Synthesis, Chemistry, and Photochemical Substitutions of 6,11-Dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones

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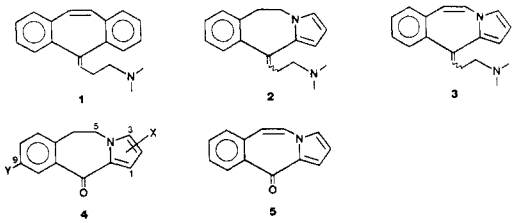
A series of 6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones, **4**, has been prepared as intermediates for potential CNS drugs. Substituents in the pyrrole ring of **4** were introduced by Friedel–Crafts cyclization of pyrrole-substituted 1-(2-phenethyl)pyrrole-2-carboxylic acid derivatives (**6**) and by electrophilic substitution on the parent ketone **4a**. Substituents in the benzene ring of **4** were introduced by Friedel–Crafts cyclization of substituted 2-(2-pyrrol-1-ylethyl)benzoic acids (**12**). Novel and efficient photochemical reactions were discovered for the direct introduction of the cyano and trifluoromethyl groups into the pyrrole ring of **4a**. The latter reaction was extended to yield a series of trifluoromethylated heterocycles.

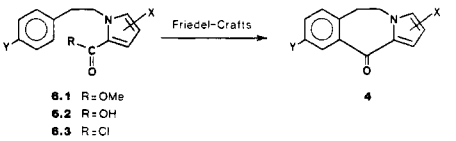
Introduction

The dibenzo[*a*,*d*]cycloheptene ring system has been a rich source of very useful drugs, particularly for treatment of diseases implicating the central nervous system.[1] One of these drugs, cyclobenzaprine (**1**; 3-(5*H*-dibenzo[*a*,*d*]-cyclohepten-5-ylidene)-*N*,*N*-dimethyl-1-propylamine), after demonstration of its effectiveness in animal models in these laboratories,[2] has recently been introduced as a new and useful skeletal muscle relaxant.[3] The therapeutic utility of cyclobenzaprine prompted us to investigate some heteroanalogues of this tricyclic derivative in search for compounds with increased biological efficacy. The pyrrolo[2,1-*b*][3]benzazepine system, with a nitrogen at a bridgehead position, appeared to be an attractive target because it had been little studied and also because it would give rise to compounds (e.g., **2** and **3**) that should be reasonably similar to cyclobenzaprine in molecular shape and chemical properties. In this present article we describe the synthesis and chemistry of a series of ketones **4** (6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one), and in an accompanying article, the synthesis and chemistry of the corresponding 5,6-unsaturated ketones **5** (11*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one) is presented.[4] The conversion of **4** and **5** to **2** and **3** and the related medicinal chemistry will be the subject of future publications.[3a]



At the outset of this work, only one example of the pyrrolo[2,1-*b*][3]benzazepine system, the 1-cyano ketone **4** (X = 1-CN, Y = H), had been reported.[5] The parent ring system is also incorporated into the structure of the *cephalotaxus* alkaloids, and during the course of more recent synthetic work in this area a few partially saturated derivatives of pyrrolo[2,1-*b*][3]benzazepines have been reported.[6] The small amount of work on this relatively little-explored ring system provided no effective general syntheses of ketones **4**, and it was consequently necessary to develop new approaches that would allow for the controlled introduction of substituents into the pyrrole ring and/or the benzene ring.

We have previously described[7a] an efficient synthesis of the parent acid **6.2a** (X = Y = H), and this, with the related work of Irwin and Wheeler,[7b] gave us confidence that a variety of substituted derivatives of general structure **6** could be made available. It was anticipated that such acid derivatives would serve as suitable precursors to **4** via Friedel–Crafts cyclization.



6.1 R=OMe
6.2 R=OH
6.3 R=Cl

4

This approach still contained some foreseeable (and ultimately encountered) difficulties. Principally, the well-known reactivity of the pyrrole ring toward oxidizing and electrophilic reagents could, and did, give rise to certain difficulties, which were finally resolved. This same reactivity, however, could often be turned to advantage, with some surprising results as described later. The sensitivity of the pyrrole ring to electrophilic reagents might also be anticipated to make it difficult to utilize **6** when Y was a substituent that would deactivate the benzene ring.

Results and Discussion

The synthetic approaches developed toward the successful synthesis of the 6,11-dihydro-5*H*-pyrrolo[2,1-*b*]-[3]benzazepin-11-ones **4** fell into three broad categories:

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(1) C. Kaiser and C. L. Zirkle in "Medicinal Chemistry", 3rd ed., A. Burger, Ed., Wiley-Interscience, New York, 1970; Part II, pp 1470–1497.
(2) N. N. Share and C. S. McFarlane, *Neuropharmacology*, **14**, 675 (1975).
(3) J. C. De Lee and C. A. Rockwood, *Curr. Ther. Res.*, **27**, 64 (1980).
(4) P. C. Bélanger, J. G. Atkinson, C. S. Rooney, S. F. Britcher, and D. C. Remy, following paper in this issue.
(5) R. Huisgen and E. Laschtuvka, *Chem. Ber.*, **93**, 65 (1960).
(6) (a) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975); (b) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, **97**, 2507 (1975); (c) B. Weinstein and A. R. Craig, *J. Org. Chem.*, **41**, 875 (1976).
(7) (a) J. Rokach, Y. Girard, and J. G. Atkinson, *Can. J. Chem.*, **51**, 3765 (1973); (b) W. J. Irwin and D. L. Wheeler, *Tetrahedron*, **28**, 1113 (1972).

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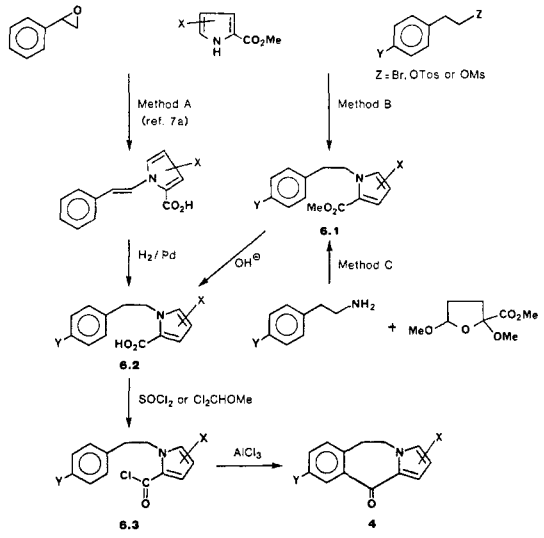
Scheme I

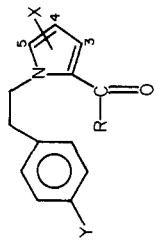


I, total synthesis of the ring system; II, introduction of substituents into the parent ketone 4; and III, modification of substituents introduced in I or II. The major successes and difficulties encountered in these approaches are detailed below.

I.1 Total Synthesis of Pyrrole-Substituted Ketones (4, X ≠ H, Y = H). The synthesis of the requisite acid derivatives **6** was carried out by three methods as summarized in Scheme I. Method A has already been described[7] and is quite satisfactory as long as the group X is resistant to catalytic hydrogenation. Method B, the alkylation of a substituted pyrrole-2-carboxylic ester with 2-phenethyl bromide, was also found to be a very satisfactory route to the esters **6.1**, particularly when X was a strong electron-withdrawing group. When X was less electron withdrawing, it was advantageous to use phenethyl tosylate to minimize competitive elimination to form styrene. Method C was used to prepare ester **6.1h** and, although quite satisfactory, was not used extensively. The preparation of the 4-substituted pyrrole-2-carboxylates was generally carried out by the recent method of Bélanger[8] or by standard methods. A minor problem was initially encountered in forming the acid chlorides **6.3**, using $SOCl_2$, in that a few percent of pyrrole ring chlorination[9] was found to occur when X was not a strong electron-withdrawing group; however, the use of dichloromethyl methyl ether[10] easily circumvented this problem. It may be noted in passing that all the pyrrole acid chlorides **6.3** encountered in this work were quite resistant to hydrolysis and could even be purified by chromatography on silica gel. Table I summarizes the various acid derivatives, **6**, prepared in this work.

One of the anticipated difficulties was soon encountered when it was found that the parent acid **6.2a** (X = H) and acid chloride **6.3a** (X = H) underwent extensive decomposition under a wide variety of Friedel–Crafts conditions (**6.2**, PPA, PPA in toluene, HF, HF/ether, H_2SO_4/H_2O, $SnCl_4/(CF_3CO)_2O$;[6c] **6.3**, $AlCl_3$ in CS_2 or $CHCl_2CHCl_2$, $SnCl_4$ in C_6H_6). Finally, under the mildest conditions found to effect the cyclization ($AlCl_3$ in CH_3NO_2, 0 °C, 3 h) a low yield of a compound of twice the expected molecular weight (394 vs. 197) was isolated. In addition to the mass spectrum, the ^1H NMR spectrum showed the

Table I. Substituted 1-(2-Phenethyl)pyrrole-2-carboxylic Acids, Esters, and Chlorides (Scheme I)



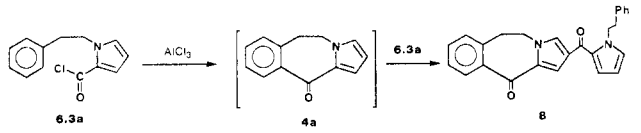
6.1, R = OCH_3
6.2, R = OH
6.3, R = Cl

X	Y	compd	method	mp, °C	% yield	compd	mp, °C	% yield	compd	mp, °C	% yield
H	H	6.1a	A			6.2a	124–125	90	6.3a	85–86	83
H	H	6.1a	B	oil		6.2a	124–125	95			
4-CN	H	6.1b	B	109–110	55	6.2b	188–189	100	6.3b	114–115	92
4-Cl	H	6.1c	B	oil	77	6.2c	117–120	91	6.3c	91–92	100
4-Br	H	6.1d	B	62–63	95	6.2d	125–127	100	6.3d	101–103	94
4-NO_2	H	6.1e[a]	B	112–114	78	6.2e	193–194	100	6.3e	119–120	75
4,5-Br_2	H				74	6.2f[b]	178–179	77	6.3f	95–96	97
3,4,5-Br_3	H	6.1g	B	109–110	90	6.2g	190–192	84	6.3g	144–145	84
H	CH_3	6.1h	C	oil	91						
3,4,5-Br_3	CH_3	6.1i[c]		88–90	89	6.2i	170–173	68	6.3i	81–83	92
3,4,5-Br_3	SCH_3	6.1j	B	108–109	63	6.2j	184–185	90	6.3j	96–97	88
3,4,5-Br_3		6.1k	B	180–182	45	6.2k	200–202 dec	100	6.3k	156–158	98

[a] Ethyl ester. [b] Prepared by bromination of **6.2a** in HOAc. [c] Prepared by bromination of **6.1h** in $CHCl_3$.

(8) P. Bélanger, *Tetrahedron Lett.* 2505 (1979).
(9) For another example of chlorination by $SOCl_2$, see: J. R. Merchant and D. V. Rege, *Tetrahedron*, **27**, 4837 (1971).
(10) H. C. J. Ottenheijm and J. H. M. de Man, *Synthesis*, 163 (1975).

characteristic AA'BB' pattern for the bridging methylenes of the tricyclic system at δ 3.27 and 4.30 and the two triplets normally seen in the *N*-phenethylpyrroles at δ 3.02 and 4.52. This unexpected compound was assigned structure **8**, the product of subsequent rapid acylation of initially formed **4a** by the acid chloride **6.3a**. The site of acylation is assigned as position 2 of the pyrrolo[2,1-*b*][3]benzazepine ring on the basis of the small (2 Hz) coupling constant for H_1 (δ 7.80) with H_3 (hidden under the aromatics) and in analogy with other acylations described later.[11]



Since electron-withdrawing groups on the pyrrole ring might circumvent the problems encountered, the 4,5-dibromo acid **6.2f** (X = 4,5-Br_2) was prepared by direct bromination of **6.2a** (X = H). Friedel–Crafts cyclization of the corresponding acid chloride under the conditions of Huisgen and Laschtuvka[5] was then found to give good yields of the corresponding ketone **4f**. Catalytic hydrogenolysis of the bromine atoms then proceeded smoothly to give the parent ketone **4a** (X = H) in high yield. For subsequent preparations of large quantities of the parent ketone **4a** by this method, it was found more practical to start with methyl 3,4,5-tribromopyrrole-2-carboxylate (method B, Scheme I), carrying through to ketone **4g** followed by hydrogenolysis.

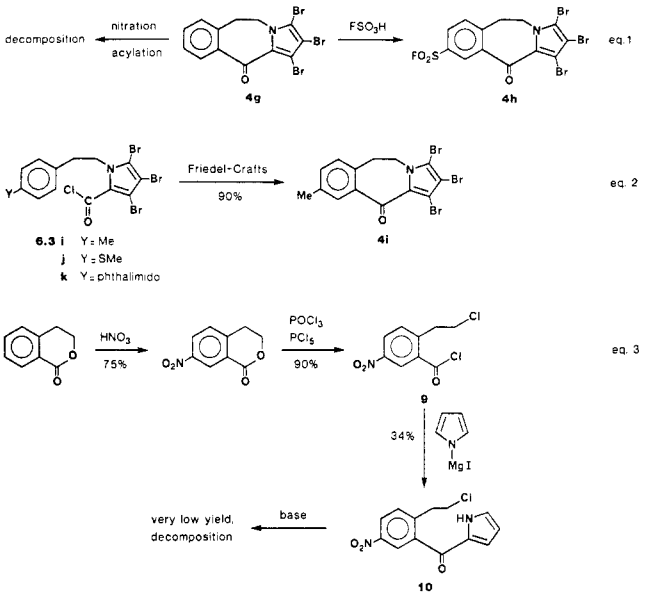
It was also found that the conditions for the Friedel–Crafts reaction described by Huisgen and Laschtuvka[5] ($AlCl_3$ in refluxing tetrachloroethane) were much more vigorous than necessary, and we routinely carried out the reaction in refluxing methylene chloride over a 30-min period or in nitromethane at 0 °C for 3 h. In this way ketones **4b–g** and **4i** (Table II) were then synthesized without incident.

The synthesis of other pyrrole-substituted ketones **4** by direct substitution into the constructed tricyclic nucleus and by modification of substituents is described in sections II and III below.

I.2 Total Synthesis of Benzene Ring Substituted Ketones (4, X = H, Y ≠ H). For medicinal chemical reasons, we also wished to develop syntheses of ketones **4** bearing a substituent in the 9-position of the pyrrolo[2,1-*b*][3]benzazepine structure. This proved to be unexpectedly difficult, and in this section we detail the major unsuccessful efforts and the solution to this problem.

The obvious approach was to build on the chemistry described above. Thus, the readily available, fully blocked (in the pyrrole ring) 1,2,3-tribromo ketone **4g** was expected to undergo electrophilic substitution mainly in the desired 9-position. Nitration under a variety of conditions ($NO_2^+BF_4^-$, 90% HNO_3–HOAc, $NaNO_3$–H_2SO_4, HNO_3–H_2SO_4) gave only very polar, noncharacterizable material. We conclude that in spite of being fully substituted, the pyrrole nucleus was still being attacked preferentially, with subsequent extensive decomposition. A similar result was observed upon attempted Friedel–Crafts reactions, where again extensive decomposition was observed, when reaction occurred. The only successful reaction encountered was fluorosulfonation, which gave a 76% crude yield of the 9-fluorosulfonyl ketone **4h**, mp

Scheme II

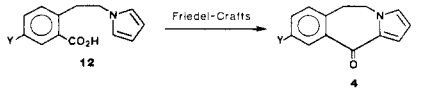


248–249 °C. It proved to be a difficult compound to purify and as there are no efficient methods for replacing the sulfur by other elements, this approach was not pursued further (Scheme II, eq 1).

Another approach (Scheme II, eq 2) was the attempted Friedel–Crafts cyclization of the acid chlorides **6.3i–k**. This approach again met with very limited success, the tribromo 9-methyl ketone **4i** being the only instance a tricyclic product was obtained, although in 90% yield. Hydrogenation of **4i** cleanly removed the bromine atoms to give a quantitative yield of the 9-methyl ketone **4j**. The remaining acid chlorides failed to undergo the Friedel–Crafts cyclization prior to extensive decomposition, probably because the substituents Y all have positive σ_{meta} values.[12] The requisite acid derivatives were prepared by methods B and C (Scheme I).

A third approach was explored via the synthesis of ketone **10** (Scheme II, eq 3), followed by attempted intramolecular N-alkylation. The sequence failed at the last step, with either no reaction occurring or else giving rise to very bad mixtures that may have contained traces of desired product. We surmise that a major source of difficulty was a competing elimination from the phenethyl chloride unit, giving rise to styrenes.

In view of the disappointing results described above, our attention was then directed to acids of type **12**, in which it was hoped that the high reactivity of the pyrrole ring would facilitate the desired Friedel–Crafts reactions. To anticipate the results, our expectations were fully realized, and a viable, practical synthesis of the 9-substituted ketones **4** was at last in hand.

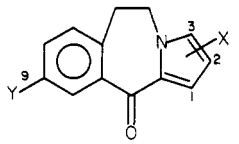


Acids of structure **12** are not described in the literature and it was necessary to devise a suitable synthesis. Our experience with several compounds related to **9** (Scheme II) precluded any attempts at N-alkylation of pyrrole with the phenethyl halide moiety because of the very rapid competing relactonization of such compounds. However, we felt that lactam formation from a 2-(2-aminoethyl)-

(11) For a discussion of the NMR spectra of pyrroles, see: (a) A. Gossauer; "Die chemie der Pyrrole"; Springer-Verlag; Berlin, 1974; pp 77–94; (b) R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles"; Academic Press, New York, 1977, pp 472–478.

(12) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

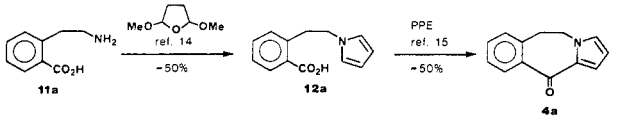
Table II. Substituted 6,11-Dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4)



X	Y	precursor	ketone	mp, °C	% yield
Scheme I					
H	H	4g	4a[a]	54-55	90
2-CN	H	6.3b	4b	146-147	98
2-Cl	H	6.3c	4c	100-105	73
2-Br	H	6.3d	4d	101-103	81
2-NO_2	H	6.3e	4e	174-176	91
2,3-Br_2	H	6.3f	4f	135-137	69
1,2,3-Br_3	H	6.3g	4g	169-171	97
Scheme II					
1,2,3-Br_3	SO_2F	4g	4h	248-249	76
1,2,3-Br_3	CH_3	6.3i	4i	160-163	90
H	CH_3	4i	4j[a]	oil	100
Scheme III					
H	9-NO_2	12b	4k	191-193	45
H	9-I	12c	4l	120-122	37
Scheme IV					
2-$COCH_3$	H	4a	4m	162-163	66
2-$COCH(CH_3)_2$	H	4a	4n	124-126	44
2-CO-*n*-C_4H_9	H	4a	4o	137-138	83
3-CO-*n*-C_4H_9	H	4a	4p	73-74	15
2-$SO_2N(CH_3)_2$	H	4a	4q	134-137	45
2-$SOCH_3$	H	4a	4r	115-117	10.3
3-$SOCH_3$	H	4a	4s	oil	3.2
2-SO_2CH_3	H	4r	4t	196-197	85
3-SO_2CH_3	H	4s	4u	152-154	63
2-SCF_3	H	4a	4v	77-78	28
3-SCF_3	H	4a	4w	94-95	54
3-Cl	H	4a	4x	69-70	71
1,3-Cl_2	H	4a	4y	87-88	34
3-Br	H	4a	4z	80-82	51
Scheme V					
3-CN	H	14	4aa	130-131	70
Scheme VI					
3-CF_3	H	4a	4bb	90-93	50
1-CF_3	H	4a	4cc	102-103	5
1,3-$(CF_3)_2$	H	4a	4dd		traces
Chart I					
2-CHO	H	4b	4ee	135-136	81
2-$CONH_2$	H	4b	4ff	225-228	88
2-CO_2H	H	4ff	4gg	289-293	89
2-CO_2CH_3	H	4gg	4hh	122-123	87
2-$CON(CH_3)_2$	H	4gg	4ii	148-149	94
H	9-NH_2	4k	4jj	166-167	97
H	9-$NHCOCH_3$	4jj	4kk	169-170	90
H	9-Cl	4jj	4ll	93-94	62
H	9-CN	4jj	4mm	127-128	62
H	9-CO_2H	4mm	4nn	270-272	92
H	9-SCF_3	4l	4oo	81-83	90

[a] Prepared by hydrogenation of the tribromo precursor.

benzoic acid (**11a**) might be sufficiently slow to allow formation of a pyrrole ring from the amino group and a 2,5-dialkoxytetrahydrofuran. Preliminary experiments carried out on the known[13] **11a** through to the parent ketone **4a** were sufficiently encouraging to embark on a total synthesis as outlined in Scheme III.



Based on Smith and Kan's[13] cyclization of β-phenethyl isothiocyanate to 1-thio-3,4-dihydroisocarbostyryl, we have developed a new two-step synthesis of 3,4-dihydroisocarbostyryl that proceeds in about 50% overall yield and that is easily adaptable to large-scale preparations. The initial cyclization to obtain the thiolactam (Scheme III) was effected in 55–60% yield, using PPA instead of $AlCl_3$ in CS_2, which was reported[13] to give a 40% yield. Subsequent to completion of this work, Bose[16] has reported the same cyclization using $AlCl_3$–H_2SO_4–CH_2Cl_2, and his conditions may be slightly superior as he reports a yield of 80%. The thiolactam was then converted in over 90% yield to 3,4-dihydroisocarbostyryl by treatment with basic

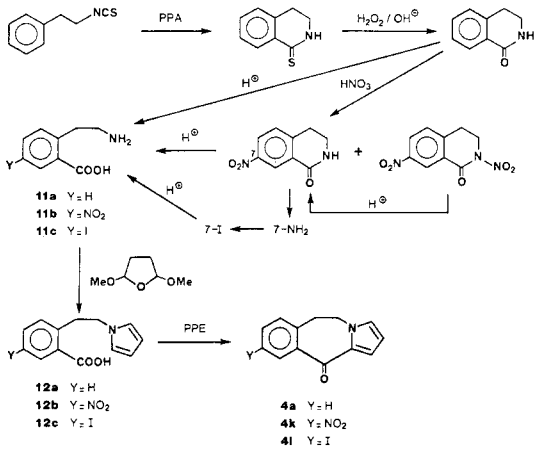
(13) P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 4753 (1960).

(14) A. D. Josey, "Organic Syntheses", Wiley, New York, 1973, Collect. Vol. V, p 716.

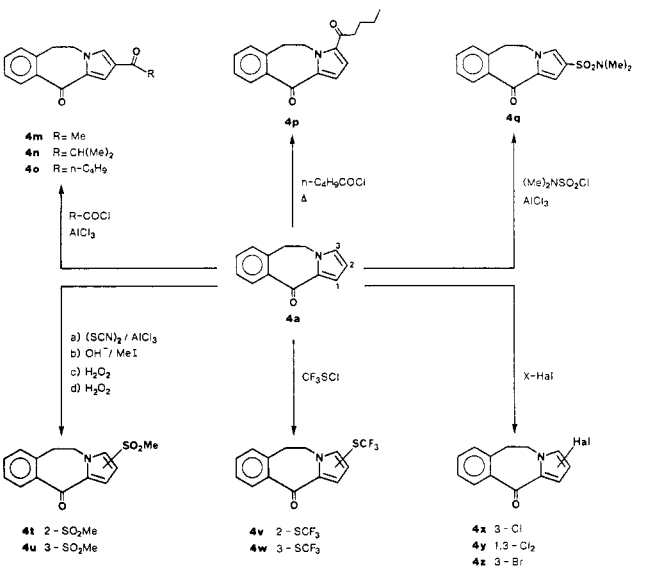
(15) M. P. Cava, N. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969).

(16) A. K. Bose, B. Ram, W. A. Hoffman III, A. J. Hutchison, and M. S. Manhas, *J. Heterocycl. Chem.*, **16**, 1313 (1979).

Scheme III



Scheme IV



hydrogen peroxide. Nitration with 1 equiv of fuming nitric acid in sulfuric acid at 0 °C gave a 95% yield of the known[17] 7-nitro-3,4-dihydroisocarbostyryl. When the nitration was carried out using excess nitric acid as solvent, a 1:1 mixture of the desired compound and a dinitro compound was obtained. The latter was proven to be the 2,7-dinitro derivative by the absence of the NH in the infrared spectrum and by acid hydrolysis (86% yield) to the 7-nitro compound. The ^1H NMR spectra of both compounds are straightforward and unambiguously indicate the 7-nitro structure. Hydrolysis of the nitro lactam to the desired amino acid **11b** required rather vigorous conditions (concentrated HCl, sealed tube, 150 °C, 24 h) but gave an 80% yield on the basis of recovered starting material. The critical step of pyrrole formation was dramatically improved by using much milder conditions (H_2O–HOAc (6:1), 50 °C, 2 h) than those reported,[14] giving rise to a 96% yield of the desired acid **12b**, thus completely circumventing relactamization. The last step was accomplished in 45% yield after chromatographic purification, and although this yield is only modest, a viable synthesis of the 9-substituted ketone **4k** was in hand.

7-Iodo-3,4-dihydroisocarbostyryl was also prepared from the 7-nitro compound by standard reactions and was carried through the sequence (**11c** → **12c**) to give the 9-iodo ketone **4l**. Further transformations of **4k** and **4l** are described in Section III below.

II.1 Electrophilic Substitution into the Pyrrole Ring of Ketone 4a. As previously discussed, the reactivity of the pyrrole nucleus was a two-edged sword, giving rise to a number of difficulties already mentioned, but which could be turned to advantage, as detailed in the present section.

Scheme IV summarizes the major electrophilic reactions investigated. In several cases, the effect of an added Lewis acid ($AlCl_3$) was compared with the results of the corresponding uncatalyzed reaction, and it was generally found that in the absence of $AlCl_3$, 3-substitution predominated, whereas in its presence, the 2-position become the predominant or exclusive site of attack.

Thus heating ketone **4a** in excess pentanoyl chloride at 120 °C for several hours gave the 3-substituted ketone **4p** in low yield (15%) as the only isolable compound. In sharp contrast, when the acylation was carried out in the presence of 2 equiv of $AlCl_3$ in methylene chloride, the reaction was complete after 15 min at room temperature and the 2-substituted ketone **4o** was obtained as the sole isolable product in 83% yield. Similarly the 2-acetyl (**4m**), 2-isobutyryl (**4n**), and 2-dimethylsulfamoyl (**4q**) ketones were obtained, although the latter required 20 min of refluxing in nitromethane to complete the reaction. The lesser reactivity of the sulfonyl chloride unit was also reflected in the fact that methanesulfonyl chloride could not be induced to react under forcing conditions and that 2-propanesulfonyl chloride decomposed, apparently with loss of SO_2 and the formation of propylene, without giving any sulfone product. It is important to note that a minimum of 2 equiv of $AlCl_3$ are necessary to bring these acylations to completion; with less than 2 equiv the yield drops off, roughly in proportion to the deficiency of catalyst. When the ketone **4** and $AlCl_3$ are mixed in the reaction solvent, a solid precipitate is observed. This is attributed to the formation of a stable complex, **13**, which completely ties up 1 equiv of catalyst, the second equivalent then being necessary to effectuate the Friedel–Crafts reaction.

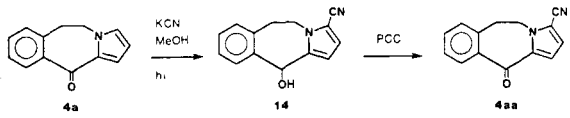
The reaction of **4a** with thiocyanogen showed a similar shift in site of substitution, giving a 9:1 preponderance of 3- over 2-substitution without $AlCl_3$ and a 3:7 ratio in the presence of the catalyst, as deduced from the ^1H NMR of the crude reaction mixture. The crude mixture of thiocyanates so obtained was converted to the methyl sulfones **4t** and **4u** by the following sequence: (a) hydrolysis and simultaneous methylation with $KOH/CH_3OH/CH_3I$, (b) oxidation to the sulfoxides **4r** and **4s** with hydrogen peroxide, (c) chromatographic separation of the sulfoxides, and (d) oxidation to the sulfones **4t** and **4u**. As might be intuitively deduced, this was a messy sequence and the sulfones **4t** and **4u** were obtained in only 8.7% and 2% overall yields, respectively, from **4a**.

The directing effect of $AlCl_3$ on the site of electrophilic substitution can be rationalized qualitatively by the formation of a complex, **13**, between the catalyst and the ketone in which a partial positive charge results at positions 1 and 3, thus deactivating them relative to position 2. This rationale is very similar to that put forward by Sonnet[18] to explain the predominance of 4-substitution in ternary iminium salts of pyrrole-2-carboxaldehydes. Most 2-acylpyrroles undergo substitution principally in the 4-position without the need for such complexation, but in the case of **4a**, the "meta"-directing effect of the carbonyl group is attenuated considerably since it is cross-conjugated with the benzene ring. The result is that most of

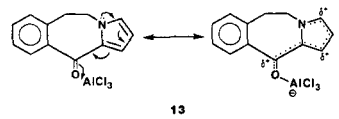
(17) M. Tomita, S. Minami, and S. Uyeo, *J. Chem. Soc. C*, 183 (1969).

(18) P. E. Sonnet, *J. Org. Chem.*, **37**, 925 (1972).

Scheme V



the uncatalyzed electrophilic substitutions occur α to the pyrrole nitrogen as is the case for most pyrroles when this position is free.



13

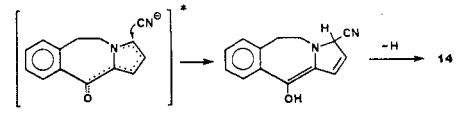
Reaction of ketone **4a** with CF_3SCl in chloroform in the presence of pyridine gave a 28% yield of the 2-isomer **4v** and 54% of the 3-isomer **4w** after chromatographic separation. In contrast, treatment of **4a** with 2-propanesulfenyl chloride gave a 71% yield of the 3-chloro ketone **4x**, with no evidence of sulfenylation. Chlorination with a slight excess of SO_2Cl_2 in $CHCl_3$ gave a mixture of the same 3-chloro ketone (45%) and a dichloro ketone (34%), to which we assign the 1,3-dichloro structure **4y** on the basis of a one-proton singlet in the NMR spectrum at δ 6.30, which because of its relatively high-field position is assigned to a proton at C_2. Bromination, even in the presence of $AlCl_3$, gave a 51% yield of the 3-bromo ketone **4z** as the only product isolated in pure form after chromatography.

II.2 Photochemical Cyanation of Ketone 4a. As part of the exploration of the chemistry of the pyrrolobenzazepinones, a strikingly efficient and clean photochemical cyanation of ketone **4a** was discovered.[19] Thus, irradiation through Pyrex of a solution of **4a** and KCN in methanol for about 8 h resulted in essentially complete (TLC) conversion to a single cyano alcohol, isolated in 60–70% yield, and which is assigned structure **14** (Scheme V). The overall result is the addition of the elements of HCN to ketone **4a**.[20] Oxidation with pyridinium chlorochromate gave cyano ketone **4aa** in 70% yield.

That no deep-seated structural rearrangement had occurred was assured by the fact that the derived ketone **4aa** had all the chemical and spectroscopic properties typical of these ketones. That cyanation had occurred in the pyrrole ring to give structure **14** was deduced from the presence of only two protons as two doublets, in the region expected for pyrrole protons, at δ 6.15 and 6.63 with a coupling constant of 4 Hz, and which are assigned to H_1 and H_2, respectively. The remaining four aromatic protons are present as a broadened singlet at δ 7.17 as expected for a benzene ring carrying only aliphatic substituents. The cyano group was assigned to the 3-position on the following grounds: (a) the relatively large coupling constant of 4 Hz seen between the pyrrole protons in both alcohol **14** and ketone **4aa** is a characteristic that we and others[11] have observed for protons in the 3- and 4-positions of various pyrroles (for a discussion of the ^1H NMR spectra of the pyrrolo[2.1-*b*][3]benzazepines, see the last section of this paper), (b) ketone **4aa** obtained by oxidation of **14** was clearly different from the 2-cyano ketone **4b** that we had previously synthesized (Scheme I, method B), (c) in addition to the NMR evidence, the 1-cyano alcohol structure was ruled out on the grounds of its stability, since such a structure would be expected to cyclize readily to a lactone as found by Letsinger and Colb.[20] The NMR spectrum of the protons of the ethylene bridge in alcohol **14**, which was very complex and spread over the range of δ 2.8 to 4.4, returned to the familiar AA'BB' pattern seen in all the ketones **4**, showing multiplets centered at δ 3.35 (Ar CH_2) and δ 4.46 (NCH_2); a sharp singlet for one proton (H_{11}) was also present at δ 5.73 in the alcohol. The IR spectra were in complete agreement with structures **14** and **4aa**: **14** ν_{KBr} 3450 (s, OH), 2210 (CN) cm^{-1}; **4aa** ν_{KBr} 2210 (CN), 1625 (s, C=O) cm^{-1}.

No such photochemical cyanation of pyrroles appears to have been reported,[19] and although work is continuing on this very interesting and useful reaction, we can report on some initial explorations of this area. Thus 1-benzyl-2-acetylpyrrole, methyl 1-(2-phenethyl)pyrrole-2-carboxylate, and 2-acetylfuran failed to undergo any significant reaction under the conditions in which **4a** reacted smoothly. Ketone **4a** was also irradiated in the presence of dimethylamine, sodium methanesulfinate, and sodium thiophenoxide without giving any clean adducts, although reduction of the ketone and decomposition was quite extensive in the presence of these nucleophiles. These results are in line with the report[19] that photochemical nucleophilic substitutions often give variable yields of the desired adducts.

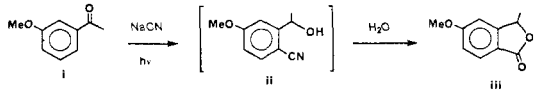
We can only make limited speculation regarding the mechanism of this (unique) reaction as we have not investigated the photochemistry in a quantitative way. The chromophore of **4a** (a roughly coplanar diaryl ketone structure) may be such as to give rise to a highly polarized excited state such as **15**, which can be attacked by cyanide to give **16**, which by tautomerization yields the alcohol **14**. Why such a proposed structure as **15** fails to react with the other nucleophiles investigated is not clear, but it is probably due to the fact that considerable reduction of the starting ketone was observed with these other nucleophiles. The formation of **14** almost certainly does not go through a prior oxidative cyanation to form ketone **4aa** followed by a light-catalyzed reduction of the carbonyl group in the methanol solvent since prolonged irradiation of **4aa** in methanol gives only traces of 14 (TLC) and ultimately forms only very polar decomposition products.



II.3 Photochemical Trifluoromethylation of Ketone 4a. The report[21] that irradiation of trifluoromethyl iodide in the presence of $\alpha,\beta,\gamma,\delta$-unsaturated ketones gave rise to the corresponding trifluoromethylated olefins prompted us to investigate this reaction as a means of introducing trifluoromethyl groups into the pyrrole nucleus of ketone **4a**. We were very pleased to find that the reaction proceeded very smoothly and has proved to be a very practical method for the introduction of trifluoromethyl groups into

(19) For a review of photochemical cyanation of aromatic nuclei, see: J. Cornelisse and E. Havinga, *Chem. Rev.*, **75**, 353 (1975).

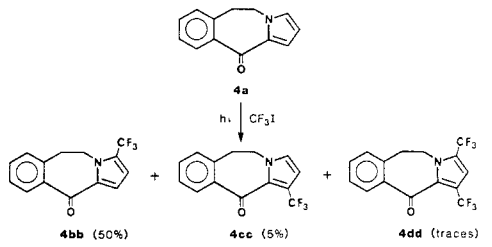
(20) At least one such analogous photoaddition of the elements of HCN to an aromatic ketone has been reported. The principal product of photolysis of i with aqueous NaCN is the lactone iii, which is thought to arise by ready cyclization and hydrolysis of the initial adduct ii. R.



L. Letsinger and A. L. Colb, *J. Am. Chem. Soc.*, **94**, 3665 (1972).

(21) G. H. Rasmusson, R. D. Brown, and G. E. Arth, *J. Org. Chem.*, **40**, 672 (1975).

Scheme VI



ketone **4a** and a number of other aromatic nuclei as detailed below.

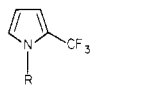
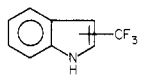
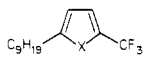
The irradiation through Pyrex of **4a** dissolved in acetonitrile containing trifluoromethyl iodide and pyridine for 30 h gave a mixture containing starting material plus two monotrifluoromethylated ketones and traces of a bis-trifluoromethylated ketone. The major component, isolated in 50% yield after chromatography, was assigned the 3-trifluoromethyl structure **4bb** (Scheme VI) on the basis of evidence similar to that presented for the product of photocyanation (**14**) and the derived ketone (**4aa**). In the IR spectrum, a carbonyl peak typical of the pyrrolo[2,1-*b*][3]benzazepinones was present at 1630 cm^{-1}, with no other distinct functional groups being identified. The key feature of the ^1H NMR spectrum was the presence of a one-proton doublet at δ 6.60 with a coupling constant of 4 Hz. The observation of only one proton in the high-field pyrrole region appearing as a doublet gave definite proof that substitution had occurred in the pyrrole ring. If substitution had occurred in the benzene ring, the proton would have appeared as a triplet or a doublet of doublets; furthermore, the observation of the large coupling constant of 4 Hz is typical of that between H_1 and H_2 as discussed above. The remaining aromatic protons, including H_1, are present as a complex four-proton pattern at δ 7.05–7.55 for H_1, H_7, H_8, and H_9 and a one-proton multiplet at δ 8.07 for H_{10}; the ethylene bridge presents the typical AA′BB′ pattern of two multiplets centered at δ 3.33 and 4.40.

The minor component (5% yield) also had the typical carbonyl band at 1635 cm^{-1} in the IR spectrum and in the ^1H NMR two protons were seen at δ 6.50 and 6.70 as a pair of doublets with a coupling constant of 2 Hz and are assigned to H_2 and H_3, respectively. By arguments similar to those given above, the compound is assigned the 1-trifluoromethyl structure **4cc**.

Trace amounts of a bis-trifluoromethylated ketone were isolable on prolonged irradiation and it is tentatively assigned the 1,3-bis(trifluoromethyl) structure **4dd** on the basis of its mass spectrum (M^+ at 333) and a one-proton singlet in the NMR at δ 6.90.

Trifluoromethyl aromatic compounds have generally been prepared by the action of various fluorinating agents, such as HF, SbF_3, SbF_5, SF_4, or RSF_3, on compounds bearing a trichloromethyl group or carboxylic acid derivative.[22] The drastic experimental conditions implied by this chemistry, coupled to the synthetic necessity of using an already substituted precursor, has limited the application of these methods. As a result, trifluoromethyl substituents are largely unknown in the more sensitive heterocycles such as pyrrole, thiophene, furan, and indole. In a gratifying extension of the trifluoromethylation of ketone **4a**, we have now found that representative examples of all these nuclei could be trifluoromethylated in 40% to 60% yields (60–90% based on recovered starting materials), as summarized in Table III. Thus, a very mild

Table III. Trifluoromethylated Heterocycles

product		% yield[a]
	R = $CH_2C_6H_5$	60 (71)
	R = 4-$C_6H_4CH_3$	60 (91)
	2-CF_3	30 (46)[b]
	3-CF_3	15 (23)[b]
	X = O	51 (59)
	X = S	40 (73)

[a] Isolated yields (yields based on recovered starting material). [b] *N*-(trimethylsilyl)indole was the actual substrate as indole itself gave very low yields.

Scheme VII

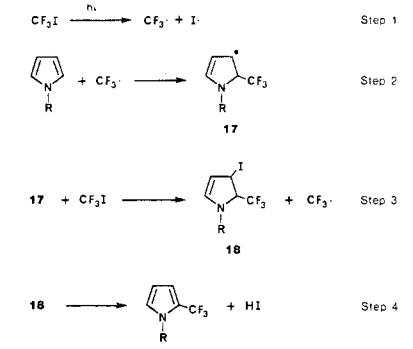
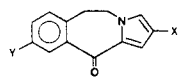


Chart I



Y=H		X=H	
4ee	X=CHO	**4jj**	Y=NH_2
4ff	X=$CONH_2$	**4kk**	Y=NHCOMe
4gg	X=CO_2H	**4ll**	Y=Cl
4hh	X=CO_2Me	**4mm**	Y=CN
4ii	X=$CON(Me)_2$	**4nn**	Y=CO_2H
		4oo	Y=SCF_3

and quite general method for preparing electron-rich trifluoromethylated heterocycles in preparatively useful yields is now available.[23]

The photolysis of CF_3I has been shown to yield $CF_3\cdot$ and I· radical[25] (Scheme VII, step 1). Scheme VII (illustrated with a pyrrole) shows the possible sequence initiated by an addition of $CF_3\cdot$ radical (step 2) and leading to products (steps 3, 4). Step 3 is a propagation step. The formation of 18 by a combination of 17 and I· radical is unlikely, being of very low probability. The direction of addition observed in the case of pyrroles, furans, and thiophenes is the one expected of radical addition to these heterocycles.[26] Indoles, however, are reported to be quite unreactive toward homolytic substitution, and mixtures and very low yields are often obtained,[27] and no clear picture seems available for the substitution pattern. In the homolytic substitution of *N*-(trimethylsilyl)indole with $CF_3\cdot$ radical we observe a preference for C_2 over C_3 attack. The extent of substitution in the aromatic ring is probably minimal since we

(22) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, 1969, pp 410–412.

(23) After this work was completed, a publication appeared that described a similar photochemical trifluoromethylation of pyrrole and *N*-methylpyrrole: Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami, and T. Nakano, *Chem. Pharm. Bull.*, **26**, 1247 (1978).

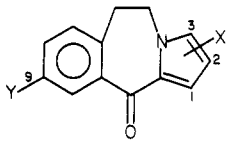
(24) Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzawa, *J. Org. Chem.*, **39**, 1836 (1974).

(25) A. Schönberg, "Preparative Organic Photochemistry", 2nd ed., Springer-Verlag, New York, 1968, pp 173–174.

(26) G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1173 (1972).

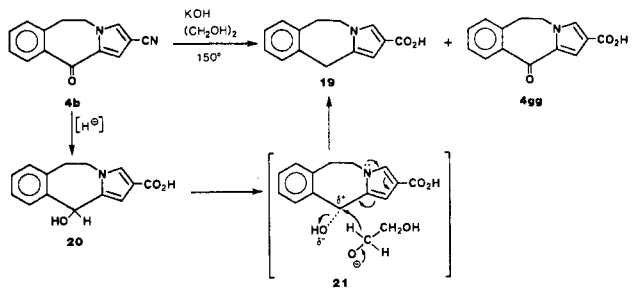
(27) W. A. Remers in "The Chemistry of Heterocyclic Compounds", W. J. Houlihan, Ed., Wiley, New York, 1972, Part 1, pp 179–181.

Table IV. Ultraviolet Spectra of Representative 6,11-Dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4)



compd	λ_{max}^{EtOH} (log ϵ)			
2-$COCH_3$ (4m)	212 (4.31)	247 (4.30)	321 (4.16)	
2-$SO_2N(CH_3)_2$ (4q)	209 (4.44)	262 (4.03)	309 (4.16)	
3-CN (4aa)	209 (4.21)	231 (4.15)	268 (4.00)	314 (4.21)
3-CN, 11-OH (14)	209 (4.30)	261 (4.18)		
9-NO_2 (4k)	208 (4.18)	246 (4.25)	340 (4.06)	
9-NH_2 (4jj)	206 (4.20)	238 (4.27)	325 (4.18)	
9-CN (4mm)	202 (4.54)	223 (4.62)	250 (4.20)	337 (4.14)

Scheme VIII



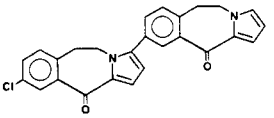
could not identify such products in the reaction mixture.

III. Modification of Existing Functional Groups. The third general method for preparation of other ketones of general structure 4 was the chemical modification of functionality introduced by the methods described above.

The 2-cyano ketone **4b** was transformed into the ketones **4ee** (2-CHO),[28] **4ff** (2-$CONH_2$), **4gg** (2-COOH), **4hh** (2-$COOCH_3$), and **4ii** (2-$CON(CH_3)_2$; Chart I) by standard methods and without incident except for the case of the carboxylic acid, which was obtained in two steps by the acid-catalyzed hydrolysis of the nitrile to the amide followed by nitrous acid treatment[29] of the latter to give the acid **4gg** in 78% overall yield. This two-step procedure was made necessary by an unexpected side reaction on attempted total hydrolysis of the nitrile. Basic hydrolysis of the nitrile in ethanol–water was found to be extremely slow, and recourse to KOH in ethylene glycol at 150 °C for 16 h was necessary to bring about hydrolysis. However under these conditions, a 2:1 mixture of the reduced acid **19** and the desired acid **4gg** was obtained (Scheme VIII). Wolff–Kishner reduction of **4gg** gave the same acid **19**.

This unexpected reduction of a carbonyl group to a hydrocarbon turns out to have related precedents in that sodium alkoxides were among those found by Verley in his original work to bring about the reduction of aldehydes and ketones to alcohols, and aluminum alkoxides have been reported to give the corresponding hydrocarbons from diaryl ketones and from diphenylcarbinol.[30,31] The likely intermediate, carbinol **20** (Scheme VIII), was not seen in the crude product, and under the rather vigorous conditions of the reaction it must be reduced to the hydrocarbon more rapidly than it is formed from the ketone. The well-documented[32] reactivity of (α-hydroxyalkyl)pyrroles, even to nucleophilic displacement under basic conditions, and the high temperature of the reaction leads to a suggested transition state such as **21**, with considerable S_N1 character, for the second hydride transfer from ethylene glycol. The elimination of OH^- may also be assisted by hydrogen bonding, either intramolecular or intermolecular with the solvent.

From the 9-nitro and 9-iodo ketones (**4k** and **4l**, Scheme III), the corresponding ketones **4jj** (9-NH_2), **4kk** (9-NHAc), **4ll** (9-Cl), **4mm** (9-CN), **4nn** (9-CO_2H), and **4oo** (9-SCF_3) were obtained by straightforward reactions (Chart I). The only reaction that initially gave some difficulty was the Sandmeyer reaction to obtain the 9-Cl ketone. When carried out in dilute HCl with CuCl alone, only a 22% yield of the desired chloro derivative **4ll** was obtained along with an equal amount of a product resulting from coupling of the 9-radical (or cation) intermediate with formed **4ll**, to which structure **22** is tentatively assigned, based on the mass spectrum and ^1H NMR spectrum (see Experimental Section).



This side reaction was effectively suppressed, however, by running the Sandmeyer reaction in 10 N HCl, using a mixture of CuCl and $CuCl_2$,[33] whence a 62% yield of the 9-Cl ketone could be isolated.

Because of the relatively few examples of ketones of type 4, we have summarized in Table IV the ultraviolet spectra of several representative ketones prepared during the course of this work.

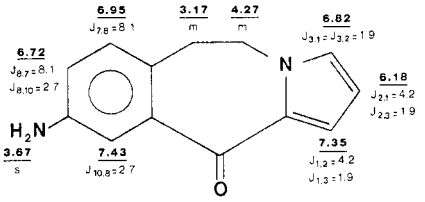
IV. ^1H NMR Spectra. The ^1H NMR spectral behavior of these tricyclic ketones warrants some observations as it was used routinely for structure determination in several cases. The two methylene groups are centered at about δ 3.3 and 4.3 for the benzylic CH_2 and the CH_2 α to nitrogen, respectively. The shape of the absorption is characteristic throughout the series showing an AA'BB' pattern.

Another characteristic of this system is the H_{10} proton, which is deshielded by about 1 ppm due to its position in the plane of the carbonyl. The chemical shift of H_{10} is invariably at the lowest field position in the spectra and is usually located around δ 8.1–8.2, appearing roughly as a doublet of doublets due to ortho and meta coupling.

The pyrrole protons are also characteristic.[11] In the unsubstituted ketone 4, H_2 is located at δ 6.2, appearing as a doublet of doublets with coupling constants of 2 and

(28) J. Van Es and B. Staskun, *J. Chem. Soc.*, 5775 (1965).
(29) J. March, "Advanced Organic Chemistry", 2nd ed., McGraw-Hill, New York, 1977, p 353.
(30) For a review of the Meerwein–Ponndorff–Verley (MPV) reduction, see: A. L. Wilds in "Organic Reactions", R. Adams, Ed., Wiley, New York, 1944, Vol. 2, pp 178–223.
(31) For a recent reference to intramolecular MPV reductions and the effect of different cations, see: E. W. Warnhoff, P. Reynolds-Warnhoff, and M. Y. H. Wong, *J. Am. Chem. Soc.*, **102**, 5956 (1980).
(32) Reference 11b, pp 355–361.
(33) H. H. Hodgson and D. D. R. Sibbald, *J. Chem. Soc.*, 393 (1944).

Chart II. ^{1}H NMR Parameters of Ketone 4jj



4 Hz. For substituents located in position 3, the key feature is the presence of a doublet with a coupling constant of 4 Hz in the region of δ 6.2–6.9 assigned to proton H_2. In most cases, the H_1 proton is buried within the complex pattern for H_7, H_8, and H_9 due to its coplanarity with the carbonyl.

In the case of 2-substitution, depending on the nature of the substituents, either H_1 or H_3 is sufficiently removed from the aromatic absorptions to be easily detected by their characteristic doublet with a coupling constant of 2 Hz.[34]

The above salient features are particularly well-demonstrated in the 9-amino ketone **4jj**, in which every aromatic proton could be distinguished, even at 60 MHz. The chemical shifts and coupling constants (in $CDCl_3$) could be assigned unambiguously as shown in Chart II.

Summary

Two independent and quite flexible syntheses of the 6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one system (4) have been developed, allowing the introduction of a variety of substituents into either the pyrrole ring or the benzene ring. Electrophilic reactions were found to permit the introduction of further substituents into the pyrrole ring in either position 2 or position 3, depending on the reaction and the conditions. Two novel and very useful photochemical reactions were also discovered that brought about the introduction of cyano and trifluoromethyl groups into the pyrrole ring. The latter photochemical reaction is of particular value as other methods of preparing electron-rich aromatic compounds containing trifluoromethyl groups are severely limited by the strong electrophilic reagents generally employed, which would cause extensive decomposition of sensitive substrates.

Experimental Section

Melting points were taken on a Thomas Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 267 grating spectrophotometer. All IR spectra were run as KBr pellets for solids or as neat films on NaCl plates for liquids. A Varian EM-360 and a Varian T-60 spectrometer were used to record ^{1}H NMR spectra in deuteriochloroform unless indicated otherwise. Proton chemical shifts are relative to tetramethylsilane (Me_4Si) as internal standard, while fluorine chemical shifts are relative to fluorotrichloromethane. GC analyses were performed on a Hewlett-Packard Model 5700 A/3370B instrument with a 6 ft × 2 mm column packed with 1% OV-17 on 100–200 Gas-Chrom Q and a Varian 1400 instrument with a 5 ft × $^1/_8$ in. column packed with 1.5% OV-101 on 100–120-mesh Chromosorb G-HP. Elemental analyses were performed by Dr. C. Daesslé of Montreal. The low-resolution mass spectral analyses were performed by the Morgan-Schaffer Corp., Montreal, and the high-resolution mass spectra were run on a VG-MM7035 instrument.

Substituted Methyl 1-(2-Phenethyl)pyrrole-2-carboxylates (6.1a–e, g, j, k) (Method B, Scheme I). To a suspension of K_2CO_3 (75 g, 0.57 mol) in DMF (300 mL) were added successively phenethyl bromide (84 g, 0.46 mol) and 2-carbomethoxy-4-cyanopyrrole[8] (63.5 g, 0.42 mol). The reaction mixture was heated at 85 °C for 4 h and then poured into H_2O (1 L) and extracted with ether (3 × 100 mL). The organic layers were washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was triturated with the minimum amount of cold ether and filtered, affording 82.8 g (77%) of ester **6.1b**: mp 109–110 °C; IR 2210 (CN), 1710 cm^{-1} (CO_2Me); ^{1}H NMR δ 3.02 (t, 2 H, Ar CH_2, J = 7 Hz), 3.87 (s, 3 H, OCH_3), 4.53 (t, 2 H, CH_2N, J = 7 Hz), 6.95 (d, 1 H, H_3, $J_{3,5}$ = 2 Hz), 7.20 (m, 6 H, H_5 and Ar). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.42; H, 5.87; N, 10.97.

Compounds **6.1a**, **6.1d–e**, and **6.1g** were similarly prepared. Compound **6.1c** was prepared with phenethyl tosylate, and **6.1j** and **6.1k** were prepared with the corresponding mesylates. Yields and melting points of the esters thus prepared are reported in Table I.

Methyl 1-(2-*p*-Tolylethyl)pyrrole-2-carboxylate (6.1h; Method C, Scheme I). A mixture of 2-*p*-tolylethylamine (12.8 g, 0.095 mol) and methyl 2,5-dimethoxytetrahydrofuran-2-carboxylate (18 g, 0.095 mol) was refluxed in HOAc (60 mL) for 5 h. The reaction mixture was then poured into an ice–water suspension of Na_2CO_3 and extracted with ether. The ethereal layer was washed with H_2O, dried, and evaporated to dryness, yielding 21 g (91%) of ester **6.1h** as an oil: IR 1710 cm^{-1} (CO_2Me); ^{1}H NMR δ 2.30 (s, 3 H, CH_3), 2.98 (m, 2 H, Ar CH_2), 3.75 (s, 3 H, OCH_3), 4.45 (m, 2 H, CH_2N), 6.00 (dd, 1 H, H_4, $J_{4,3}$ = 4 Hz, $J_{4,5}$ = 2 Hz), 6.60 (t, 1 H, H_5, $J_{5,3}$ = $J_{5,4}$ = 2 Hz), 6.90 (dd, 1 H, H_3, $J_{3,4}$ = 4 Hz, $J_{3,5}$ = 2 Hz), 7.00 (s, 4 H, Ar).

Methyl 3,4,5-Tribromo-1-(2-*p*-tolylethyl)pyrrole-2-carboxylate (6.1i). Bromination of **6.1h** (20 g, 0.082 mol) was carried out in $CHCl_3$ (200 mL) by the dropwise addition of Br_2 (42 g, 0.26 mol). The temperature of the reaction mixture was kept below 10 °C during the addition and then kept at this temperature for an additional 30 min. The resulting solution was washed with a solution of $NaHSO_3$ and then with H_2O, dried (Na_2SO_4), and evaporated to dryness, yielding 36 g (89%) of ester **6.1i** as an oil that crystallized on standing: mp 88–90 °C; IR 1700 cm^{-1} (CO_2Me); ^{1}H NMR δ 2.30 (s, 3 H, CH_3), 2.93 (m, 2 H, Ar CH_2), 3.87 (s, 3 H, OCH_3), 4.56 (m, 2 H, CH_2N), 7.06 (s, 4 H, Ar). Anal. Calcd for $C_{15}H_{14}Br_3NO_2$: C, 37.53; H, 2.94; N, 2.92; Br, 49.95. Found: C, 37.20; H, 2.94; N, 2.86; Br, 49.82.

1-(2-Phenethyl)pyrrole-2-carboxylic Acid (6.2a; Method A, Scheme I). *N-trans*-Styrylpyrrole-2-carboxylic acid (24.4 g, 0.115 mol), prepared from styrene oxide and ethyl pyrrole-2-carboxylate as previously reported,[7a] was suspended in EtOH (200 mL) and hydrogenated under 3 atm of H_2 in the presence of 10% Pd/C (1 g) until uptake of H_2 ceased. After removal of the catalyst by filtration, the ethanolic solution was evaporated to dryness, affording 22.2 g (90%) of acid **6.2a**: mp 124–125 °C; IR 1675 cm^{-1} (CO_2H); ^{1}H NMR δ 3.02 (t, 2 H, Ar CH_2, J = 7 Hz), 4.50 (t, 2 H, CH_2N, J = 7 Hz), 6.08 (dd, 1 H, H_4, $J_{4,5}$ = 2 Hz, $J_{4,3}$ = 4 Hz), 6.65 (t, 1 H, H_5, $J_{5,4}$ = $J_{5,3}$ = 2 Hz), 6.9–7.4 (m, 6 H, H_3, Ar), 11.70 (s, 1 H, CO_2H, exchangeable). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.50; H, 5.92; N, 6.46.

Substituted 1-(2-Phenethyl)pyrrole-2-carboxylic Acids (6.2a–e,g–k; Method B, Scheme I). To a mixture of methyl 4-cyano-1-(2-phenethyl)pyrrole-2-carboxylate (**6.1b**; 482 g, 1.90 mol) in EtOH (1 L) was added NaOH (6 N, 350 mL) and the resulting mixture was refluxed until disappearance of starting material by TLC (about 2 h). The EtOH was stripped off and the concentrated mixture was diluted wiith cold water (2 L) and acidified with concentrated HCl. The resulting precipitate was then filtered, washed with H_2O, and air-dried to yield 455 g (quantitative) of compound **6.2b**: mp 188–189 °C; IR 2225 (CN), 1680 cm^{-1} (CO_2H); ^{1}H NMR δ 3.00 (t, 2 H, Ar CH_2, J = 7 Hz), 4.57 (t, 2 H, CH_2N, J = 7 Hz), 7.20 (m, 6 H, H_5, Ar), 7.77 (d, 1 H, H_3, $J_{3,5}$ = 2 Hz). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.84; H, 5.10; N, 11.54.

Compounds **6.2a**, **6.2c–e**, and **6.2g–k** were similarly prepared. Yields and melting points of the acids thus prepared are reported in Table I.

4,5-Dibromo-1-(2-phenethyl)pyrrole-2-carboxylic Acid (6.2f). To a solution of **6.2a** (30 g, 0.14 mol) in HOAc (100 mL) was added Br_2 (44.6 g, 0.28 mol) dropwise and the mixture was stirred at room temperature for 15 min. The crystalline precipitate was filtered, washed with H_2O, and air-dried to afford 40 g (77%) of compound **6.2f**. A sample was recrystallized from MeOH: mp

(34) P. Fournari, M. Farnier, and C. Fournier, *Bull. Soc. Chem. Fr.*, 283 (1972).

178–179 °C; IR 1675 cm^{-1} (CO_2H); ^1H NMR δ 2.92 (t, 2 H, Ar CH_2, J = 7 Hz), 4.62 (t, 2 H, CH_2N, J = 7 Hz), 7.07 (s, 1 H, H_3), 7.15–7.50 (m, 5 H, Ar). The product contained a few percent of monobromo material as indicated by high-carbon and low-bromine analyses. Since this intermediate was not used extensively, no further attempts were made to obtain pure material. Anal. Calcd for $C_{13}H_{11}Br_2NO_2$: C, 41.90; H, 2.95; Br, 43.0; N, 3.76. Found: C, 42.57; H, 3.10; Br, 35.88; N, 3.92.

Substituted 1-(2-Phenethyl)pyrrole-2-carboxylic Acid Chlorides (6.3a, c, i–k; Dichloromethyl Methyl Ether Method, Scheme I). Dichloromethyl methyl ether (25 mL) was added slowly to **6.2a** (4 g, 0.019 mol) and the mixture was refluxed for 30 min to yield a clear solution. This solution was concentrated under vacuum and the resulting residue was dissolved in ether, treated with charcoal, filtered, and evaporated to dryness. The crude product was chromatographied on silica gel eluting wiith 40% EtOAc in hexane to afford 3.6 g (83%) of pure **6.3a**: mp 85–86 °C; IR 1725 cm^{-1} (CO); ^1H NMR δ 2.98 (t, 2 H, Ar CH_2, J = 7 Hz), 4.40 (t, 2 H, CH_2N, J = 7 Hz), 6.12 (dd, 1 H, H_4, $J_{4,3}$ = 4 Hz, $J_{4,5}$ = 2 Hz), 6.74 (t, 1 H, H_5, $J_{5,4} = J_{5,3}$ = 2 Hz), 7.00–7.40 (m, 6 H, H_3, Ar). Anal. Calcd for $C_{13}H_{11}ClNO$: C, 67.11; H, 4.73; Cl, 15.25; N, 6.02. Found: C, 67.10; H, 5.45; Cl, 15.56; N, 5.96.

The acid chlorides **6.3c** and **6.3i–k** were similarly prepared. Yields and melting points are reported in Table I.

Substituted 1-(2-Phenethyl)pyrrole-2-carboxylic Acid Chlorides (6.3b,d–g; Thionyl Chloride Method, Scheme I). $SOCl_2$ (1 L) was added slowly to 4-cyano-1-(2-phenethyl)-pyrrole-2-carboxylic acid (**6.2b**; 455 g, 1.90 mol). The reaction was exothermic during the addition. The reacting mixture was then refluxed for 30 min and the excess of $SOCl_2$ was stripped off under vacuum. The resulting residue was triturated with hexane and filtered, yielding 452 g (92%) of acid chloride **6.3b**: mp 114–115 °C; IR 2250 (CN), 1750 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 3.00 (t, 2 H, Ar CH_2, J = 7 Hz), 4.57 (t, 2 H, CH_2N, J = 7 Hz), 7.23 (m, 6 H, H_5, Ar), 7.67 (d, 1 H, H_3, $J_{3,5}$ = 2 Hz). Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; Cl, 13.71; N, 10.83. Found: C, 63.81; H, 4.74; Cl, 13.30; N, 10.83.

Similarly, compounds **6.3d–g** were prepared. Yields and melting points are reported in Table I.

6,11-Dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4a). A suspension of 1,2,3-tribromo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*]-[3]benzazepin-11-one (**4g**, see below; 43 g, 0.10 mol) and Et_3N (30 mL) in MeOH (200 mL) was hydrogenated in the presence of 10% Pd/C (0.5 g) under 3 atm of H_2 until uptake ceased. The catalyst was filtered and the filtrate evaporated to dryness. The resulting residue was dissolved in H_2O (100 mL) and ether (100 mL). After decantation of the ethereal layer, the aqueous layer was washed once with ether (100 mL). The organic layers were combined, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, leaving 17.7 g (90%) of crude ketone **4a**, which crystallized on standing: mp 54–55 °C; IR 1615 cm^{-1} (CO); ^1H NMR δ 3.32 (m, 2 H, Ar CH_2), 4.32 (m, 2 H, CH_2N), 6.22 (dd, 1 H, H_2, $J_{2,3}$ = 2 Hz, $J_{2,1}$ = 4 Hz), 6.85 (t, 1 H, H_3, $J_{3,2} = J_{3,1}$ = 2 Hz), 7.10–7.52 (m, 4 H, H_1, H_7, H_8, H_9), 8.18 (m, 1 H, H_{10}). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.29; H 5.67; N, 6.90.

Similarly, compound **4a** was also prepared by hydrogenation of 2,3-dibromo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**4f**) in quantitative yield.

Substituted 6,11-Dihydro-5*H*-pyrrolo[2,1-*b*][3]benz-azepin-11-ones (4b–g,i) (Scheme I). $AlCl_3$ (80 g, 0.60 mol) was added to a solution of 4-cyano-1-(2-phenethyl)pyrrole-2-carboxylic acid chloride (**6.3b**; 50 g, 0.19 mol) in CH_2Cl_2 (500 mL) and refluxed for 30 min. After cooling, the reaction mixture was poured into ice–water, and the insolubles were filtered. The organic layer was decanted and the aqueous solution was washed once with CH_2Cl_2 (500 mL). The organic layers were combined, washed with H_2O, dried (Na_2SO_4), and concentrated under vacuum, leaving the crude ketone derivative. Trituration with ether (500 mL) afforded after filtration 36 g (84%) of pure **4b**. A second crop (6.2 g, 14%) was obtained from the mother liquors; mp 146–147 °C; IR 2238 (CN), 1635 cm^{-1} (CO); ^1H NMR δ 3.37 (m, 2 H, Ar CH_2), 4.47 (m, 2 H, CH_2N), 7.43 (d, 1 H, H_3, $J_{3,1}$ = 2 Hz), 7.50 (m, 3 H, H_7, H_8, H_9), 7.97 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 8.03 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 76.07; H, 4.64; N, 12.72.

Compounds **4d–g** and **4i** were similarly prepared. For the preparation of **4c**, nitromethane was used as solvent instead of CH_2Cl_2 and the reacting mixture was kept at 0 °C for 3 h. Yields and melting points are reported in Table II.

9-(Fluorosulfonyl)-1,2,3-tribromo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3b]benzazepin-11-one (4h; Eq 1, Scheme II). To 20 mL of fluorosulfonic acid stirred at room temperature was added **4g** (1.0 g, 2.3 mmol). The solution was heated at 160 °C for 3 h, cooled, and poured onto 100 g of cracked ice. The solid brown precipitate was filtered, washed with H_2O, and air-dried. It was slurried well with 25 mL of EtOAc to remove starting material, and the insoluble, light-brown solid recovered by filtration to yield 902 mg (76%) of **4h**: mp 248–249 °C; IR 1620 (CO), 1205, 1410 cm^{-1} (SO_2F); ^1H NMR (Me_2SO-d_6) δ 3.47 (m, 2 H, Ar CH_2), 4.40 (m, 2 H, CH_2N), 7.60 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 7.97 (dd, 1 H, H_8, $J_{8,7}$ = 8 Hz, $J_{8,10}$ = 2 Hz), 8.33 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz); mass spectrum, m/e 513, 515, 517, 519 (M^+).

9-Methyl-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4j). The title compound was prepared by hydrogenation of 9-methyl-1,2,3-tribromo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]-benzazepin-11-one (**4i**) as described for the preparation of **4a**. Compound **4j** was obtained in quantitative yield as an oil: IR 1625 cm^{-1} (CO); ^1H NMR δ 2.36 (s, 3 H, CH_3), 3.23 (m, 2 H, Ar CH_2), 4.30 (m, 2 H, CH_2N), 6.22 (dd, 1 H, H_2, $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.80 (t, 1 H, H_3, $J_{3,1} = J_{3,2}$ = 2 Hz), 7.0 (d, 1 H, H_7, $J_{7,8}$ = 7 Hz), 7.2 (d, 1 H, H_8, $J_{8,7}$ = 8 Hz), 7.35 (dd, 1 H, H_1, $J_{1,2}$ = 4 Hz, $J_{1,3}$ = 2 Hz), 7.88 (br s, 1 H, H_{10}).

9-Nitro-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4k; Scheme III). β-Phenethyl isothiocyanate (250 g, 1.53 mol) was added portionwise to preheated (100 °C) PPA (1 kg). The reaction was exothermic with gas evolution. When the evolution of gas had ceased, the reaction mixture was heated at 145 °C for 15 min and then poured slowly into cold H_2O. The precipitate formed was filtered, washed with H_2O, and air-dried, affording 142 g (57%) of 1-thio-3,4-dihydroisocarbostyril: mp 98–99 °C (lit.[13] mp 98–99 °C). The following procedure[35] was then used to convert the thiolactam to the lactam.

To a solution of KOH/H_2O/MEOH (60 g/150 mL/900 mL) was added H_2O_2 (30%, 220 mL) at 0 °C. The 1-thio-3,4-dihydroisocarbostyryl (71 g, 0.44 mol) was then added portionwise to the resulting solution, at such a rate as to keep the temperature of the reaction mixture between 15 and 30 °C (ice bath). After addition, the reaction was stirred for 30 min at room temperature. The white precipitate was filtered and washed with MEOH and the filtrate evaporated to dryness. The resulting residue was partitioned between H_2O and ether, decanted, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, leaving 50 g (78%) of 3,4-dihydroisocarbostyryl: mp 64–66 °C (lit.[36] mp 73 °C). After acidification of the aqueous layer and extraction with ether, a second crop of 10 g (16%) was obtained.

Fuming HNO_3 (17 mL) was added to concentrated H_2SO_4 (670 mL) at 0 °C and then 3,4-dihydroisocarbostyryl (50 g, 0.34 mol) was added portionwise, maintaining the temperature below 0 °C. After 30 min at 0 °C, the solution was poured into ice–water (8 L). The crystalline precipitate was collected, washed with H_2O, and air-dried, affording 62 g (95%) of 7-nitro-3,4-dihydroisocarbostyryl: mp 225–230 °C. A sample was recrystallized from acetone: mp 230–232 °C (lit.[17] mp 216–218 °C); IR 3170 (NH), 1670 (C=O), 1510, 1335 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 3.05 (m, 2 H, Ar CH_2), 3.43 (m, 2 H, CH_2N), 7.58 (d, 1 H, H_5, $J_{5,6}$ = 9 Hz), 8.28 (br s, 1 H, NH, exchangeable), 8.30 (dd, 1 H, H_6, $J_{6,5}$ = 9 Hz, $J_{6,8}$ = 3 Hz), 8.52 (d, 1 H, H_8, $J_{8,6}$ = 3 Hz). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.09; H, 4.49; N, 14.66.

When the nitration was carried out by adding 3,4-dihydroisocarbostyryl (4.0 g, 0.027 mol) portionwise to fuming HNO_3 (20 mL) at −10–15 °C and then at 0 °C for 1 h, there was obtained, after pouring into ice–water and filtration, a mixture (5.0 g) in a 1:1 ratio of the desired product and of 2,7-dinitro-3,4-dihydroisocarbostyryl. The pure dinitro derivative was obtained by chromatography (silica gel, EtOAc): mp 120–121 °C; IR 1705 (C=O), 1525, 1350 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 3.20 (m,

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2 H, Ar CH_2), 4.04 (m, 2 H, CH_2N), 7.68 (d, 1 H, H_5, $J_{5,6}$ = 8 Hz), 8.43 (dd, 1 H, H_6, $J_{6,5}$ = 8 Hz, $J_{6,8}$ = 3 Hz), 8.92 (d, 1 H, H_8, $J_{8,6}$ = 3 Hz).

Treatment of the dinitro derivative (1.0 g, 4 mmol) with concentrated HCl (1 mL) and MeOH (5 mL) at reflux for 5 min afforded after cooling and filtration 0.7 g (86%) of the pure 7-nitro derivative, identical with that obtained previously.

A mixture of 7-nitro-3,4-dihydroisocarbostyryl (10 g, 0.052 mol) and concentrated HCl (100 mL) was heated in a pressure vessel at 150 °C for 24 h. After evaporation to dryness, the residue was taken up in H_2O (100 mL) and the unreacted product was filtered (2.0 g). The aqueous solution was then neutralized by addition of NH_4OH from which the free amino acid derivative crystallized. After filtration and air-drying, 7.0 g (64%) of 2-(2-aminoethyl)-5-nitrobenzoic acid (**11b**) was obtained: mp 230–232 °C; IR 3300–2400 (br, NH_3^+), 1635 (CO_2^-), 1510, 1335 cm^{-1} (NO_2); ^1H NMR (D_2O + DCl) δ 3.35 (s, 4 H, $(CH_2)_2$), 7.57 (d, 1 H, H_3, $J_{3,4}$ = 9 Hz), 8.27 (dd, 1 H, H_4, $J_{4,3}$ = 9 Hz, $J_{4,6}$ = 3 Hz), 8.53 (d, 1 H, H_6, $J_{6,4}$ = 3 Hz). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.73; H, 4.93; N, 13.15.

2,5-Dimethoxytetrahydrofuran (55 g, 0.42 mol) was added to a suspension of **11b** (44 g, 0.21 mol) in H_2O (600 mL) and HOAc (100 mL). The reaction mixture was then heated at 50 °C for 2 h. After cooling, the precipitate was filtered, washed with H_2O, and dried, affording 51.5 g (96%) of crude 2-(2-pyrrol-1-ylethyl)-5-nitro benzoic acid (**12b**), which was used as such for the next step. An analytical sample was recrystallized from toluene: mp 147–149 °C; IR 3300–2200 (OH), 1700 (CO_2H), 1520, 1340 cm^{-1} (NO_2); ^1H NMr (Me_2SO-d_6) δ 3.43 (m, 2 H, Ar CH_2), 4.12 (m, 2 H, CH_2N), 5.90 (t, 2 H, H_3, H_4 (pyrrole), J = 2 Hz), 6.64 (t, 2 H, H_2, H_5 (pyrrole), J = 2 Hz), 7.32 (d, 1 H, H_3, $J_{3,4}$ = 8 Hz), 7.92 (br s, 1 H, OH, exchangeable), 8.12 (dd, 1 H, H_4, $J_{4,3}$ = 8 Hz, $J_{4,6}$ = 2 Hz), 8.52 (d, 1 H, H_6, $J_{6,4}$ = 2 Hz). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.63; H, 4.66; N, 10.61.

The intermediate **12b** (51 g, 0.20 mol) was added to a solution of polyphosphate ester[15] in $CHCl_3$ (500 mL) and the mixture was refluxed for 1.5 h. The reaction mixture was concentrated under vacuum and diluted with H_2O. The dark mixture was extracted with $CHCl_3$ (2 × 700 mL), washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The oily residue was passed quickly through a silica gel column (1 kg). Elution with $CHCl_3$ afforded 21.7 g (45%) of final product **4k**: mp 191–193 °C; IR 1610 (C=O), 1525, 1335 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 3.46 (m, 2 H, Ar CH_2), 4.46 (m, 2 H, CH_2N), 6.30 (dd, 1 H, H_2, $J_{2,1}$ = 2 Hz, $J_{2,3}$ = 4 Hz), 7.27 (m, 2 H, H_1, H_3), 7.67 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 8.30 (dd, 1 H, H_8, $J_{8,7}$ = 8 Hz, $J_{8,10}$ = 3 Hz), 8.62 (d, 1 H, H_{10}, $J_{10,8}$ = 3 Hz). Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.40; H, 4.18; N, 11.62.

9-Iodo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4l; Scheme III). A suspension of 7-nitro-3,4-dihydroisocarbostyryl (20 g, 0.104 mol) in MeOH (350 mL) was hydrogenated in the presence of 10% Pd/C (2 g) until H_2 uptake ceased. The catalyst was filtered, and the filtrate evaporated to dryness. The residue was triturated with ether and filtered, yielding 15.7 g (93%) of 7-amino-3,4-dihydroisocarbostyryl: mp 123–125 °C; IR 3460, 3400, 3340, 3240 (NH_2, NH), 1680–1625 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 2.66 (m, 2 H, Ar CH_2), 3.30 (m, 2 H, CH_2N), 5.06 (br s, 2 H, NH_2, exchangeable), 6.63 (dd, 1 H, H_6, $J_{6,5}$ = 9 Hz, $J_{6,8}$ = 3 Hz), 6.91 (d, 1 H, H_5, $J_{5,6}$ = 9 Hz), 7.10 (d, 1 H, H_8, $J_{8,6}$ = 3 Hz), 7.68 (br s, 1 H, NH, exchangeable).

A solution of $NaNO_2$ (20.95 g, 0.304 mol) in H_2O (125 mL) was added dropwise to a solution of 7-amino-3,4-dihydroisocarbostyryl (44.87 g, 0.277 mol) in 3 N HCl (400 mL) at 0–5 °C over 30 min. After stirring at 0 °C for 1 h, the cold diazonium salt was added slowly to a cold solution (0 °C) of KI (137.95 g, 0.831 mol) in H_2O (175 mL). The mixture was stirred vigourously and allowed to warm to room temperature over 4 h. The reaction mixture was decanted from a black extractable residue and extracted with $CHCl_3$. The balck residue was triturated with hot $CHCl_3$. The $CHCl_3$ fractions were combined, washed (10% $NaHSO_3$), dried ($MgSO_4$), and concentrated in vacuo to leave a yellow solid. The solid was triturated with cyclohexane and filtered to collect 21.2 g (28%) of 7-iodo-3,4-dihydroisocarbostyryl: mp 155–165 °C; IR 3170 (NH), 1650 cm^{-1} (C=O); ^1H NMR δ 2.91 (m, 2 H, Ar CH_2), 3.57 (m, 2 H, CH_2N), 6.95 (d, 1 H, H_5, $J_{5,6}$ = 8 Hz), 7.20–8.20 (br s, 1 H, NH, exchangeable), 7.77 (dd, 1 H, H_6, $J_{6,5}$ = 8 Hz, $J_{6,8}$ = 2 Hz), 8.32 (d, 1 H, H_8, $J_{8,6}$ = 2 Hz). GC analysis showed 95.7% of 7-iodo-3,4-dihydroisocarbostyryl and 4.3% of 3,4-dihydroisocarbostyryl.

A mixture of 7-iodo-3,4-dihydroisocarbostyryl (29.6 g, 0.11 mol) and concentrated HCl (800 mL) was heated in a pressure vessel at 150 °C, 600 psi, for 30 h. The reaction was cooled, diluted wiith H_2O, and concentrated in vacuo to a beige solid. The crude product was recrystallized from isopropyl alcohol to yield 21.5 g (60%) of 2-(2-aminoethyl)-5-iodobenzoic acid hydrochloride (**11c**.HCl): mp 190–195 °C; homogeneous by TLC (silica gel: 5BuOH–3HOAc–2H_2O); IR 1700 cm^{-1} (CO_2H); ^1H NMR (Me_2SO-d_6 + D_2O) δ 3.16 (m, 4 H, $(CH_2)_2$), 7.50 (d, 1 H, H_3, $J_{3,4}$ = 10 Hz), 8.10 (dd, 1 H, H_4, $J_{4,3}$ = 10 Hz, $J_{4,6}$ = 3 Hz), 8.83 (d, 1 H, H_6, $J_{6,4}$ = 3 Hz).

2,5-Dimethoxytetrahydrofuran (10.44 g, 0.079 mol) was added to a mixture of **11c**·HCl (21.48 g, 0.066 mol), NaOAc (5.41 g, 0.066 mol), H_2O (300 mL), and HOAc (50 mL). The reaction mixture was heated to 50 °C for 1 h, cooled, diluted with H_2O, and extracted in portions with $CHCl_3$ (800 mL). The $CHCl_3$ was washed (H_2O), dried ($MgSO_4$), and concentrated in vacuo to yield 18.9 (84%) of 5-iodo-2-(2-pyrrol-1-ylethyl)benzoic acid (**12c**): mp 92–95 °C; homogeneous by TLC (silica gel: 2MeOH–8C_6H_{12}); IR 1675 cm^{-1} (CO_2H); ^1H NMR δ 3.25 (m, 2 H, Ar CH_2), 4.15 (m, 2 H, CH_2N), 5.93 (t, 2 H, H_3, H_4 (pyrrole), J = 2 Hz), 6.50 (t, 2 H, H_2, H_5 (pyrrole), J = 2 Hz), 6.80 (d, 1 H, H_3, $J_{3,4}$ = 10 Hz), 7.76 (dd, 1 H, H_4, $J_{4,3}$ = 10 Hz, $J_{4,6}$ = 2 Hz), 8.50 (d, 1 H, H_6, $J_{6,4}$ = 2 Hz), 11.40 (br s, 1 H, OH, exchangeable).

The intermediate **12c** (18.90 g, 0.055 mol) was stirred wiith polyphosphate ester[15] (200 mL) at room temperature for 6 h. The dark syrupy reaction mixture was diluted by slow addition to an ice–water mixture and then extracted with benzene. The benzene fractions were combined, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to a black oil. Chromatography (silica gel, $CHCl_3$) yielded 6.65 g (37%) of pure **4l**. An analytical sample was recrystallized from cyclohexane: mp 120–122 °C; IR 1600 cm^{-1} (C=O); ^1H NMR δ 3.26 (m, 2 H, Ar CH_2), 4.33 (m, 2 H, CH_2N), 6.23 (dd, 1 H, H_2, $J_{2,1}$ = 2 Hz, $J_{2,3}$ = 4 Hz), 6.93 (m, 2 H, H_3, H_7), 7.37 (dd, 1 H, H_1, $J_{1,3}$ = 2 Hz, $J_{1,2}$ = 4 Hz), 7.76 (dd, 1 H, H_8, $J_{8,7}$ = 5 Hz, $J_{8,10}$ = 2 Hz), 8.46 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz). Anal. Calcd for $C_{13}H_{10}INO$: C, 48.31; H, 3.11; N, 4.34; I, 39.28. Found: C, 48.15; H, 3.26; N, 4.20; I, 38.93.

2-Acyl-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4m–o; Scheme IV). To a solution of **4a** (5.0 g, 0.025 mol) in CH_2Cl_2 (100 mL) was added portionwise $AlCl_3$ (13.3 g, 0.10 mol) followed by the dropwise addition of acetyl chloride (2.5 g, 0.032 mol). The reaction mixture was stirred at room temperature for 15 min and poured onto ice. The organic layer was decanted, filtered through K_2CO_3, dried (Na_2SO_4), and evaporated to dryness. The resulting residue was then purified by chromatography [silica gel, eluting with benzene and then with ethyl acetate/benzene (5:95)], affording 4.0 g (66%) of pure **4m**: mp 162–163 °C; IR 1675, 1625 cm^{-1} (C=O); ^1H NMR δ 2.40 (s, 3 H, CH_3), 3.33 (m, 2 H, Ar CH_2), 4.39 (m, 2 H, CH_2N), 7.10–7.55 (m, 4 H, H_3, H_7, H_8, H_9), 7.66 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), and 8.12 (m, 1 H, H_{10}). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.45; H, 5.41; N, 5.75.

Compounds **4n** and **4o** were prepared similarly as summarized in Table II.

3-Pentanoyl-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4p; Scheme IV). Valeryl chloride (6 mL) was added to compound **4a** (500 mg, 2.54 mmol) and the mixture was heated neat at 120 °C under pressure for 6 h. The excess of valeryl chloride was hydrolyzed by heating the reacting mixture in ethanolic NaOH solution for 15 min. After evaporation to dryness, the residue was taken up in $CHCl_3$, washed with H_2O, decanted, treated with charcoal, dried (Na_2SO_4), and evaporated to dryness, leaving 110 mg (15%) of crude final product (**4p**) as an oil. A sample was purified by chromatography on silica gel, eluting with 25% EtOAc in hexane, to afford pure **4p**: mp 73–74 °C; IR 1630, 1670 cm^{-1} (CO); ^1H NMR δ 0.75–1.85 (m, 7 H, C_3H_7), 2.03 (t, 2 H, $COCH_2$, J = 7 Hz), 3.25 (m, 2 H, Ar CH_2), 4.82 (m, 2 H, CH_2N), 6.90 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.0–7.5 (m, 4 H, H_1, H_7, H_8, H_9), 7.98 (m, 1 H, H_{10}). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.67; H, 6.79; N, 5.28.

2-(Dimethylsulfamoyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4q; Scheme IV). Dimethylsulfamoyl

chloride (0.9 g, 5 mmol) was added to a mixture of **4a** (1.0 g, 4 mmol) and $AlCl_3$ (2.5 g, 15 mmol) in nitromethane (20 mL). After refluxing for 20 min, the reaction mixture was poured into ice–water and extracted with ether (2 × 50 mL). The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, leaving an oil, which was chromatographed [silica gel, EtOAc/benzene (25:75 and then 40:60)], affording 690 mg (45%) of pure product **4q**: mp 134–137 °C; IR 1625 (C=O), 1330, 1140 cm^{-1} (SO_2); ^1H NMR δ 2.66 [s, 6 H, $(CH_3)_2$], 3.33 (m, 2 H, Ar CH_2), 4.38 (m, 2 H, CH_2N), 7.00–7.50 (m, 5 H, Ar), 8.03 (m, 1 H, H_{10}).

2- and 3-(Methylsulfinyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4r,s). A cooled solution of thiocyanogen[37] prepared from $Pb(SCN)_2$ (160 g, 0.5 mol) and Br_2 (80 g, 0.5 mol) in CH_2Cl_2 (800 mL) was added dropwise to a cooled mixture (0 °C) of **4a** (24.5 g, 0.12 mol) and $AlCl_3$ (30 g, 0.23 mol) in CH_2Cl_2 (300 mL) and the mixture stirred at 0 °C for 1 h. The reacting mixture was poured into ice–water (2 L) filtered through Celite and decanted. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, leaving 30 g of a bad, oily mixture, the IR spectrum of which showed a thiocyanate band: IR 2170 (SCN), 1630 cm^{-1} (C=O).

The thiocyanate mixture was dissolved in MeOH (300 mL) and then iodomethane (40 g, 0.28 mol) and KOH (50 mL, 6 N) were added successively under nitrogen. The resulting mixture was refluxed for 1 h and cooled to room temperature and the methanolic solution was decanted from a gummy insoluble tar. After evaporation, the residue was taken up in ether, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, affording 20 g of an oil containing the methyl sulfide derivative on the basis of the NMR spectrum that showed an SCH_3 absorption at δ 2.30.

Without further purification the above intermediate was dissolved in HOAc (100 mL) and oxidized by addition of H_2O_2 (30%, 5 mL). After stirring for 2 h at room temperature, the reaction mixture was poured into a NaOH solution and extracted with $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and concentrated under vacuum. From the resulting oily residue there was obtained, after chromatography (silica gel, EtOAc), 3-(methylsulfinyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**4s**; 1.0 g) as an oil [IR 1625 cm^{-1} (C=O); ^1H NMR δ 2.97 (s, 3 H, CH_3), 3.37 (m, 2 H, Ar CH_2), 4.64 (m, 2 H, CH_2N), 6.67 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.10–7.53 (m, 4 H, H_1, H_7, H_8, H_9), 8.03 (m, 1 H, H_{10},] and 2-(methylsulfinyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**4r**; 3.2 g): mp 115–117 °C; IR 1625 cm^{-1} (C=O); ^1H NMR 2.82 (s, 3 H, CH_3), 3.33 (m, 2 H, Ar CH_2), 4.38 (m, 2 H, CH_2N), 7.05–7.55 (m, 5 H, Ar), 8.10 (m, 1 H, H_{10}).

2- and 3-(Methylsulfonyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4t,u; Scheme IV). The 2-methylsulfinyl derivative **4r** (2.55 g, 10 mmol) was oxidized with H_2O_2 (30%, 2 mL) in HOAc (50 mL). After stirring at room temperature for 18 h, the reacting mixture was heated to 50 °C for 2 h to complete the reaction. The resulting mixture was poured into a NaOH solution from which the final product crystallized. The crystals were filtered off, washed with H_2O, and air-dried to give 2.3 g (85%) of compound **4t**; mp 196–197 °C; IR 1625 (C=O), 1300, 1135 cm^{-1} (SO_2); ^1H NMR δ 3.10 (s, 3 H, CH_3), 3.28 (m, 2 H, Ar CH_2), 4.44 (m, 2 H, CH_2N), 7.10–7.70 (m, 5 H, Ar), 8.17 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.08; S, 11.65. Found: C, 61.30; H, 4.91; N, 4.90; S, 11.79.

Compound **4u** was similarly prepared from **4s** in 63% yield: mp 152–154 °C; IR 1630 (C=O), 1310, 1130 cm^{-1} (SO_2); ^1H NMR δ 3.10 (s, 3 H, CH_3), 3.33 (m, 2 H, Ar CH_2), 4.70 (m, 2 H, CH_2N), 6.83 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.05–7.50 (m, 4 H, H_1, H_7, H_8, H_9), 8.00 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.08; S, 11.65. Found: C, 61.20; H, 4.83; N, 4.94; S, 11.65.

2- and 3-[(Trifluoromethyl)thio]-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4v,w; Scheme IV). To a solution of **4a** (10 g, 0.05 mol) in alcohol-free $CHCl_3$ (75 mL) and pyridine (20 mL) was added trifluoromethane sulfenyl chloride (20 g, 0.16 mol). The reaction mixture was stirred at room temperature for 2 h. It was then poured into H_2O (100 mL), and the organic layer was washed successively with 1 N HCl, 5% $NaHCO_3$, and H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with 25% ether in hexane, to yield firstly 8.1 g (54%) of the 3-(trifluoromethyl)thio isomer **4w** [mp 94–95 °C; IR 1622 (C=O), 1155, 1130, 1100 cm^{-1} (SCF_3); ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.48 (m, 2 H, CH_2N), 6.70 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.10–7.50 (m, 4 H, H_1, H_7, H_8, H_9), 8.10 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{10}F_3NOS$: C, 56.94; H, 2.73; F, 19.30; N, 4.74; S, 10.86. Found: C, 56.73; H, 2.71; F, 18.98; N, 4.86; S, 10.43] and secondly 4.2 g (28%) of the 2-(trifluoromethyl)thio isomer **4v** [mp 77–78 °C; IR 1625 (C=O), 1140, 1110 cm^{-1} (SCF_3); ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.37 (m, 2 H, CH_2N), 7.03 (d, 1 H, H_3, $J_{3,1}$ = 2 Hz), 7.43 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 7.10–7.40 (m, 3 H, H_7, H_8, H_9), 8.10 (m, 1 H, H_{10}). Anal. Calcd fro $C_{14}H_{10}F_3NOS$: C, 56.94; H, 2.73; F, 19.30; N, 4.74; S, 10.86. Found: C, 56.69; H, 2.77; F, 19.07; N, 4.81; S, 10.43.

3-Chloro- and 1,3-Dichloro-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4x,y; Scheme IV). To a solution of **4a** (756 mg, 3.8 mmol) in $CHCl_3$ (5 mL) was added SO_2Cl_2 (0.453 mL, 5.6 mmol) and the mixture was stirred for 30 min. The reaction mixture was diluted with $CHCl_3$ (50 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue (1 g) was purified by preparative TLC, eluting with toluene, to yield 400 mg (45%) of the monochloro derivative **4x** [mp 69–70 °C; IR 1620 cm^{-1} (C=O); ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.30 (m, 2 H, CH_2N), 6.27 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.10–7.50 (m, 4 H, H_1, H_7, H_8, H_9), 8.03 (m, 1 H, H_{10})] 350 mg (34%) of the 1,3-dichloro derivative **4y** [mp 87–88 °C; IR 1615 cm^{-1} (C=O); ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.33 (m, 2 H, CH_2N), 6.30 (s, 1 H, H_2), 7.10–7.50 (m, 3 H, H_7, H_8, H_9), 8.07 (m, 1 H, H_{10}). Anal. Calcd for $C_{13}H_9Cl_2NO$: C, 58.65; H, 3.40; Cl, 26.60; N, 5.25. Found: C, 58.85; H, 3.36; Cl, 26.31; N, 5.47.

When **4a** (300 mg, 1.5 mmol) was added to a 1 M solution of 2-propanesulfenyl chloride in CCl_4 (5 mL) and kept at room temperature for 20 h, there was obtained after evaporation and purification by chromatography (silica gel, benzene) 250 mg (71%) of pure 3-chloro derivative **4x**. IR and NMR spectral data were identical with those described above; mass spectrum, *m/e* 231 (M^+).

3-Bromo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4z; Scheme IV). $AlCl_3$ (1.5 g, 11 mmol) was added to a cooled solution of **4a** (1.97 g, 10 mmol) in $CHCl_3$ (45 mL) and the mixture was stirred at 0 °C for 15 min. A solution of Br_2 (1.6 g, 10 mmol) in $CHCl_3$ (5 mL) was then added and the mixture was stirred for 15 min in the cold. The reaction mixtures was poured into an ice–water mixture and decanted, and the aqueous phase was washed with $CHCl_3$. The organic layers were combined, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The resulting oily residue (2.8 g) was purified by chromatography [silica gel, EtOAc/benzene (5:95)], affording 1.42 g (51%) of pure product **4z**: mp 80–82 °C; IR 1620 cm^{-1} (C=O); ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.32 (m, 2 H, CH_2N), 6.30 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.05–7.55 (m, 4 H, H_1, H_7, H_8, H_9), and 8.04 (m, 1 H, H_{10}). Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.56; H, 3.63; Br, 28.94; N, 5.07. Found: C, 56.54; H, 3.65; Br, 28.84; N, 5.05.

3-Cyano-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4aa; Scheme V). A mixture of **4a** (7.0 g, 0.036 mol) and KCN (5 g, 0.077 mol) in MeOH (400 mL) was irradiated with a 450-W lamp for 8 h. The solvent was stripped off and the resulting residue was taken up in H_2O and $CHCl_3$. After decantation, the organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, affording a semisolid residue, which was triturated with ether and filtered, affording 4.16 g of 3-cyano-11-hydroxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (**14**). A second crop (0.87 g) was obtained from the filtrate to give a total yield of 63%. An analytical sample was recrystallized from benzene/hexane: mp 146–148 °C; IR 3450 (OH), 2210 cm^{-1} (CN); ^1H NMR δ 2.50 (br s, 1 H, OH, exchangeable), 2.80–4.70 [m, 4 H, $(CH_2)_2$], 5.73 (s, 1 H, CH), 6.15 (d, 1 H, H_1, $J_{2,1}$ = 4 Hz), 6.63 (d, 1 H, H_2, $J_{1,2}$ = 4 Hz), 7.17 (s, 4 H, Ar). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.04; H, 5.05; N, 12.47.

A solution of **14** (4.0 g, 0.018 mol) in CH_2Cl_2 (100 mL) was

(37) J. L. Wood and L. F. Fieser, *J. Am. Chem. Soc.*, **63**, 2323 (1941).

(38) **Note Added in Proof**: The utilization of a number of these ketones for certain medicinal chemical purposes has now been described: (a) D. C. Remy, S. F. Britcher, P. S. Anderson, P. C. Bélanger, Y. Girard, and B. V. Clineschmidt, *J. Med. Chem.*, **25**, 231 (1982); (b) D. C. Remy, S. F. Britcher, S. W. King, P. S. Anderson, C. A. Hunt, W. C. Randall, P. Bélanger, J. G. Atkinson, Y. Girard, C. S. Rooney, J. J. Fuentes, J. A. Totaro, J. L. Robinson, E. A. Risely, and M. Williams, *ibid.*, **26**, 974 (1983).

stirred at room temperature with pyridinium chlorochromate (6.0 g, 0.028 mol) for 3 h. The reaction mixture was diluted with ether (100 mL) and filtered through Florisil, and the solid obtained after evaporation to dryness was chromatographed on silica gel, eluting with EtOAc/benzene (5:95). The final product **4aa** (2.82 g) was obtained in 70% yield. An analytical sample was recrystallized from MeOH: mp 130–131 °C; IR 2100 (CN), 1625 cm^{-1} (C=O); ^1H NMR δ 3.35 (m, 2 H, Ar CH_2), 3.46 (m, 2 H, CH_2N), 6.73 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.05–7.55 (m, 4 H, H_1, H_7, H_8, H_9), 8.00 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.55; H, 4.65; N, 12.69.

1- and 3-(Trifluoromethyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones (4bb,cc; Scheme VI). To a solution of CF_3I (30 g, 0.15 mol) and pyridine (20 mL) in CH_3CN (300 mL) was added **4a** (8.9 g, 0.045 mol) and the solution irradiated with a 450-W lamp for 18 h. The mixture was evaporated to dryness and upon ether treatment the precipitate of pyridine hydroiodide was filtered off. The filtrate was concentrated and taken up in a solution of CF_3I (25 g, 0.13 mol) in pyridine/CH_3CN as above. After irradiation for an additional 12 h, followed by the above workup, a crystalline residue containing a mixture of starting material and two different trifluoromethylated derivatives was obtained. The separation of the components was carried out by chromatography (silica gel, benzene), affording, firstly 4.5 g (50%) of the 3-trifluoromethylated compound **4bb** [mp 90–93 °C; IR 1630 cm^{-1} (C=O); ^1H NMR δ 3.33 (m, 2 H, Ar CH_2), 4.40 (m, 2 H, CH_2N), 6.60 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 7.05–7.55 (m, 4H, H_1, H_7, H_8, H_9), and 8.07 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{10}F_3NO$: C, 63.40; H, 3.77; F, 21.51; N, 5.28. Found: C, 63.20; H, 3.60; F, 21.35; N, 5.20], secondly 0.4 g (5%) of the 1-trifluoromethylated derivative **4cc** [mp 102–103 °C; IR 1635 cm^{-1} (C=O); ^1H NMR δ 3.28 (m, 2 H, Ar CH_2), 4.36 (m, 2 H, CH_2N), 6.50 (d, 1 H, H_2, $J_{2,3}$ = 2 Hz), 6.70 (d, 1 H, H_3, $J_{3,2}$ = 2 Hz), 7.05–7.55 (m, 3 H, H_7, H_8, H_9), 8.16 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{10}F_3NO$: C, 63.40; H, 3.77; F. 21.51; N, 5.28. Found: C, 63.27; H, 3.74; F, 21.33; N, 5.19], and finally 2.0 g (22%) of the starting material. In another preparation, in which a larger excess of CF_3I was used, a small amount of 1,3-bis(trifluoromethyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**4dd**) was observed as deduced from the mass spectrum, *m/e* 333 (M^+), and the NMR spectrum, which showed a singlet for H_2 at δ 6.90.

2-Formyl-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4ee). 2-Cyano-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**4b**; 10 g, 45 mmol) and nickel–aluminum alloy (10 g) were added to 75% formic acid[28] (100 mL) and brought to reflux for 90 min. The suspension was filtered, the solid was washed with EtOH, and the filtrate was stripped to dryness. The residue was taken up in $CHCl_3$ (500 mL), and the resulting solution was washed with NaOH (2N) and H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel, eluting with $CHCl_3$, to yield 8.7 g (81%) of **4ee**: mp 135–136 °C; IR 1680 cm^{-1} (C=O; ^1H NMR δ 3.33 (m, 2 H, Ar CH_2), 4.40 (m, 2 H, CH_2), 7.10–7.55 (m, 4 H, H_3, H_7, H_8, H_9), 7.60 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 8.03 (m, 1 H, H_{10}), 9.67 (s, 1 H, CHO). Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.31; H, 5.3; N, 6.14.

2-Carboxamido-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4ff). Compound **4b** (30 g, 0.135 mol) was suspended in HOAc (100 mL) and concentrated HCl (100 mL) and then refluxed for a period of 2 h. The resulting solution was cooled and poured into H_2O. The crystals were filtered, washed with H_2O, and air-dried to yield 27 g (88%) of **4ff**: mp 225–228 °C; IR 1660, 1620 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 3.30 (m, 2 H, Ar CH_2), 4.40 (m, 2 H, CH_2N), 7.00 (br s, 2 H, NH_2, exchangeable), 7.40 (d, 1 H, H_3, $J_{3,1}$ = 2 Hz), 7.10–7.60 (m, 4 H, H_1, H_7, H_8, H_9), 8.00 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.26; H, 5.07; N, 10.75.

2-Carboxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4gg). Compound **4ff** (27 g, 0.112 mol) was dissolved in 50% H_2SO_4 (300 mL) and $NaNO_2$[29] (25 g, 0.36 mol) in H_2O (75 mL) was added dropwise over 30 min while the reaction mixture was maintained at 50 °C. The suspension was filtered, washed with H_2O, and air-dried to give 24 g (89%) of **4gg**: mp 289–293 °C; IR 1665 (CO_2H), 1620 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 3.33 (m, 2 H, Ar CH_2), 4.47 (m, 2 H, CH_2N), 7.10–7.60 (m, 4 H, H_3, H_7, H_8, H_9), 7.77 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), and 8.03 (m, 1 H, H_{10}). Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.80. Found: C, 69.97; H, 4.49; N, 6.03.

2-Carbomethoxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4hh). Acid **4gg** (25.5 g, 0.106 mol) was added to a saturated MeOH solution of HCl (300 mL) and the mixture refluxed for 4 h. The volatiles were removed under vacuum, and the residue was taken up in CH_2Cl_2 (300 mL). The organic layer was washed with 2 N NaOH and brine and dried (Na_2SO_4). Concentration to a small volume left a residue that was triturated with ether. The solid was filtered and air-dried to yield 23.5 g (87%) of **4hh**: mp 122–123 °C; IR 1710 (CO_2CH_3), 1625 cm^{-1} (C=O); ^1H NMR δ 3.37 (m, 2 H, Ar CH_2), 3.87 (s, 3 H, CH_3), 4.43 (m, 2 H, CH_2N), 7.05–7.55 (m, 4 H, H_3, H_7, H_8, H_9), 7.73 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 8.17 (m, 1 H, H_{10}). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.19; H, 5.25; N, 5.46.

2-(Dimethylcarboxamido)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4ii). Compound **4gg** (24 g, 0.10 mol) in $SOCl_2$ (100 mL) was refluxed for 15 min. The volatiles were removed under vacuum, leaving a residue that was triturated in ether. The resulting solid was filtered and air-dried to yield 23 g (89%) of 2-(chlorocarbonyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*]-[3]benzazepin-11-one: mp 147–148.5 °C. Without further purification, it was taken up in CH_2Cl_2 (100 mL) and gaseous dimethylamine was bubbled in for a period of 1 h. The reaction mixture was poured into H_2O, and the organic layer was washed with brine and dried (Na_2SO_4). After evaporation, the residue was triturated with ether to afford 22.3 g (94%) of **4ii** as a brown solid, which after crystallization from ether/hexane melted at 148–149 °C: IR 1610, 1590 cm^{-1} (C=O); ^1H NMR δ 3.07 (s, 6 H, $(CH_3)_2$), 3.33 (m, 2 H, Ar CH_2), 4.48 (m, 2 H, CH_2N), 7.20–7.70 (m, 5 H, Ar), 8.00 (m, 1 H, H_{10}). Anal. Calcd for $C_{16}H_{16}N_2O_2 \cdot {}^1/_2H_2O$: C, 69.30; H, 6.18; N, 10.10. Found: C, 69.74; H, 5.83; N, 10.07.

9-Amino-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4jj). A suspension of **4k** (20.5 g, 0.085 mol) in MeOH (300 mL) was hydrogenated over 10% Pd/C (1.0 g) until uptake of H_2 had ceased. MeOH (300 mL) was added to the resulting mixture and heated to dissolve the final product, which had crystallized out during the hydrogenation. The catalyst was then filtered off and the filtrate evaporated to dryness. The residue was triturated with the minimum amount of ether and filtered, affording 17.5 g (97%) of amino derivative **4jj**: mp 166–167 °C; IR 3440, 3340 (NH_2), 1625 cm^{-1} (C=O); ^1H NMR δ 3.17 (m, 2 H, Ar CH_2), 3.67 (s, 2 H, NH_2, exchangeable), 4.27 (m, 2 H, CH_2N), 6.18 (dd, 1 H, H_2, $J_{2,1}$ = 4.2 Hz, $J_{2,3}$ = 1.9 Hz), 6.72 (dd, 1 H, H_8, $J_{8,7}$ = 8 Hz, $J_{8,10}$ = 2.7 Hz), 6.82 (t, 1 H, H_3, $J_{3,1}$ = $J_{3,2}$ = 1.9 Hz), 6.95 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 7.35 (dd, 1 H, H_1, $J_{1,2}$ = 4.2 Hz, $J_{1,3}$ = 1.9 Hz), 7.43 (d, 1 H, H_{10}, $J_{10,8}$ = 2.7 Hz). Anal. Calcd for $C_{13}H_{12}NO$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.42; H, 5.74; N, 13.18.

9-Acetamido-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4kk). A mixture of acetic anhydride (0.8 g, 8 mmol) and **4jj** (1.06 g, 5 mmol) was heated on a steam bath for 5 min to obtain a clear solution. After evaporation, the residue was dissolved in $CHCl_3$, washed successively with dilute NaOH and H_2O, and then dried (Na_2SO_4) and reevaporated to dryness. Subsequent trituration with the minimum amount of ether and filtration afforded 1.15 g (90%) of desired product **4kk**: mp 169–170 °C; IR 3300 (NH) 1675, 1610 cm^{-1}(C=O); ^1H NMR δ 2.15 (s, 3 H, CH_3), 3.25 (m, 2 H, Ar CH_2), 4.30 (m, 2 H, CH_2N), 6.17 (dd, 1 H, H_2, $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.80 (t, 1 H, H_3, $J_{3,1}$ = $J_{3,2}$ = 2 Hz), 7.08 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 7.30 (dd, 1 H, H_1, $J_{1,2}$ = 4 Hz, $J_{1,3}$ = 2 Hz), 7.90 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz), 8.15 (dd, 1 H, H_8, $J_{8,7}$ = 8 Hz, $J_{8,10}$ = 2 Hz), 8.77 (br s, 1 H, NH, exchangeable). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.60; H, 5.43; N, 11.14.

9-Chloro-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4ll). A solution of $NaNO_2$ (3.45 g, 0.05 mol) in H_2O (5 mL) was added dropwise to a cooled suspension of **4jj** (10.6 g, 0.05 mol) in 10 N HCl (500 mL). A solution was obtained after stirring for 30 min at 0 °C. A mixture of pulverized CuCl (5.5 g, 0.056 mol) and $CuCl_2 \cdot 2H_2O$ (9.5 g, 0.056 mol) was then added protionwise to the diazonium salt solution from which a solid precipitated. The reaction mixture was then allowed to stir at room temperature for 20 min and then heated with caution at 50 °C. A strong evolution of gas (N_2) was observed. After 15 min

at 50 °C, the reaction mixture was cooled, ice was added, and the mixture was extracted with $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, leaving 11.4 g of crude product. Purification of chromatography [silica gel, EtOAc/benzene (5:95)] yielded 7.2 g (62%) of pure **4ll**: mp 93–94 °C; IR 1610 cm^{-1} (C=O); ^1H NMR δ 3.27 (m, 2 H, Ar CH_2), 4.32 (m, 2 H, CH_2N), 6.20 (dd, 1 H, H_2, $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.87 (t, 1 H, H_3, $J_{3,1}$ = $J_{3,2}$ = 2 Hz), 7.12 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 7.22–7.50 (m, 2 H, H_8, H_1), 8.13 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz). Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.33; H, 4.32; Cl, 15.30; N, 6.04. Found: C, 67.17; H, 4.05; Cl, 15.18; N, 6.12.

When the above reaction was carried out with CuCl and dilute HCl (0.2 N), a mixture of desired product and dimer was obtained. Separation by chromatography [silica gel, EtOAc/benzene (5:95)] afforded successively the chloro derivative **4ll**, mp 88–90 °C in 22% yield, and 9-chloro-2-(11-oxo-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-9-yl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**22**) in 20% yield: mp 205–212 °C; IR 1625 cm^{-1} (C=O); ^1H NMR δ 3.30 (m, 4 H, Ar CH_2 and Ar CH_2'), 4.35 (m, 4 H CH_2N and $CH_2'N$), 6.22 (dd, 1 H, H_2', $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.35 (d, 1 H, H_2, $J_{2,1}$ = 4 Hz), 6.85 (t, 1 H, H_3', $J_{3,1}$ = $J_{3,2}$ = 2 Hz), 7.07 (d, 1 H, H_7', $J_{7,8}$ = 8 Hz), 7.12–7.57 (m, 5 H, H_1, H_1', H_7, H_8, H_8'), 8.03 and 8.13 (2 d, 2 H, H_{10} and H_{10}', $J_{10,8}$ = 2 Hz); mass spectrum, *m/e* 426 (M^+). Anal. Calcd for $C_{26}H_{19}ClN_2O_2$: C, 73.24; H, 4.46; Cl, 8.31; N, 6.57. Found: C, 73.25; H, 4.89; Cl, 7.87; N, 5.95.

9-Cyano-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4mm). A solution of $NaNO_2$ (4.0 g, 0.057 mol) in H_2O (60 mL) was added dropwise to a cooled suspension of **4jj** (12 g, 0.057 mol) in 1 N HCl (240 mL). After 10 min at 0 °C, the diazonium salt solution was neutralized by the addition of K_2CO_3. This neutral solution was then added dropwise to a cooled solution of CuCN (12 g, 0.13 mol) and KCN (18 g, 0.28 mol) in H_2O (300 mL). During the addition, gas evolution (N_2) and a precipitate were observed. The addition completed, the reaction mixture was stirred at 0 °C for an additional hour and the precipitate collected by filtration. The solid was dissolved in $CHCl_3$, washed with H_2O, treated with charcoal, dried (Na_2SO_4), and evaporated to dryness, affording 12 g of crude product. Purification by chromatography [silica gel, eluting successively with EtOAc/benzene (5:95, 10:90, and then 15:85)] gave 7.85 g (62%) of pure compound **4mm**: mp 127–128 °C; IR 2215 (CN), 1625 cm^{-1} (C=O); ^1H NMR δ 3.33 (m, 2 H, Ar CH_2), 4.33 (m, 2 H, CH_2N), 6.20 (dd, 1 H, H_2, $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.86 (t, 1 H, H_3, $J_{3,1}$ = $J_{3,2}$ = 2 Hz), 7.27 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 7.30 (dd, 1 H, H_1, $J_{1,2}$ = 4 Hz, $J_{1,3}$ = 2 Hz), 7.62 (dd, 1 H, H_8, $J_{8,7}$ = 8 Hz, $J_{8,10}$ = 2 Hz), 8.33 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.54; H, 4.63; N, 12.65.

9-Carboxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4nn). A mixture of **4mm** (300 mg, 1.35 mmol), KOH (180 mg, 5.0 mmol), EtOH (3 mL), and H_2O (3 mL) was refluxed for 2 h. The reaction was cooled and acidified with 3 N HCl. The precipitate was collected, washed with H_2O, and air-dried to yield 300 mg (92%) of **4nn**: mp 270–272 °C; IR 1680 cm^{-1} (CO_2H); ^1H NMR (Me_2SO-d_6) δ 3.38 (m, 2 H, Ar CH_2), 4.45 (m, 2 H, CH_2N), 6.23 (dd, 1 H, H_2, $J_{2,1}$ = $J_{2,3}$ = 3 Hz), 7.24 (m, 2 H, H_1, H_3), 7.47 (d, 1 H, H_7, $J_{7,8}$ = 8 Hz), 8.02 (dd, 1 H, $H_{8,7}$ = 8 Hz, $J_{8,10}$ = 2 Hz), 8.65 (d, 1 H, H_{10}, $J_{10,8}$ = 2 Hz). Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.40, H, 4.60; N, 5.74.

9-[(Trifluoromethyl)thio]-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (4oo). A mixture of **41** (2.40 g, 7.43 mmol), copper electrolytic dust (5.40 g, 80.9 mmol), bis[(trifluoromethyl)thio]mercury (8.98 g, 22.3 mmol), and DMF (20 mL) was heated with stirring on the steam bath for 5 h. The reaction mixture was cooled and benzene (75 mL) added. Then 10% NaOH (50 mL) was added dropwise. After stirring at room temperature 1 h, the mixture was filtered through Celite. The inorganic residues were washed with benzene. The filtrate and washings were combined, and the benzene phase was separated. The benzene was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to yield 2.0 g (90%) of **4oo**: mp 81–83 °C; ^1H NMR δ 3.30 (m, 2 H, Ar CH_2), 4.33 (m, 2 H, CH_2N), 6.23 (dd, 1 H, H_2, $J_{2,1}$ = 4 Hz, $J_{2,3}$ = 2 Hz), 6.83 (t, 1 H, H_3, $J_{3,1}$ = $J_{3,2}$ = 2 Hz), 7.23 (d, 1 H, H_7, $J_{7,8}$ = 10 Hz), 7.33 (dd, 1 H, H_1, $J_{1,2}$ = 4 Hz, $J_{1,3}$ = 2 Hz), 7.70 (dd, 1 H, H_8, $J_{8,7}$ = 10 Hz, $J_{8,10}$ = 3 Hz), 8.40 (d, 1 H, H_{10}, $J_{10,8}$ = 3 Hz); ^{19}F NMR δ 41.9 (s, CF_3). Anal. Calcd for $C_{14}H_{10}F_3NOS$: C, 56.56; H, 3.90; F, 19.17; N, 4.71; S, 10.78. Found: C, 56.60; H, 3.68; F, 12.96; M, 4.82; S, 10.71. Upon repeated analysis, fluorine was inexplicably far off, although the material was excellent by NMR and GC analysis showed that it was 96% pure.

2-Carboxy- and 2-Carbomethoxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (19). A. From 4b. Compound **4b** (20 g, 0.09 mol) and KOH (10 g, 0.18 mol) in ethylene glycol (100 mL) were heated overnight at 150 °C. The reaction mixture was poured into H_2O (300 mL) and extracted several times with $CHCl_3$. The aqueous layer was acidified with 6 N HCl and the solid was filtered, washed with H_2O, and air-dried to yield 17.4 g of a mixture of **4gg** and **19**: mp 215–220 °C dec.

A sample (500 mg) dissolved in MeOH (10 mL) was treated with diazomethane to yield a mixture of methyl esters, which were separated by preparative TLC, developing with EtOAc/toluene (1:4). The band R_f 0.6 yielded 270 mg of the methyl ester of **19**: mp 124–126 °C; IR 1700 cm^{-1} (CO_2CH_3); ^1H NMR δ 3.20 (m, 2 H, Ar CH_2), 3.73 (s, 3 H, CH_3), 4.00 (s, 2 H, CH_2), 4.20 (m, 2 H, CH_2N), 6.33 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 7.13 (m, 5 H, Ar). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.46, N, 5.78.

Base hydrolysis of this ester yielded purified acid **19**, mp 217–219 °C dec, identical with a sample prepared as described below. The band R_f 0.4 yielded 134 mg of **4hh**, mp 125–126 °C, hydrolysis of which yielded acid **4gg**, mp 288 °C dec.

B. From 4gg. A mixture of **4gg** (0.5 g, 2 mmol), hydrazine (85%, 0.5 g), and KOH (0.5 g) was dissolved in ethylene glycol (5 mL) and heated at 220 °C for 4 h. The reaction mixture was poured into H_2O, acidified with 6 N HCl, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated to a small volume, which was triturated in ether. The solid was filtered, washed with ether, and air-dried to afford 382 mg (81%) of **19**: mp 217–219 °C; IR 3200–2500 (OH), 1670 cm^{-1} (CO_2H); ^1H NMR (Me_2SO-d_6) δ 3.17 (m, 2 H, Ar CH_2), 4.00 (s, 2 H, CH_2), 4.20 (m, 2 H, CH_2N), 6.17 (d, 1 H, H_1, $J_{1,3}$ = 2 Hz), 7.17 (s, 5 H, Ar), 11.60 (br s, 1 H, OH, exchangeable). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.98; H, 5.95; N, 5.75.

Photochemical Trifluoromethylation of Heterocycles (Table III). A solution of *N*-benzylpyrrole (3.0 g, 19 mmol), CF_3I (10 g, 51 mmol), and pyridine (5 mL) in CH_3CN (50 mL) was irradiated with a 450-W medium-pressure Hanovia lamp for 18 h. The resulting mixture was concentrated under vacuum and partitioned betweens ether and H_2O. After decantation, the ethereal layer was washed successively with a solution of $Na_2S_2O_3$ and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to dryness, leaving 3.9 g of an oily residue that was chromatographed on silica gel, eluting with hexane, to afford 125 mg (2.2%) of *N*-benzyl-2,5-bis(trifluoromethyl)pyrrole [^1H NMR δ 5.35 (s, 2 H, CH_2), 6.60 (s, 2 H, pyrrole protons), 6.7–7.4 (m, 5 H, Ar); high-resolution mass spectrum, *m/e* 293.0634 (M^+; $C_{13}H_9F_6N$ requires 293.0639)], 2.43 g (57%) of *N*-benzyl-2-(trifluoromethyl)pyrrole [^1H NMR δ 5.15 (s, 2 H, CH_2), 6.10 (t, 1 H, H_4, (pyrrole), $J_{4,3}$ = $J_{4,5}$ = 3.5 Hz), 6.60 (m, 2 H, H_3, H_5), 6.8–7.4 (m, 5 H, Ar); high-resolution mass spectrum, *m/e* 225.0767 (M^+; $C_{12}H_{10}F_3N$ requires 225.0765). Anal. Calcd for $C_{12}H_{10}F_3N$: C, 63.99; H, 4.48; F, 25.31; N, 6.22. Found: C, 64.20; H, 4.38; F, 25.12; N, 6.40], and finally 480 mg (16%) of the starting material.

When *N*-*p*-tolylpyrrole (5.0 g, 32 mmol) was irradiated in the presence of CF_3I (15 g, 77 mmol) under similar conditions, there was obtained after chromatography on silica gel (hexane) 4.2 g (60% of *N*-*p*-tolyl-2-(trifluoromethyl)pyrrole [^1H NMR δ 2.33 (s, 3 H, CH_3), 6.15 (t, 1 H, H_4 (pyrrole), $J_{4,3}$ = $J_{4,5}$ = 3.5 Hz), 6.7 (m, 2 H, H_3, H_5), 7.15 (s, 4 H, Ar); high-resolution mass spectrum, *m/e* 225.0753 (M^+; $C_{12}H_{10}F_3N$ requires 225.0765)] and 1.7 g (34%) of the starting material.

Under similar conditions, the trifluoromethylation of *N*-(trimethylsilyl)indole (5.0 g, 16 mmol) for 48 h afforded after methanolic hydrolysis and chromatography on silica gel (10% ETOAc/hexane) 1.5 g (30%) of 2-(trifluoromethyl)indole, mp 107–108 °C (lit.[24] mp 102 °C), followed by 1.1 g (35%) of indole and 750 mg (15%) of 3-(trifluoromethyl)indole, mp 109–110 °C (lit.[24] mp 110 °C).

Trifluoromethylation of 2-nonylfuran (1.9 g, 10 mmol) for 40 h yielded after chromatography (hexane) 1.45 g of a 60:40 mixture

(determined by GC) of 2-nonyl-5-(trifluoromethyl)furan and the starting material. A sample was purified by GC: ^{1}H NMR δ 0.6–2.0 n, 17 H, C_8H_{17}), 2.65 (t, 2 H, CH_2, J = 7 Hz), 6.0 (d, 1 H, H_3, $J_{3,4}$ = 4 Hz), 6.7 (m, 1 H, H_4); high-resolution mass spectrum, m/e 262.1543 (M^+; $C_{14}H_{21}F_3O$ requires 262.1542).

Similarly, 2-nonylthiophene (500 mg, 2.4 mmol) was trifluoromethylated for 26 h to afford after chromatography (hexane) 340 mg of a 70:25:5 mixture (determined by GC) of 2-nonyl-5-(trifluoromethyl)thiophene, starting material, and 3(4),5-bis-(trifluoromethyl)-2-nonylthiophene. A sample was purified by GC: ^{1}H NMR δ 0.6–2.0 (m, 17 H, C_8H_{17}), 2.82 (t, 2 H, CH_2, J = 7 Hz), 6.75 (m, 1 H, H_3), 7.25 (m, 1 H, H_4); high-resolution mass spectrum, m/e 278.1280 (M^+; ($C_{14}H_{21}F_3S$ requires 278.1245); ditrifluoromethylated derivative, high-resolution mass spectrum, m/e 346.1163 (M^+; $C_{15}H_{20}F_6S$ requires 346.1137).

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Registry No. **4a**, 62541-43-9; **4b**, 62541-38-2; **4c**, 62541-40-6; **4d**, 62541-39-3; **4e**, 69624-13-1; **4f**, 62541-37-1; **4g**, 62541-42-8; **4h**, 86307-67-7; **4i**, 69624-14-2; **4j**, 86288-45-1; **4k**, 62541-68-8; **4l**, 62541-64-4; **4m**, 62541-56-4; **4n**, 62541-57-5; **4o**, 62541-55-3; **4p**, 86288-46-2; **4q**, 62541-58-6; **4r**, 86288-47-3; **4s**, 86288-48-4; **4t**, 86288-49-5; **4u**, 86288-50-8; **4v**, 62541-52-0; **4w**, 62541-51-9; **4x**, 86288-51-9; **4y**, 86288-52-0; **4z**, 86288-53-1; **4aa**, 62541-41-7; **4bb**, 62541-53-1; **4cc**, 62541-54-2; **4dd**, 86307-68-8; **4ee**, 62541-45-1; **4ff**, 62541-46-2; **4gg**, 62541-47-3; **4hh**, 62541-50-8; **4ii**, 62541-49-5; **4jj**, 62541-69-9; **4kk**, 86288-54-2; **4ll**, 69624-15-3; **4mm**, 69624-17-5; **4nn**, 86288-55-3; **4oo**, 62541-65-5; **6.1a**, 73259-61-7; **6.1b**, 66491-00-7; **6.1c**, 86307-69-9; **6.1d**, 86288-56-4; **6.1e**, 86288-57-5; **6.1g**, 86288-58-6; **6.1h**, 72791-94-7; **6.1i**, 86288-59-7; **6.1j**, 86288-60-0; **6.1k**, 86288-61-1; **6.2a**, 62541-29-1; **6.2b**, 66491-01-8; **6.2c**, 62569-72-6; **6.2d**, 86288-62-2; **6.2e**, 69624-08-4; **6.2f**, 62541-35-9; **6.2g**, 62541-32-6; **6.2i**, 69624-09-5; **6.2j**, 86288-63-3; **6.2k**, 86288-64-4; **6.3a**, 86288-65-5; **6.3b**, 66491-02-9; **6.3c**, 86288-66-6; **6.3d**, 86288-67-7; **6.3e**, 86288-68-8; **6.3f**, 62541-36-0; **6.3g**, 86288-69-9; **6.3i**, 86288-70-2; **6.3j**, 86288-71-3; **6.3k**, 86288-72-4; **11b**, 62541-66-6; **11c**·HCl, 62541-62-2; **12b**, 62541-67-7; **12c**, 62541-63-3; **14**, 86288-73-5; **19**, 86288-74-6; **19** methyl ester, 86288-75-7; **22**, 86288-76-8; CF_3I, 2314-97-8; 2-carbomethoxypyrrole, 1193-62-0; 2-carbomethoxy-4-cyanopyrrole, 937-18-8; 2-carbomethoxy-4-chloropyrrole, 1194-96-3; 2-carbomethoxy-4-bromopyrrole, 934-05-4; 2-carbomethoxy-4-nitropyrrole, 13138-74-4; 2-carbomethoxy-3,4,5-tribromopyrrole, 1198-67-0; phenethyl bromide, 103-63-9; phenethyl tosylate, 4455-09-8; 2-*p*-tolylethylamine, 3261-62-9; *p*-(methylthio)phenethyl mesylate, 86288-77-9; *p*-phthalimidophenethyl mesylate, 86288-78-0; methyl 2,5-dimethoxytetrahydrofuran-2-carboxylate, 39658-49-6; *N*-*trans*-styrylpyrrole-2-carboxylic acid, 34600-57-2; β-phenethyl isothiocyanate, 2257-09-2; 1-thio-3,4-dihydroisocarbostyryl, 6552-60-9; 3,4-dihydroisocarbostyryl, 1196-38-9; 7-nitro-3,4-dihydroisocarbostyryl, 22245-96-1; 2,7-dinitro-3,4-dihydroisocarbostyryl, 86288-79-1; 2,5-dimethoxytetrahydrofuran, 696-59-3; 7-amino-3,4-dihydroisocarbostyryl, 66491-03-0; 7-iodo-3,4-dihydroisocarbostyryl, 66491-04-1; valeryl chloride, 638-29-9; dimethylsulfamoyl chloride, 13360-57-1; thiocyanogen, 505-14-6; 2-thiocyanato-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-80-4; 3-thiocyanato-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-81-5; 2-(methylthio)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]-benzazepin-11-one, 86288-82-6; 3-(methylthio)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-83-7; trifluoromethanesulfenyl chloride, 421-17-0; 2-(chlorocarbonyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 62541-48-4; *N*-benzylpyrrole, 2051-97-0; *N*-benzyl-2,5-bis(trifluoromethyl)pyrrole, 86288-84-8; *N*-benzyl-2-(trifluoromethyl)pyrrole, 86288-85-9; *N*-*p*-tolylpyrrole, 827-60-1; *N*-*p*-tolyl-2-(trifluoromethyl)pyrrole, 86288-86-0; *N*-(trimethylsilyl)indole, 17983-42-5; 2-(trifluoromethyl)indole, 51310-54-4; 3-(trifluoromethyl)indole, 51310-55-5; 2-nonylfuran, 68532-53-6; 2-nonyl-5-(trifluoromethyl)furan, 86288-87-1; 2-nonylthiophene, 57754-07-1; 2-nonyl-5-(trifluoromethyl)thiophene, 86288-88-2; bis(trifluoromethyl)-2-nonylthiophene, 86307-66-6.

Synthesis of 2-, 3-, and 9-Substituted 11-Oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines

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Syntheses of nuclear-substituted 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines by three reaction sequences are described. The first and most successful route involves an internal Friedel–Craft cycliacylation of substituted *N*-(*Z*)-styrylpyrrole-2-carboxylic acids, the latter obtained via photoisomerization of the easily prepared *E* acids. The second path has as its key steps the cyclization of the acid chlorides of substituted *N*-(α,β-dichlorophenethyl)pyrrole-2-carboxylic acids followed by a chromous chloride reduction to generate the 5,6-double bond. Another route, employed with only limited success, involves cyclization of the acid chlorides of substituted *N*-(β-chlorophenethyl)pyrrole-2-carboxylic acids, followed by base-catalyzed elimination of HCl to form the 5,6-double bond. These substituted ketones are representatives of a novel tricyclic system and have been used for further elaboration into agents having muscle relaxant and other biological activities.

Introduction

The successful introduction[1,2] of cyclobenzaprine (1; 3-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*,*N*-dimethyl-1-propylamine) as a therapeutically useful skeletal muscle relaxant has stimulated efforts in these laboratories to discover novel structures with improved clinical efficacy. With use of the 5*H*-dibenzo[*a*,*d*]cycloheptene system as a lead, one of the target molecules selected was that in which one of the benzene rings of 1 was replaced by a pyrrole nucleus, affording the novel tricyclic system, pyrrolo[2,1-*b*][3]benzazepin-11-one 4 in which the pyrrole nitrogen is located at a bridgehead position. It was decided

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