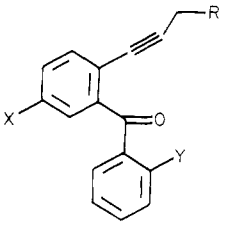
Table I. Substituted o-Iodobenzophenones



X	Y	mp, °C	% yield[b]	formula[d,e]
Cl	Cl	64-66	34	$C_{13}H_7Cl_2IO$
Cl	H	80-82	52	$C_{13}H_8ClIO$
Cl	F	78-81	47	$C_{13}H_7ClFIO$
H	Cl	62-64	35	$C_{13}H_8ClIO$
H	H	29-31[a]	77[c]	$C_{13}H_9IO$

[a] Lit. mp 32.5 °C: *J. Chem. Soc.* 1958, 1382. [b] Yields are not optimized. [c] Yield based on crude oil. [d] All spectroscopic data are consistent with assigned structures. [e] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds.

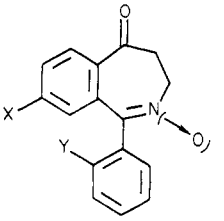
Table II. Acetylenic Benzophenones



X	Y	R	mp, °C	% yield[b]	formula[c,d]
Cl	Cl	Phth	144-145	39	$C_{24}H_{13}Cl_2NO_3$
Cl	H	Phth	148-150	46	$C_{24}H_{14}ClNO_3$
Cl	F	Phth	155-161	80	$C_{24}H_{13}ClFNO_3$
H	Cl	Phth	149-150	64	$C_{24}H_{14}ClNO_3$
H	H	Phth	164-165	58	$C_{24}H_{15}NO_3$
Cl	Cl	NH_2	81-82	90	$C_{16}H_{11}Cl_2NO$
Cl	H	NH_2	68-69	80	$C_{16}H_{12}ClNO$
Cl	F	NH_2	89-91	78	$C_{16}H_{11}ClFNO$
H	Cl	NH_2	160-162[a]	88	$C_{16}H_{13}Cl_2NO$
H	H	NH_2	157-158[a]	56	$C_{16}H_{14}ClNO$

[a] Melting points, yields, and analyses are based on the hydrochloride salt. [b] Yields have not been optimized. [c] All spectroscopic data are consistent with assigned structure. [d] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds.

Table III. 1-Phenyl-2-benzazepin-4-ones



X	Y	→O	mp, °C	% yield[c]	formula[d,e]
Cl	Cl		134-135	62	$C_{16}H_{11}Cl_2NO$
Cl	H		185-186[a,b]	60	$C_{17}H_{16}ClNO_4S$
Cl	F		109-111	56	$C_{16}H_{11}ClFNO$
H	Cl		135-137	43	$C_{16}H_{12}ClNO$
H	H		196-198[a]	39	$C_{17}H_{17}NO_4S$
Cl	F	O	166-168	51	$C_{16}H_{11}ClFNO_2$
Cl	Cl	O	184-187	50	$C_{16}H_{11}Cl_2NO_2$

[a] Compound characterized as methanesulfonate salt. [b] Lit.[3] mp 185-186 °C: Gschwend, H. U.S. Patent 3 947 585. [c] Yields are not optimized. [d] All spectroscopic data are consistent with assigned structure. [e] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds.

Table IV. Summary of Crystal Data for Compound 16

formula	$C_{16}H_{11}Cl_2NO_2$	α	98.48 (2)°
fw	320.17	β	102.53 (2)°
space group	$P\bar{1}$	γ	111.77 (1)°
a	8.145 (2) Å	Z	2
b	9.737 (2) Å	d_{calcd}	1.504 g cm^{-3}
c	10.159 (3) Å	μ (Cu Kα)	41.7 cm^{-1}

Table V. Summary of Experimental Details for Crystallographic Analysis of Compound 16

crystal	0.05 × 0.20 × 0.35 mm
max θ	57°
no. of reflections	1515
absorption correction	yes
least-squares refinement	full matrix
heavier atoms	anisotropic
hydrogen atoms	isotropic
final R	0.056
final R_w	0.063
final difference map largest peak, e A^{-3}	±0.5

either cold concentrated sulfuric acid or with mercuric sulfate in formic acid gave, after basification of the reaction medium, the 2-benzazepin-5-one **9**, presumably via the amino ketone **8**.

Tables I–III contain additional derivatives of **5**–**7** and **9** which were prepared in an analogous fashion.

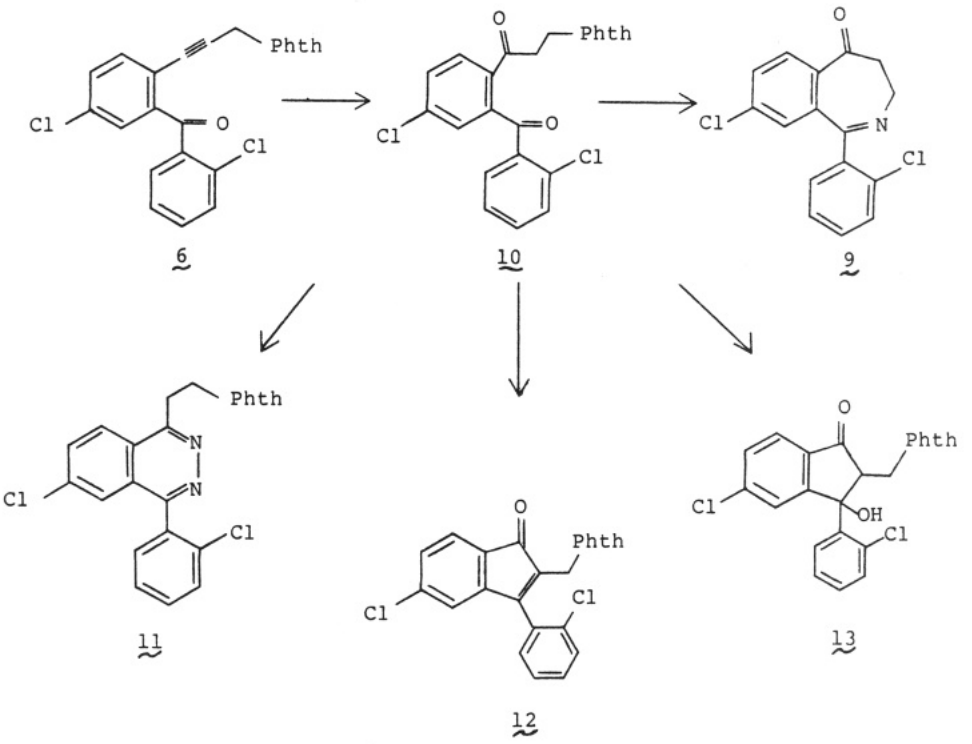
The sequence of steps for converting the phthalimide **6** into the ketone **9** could be reversed, although the overall yield of **9** was reduced. Hydration of the acetylene **6** with mercuric sulfate in formic acid gave the diketone **10**. Removal of the phthaloyl protecting group from **10** by using 40% aqueous methylamine under carefully controlled reaction conditions gave **9**. This deprotection step was accompanied by the formation of varying amounts of unidentified highly polar side products.

The ability of the diketone **10** to undergo side reactions prior to deprotection of the amine was briefly explored. Reaction of **10** with hydrazine in ethanol, the classical method for removing a phthaloyl group, did not yield **9** but only the phthalazine **11** (Scheme II). Acid or base treatment of **10** yielded products derived from aldol condensations. Compound **10** when heated in 70% sulfuric acid on a steam bath gave the indenone **12** and when reacted with dimethylformamide dimethyl acetal in dimethylformamide yielded indanone **13**.

The synthesis of nitrone **14**, was carried out either by the oxidation of the imine group in **9** or in four steps by starting with **5**. Oxidation of **9** with *m*-chloroperbenzoic acid[7] gave a mixture of the desired *N*-oxide **14** and the isomeric oxazirane **15** (Scheme III). If the reaction mixture was washed rapidly with cold dilute sodium bicarbonate solution, then the isolation of pure **14** could be achieved by fractional crystallization or plug filtration through silica gel. If, however, the mixture was treated with acid or stronger base, the oxazirane **15** rearranged to aziridine **16**. Compounds **14** and **16** were not easily separated by either fractional crystallization or column chromatography. Treatment of pure **15** with sodium hydroxide resulted in the formation of the rearranged product

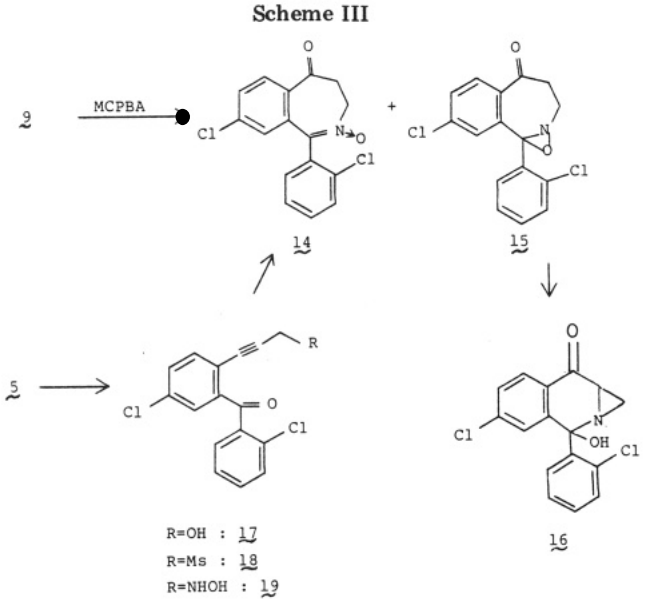
(7) For analogous reactions in the 1,4-benzodiazepines, see: Metlesics, W.; Silverman, G.; Sternbach, L. H. *J. Org. Chem.* **1963**, *28*, 2459.
(8) Makaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8642.
(9) Pappas, N.; Nace, H. *J. Am. Chem. Soc.* **1959**, *81*, 4556.

Scheme II



[a] Phth = phthalimido.

Scheme III



16. The structure of **16** was confirmed by X-ray analysis (see Tables IV and V and Figure 1.

An alternate synthesis of the *N*-oxide **14**, using the readily available acetylene propargyl alcohol, was developed in order to circumvent the separation problems mentioned above. Propargyl alcohol was coupled with iodobenzophenone **5** in the presence of dichlorobis(triphenylphosphine)palladium(II) to give the acetylene **17**. Transformation of the hydroxyl group in **17** into a hydroxylamine group was accomplished first by treatment of **17** with methanesulfonyl chloride and triethylamine to give the mesylate **18**. Displacement of the mesylate with hydroxylamine in ethanol gave **19**. Hydration of **19** with mercuric sulfate in formic acid led to the 2-benzazepin-5-one *N*-oxide **14**.

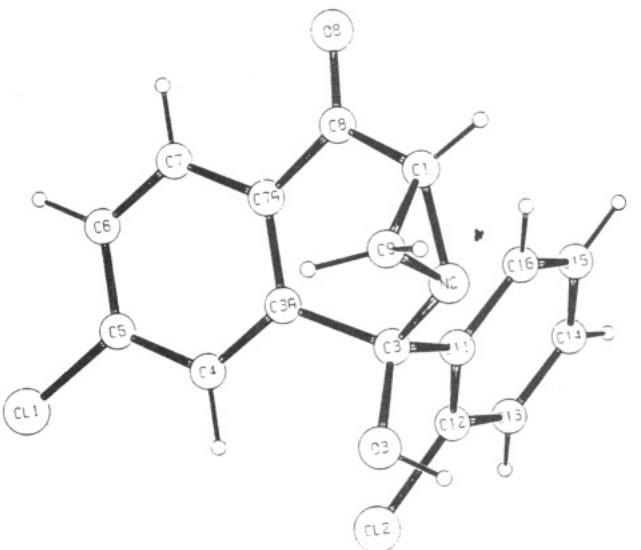
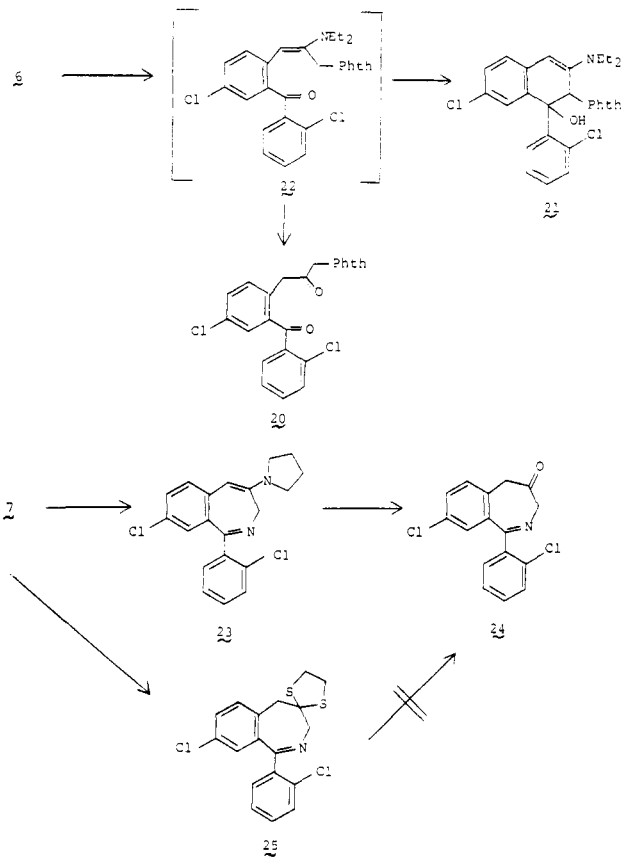


Figure 1. Structure of compound **16** as determined by X-ray analysis.

In a formal sense the preparation of the isomeric 2-benzazepin-4-one compound **24** from either **6** or **7** could be accomplished simply by reversing the reactivity of the acetylene to hydration, relative to treatment with either sulfuric acid or mercuric sulfate. The methodology required for the desired change in functionalization was developed following the isolation and identification of the byproducts formed as a result of extending the reaction times used in the coupling of **5** with propargylphthalimide. Reaction times in excess of 24 h resulted in the formation of compounds such as the diketone **20** (Scheme IV) and the dihydronaphthalene derivative **21**. Both **20** and **21** are probably derived from the same intermediate, the enamine **22**, which is formed by a nucleophilic addition of diethylamine to the acetylene in **6**. Removal of the phthaloyl

Scheme IV



group from **20** and cyclization of the resulting amino ketone to benzazepinone **24** under a variety of conditions, however, was unsuccessful.

The reaction of **7** in which the phthaloyl group has already been removed with an excess of pyrrolidine, a better nucleophile than diethylamine, at room temperature gave the enamine **23** in high yield. Not only had nucleophilic addition of pyrrolidine occurred but the intermediate had also cyclized to the benzazepine. Hydrolysis of the enamine **23** with aqueous hydrochloric acid gave the 2-benzazepin-4-one **24**.

The addition of ethanedithiol to **7** in dimethylformamide containing a catalytic amount of sodium hydride gave the thioketal **25**. Thus far, we have been unable to hydrolyze the thioketal group of **25** to give **24**. The thioketal was inert to reagents such as cupric chloride[8] and mercuric chloride.[9] Methods which facilitate hydrolysis of the thioketal by oxidation or alkylation of the sulfur atoms of the thioketal such as *N*-bromosuccinimide[10] and methyl iodide[11] gave complex reaction mixtures.

In conclusion, the palladium-catalyzed coupling of a monosubstituted acetylene to an aryl iodide provided a facile entry into the 2-benzazepine ring system. The acetylene group of the coupled product was easily transformed into the desired ketone functionality. The utility of these 2-benzazepines and the synthesis of 2-benzazepines with other functional groups will be discussed in forthcoming papers from these laboratories.

Crystallography

Crystals of **16** were obtained from tetrahydrofuran. All intensity data were measured on a Hilger Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The crystal data are given in Table IV. A multiple-solution procedure[12] was used to solve the structure. Experimental details are summarized in Table V.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal Me_4Si. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively.

2′,5-Dichloro-2-iodobenzophenone (5). Sodium nitrite (76 g, 1.1 mol) was added portionwise to 450 mL of concentrated sulfuric acid which was cooled to 10 °C followed by heating to 80 °C until solution was complete. The solution was cooled to 30 °C, and 266 g (1 mol) of **4**[13] was added in portions to maintain a temperature of between 30 and 40 °C. After being stirred for 1 h, the mixture was poured into 3 L of ice–water and the resulting solution filtered through a pad of Celite. A solution of 200 g (1.8 mol) of sodium tetrafluoroborate in 800 mL of water was added slowly to the filtrate. The resulting precipitate was collected by filtration and washed with a small amount of water.

The moist precipitate was slurried in 3 L of water, and a solution of 332 g (2 mol) of potassium iodide in 1 L of water was added dropwise. The mixture was stirred at room temperature overnight. The resulting precipitate was collected by filtration and added to 1 L of boiling ether. The insoluble material was removed by filtration and the ether solution concentrated to ca. 300 mL. Petroleum ether was added, and the resulting precipitate was collected by filtration to give 128 g (mp 58–60 °C; 34%)[14] of **5** as a pale yellow solid. Recrystallization of a small sample of **5** from a mixture of ether and petroleum ether gave **5** as pale yellow prisms: mp 64–66 °C; IR ($CHCl_3$) 1680 cm^{-1}; mass spectrum, *m/e* 376 (M^+).

Anal. Calcd for $C_{13}H_7Cl_2IO$: C, 41.42; H. 1.87. Found: C, 41.60; H, 1.92.

***N*-[[4-Chloro-2-(2-chlorobenzoyl)phenyl]-3-propynyl]isoindole-1,3(2*H*)-dione (6).** Successively to a solution of 400 mL of CH_2Cl_2 and 200 mL of diethylamine under an atmosphere of argon were added 0.71 g (4 mmol) of palladium chloride, 2.1 g (8 mmol) of triphenylphosphine,[15] 0.8 g of cuprous iodide, 72.5 g (0.192 mol) of **5**, and 40 g (0.216 mol) of *N*-propargylphthalimide.[16] The mixture was stirred at room temperature under argon for 20 h and then concentrated in vacuo to dryness. The residue was triturated with 200 mL of 2-propanol. The resulting precipitate was collected by filtration and successively washed with 2-propanol and ether. The crude product was recrystallized from acetone to give 32.5 g (39%) of **6** as cream-colored prisms: mp 144–145 °C; IR ($CHCl_3$) 1775, 1723 (imide C=O), 1680 cm^{-1} (ketone C=O); NMR ($CDCl_3$) δ 4.34 (s, 2, CH_2), and 7.1–7.9 (m, 11, arom H); mass spectrum, *m/e* 433 (M^+).

Anal. Calcd for $C_{24}H_{14}ClNO_3$: C, 66.38; H, 3.02; N, 3.22. Found: C, 66.58; H, 2.99; N, 3.05.

3-Amino-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]propane (7). A mixture of 350 g (0.8 mol) of **6**, 250 mL of 40% aqueous methylamine, and 900 mL of 95% ethanol was stirred at room temperature for 2 h. Water (450 mL) was added dropwise, producing a clear yellow solution which was stirred for 30 min. The slow addition of 3 L of water precipitated the product which was collected by filtration to give 238 g (mp 79–80 °C; 97%) of **7** as a pale yellow solid. Recrystallization of a small sample from ether gave **7** as pale yellow prisms: mp 81–82 °C; IR ($CHCl_3$) 3390 (NH_2), 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.07 (s, 2, NH_2), 3.29

(10) Corey, E. J.; Erickson, B. *J. Org. Chem.* **1971**, *36*, 3553.
(11) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.
(12) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.
(13) Sternbach, L. H.; Reeder, E.; Keller, O.; Metlesics, W. *J. Org. Chem.* **1961**, *26*, 4488.
(14) The yield of this reaction has been increased to 70% by the use of ethyl acetate as a cosolvent in the decomposition of the diazonium salt with potassium iodide. This improvement was conducted by Dr. J. W. Scott of our Kilo Laboratory.
(15) The reaction was also done by using phthalimidodichlorobis(triphenylphosphine)palladium(II) as a catalyst.
(16) Gaudemar, M. *Ann. Chim. (Paris)* **1956**, *1*(13), 161.

(s, 2, CH_2), 7.3–7.7 (m, 7, arom H); mass spectrum, m/e 303 (M^+).

Anal. Calcd for $C_{16}H_{11}Cl_2NO$: C, 63.18; H, 3.64; N, 4.60. Found: C, 63.39; H, 3.57; N, 4.44.

8-Chloro-1-(2-chlorophenyl)-3,4-dihydro-5*H*-2-benzazepin-5-one (9). Method A. Compound **7** (32.4 g, 106 mmol) was added portionwise to a solution of 6.9 g (25 mmol) of mercuric sulfate and 30 mL of formic acid in 150 mL of CH_2Cl_2 which was cooled in an ice bath. The mixture was stirred at 0 °C for 2 h, poured over ice, and neutralized with ammonium hydroxide. The aqueous solution was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried (Na_2SO_4), and concentrated in vacuo to give 33.3 g of a dark brown oil. The oil was dissolved in 106 mL of a 1 M methanol solution of methanesulfonic acid, filtered through Celite, and concentrated to a small volume. The addition of ether to the residue gave 20.2 g (62%) of the methanesulfonate salt of **9** as an off-white solid. Recrystallization from a mixture of methanol and ether gave the salt of **9** as off-white prisms: mp 180–181 °C;[2] IR (KBr) 2800, 2600 cm^{-1} (NH^+), 1693 (C=O); NMR (Me_2SO-d_6) δ 3.25 (m, 2) and 4.09 (m, 2) (A_2B_2 system, CH_2CH_2), 7.05 (d, J = 2 Hz, 1, arom H), 7.4–7.9 (m, 6, arom H), 11.51 (s, 1, NH^+).

Anal. Calcd for $C_{17}H_{15}Cl_2NO_4S$: C, 51.01; H, 3.78; N, 3.50. Found: C, 51.19; H, 3.57; N, 3.43.

A small sample of the methanesulfonate salt of **9** was partitioned between CH_2Cl_2 and ammonium hydroxide. The CH_2Cl_2 solution was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue crystallized from ether to give **9** as a yellow solid. Recrystallization from a mixture of ether and petroleum ether gave **9** as pale yellow prisms: mp 134–135 °C; IR ($CHCl_3$) 1675 (C=O), 1620 cm^{-1} (C=N); NMR ($CDCl_3$) δ 3.07 (m, 2) and 3.95 (m, 2) (A_2B_2 system, CH_2CH_2), 6.99 (d, J = 2 Hz, 1, arom H), 7.2–7.6 (m, 5, arom H), 7.86 (d, J = 9 Hz, 1, arom H); mass spectrum, m/e 303 (M^+).

Anal. Calcd for $C_{16}H_{11}Cl_2NO$: C, 63.18; H, 3.65; N, 4.60. Found: C, 63.00; H, 3.78; N, 4.31.

Method B. A solution of 100 g (0.33 mol) of **7** in 160 mL of CH_2Cl_2 was added dropwise to 250 mL of concentrated sulfuric acid which was cooled to 0 °C. The mixture was stirred at 0 °C for 4 h, poured over ice, and neutralized with ammonium hydroxide. The aqueous solution was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. A solution of 32 g (0.33 mol) of methanesulfonic acid in 75 mL of 2-propanol was added to an ice-cold solution of the residue in 200 mL of 2-propanol. The resulting precipitate was collected by filtration to give 55.7 g (42%) of the methanesulfonate salt of **9** as off-white crystals, mp 175–178 °C.

2-[[4-Chloro-2-(2-chlorobenzoyl)phenyl]-3-oxopropyl]-1*H*-isoindole-1,3(2*H*)-dione (10). Compound **6** (21.6 g, 50 mmol) was added portionwise to a mixture of 1.0 g (3.3 mmol) of mercuric sulfate, 5 mL of water, 55 mL of formic acid, and 50 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 40 min, poured into ice, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to dryness. Crystallization of the residue from a mixture of ethyl acetate and ether gave 20.8 g (92%) of **10** as off-white crystals. Recrystallization of a sample from a mixture of methanol and CH_2Cl_2 gave **10** as white prisms: mp 133–134 °C; IR ($CHCl_3$) 1776, 1718 (imide C=O), 1693 cm^{-1} (ketone C=O).

Anal. Calcd for $C_{24}H_{15}Cl_2NO_4$: C, 63.73; H, 3.34; N, 3.10. Found: C, 63.47; H, 3.35; N, 3.33.

Methanesulfonate of 8-Chloro-3,4-dihydro-1-(2-chlorophenyl)-5*H*-2-benzazepin-5-one (9) from 10. A mixture of 4.5 g (10 mmol) of **10**, 30 mL of ethanol, and 10 mL of 40% aqueous methylamine was stirred at room temperature 1 h. The reaction mixture was poured into ice–water and extracted with ether. The ether solution was extracted with cold dilute HCl. The aqueous acid extract was neutralized with cold dilute ammonium hydroxide and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried (Na_2SO_4), diluted with 10 mL of a 1 M methanol solution of methanesulfonic acid, and concentrated in vacuo to dryness. The residue crystallized from 2-propanol to give 0.8 g (mp 183–184 °C; 20%) of **9** as off-white needles which were identical in every respect with an authentic sample.

2-[1-[6-Chloro-4-(2-chlorophenyl)-1-phthalazinyl]-ethyl]-1*H*-isoindole-1,3(2*H*)-dione (11). A mixture of 2.2 g (5 mmol) of **10**, 100 mL of ethanol, and 0.3 mL of 85% hydrazine hydrate was heated on a steam bath for 2 h. The reaction mixture was concentrated in vacuo to a small volume, and 1.3 g (58%) of crude **11** was separated by filtration. Recrystallization from ethanol gave **11** as colorless needles: mp 190–191 °C; IR ($CHCl_3$) 1775, 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.78 (dd, 2) and 4.37 (dd, 2) (A_2B_2 system, J = 6, 8 Hz, CH_2CH_2), 7.4–7.9 (m, 10, arom H), 8.28 (d, J = 9 Hz, 1, arom H); mass spectrum, m/e 447 (M^+).

Anal. Calcd for $C_{24}H_{15}Cl_2N_3O_2$: C, 64.30; H, 3.37; N, 9.37. Found: C, 64.29; H, 3.39; N, 9.37.

2-[[5-Chloro-3-(2-chlorophenyl)-1-oxo-1*H*-inden-2-yl]-methyl]-1*H*-isoindole-1,3(2*H*)-dione (12). A mixture of 2 g (4.4 mmol) of **10** and 20 mL of 70% (v/v) sulfuric acid was heated on a steambath for 45 min. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to dryness. The residue (1.7 g) crystallized from a mixture of CH_2Cl_2, ether, and petroleum ether to give 1.3 g (mp 187–188 °C; 67%) of **12** as a yellow solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **12** as pale yellow needles: mp 187–188 °C; IR ($CHCl_3$) 1775 (imide C=O), 1720 cm^{-1} (imide, ketone C=O); NMR ($CDCl_3$) δ 4.45 (d, 1) and 4.73 (d, 1) (AB system, J = 17 Hz, CH_2), 6.68 (d, J = 2 Hz, 1, arom H), 7.1–7.5 (m, 6, arom H), 7.66 (m, 4, arom H); mass spectrum, m/e 433 (M^+).

Anal. Calcd for $C_{24}H_{13}Cl_2NO_3$: C, 66.38; H, 3.02; N, 3.23. Found: C, 66.44; H, 3.09; N, 3.38.

2-[[5-Chloro-3-(2-chlorophenyl)-2,3-dihydro-3-hydroxy-1-oxo-1*H*-inden-2-yl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (13). A mixture of 4.5 g (10 mmol) of **10**, 15 mL of dimethylformamide, and 10 mL of dimethylformamide dimethyl acetal was stirred at room temperature for 5 h. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was separated, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to dryness. The residue crystallized from a mixture of CH_2Cl_2 and ether to give 2 g (44%; mp 239–240 °C) of crude **13**. Recrystallization from a mixture of CH_2Cl_2 and ether gave **13** as cream-colored needles: mp 251–252 °C; IR (KBr) 3425 (OH), 1775, 1720 (imide C=O), 1700 cm^{-1} (ketone C=O); NMR (Me_2SO-d_6) δ 3.34 (s, 1, OH), 3.9–4.2 (m, 3, CH_2CH), 6.90 (t, J = 7 Hz, 1, arom H), 7.0–7.2 (m, 2, arom H), 7.36 (d, J = 8 Hz, 1, arom H), 7.5–7.8 (m, 7, arom H); mass spectrum, m/e 451 (M^+).

Anal. Calcd for $C_{24}H_{15}Cl_2NO_4$: C, 63.73; H, 3.34; N, 3.06. Found: C, 63.44; H, 3.51; N, 3.06.

8-Chloro-1-(2-chlorophenyl)-3,4-dihydro-5*H*-2-benzazepin-5-one 2-Oxide (14) and 8-Chloro-9b-(2-chlorophenyl)-3,4-dihydro-9a*H*-oxazirino[3,2-*a*][2]benzazepin-5-(5*H*)-one (15). A solution of 1.9 g (6.2 mmol) of **9** and 1.9 g (9.4 mmol) of 85% *m*-chloroperoxybenzoic acid in 30 mL of CH_2Cl_2 was stirred at 0 °C for 30 min. The mixture was washed with ice-cold dilute $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to dryness. The residue was purified by column chromatography (SiO_2, 20 g; eluent, CH_2Cl_2 and then 10% Et_2O in CH_2Cl_2) to give as the first product band 0.9 g of **15** as a foam:[17] IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.05 (m, 2, 2-CH), 3.49 (m, 1, CH), 3.80 (m, 1, CH), 7.2–7.7 (m, 10, arom H); mass spectrum, m/e 319 (M^+).

The second product band gave 0.5 g (mp 185–190 °C; 25%) of **14** as a pale yellow solid. Recrystallization from a mixture of ether and CH_2Cl_2 gave **14** as colorless prisms: mp 195–198 °C; IR ($CHCl_3$) 1693 (C=O); NMR ($CDCl_3$) δ 3.37 (m, 2, C_4 H), 4.09 (m, 2, C_3 H), 6.87 (d, J = 2 Hz, 1, arom H), 7.3–7.5 (m, 5, arom H), 7.82 (d, J = 8 Hz, 1, arom H); mass spectrum, m/e 319 (M^+).

Anal. Calcd for $C_{16}H_{11}Cl_2NO$: C, 60.02; H, 3.46; N, 4.37. Found: C, 60.27; H, 3.61; N, 4.13.

5-Chloro-3-(2-chlorophenyl)-1,3-dihydro-3-hydroxyazirino[1,2-*b*]isoquinolin-8(8a*H*)-one (16). A solution of 2.0 g (6.2 mmol) of **15** and 5 mL of 3 N aqueous sodium hydroxide in 50 mL of THF was stirred at room temperature for 10 min. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give 1.2 g (60%) of **16** as a pale yellow solid. Recrystallization from ether gave **16** as pale yellow prisms: mp 150–152 °C; IR (KBr) 3150–3080 (OH), 1683 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.15 (d, J = 3 Hz, 1, CH), 2.44 (d, J = 6 Hz, 1, CH), 3.11 (dd, J = 3, 6 Hz, 1, CH), 5.19 (s, 1 OH), 6.61 (dd, J = 2, 8

(17) The instability of this compound did not permit a correct elemental analysis to be obtained.

Hz, 1, arom H), 7.0–7.7 (m, 5, arom H), 7.85 (d, J = 8 Hz, 1, arom H); mass spectrum, m/e 319 (M^+).

Anal. Calcd for $C_{16}H_{11}Cl_2NO_2$: C, 60.02; H, 3.46; N, 4.37. Found: C, 59.96; H, 3.38; N, 4.65.

3-Hydroxy-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]propyne (17). Dichlorobis(triphenylphosphine)palladium(II) (0.8 g, 1.1 mmol), 0.2 g (1 mmol) of cuprous iodide, 36 g (100 mmol) of **5**, and 12 mL of propargyl alcohol were added successively to a solution of 200 mL of diethylamine and 200 mL of CH_2Cl_2 under a constant stream of argon. The mixture was stirred at room temperature for 3 h and concentrated in vacuo to dryness. The residue was dissolved in CH_2Cl_2 and washed with water, 1 N aqueous HCl, and aqueous $NaHCO_3$. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentration in vacuo to dryness. Purification of the residue (SiO_2, 50 g; eluent, 5% ether in CH_2Cl_2) gave 27.5 g (90%) of **17** as a red oil which was used without further purification:[13] IR ($CHCl_3$) 3420 (OH), and 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.56 (br s, 1, OH), 4.15 (s, 2, CH_2), 7.2–7.6 (m, 7, arom H); mass spectrum, m/e 304 (M^+).

3-[(Methanesulfonyl)oxy]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]propyne (18). A solution of 8.0 mL (0.103 mol) of methanesulfonyl chloride in 20 mL of CH_2Cl_2 was added dropwise to a solution of 22.5 g (0.074 mol) of crude **17** and 21 mL (0.15 mol) of triethylamine in 250 mL of CH_2Cl_2 which was cooled in an ice bath. The mixture was stirred for 20 min and then washed with water, 1 N aqueous HCl, and aqueous $NaHCO_3$. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to dryness. Trituration of the residue with ether gave 17.0 g (mp 101–103 °C; 60%) of **18** as off-white crystals. Recrystallization of a sample from ether gave **18** as colorless prisms: mp 104–105 °C; IR (KBr) 1670 (C=O), 1346, 1173 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 3.09 (s, 3, CH_3), 4.81 (s, 2, CH_2), 7.3–7.6 (m, 7, arom H); mass spectrum, m/e 382 (M^+).

Anal. Calcd for $C_{17}H_{12}Cl_2SO_4$: C, 53.28; H, 3.16. Found: C, 53.35; H, 3.17.

3-(Hydroxyamino)-1-[4-chloro-2-(2-chlorobenzoyl)-phenyl]propyne (19). A solution of 13.6 g (0.2 mol) of hydroxylamine hydrochloride in 40 mL of water was added to a mixture of 40 mL of a 4.3 M methanol solution of sodium methoxide, 250 mL of methanol, and 250 mL of THF. The resulting precipitate was removed by filtration, and 12.8 g (0.033 mol) of **18** was added to the filtrate. The resulting solution was stirred at room temperature for 23 h and concentrated in vacuo to a small volume. The residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to dryness. Purification of the residue by column chromatography (SiO_2, 100 g; eluent, CH_2Cl_2 and then 20% ether in CH_2Cl_2) gave in the later eluent 3.6 g (33%) of **19** as pale yellow prisms: mp 111–112 °C; IR (KBr) 3420 (OH), 3280 (NH), 1666 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.64 (s, 2, CH_2), 5.32 (br s, 2, NHOH), 7.3–7.7 (m, 7, arom H); mass spectrum, m/e 319 (M^+).

Anal. Calcd for $C_{16}H_{11}Cl_2NO_2$: C, 60.02; H, 3.46; N, 4.38. Found: C, 60.19; H, 3.33; N, 4.35.

The hydrochloride salt of **19** was prepared by dissolving the free base of **19** in an excess of methanolic hydrogen chloride and precipitating the salt with a mixture of ether and petroleum ether. The salt of **19** formed pale yellow needles, mp 136–137 °C.

Anal. Calcd for $C_{16}H_{11}Cl_2NO_2$·HCl: C, 53.88; H, 3.39; N, 3.93. Found: C, 53.87; H, 3.46; N, 3.89.

8-Chloro-1-(2-chlorophenyl)-3,4-dihydro-5*H*-2-benzazepin-5-one 2-Oxide (14). A solution of 0.5 g (1.5 mmol) of **19** in 30 mL of CH_2Cl_2 was added dropwise over 15 min to a stirred ice-cooled mixture of 0.1 g (0.3 mmol) of mercuric sulfate, 7 mL of 95% formic acid, and 1 mL of water. The reaction mixture was stirred at room temperature for 2 h, poured into excess dilute ice-cold amonium hydroxide and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to dryness. The residue (0.4 g) crystallized from a mixture of ethyl acetate and ether to give 0.1 g of **14** as off-white crystals, mp 186–187 °C. All spectral data were identical with those of an authentic sample.

2-[3-[4-Chloro-2-(2-chlorobenzoyl)phenyl]-2-oxopropyl]-1*H*-isoindole-1,3(2*H*)-dione (20) and 2-[7-Chloro-1-(2-chlorophenyl)-3-(diethylamino)-1,2-dihydro-1-hydroxy-2-naphthalenyl]-1*H*-isoindole-1,3(2*H*)-dione (21). Dichlorobis(triphenylphosphine)palladium(II) (0.7 g, 1 mmol), 0.2 g (1 mmol) of cuprous iodide, 17.2 g (50 mmol) of **6**, and 10 g (54 mmol) of *N*-propargylphthalimide were successively added to a solution of 100 mL of diethylamine and 200 mL of CH_2Cl_2 under a constant stream of argon. The mixture was stirred at room temperature for 5 days and concentrated in vacuo to dryness. The residue was dissolved in CH_2Cl_2 and washed with water. The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to dryness. Purification by column chromatography (SiO_2, 250 g; eluent, CH_2Cl_2 and then 5% ether in CH_2Cl_2) gave as the first product band 3.3 g (7%) of **21** as a yellow solid. Recrystallization from ether gave **21** as yellow needles: mp 204–206 °C; IR ($CHCl_3$) 3550 (OH), 1780, 1768, 1713 (imide C=O), 1632 cm^{-1} (N—CH=CH); NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 6, 2-CH_3), 3.86 (q, J = 7 Hz, 2, CH_2), 3.88 (q, J = 7 Hz, 2, CH_2), 4.43 (s, 1, OH), 5.85 (d, J = 2 Hz, 1, CH—N), 6.11 (d, J = 2 Hz, 1, CH=), 6.82 (d, J = 2 Hz, 1, arom H), 7.0–7.9 (m, 10, arom H); mass spectrum, m/e 506 (M^+).

Anal. Calcd for $C_{28}H_{24}Cl_2N_2O_3$: C, 66.28; H, 4.77; N, 5.52. Found: C, 66.42; H, 4.69; N, 5.53.

The second product band to be eluted gave 0.5 g (3%; mp 145–147 °C) of **6** which was identical with an authentic sample.

The third product band to be eluted gave 2.5 g (11%) of **20** as an off-white solid. Recrystallization from a mixture of ether and CH_2Cl_2 gave **20** as colorless needles: mp 172–173 °C; IR ($CHCl_3$) 1782, 1721 (imide, ketone C=O), 1675 cm^{-1} (ketone C=O); NMR ($CDCl_3$) δ 4.18 (s, 2, CH_2), 4.75 (s, 2, CH_2), 7.2–7.9 (m, 11, arom H); mass spectrum, m/e 451 (M^+).

Anal. Calcd for $C_{24}H_{15}Cl_2NO_4$: C, 63.79; H, 3.65; N, 3.38. Found: C, 63.80; H, 3.42; N, 3.10.

8-Chloro-1-(2-chlorophenyl)-4-(1-pyrrolidinyl)-3*H*-2-benzazepine (23). A solution of 3 g (10 mmol) of **7** in 30 mL of pyrrolidine was stirred at room temperature for 7 h. The reaction mixture was concentrated in vacuo and diluted with ether, and the resulting precipitate was collected by filtration to give 2.6 g (72%) of **23** as a yellow solid. Recrystallization from a mixture of CH_2Cl_2, ether, and petroleum ether gave **23** as yellow prisms: mp 139–140 °C; IR ($CHCl_3$) 1613 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.90 (m, 4, CH_2CH_2) 3.34 (m, 4, 2 CH_2–N), 3.86 (s, 2, C_3 H), 5.53 (s, 1, C_5 H), 6.85 (s, 1, arom H), 7.2–7.5 (m, 6, arom H); mass spectrum, m/e 356 (M^+).

Anal. Calcd for $C_{20}H_{18}Cl_2N_2$: C, 67.23; H, 5.08; N, 7.84. Found: C, 67.51; H, 5.12; N, 7.80.

Methanesulfonate of 8-Chloro-1-(2-chlorophenyl)-3,5-dihydro-4*H*-2-benzazepin-4-one (24). A solution of 4 g (11 mmol) of **23** in an excess of 1 N HCl was neutralized with dilute, ice-cold $NaHCO_3$ and extracted with ether. The ether solution was dried (Na_2SO_4), acidified with 11 mL of 1 M methanol solution of methanesulfonic acid in methanol, and concentrated in vacuo to dryness. The residue crystallized from CH_2Cl_2 to give 3.6 g (80%; mp 177–178 °C) of **24** as a yellow solid. Recrystallization from CH_2Cl_2 gave **24** as pale yellow plates: mp 182–183 °C; IR (KBr) 3460 (OH), 1732 (C=O), 1162 cm^{-1} (SO_3); NMR (Me_2SO-d_6) δ 2.44 (s, 3, CH_3), 3.96 (s, 2, CH_2), 4.46 (s, 2, CH_2), 7.09 (d, J = 2 Hz, 1, arom H), 7.4–7.8 (m, 6, arom H), 8.0 (br s, 1 NH^+).

Anal. Calcd for $C_{17}H_{15}Cl_2NO_4S$: C, 51.01; H, 3.78; N, 3.50. Found: C, 50.98; H, 3.78; N, 3.50.

8-Chloro-1-(2-chlorophenyl)-3,5-dihydrospiro[4*H*-2-benzazepine-4,2′-[1,3]dithiolane] (25). In one portion, 30 mg (6 mmol) of a 50% mineral oil dispersion of NaH was added to a solution of 18 mL (220 mmol) of ethanedithiol in 250 mL of DMF. When all of the NaH had reacted, 18.4 g (60 mmol) of **7** was added and the resulting mixture stirred at room temperature overnight. Water was added, and the mixture was extracted with a mixture of ether and CH_2Cl_2. The organic solution was washed with water and then treated with a 5% $CuSO_4$ solution until a blue solution persisted. The resulting precipitate was removed by filtration through Celite. The organic solution was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was triturated with ether to give 13.4 g (59%; mp 158–160 °C) of **25** as a pale yellow solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave **25** as colorless prisms: mp 161–162 °C; IR ($nCHCl_3$) 1605 cm^{-1} (C=N); NMR ($CDCl_3$) δ 3.29 (s, 2, C_5 H), 3.33 (s, 4, CH_2CH_2), 3.79 (s, 2, C_3 H), 6.89 (d, J = 2 Hz, 1, arom H), 7.2–7.7 (m, 6, arom H); mass spectrum, m/e 379 (M^+).

Anal. Calcd for $C_{18}H_{15}Cl_2NS_2$: C, 56.84; H, 3.98; N, 3.68. Found: C, 56.68; H, 4.00; N, 3.44.

The methanesulfonate salt of **25** was prepared by the addition of equimolar amounts of **25** and methanesulfonic acid to methanol. The resulting salt was precipitated by the addition of ether. Recrystallization of the salt from a mixture of methanol and ether gave the methanesulfonate salt of **25** as pale yellow needles: mp 226–227 °C; IR (KBr) 3440 cm^{-1}; NMR (Me_2SO-d_6) δ 2.46 (s, 3, CH_3), 3.38 (s, 2, C_5 H), 3.43 (s, 4, CH_2CH_2), 3.86 (s, 2, C_3 H), 7.01 (d, J = 2 Hz, 1, arom H), 7.4–7.9 (m, 6, arom H), 8.5 (br s, 1, NH^+).

Anal. Calcd for $C_{19}H_{19}Cl_2NO_3S_3$: C, 47.90; H, 4.02; N, 2.94; S, 20.19. Found: C, 47.99; H, 4.12; N, 2.84; S, 20.23.

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Registry No. 4, 2958-36-3; **5** (X = Y = Cl), 76049-50-8; **5** (X = Cl; Y = H), 76049-48-4; **5** (X = Cl; Y = F), 76049-49-5; **5** (X = Y = H), 25187-00-2; **6**, 76049-54-2; **7** (X = Y = Cl; R = phth), 76049-64-4; **7** (X = Cl; Y = H; R = phth), 76049-52-0; **7** (X = Cl; Y = F; R = phth), 76049-53-1; **7** (X = H; Y = Cl; R = phth), 76049-55-3; **7** (X = Y = H; R = phth), 76049-56-4; **7** (X = Y = Cl; R = NH_2), 76049-64-4; **7** (X = Cl; Y = H; R = NH_2), 76049-61-1; **7** (X = Cl; Y = F; R = NH_2), 76049-63-3; **7**·HCl (X = H; Y = Cl; R = NH_2), 76049-66-6; **7**·HCl (X = Y = H; R = NH_2), 76049-67-7; **9** (X = Y = Cl), 76049-70-2; **9** (X = Y = Cl) methanesulfonate, 76049-71-3; **9** (X = Cl; Y = H) methanesulfonate, 58582-23-3; **9** (X = Cl; Y = F), 58583-07-6; **9** (X = H; Y = Cl), 76049-72-4; **9** (X = Y = H) methanesulfonate, 76049-74-6; **9** (X = Cl; Y = F) *N*-oxide, 76049-76-8; **9** (X = Y = Cl) *N*-oxide, 76049-78-0; **10**, 78367-91-6; **11**, 81389-12-0; **12**, 81389-13-1; **13**, 81389-14-2; **15**, 81389-15-3; **16**, 81389-16-4; **17**, 81389-17-5; **18**, 81389-18-6; **19**, 81389-19-7; **19**·HCl, 81389-20-0; **20**, 81389-21-1; **21**, 81389-22-2; **23**, 81389-23-3; **24**, 81389-25-5; **25**, 81389-26-6; **25** methanesulfonate, 81389-27-7; *N*-propargylphthalimide, 7223-50-9.

Supplementary Material Available: Tables VI–IX containing the corresponding final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **16** (4 pages). Ordering information is given on any current masthead page.

Regiochemistry of Intramolecular Munchnone Cycloadditions: Preparative and Mechanistic Implications

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A series of munchnone derivatives containing an internal π bond were generated in situ by treating several *N*-(*o*-allylphenyl)alanines with acetic anhydride. The major product obtained corresponded to intramolecular 1,3-dipolar cycloaddition of the mesoionic species across the olefinic π bond. The structures of the cycloadducts were assigned on the basis of their characteristic spectral data and by an X-ray single-crystal structure analysis. The cycloaddition reactions proceed via an initial N-acetylation of the amino acid followed by cyclodehydration to give an unstable munchnone intermediate. The azomethine ylide functionality of the mesoionic species then participates in an intramolecular 1,3-dipolar cycloaddition with the unactivated carbon–carbon double bond. The regioselectivity of the internal cycloaddition of a series of *N*-(*o*-allylphenyl)-substituted munchnones was found to be markedly dependent on the substituent groups present. It can be presumed that both steric and electronic factors are involved. Intramolecular cycloaddition of munchnones has been found to provide a valuable mechanistic tool for the study of orientational substituent effects.

1,3-Dipolar cycloadditions to olefins have been extensively studied and are now well understood primarily owing to the efforts of Huisgen and co-workers.[1-7] Experience indicates a concerted mechanism[8,9] and frontier molecular orbital theory has successfully explained relative rates and regioselectivity of these cycloadditions.[10-20] During the last decade a new impulse has been given to research in this field when it was found that various mesoionic compounds undergo 1,3-dipolar cycloaddition with different dipolarophiles.[21] Of the known mesoionic heterocycles, the structure, physical properties, and reactions of munchnones and sydnones have drawn the closest scrutiny.[21-24] Huisgen and co-workers have studied the cycloaddition reaction of munchnones with various dipolarophiles in detail and have shown that the reaction constitutes a general synthesis of pyrroles[25] and pyrrolines.[26] The reaction involves a 1,3-dipolar cycloaddition of the munchnone, behaving like a cyclic azomethine ylide, to the corresponding acetylenic or olefinic dipolarophile followed by CO_2 evolution and aromatization or tautomerization.[27,28] The reactions of sydnones closely parallel those of the related munchnones.[29-31] Studies with these two mesoionic systems have generated considerable theoretical interest and have resulted in practical, unique syntheses of nu-

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(1) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(2) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).
(3) R. Guisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, 1964, pp 806–878.
(4) R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967).
(5) R. Huisgen, H. Stangl, H. J. Stern, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).
(6) R. Huisgen, L. Mobius, G. Muller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).
(7) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968); **41**, 403 (1976).
(8) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968); **41**, 403 (1976).
(9) For an alternate view, see R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); **37**, 2181 (1972); *J. Chem. Soc. A*, 1570 (1970); *Tetrahedron*, **33**, 3009 (1977).
(10) K. Fukui, *Fortschr. Chem. Forsch.*, **15**, 1 (1970); *Acc. Chem. Res.*, **4**, 57 (1971).
(11) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, 1969.
(12) J. Klopman, Ed., "Chemical Reactivity and Reaction Paths", Wiley-Interscience, New York, 1974.
(13) W. C. Herndon, *Fortschr. Chem. Forsch.*, **46**, 141 (1974).
(14) L. Salem, *J. Am. Chem. Soc.*, **90**, 543, 553 (1968).
(15) A. Devaquet and L. Salem, *J. Am. Chem. Soc.*, **91**, 3793 (1969).
(16) R. Sustmann and G. Binsch, *Mol. Phys.*, **20**, 9 (1971).
(17) N. D. Epiotis, *Angew. Chem., Int. Ed. Engl.*, **13**, 751 (1974).
(18) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971).

0022-3263/82/1947-2447$01.25/0