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Carbocyclic Phenylhydrazines in the Fischer Indole Synthesis. 3. Some Rearrangements with 1-Phenyl-5-pyrazolidinones

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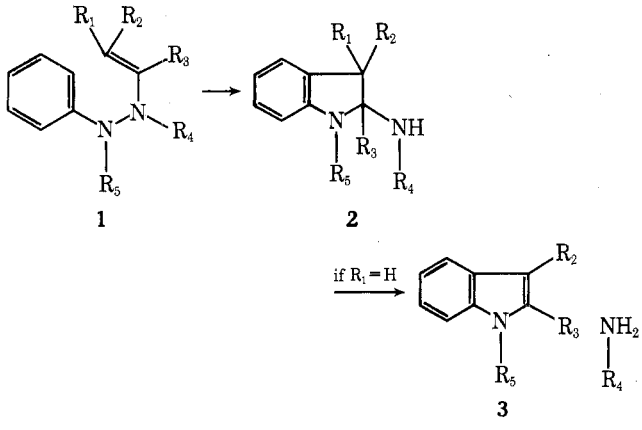
Reactions of 1-phenyl-5-pyrazolidinone **4a,b** with a variety of carbonyl compounds are described. Cyclohexanone and its higher homologues gave the novel 5-(3-aminopropanoyl)-5*H*-cycloalk[*b*]indoles **5a–g.** The carbonyl group was reduced with diborane to give 5-(3-aminopropyl)-5*H*-cycloalk[*b*]indoles **7a–c.** Loss of the side chain occurred upon treatment of **5a** and **5f** with $LiAlH_4$ to give **6a** and **6b,** respectively. Cyclopentanone and **4a,b** gave the indolines **8a,b.** Upon reduction with $LiAlH_4$, the methyl substituted compound **8b** gave the indoline **9** while the unsubstituted compound **8a** gave the indole **7d.** From the reaction of **4a** with 2,6-dichlorophenylacetaldehyde the enehydrazine **11** was isolated, which underwent thermal rearrangement to the indoline **12.**

According to Robinson and Robinson,[1] the mechanism of the Fischer indole synthesis[2] involves the formation of an enehydrazine from a phenylhydrazone followed by a [3,3] sigmatropic rearrangement to form the respective indole.

Scheme I



During the course of our investigation of the chemistry of 1-phenylpyrazolidine we have isolated[3a] 10,10-dimethyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-*a*]indole [**2**, $R_1 = R_2 = Me$; $R_3 = H$; $R_4R_5 = (CH_2)_3$]. This compound was obtained from the reaction of 1-phenylpyrazolidine with isobutyraldehyde and may be regarded as the equivalent of an intermediate of the classic Fischer indole synthesis—a stable compound because of the presence of two alkyl substituents. We have also demonstrated[4] that under our experimental conditions system **2** was not isolated but underwent further bond reorganization to form indole **3** when one of the substituents R_1 or R_2 was replaced with hydrogen. In all the cases described above, we have not isolated any compounds of the general structure **1,** the postulated precursor of **2.** To our knowledge, the literature contains only three references pertaining to the isolation and characterization of enehydrazines[5a,b,6] **1.** These compounds, when treated under conditions favorable for rearrangement, gave the respective indoles directly.

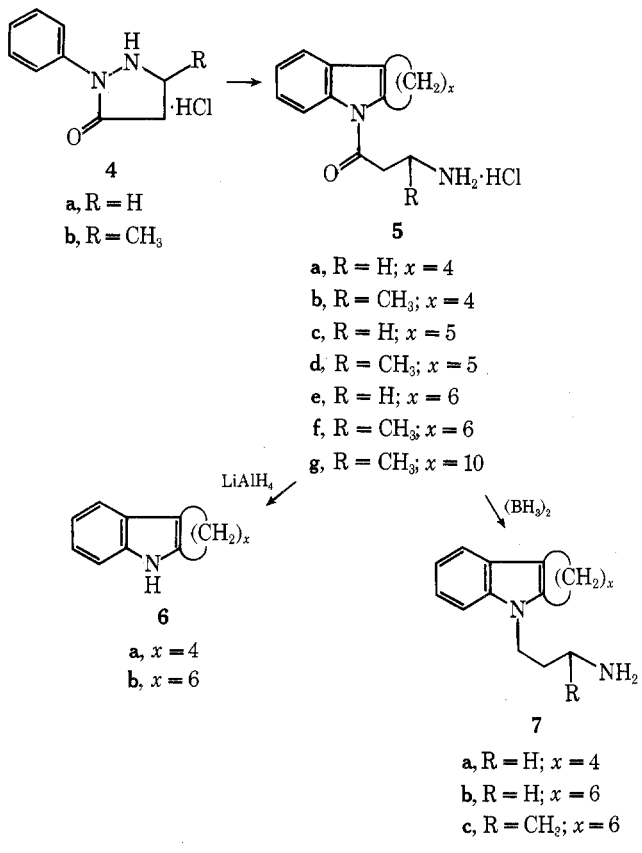
In a recent example,[7] a vinylogous hydrazide was prepared and thermally rearranged to an indoline.

We now wish to report the isolation of three compounds with the general structure **2** ($R_1 = H$) and of an enehydrazine **1,** which rearranged thermally to the indoline **2** ($R_1 = H$). These indolines did not undergo bond reorganization to give the corresponding indoles upon treatment with hydrogen chloride, but formed the indoline hydrochlorides instead.

1-Phenyl-5-pyrazolidinones **4a,b** have been known since the turn of the century as summarized recently by Jacquier et al.[8a,b] We found that their hydrochlorides[9] are capable of reacting with cyclic ketones. Equimolar amounts of 1-phenyl-5-pyrazolidinone hydrochloride (**4a**) and cyclohexanone were heated under reflux in glacial acetic acid. The novel product 9-(3-aminopropanoyl)-1,2,3,4-tetrahydrocarbazole hydrochloride (**5a**) was isolated in 86% yield and characterized by analytical and spectral data. The formation of this product was not observed, however, when the reaction was attempted in the absence of the acid. The free base of the starting material **4a** was recovered unchanged after prolonged heating to reflux with cyclohexanone in toluene. Under similar conditions 1-phenylpyrazolidine and cyclohexanone readily[4] formed the corresponding indole. The difference in reactivity with cyclohexanone parallels the basicity of the corresponding free base. We observed $pK_a = 5.0$ for 1-phenylpyrazolidine hydrochloride compared to $pK_a = 2.0$ for **4a** (CMS), the basicity of the 2-N of **4a** being lowered by the proximity of the amide.

When **5a** was treated with lithium aluminum hydide in THF we isolated tetrahydrocarbazole (**6a**). After treatment of **5a** with diborane,[10] the reduction product was 9-(3-aminopropyl)-1,2,3,4-tetrahydrocarbazole (**7a**). The maleate of

Scheme II

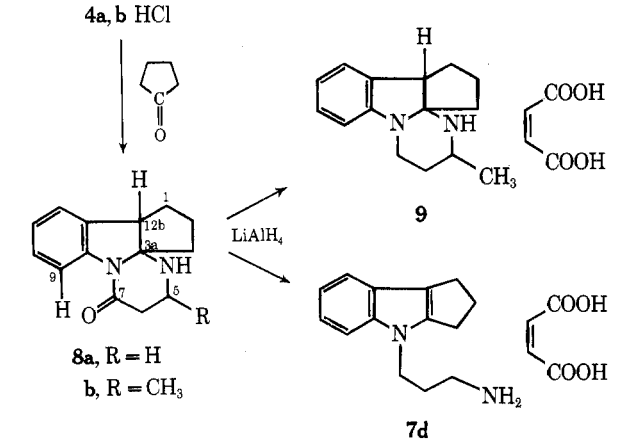


7a was found to be identical in every respect with an authentic sample prepared from cyclohexanone and 1-phenylpyrazolidine,[4] thus proving the structure of **5a.**

When 1-phenyl-3-methyl-5-pyrazolidinone hydrochloride (**4b**) and cyclohexanone were heated together in glacial acetic acid, 9-(3-aminobutanoyl)-1,2,3,4-tetrahydrocarbazole hydrochloride (**5b**) was isolated in 79% yield.

Different products were isolated, however, when cyclopentanone was used as starting material. In this case, a novel indoline **8a** was isolated in moderate yield following the reaction with **4a,** while the methyl substituted analogue **8b** was

Scheme III



isolated in 83% yield from **4b** and the same ketone. Analytical and mass spectral data support the assigned structures. While the uv spectra for both compounds show absorption usually associated with indoles (fine structure), the ^{13}C NMR spectra obtained for both **8a** and **8b** clearly established the presence of an indoline ring.

The NMR spectrum of **8a** shows the presence of a doublet at δ 4.33 ppm (1 H), which was assigned to the proton in position 12b of **8a** with coupling constants of 7 and 1–2 Hz to the vicinal methylene group. A similar doublet was observed for the compound **8b,** which is superimposed on a multiplet assigned to the proton at C-5. When the NMR spectra of the base **8a,b** were recorded in the same solvent, no absorption in the region δ 3.7–6.8 ppm was observed. To clarify the situation with respect to a possible equilibrium between **8** and the ring open tautomer, it was decided to examine the ^{13}C NMR spectra for **8a** (base and hydrochloride) and **8b** (hydrochloride).

Discussion of the ^{13}C NMR Spectra of 8a and 8b. The fully proton decoupled spectrum of **8a** HCl gave a total of 14 peaks, corresponding to the number of carbon atoms. Single-frequency off-resonance decoupling (sford) experiments were used to determine the number of protons attached to each carbon. The results are listed in Table V. These data preclude the presence of an indole in **8a,** since the spectrum displays only six peaks that can be associated with aromatic carbons.[11,12] The spectrum of **8a** compares favorably, however, with spectra[13] obtained for three related indolines which we had prepared[3a] earlier. The peak at 87.7 ppm (singlet) was assigned to the fully substituted C-3a (for the numbering see Scheme III) with two of the substituents being nitrogen. This is in good agreement with the chemical shift observed for the corresponding carbon of the three models [e.g., **2,** $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4R_5 = (CH_2)_3$]. In these cases values between 80.9 and 83.4 ppm were observed. It should be kept in mind that our models were substituted ith R_1R_2 = alkyl and R_3 = H (Figure 1), thus accounting for the shift to lower field observed for **8a.** The peak at 51.6 ppm (doublet) was assigned to the C-12b. The corresponding carbon of our models showed absorptions between ca. 40 [**2,** $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4R_5 = (CH_2)_3$; peak obscured by Me_2SO] and 47.8 ppm. These deviations are attributed to the differences in the substitution patterns. The ^{13}C NMR spectrum of the free base **8a** showed only minor changes in comparison to the spectrum of the hydrochloride. The chemical shifts for the C-3a and C-12b appeared at 90.7 and 52.7 ppm, respectively. For additional support of the above assignment, see below for the ^{13}C NMR spectrum of **12.**

The ^{13}C NMR spectrum of **8b** (see Table VI) shows the expected shifts in comparison to the spectrum of **8a** due to the presence of the additional methyl group. Particularly, the chemical shifts in **8b** assigned to C-3a and C-12b are the same as observed for **8a.** The same is true for the chemical shifts observed for the aromatic carbons. The expected shifts to lower field are observed for C-5 and C-6.

The presence of the methyl group in **8b** can give rise to diastereoisomers. That this is indeed the case is borne out by the ^{13}C NMR spectrum of **8b.** There, every peak is accompanied by a small satellite peak, indicating the presence of a second isomer to the extent of 7–8% after one recrystallization. This stereoisomerism can be attributed to the methyl group, excluding the possibility of isomerism at the juncture of the two five-membered rings, since **8a** consists of a single isomer according to the ^{13}C NMR spectrum of that compound. Further work will be required to determine the stereochemistry of **8b.**

Reduction of the Hexahydrocyclopenta[*b*]pyrimido[1,2-*a*]indol-7(6*H*)-one System (8a and 8b). When the title compound *without* the methyl group (**8a**) was treated with $LiAlH_4$ the known[4] 4-(3-aminopropyl)-1,2,3,4-tetrahydrocyclopent[*b*]indole (**7d**) was isolated and characterized as the maleic acid salt. This was found to identical in every respect with an authentic sample. The structure of this compound was also verified with the aid of its ^{13}C NMR spectrum, which clearly showed the presence of eight aromatic carbons for **7d.** In light of the results discussed above it may be as-

sumed that the lactam group in **8a** was reduced to the corresponding amine followed by opening of the perhydropyrimidine ring to form the indole **7d,** since base alone did not rearrange the skeleton of **8a** (see Experimental Section).

Surprisingly, when the title compound *with* the methyl group (**8b**) was reduced under similar conditions as employed for **8a,** the product was not the indole corresponding to **7d** but the indoline **9,** isolated and characterized as the maleic acid salt. This structure is based on the following spectral data. The NMR spectrum of **9** did not exhibit the expected triplet associated[4] with the methylene group attached to the indole nitrogen near 4.2 ppm. Instead the corresponding signal was observed in the region between 3.0 and 4.0 ppm. From the ^{13}C NMR spectrum of **9** it became clear that the product had to be assigned the cyclic tautomer with the same skeleton as the starting material **8b.** The characteristic peaks for the C-3a and C-12b were observed at 90.4 and 51.8 ppm, respectively, in addition to six low-field peaks assigned to the aromatic carbons. The spectrum also showed that the reduction product consisted of a single isomer with no detectable amount of a second isomer as was present in the starting material **8b.** The isolation of product **9** from the reduction of **8b** also proves the sequence of steps (reduction followed by ring opening) in the reduction of **8a** leading to the indole **7d.**

Additional Examples. For the results of reactions between **4a,b** and cycloheptanone, cyclooctanone, and cyclododecanone, which yielded the corresponding indoles, see Tables II and III.

To demonstrate the generality of the reduction with diborane, both compounds **5e** and **5f** were subjected to this reagent. Reduction of the free base of **5e** and the subsequent treatment with hydrogen chloride lead to the known[4] 5-(3-aminopropyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole hydrochloride (**7b**). Reduction of the free base of **5f** (mp 84–85 °C) gave 5-(3-aminobutyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole (**7c**), which was isolated as the hydrochloride in 65% yield.

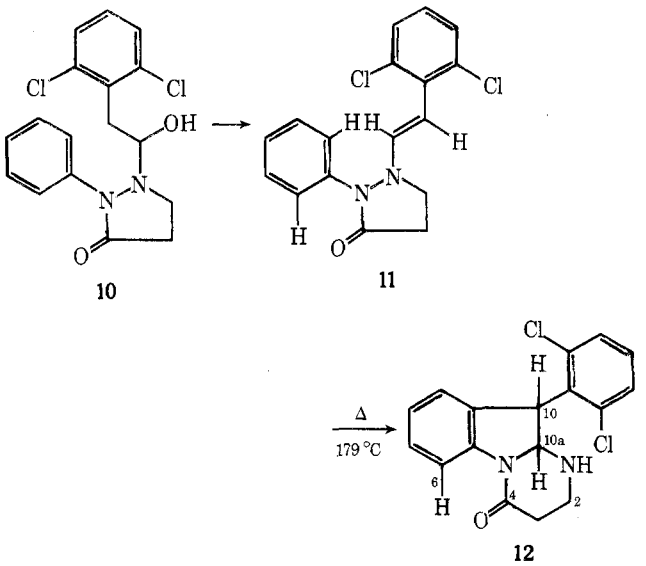
Another reductive cleavage as described above for **5a** was observed when **5f** was treated with $LiAlH_4$. Cyclooctenoindole (**6b**) was isolated and found to be identical with a commercial sample.

Isolation and Rearrangement of an Enehydrazine. Acetaldehydes did not tolerate the presence of the strong acid in attempted reactions with **4a.**

When equimolar amounts of the free base[8] 1-phenyl-5-pyrazolidinone (**4a**) and 2,6-dichlorophenylacetaldehyde[14] were mixed together, a crystalline product $C_{17}H_{16}Cl_2N_2O_2$ was isolated which we assigned structure **10** on the basis of the following data. According to the NMR spectrum of **10,** the amino alcohol seemed to dissociate at least to some degree into its components when dissolved in chloroform. Nevertheless, we were able to secure a correct elemental analysis for **10** and a mass spectrum indicating dehydration of **10** rather than reversal to the starting materials. Water was also lost when **10** was recrystallized from ethanol and a new compound $C_{17}H_{14}Cl_2N_2O$ was isolated. Analytical and spectral data are in agreement with the structure **11.** The NMR spectrum of this enehydrazine exhibits two sets of triplets at 2.82 and 3.80 ppm (J = 7.0 Hz) assigned to the methylene groups of the pyrazolidinone The two vinylic protons of **11** give rise to an AB pattern with two doublets centered at δ 5.60 and 6.73 ppm and a coupling constant of 14 Hz, indicating the presence of a trans double bond[15] in **11.** This interpretation was verified by double resonance experiments. Upon irradiation at 336 Hz, a singlet appeared at δ 6.73 ppm in place of the doublet. Absorption for two of the eight aromatic protons was observed at lower field (δ 7.85 ppm). This is interpreted as being due to the free rotation of the unsubstituted phenyl ring.

We found the enehydrazine **11** recovered unchanged even after prolonged heating to reflux in toluene. A new isomeric substance, however, was isolated after **11** was heated to 179 °C in refluxing 1,2-dichlorobenzene. The ir spectrum of the new compound possesses a NH band indicating that the original hydrazine must have undergone a cleavage. The NMR spectrum of the new compound is compatible with structure **12.** Of a total of *seven* aromatic protons we found only *one* at lower field (δ 8.10 ppm), probably due to its proximity to the carbonyl group. We assigned a broadened singlet at δ 5.44 ppm (2 H) to the protons in position 10 and 10a. Under optimal conditions this signal could be resolved to a quartet with a coupling constant J = 9 Hz and a calculated[16] $\Delta\nu$ = 6.4 Hz. The absorption for the two methylene groups no longer lends itself to first-order analysis. At δ 1.90 ppm we found a broad signal equivalent to *one* proton which could be replaced by deuterium when the sample was treated[17] with D_2O.

Scheme IV



The NMR spectrum of the hydrochloride of **12** exhibits only minor changes compared to the spectrum of the free base. The same observation was made when the NMR spectrum of **12** HCl was taken in CF_3COOH as solvent. From this we conclude that the opening of the pyrimidone ring with concomitant formation of 1-(3-aminopropanoyl)-3-(2,6-dichlorophenyl)-indole hydrochloride is not readily accomplished. This is in contrast to our observation[3a] that **2** [$R_1 = R_2 = CH_3$; R_3 = H; $R_4R_5 = (CH_2)_3$] in moderately strong acid exists in the ring open 3*H*-indole tautomeric form. We attribute the stability of **12** to the presence of a bulky substituent at C-10. It seems that not even the 1,4 axis of the 2,6-dichlorophenyl group can reach coplanarity with the phenyl ring of the potential indole. This hypothesis is supported by the ^{13}C NMR spectrum of **12.**

Discussion of the ^{13}C NMR Spectrum of 12. The fully proton decoupled spectrum of **12** gave a total of 17 peaks corresponding to the number of carbon atoms present. This implies the nonequivalency for the positions 2′,6′ and 3′,5′, respectively, of the 2,6-dichlorophenyl ring which is hindered in its free rotation. The results of the ^{13}C NMR spectrum, which are listed in Table VIII, further indicated the presence of only *one* isomer in **12.** Since isomerization is unlikely (see above), it may be concluded that the addition of the amide to the C=N double bond of the nine-membered-ring intermediate occurred in a stereospecific manner, though the stereochemistry of **12** is not known at this time.

Single-frequency off-resonance decoupling experiments (sford) were used to assign the number of protons attached to each carbon. This revealed the presence of *two* methylene

Table I. ^{13}C NMR Spectrum of 5a HCl in Me_2SO

Absorptions observed	Rel intensity	Assignment
170.8	83	C-10
135.8	80	C-8a
135.2	87	C-9a
130.1	94	C-4b
124.3	205	C-6
123.5	189	C-7
118.0	217	C-5
116.1	153	C-4a,8
35.6	156	C-12
34.8	180	C-11
26.1	132	C-1
23.4	149	C-4
21.4	137	C-2
20.7	148	C-3

and *two* methine groups and allowed the assignment of the peaks at 79.7 and 50.1 ppm to the carbons 10a (NCHN) and 10, respectively (see also arguments cited in the discussion of the ^{13}C NMR of **8a**).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 and/or T-60 spectrometer and are recorded in δ (ppm) values from Me_4Si as internal standard. ^{13}C NMR spectra were measured on a Varian XL-100 spectrometer and are recorded in parts per million values from Me_4Si as internal standard. Uv absorption spectra were measured in ethanol on a Cary spectrometer Model 14. Ir spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer.

9-(3-Aminopropanoyl)-1,2,3,4-tetrahydrocarbazole Hydrochloride (5a). A mixture of 5.0 g (0.025 mol) of 1-phenyl-5-pyrazolidinone hydrochloride[9] (**4a**) and 3.6 g (0.037 mol) of cyclohexanone was heated under reflux in 50 ml of glacial acetic acid for 3 h under an atmosphere of nitrogen. The product **5a** precipitated from the cold solution, yield 6.0 g (86%), mp 226–228 °C. A sample was recrystallized from ethanol: mp 227–229 °C; *m/e* 242 (M^+); ^{13}C NMR, see Table I; NMR ($CDCl_3$ + Me_2SO) δ 1.4–2.1 (m, 4) 2.3–3.8 (m, 8) 6.9–7.4 (m, 3, C_6H_3) 8.0–8.3 (m, 1, C_6H_1) 7.3–8.8 (broad, 3, NH_3); ir (Nujol) 2500–3400 (NH), 1692 (C=O), 1614 cm^{-1}; uv 244 nm (ϵ 21 760), 266 (11 900), 294 (6100), 301 (6050). Anal. Calcd for $C_{15}H_{18}N_2O$.HCl (278.8): C, 64.6; H, 6.9; N, 10.0; Cl, 12.7. Found: C, 65.0; H, 6.9; N, 10.0; Cl, 12.7.

Tetrahydrocarbazole (6a). A solution of 1.0 g (0.004 mol) of the free base of **5a** (mp 50–52 °C) in 50 ml of THF was added to a suspension of lithium aluminum hydride (0.5 g) in the same solvent. The mixture was stirred at room temperature overnight under an atmosphere of nitrogen. Excess of the reducing agent was decomposed by slowly adding 1.5 ml of water followed by 100 ml of ether. After filtration the solvent was evaporated to yield 0.5 g (71%) of tetrahydrocarbazole (**6a**), mp 117–118 °C, identical in every respect with a commercial sample (ir, NMR, uv, TLC), mmp 117–118 °C.

Cyclooctenoindole (6b). This compound was obtained from **5f** in 87% yield following th procedures described above. It was found to be identical in every respect with a commercial sample (ir, NMR, TLC, *m/e*, melting point, and mixture melting point).

9-(3-Aminopropyl)-1,2,3,4-tetrahydrocarbazole (7a). To 2.0 g (0.008 mol) of **5a** (free base) in 25 ml of cold THF, 25 ml of a commercial solution of diborane (1 M) was added. The mixture was kept at room temperature overnight. The solution was evaporated under reduced pressure. The residue was dissolved in ether, washed with 2 N sodium carbonate, and worked up in the usual manner to yield 1.4 g (75%) of crude **7a.** A sample was converted into the maleate, mp 194–195 °C after several recrystallizations from methanol/ether. It was identical in every respect with an authentic sample[4] (ir, NMR, uv, TLC), *m/e* 228 (M^+).

5-(3-Aminopropyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct-[*b*]indole Hydrochloride (7b) was prepared from 1.0 g (0.003 mol) of **5e** following the procedures described above: yield 0.4 g (42%); mp 210–214 °C; recrystallized from MeOH/ether; mp 242–244 °C; identical in every respect with an authentic sample.[4]

5-(3-Aminobutyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]-indole hydrochloride (7c) was prepared from **5f** in 65% yield as above: mp 239–240 °C; *m/e* 270 (M^+); NMR ($CDCl_3$ + Me_2SO) δ 1.42 (d, 3, J = 7 Hz, CH_3), 1.1–2.6 (m, 10), 2.6–3.6 (m, 5), 4.24 (t, 2, J = 8 Hz, indole NCH_2), 6.8–7.6 (m, 4, C_6H_4), 8.2–9.0 (3, NH_3); ir (Nujol)

Table II. Physical Properties and Analyses

Compd	St mat.	Yield, %	Mp, °C	*m/e* (M^+)	Empirical formula	Mol wt	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
5b	**4b**	79	215–217	256	$C_{16}H_{20}N_2O$·HCl	292.8	65.6	7.2	9.6	12.1	65.3	7.0	9.4	11.9
5c	**4a**	48	206–208	256	$C_{16}H_{20}N_2O$·HCl	292.8	65.6	7.2	9.6	12.1	65.3	7.6	9.6	12.3
5d	**4b**	23	177–178	270	$C_{17}H_{22}N_2O$·HCl	306.9	66.5	7.6	9.1		66.2	7.7	9.2	
5e	**4a**	72	195–197	270	$C_{17}H_{22}N_2O$·HCl	306.9	66.5	7.6	9.1	11.6	66.1	7.5	9.3	11.8
5f	**4b**	82	179–180	284	$C_{18}H_{24}N_2O$·HCl	320.9	67.4	7.9	8.7	11.0	67.6	8.0	8.5	11.4
5g	**4b**	65	231–233	340	$C_{22}H_{32}N_2O$·HCl	377.0	70.1	8.8	7.4	9.4	69.9	9.1	7.4	9.4

Table III. Spectral Data

Compd	Ir, cm^{-1} (NH)	(Nujol) (C=O)	Uv, nm (ϵ) in ethanol	^1H NMR in $CDCl_3$ + Me_2SO
5b	3200	1675, 1620	246 (17 100), 266 (9500), 300 (5000)	1.47 (d, 3, J = 7 Hz, CH_3), 1.6–2.2 (m, 4), 2.7–4.2 (m, 7), 7.0–7.5 (m, 3, C_6H_3), 8.0–8.2 (m, 1, C_6H_1), 7.5–8.5 (NH_3)
5c	2700–3300	1700, 1590		1.6–2.1 (m, 6, 3 CH_2), 2.4–2.9 (m, 2, CH_2), 2.9–3.8 (m, 6, 3 CH_2), 7.0–7.6 (m, 3, C_6H_3), 7.6–8.6 (m, 4, C_6H_1 + NH_3)
5d	2500–3400	1695, 1600	249 (14 900), 303 (5800)	1.47 (d, 3, J = 7 Hz, CH_3), 1.6–2.3 (m, 6, 3 CH_2), 2.5–4.3 (m, 7), 7.2–7.8 (m, 3, C_6H_3), 8.0–8.4 (m, 1, C_6H_1), 8.0–9.4 (broad, NH_3)
5e	3500	1680, 1580	248 (15 500), 271 (9500), 298 (4900) 304 (5100)	1.0–2.0 (m, 8), 2.7–3.8 (m, 8), 7.1–7.6 (m, 3, C_6H_3), 7.8–8.2 (m, 1, C_6H_1), 8.3–8.9 (broad, NH_3)
5f	3130	1680, 1600	248 (15 800), 271 (9700), 304 (5400)	1.48 (d, 3, J = 6 Hz, CH_3), 1.0–2.0 (m, 8), 2.6–4.1 (m, 7), 7.1–7.6 (m, 3, C_6H_3), 7.8–8.1 (m, 1, C_6H_1), 8.1–8.5 (NH_3)
5g	3130	1680, 1600	247 (16 300), 294 (5500), 302 (5500)	1.0–2.0 (m, 19), 2.3–4.0 (m, 7), 7.0–7.6 (m, 3, C_6H_3), 7.6–8.0 (m, 1, C_6H_1), 8.0–8.6 (NH_3)

Table IV. ^{13}C NMR Spectrum of 7d $C_4H_4O_4$ in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
168.5	123	C-1 maleic acid
146.3	70	C-4a
141.1	73	C-3a
136.7	157	C-2 maleic acid
124.5	83	C-8a
120.3	93	C-7
119.3	109	C-6
118.7	111	C-8
117.5	76	C-8b
110.4	97	C-5
41.5	117	C-9
37.1	77	C-11
28.2	138	C-1,3
24.8	102	C-2
24.5	116	C-10

Table V

^{13}C NMR Spectrum of **8a** (Free Base) in Me_2SO

Absorption observed, ppm	Rel intensity	Sford	Assignment
166.9	21		C-7
141.8	16		C-8a
133.6	36		C-12a
127.6	133		C-10
124.3	126		C-12
124.2	190		C-11
116.2	160		C-9
90.7	51		C-3a
52.7	202		C-12b
38.5	203		C-5
37.5	144		C-3
31.2	217		C-1
30.9	215		C-6
24.3	112		C-2

^{13}C NMR Spectrum of **8a** HCl in Me_2SO in Presence of $Fe(AcAc)_3$[18]

164.8	42	s	C-7
141.4	49	s	C-8a
131.2	50	s	C-12a
128.0	60	d	C-10
124.9	69	d	C-12
124.4	67	d	C-11
115.0	65	d	C-9
87.7	54	s	C-3a
51.6	98	d	C-12b
37.6	118	t	C-3
35.3	62	t	C-5
31.8	68	t	C-1
28.3	67	t	C-6
23.8	65	t	C-2

2500–3200 (NH), 1600 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2$·HCl (306.9): C, 70.5; H, 8.9; N, 9.1; Cl, 11.6. Found: C, 69.9; H, 9.1; N, 9.3; Cl, 11.9.

4-(3-Aminopropyl)-1,2,3,4-tetrahydrocyclopent[*b*]indole (7d). This compound was prepared from 0.5 g (0.002 mol) of **8a** HCl in 50 ml of ether in the presence of 1.0 g (0.025 mol) of $LiAlH_4$ and converted to the maleic acid salt, which was found to be identical with an authentic sample,[4] mmp 178–180 °C, ^{13}C NMR spectrum see Table IV.

1,2,3,4,5,12b-Hexahydrocyclopenta[*b*]pyrimido[1,2-*a*]indol-7(6*H*)-one (8a). This compound was prepared from 5.0 g (0.025 mol) of **4a** and 2.5 g (0.03 mol) of cyclopentanone in 30 ml of glacial acetic acid as described above: yield 2.0 g (30%); mp 202–203 °C; *m/e* 228 (M^+); ^{13}C NMR see Table V; NMR ($CDCl_3$ + Me_2SO) δ 1.2–2.7 (m, 6), 2.92 (t, 2, *J* = 7 Hz, O=CCH$_2$), 3.58 (t, 2, *J* = 7 Hz, C**H**$_2$NH$_2$), 4.33 (d, 1, *J* = 7 Hz, HC-12b), 7.1–7.6 (m, 3, C_6H_3), 7.9–8.2 (m, 1, C_6H_1), 10.7 (broad, 2, NH_2); ir (Nujol) 2400–2800 (NH), 1680 (C=O), 1602 cm^{-1}; uv 251 nm (ε 12 900), 278 (3300), 286 (2900). Anal. Calcd for $C_{14}H_{16}N_2O$·HCl (264.8): C, 63.5; H, 6.5; N, 10.6; Cl, 13.4. Found: C, 63.2; H, 6.6; N, 10.5; Cl, 13.6. The free base was prepred from the hydrochloride as usual: mp 130–132 °C; ^{13}C NMR see Table V; NMR (Me_2SO) δ 1.0–2.2 (m, 4), 2.2–2.6 (m, 2), 2.8–3.7 (m, 6), 6.8–7.3 (m, 3, C_6H_3), 7.7–8.0 (m, 1, C_6H_1).

1,2,3,4,5,12b-Hexahydro-5-methylcyclopenta[*b*]pyrimido-[1,2-*a*]indol-7(6*H*)-one (8b). This compound was prepared from 21.2 g (0.10 mol) of **4b** and 12.5 g (0.15 mol) of cyclopentanone in 200 ml of refluxing glacial acetic acid during 2 h; yield 23.0 g (83%); mp 243–244 °C; recrystallized from ethanol; mp 253–255 °C; *m/e* 242 (M^+); ^{13}C NMR see Table VI; NMR ($CDCl_3$ + Me_2SO) δ 1.48 (d, 3, *J* = 7 Hz, CH_3), 1.0–3.6 (m, 8, 4 CH_2), 3.6–4.4 (broad, 1, C**H**CH_3), 4.20 (d, 1, *J* = 7 Hz, HC-12b), 7.0–7.6 (m, 3, C_6H_3), 7.8–8.2 (m, 1, C_6H_1), below 9.0 (broad, 2, NH_2); ir (Nujol) 2300–2800 (NH), 1672 (C=O), 1602 cm^{-1}; uv 251 nm (ε 12 610), 278 (3230), 286 (2850). Anal. Calcd for $C_{15}H_{18}N_2O$·HCl (278.8): C. 64.6; H, 6.9; N, 10.0; Cl, 12.7. Found: C, 64.8; H, 6.8; N, 10.2; Cl, 12.8. The free base was isolated after a mixture of 0.150 g (0.005 mol) of **8b** HCl and 4 ml (0.08 mol) of 2 N NaOH was heated to reflux for 2 days in 15 ml of methanol: yield 75 mg (57%); mp 116–118 °C; *m/e* 242 (M^+); NMR ($CDCl_3$ + Me_2SO) 1.23 (d, 3, *J* = 6 Hz, CH_3), 3.0 (s, 1, exchangeable with D_2O, NH), 1.4–3.7 (m, 10), 6.8–7.4 (m, 3, C_6H_3), 7.8–8.1 (m, 1, C_6H_1).

1,2,3,4,5,6,7,12b-Octahydro-5-methylcyclopenta[*b*]pyrimido-[1,2-*a*]indole (9). To the suspension of 0.2 g (0.005 mol) of lithium aluminum hydride in 25 ml of anhydrous ether there was added 0.050 g (0.0002 mol) of **8b**. The mixture was stirred at room temperature for 2 h. After the usual workup 0.030 g (73%) of a liquid was obtained which was converted to the maleic acid salt: mp 158–159 °C; *m/e* 228 (M^+); ^{13}C NMR see Table VII; NMR ($CDCl_3$ + Me_2SO) δ 1.20 (d, 3,

Table VI. ^{13}C NMR Spectrum of 8b HCl in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
164.6	75	C-7
141.8	50	C-8a
131.4	92	C-12a
128.4	190	C-10
125.5	172	C-12
124.6	148	C-11
115.5	126	C-9
87.9	104	C-3a
51.7	216	C-12b
45.5	211	C-5
38.7	185	C-6
36.6	164	C-3
31.7	177	C-1
23.9	175	C-2
19.0	125	CH_3

Table VII. ^{13}C NMR Spectrum of 9 $C_4H_4O_4$ in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
168.1	26	C-1 maleic acid
149.0	36	C-8a
136.5	217	C-2 maleic acid
130.4	82	C-12a
128.6	140	C-12
124.9	148	C-10
118.3	155	C-11
105.8	140	C-9
90.4	130	C-3a
51.8	203	C-12b
49.4	209	C-5
37.3	160	C-7
33.5	198	C-3
32.7	176	C-6
28.8	159	C-1
25.3	177	C-2
19.0	166	CH_3

Table VIII. ^{13}C NMR Spectrum of 12 in $CHCl_3$

Absorptions observed, ppm	Rel intensity	Sford	Assignment
166.9	101	s	C-4
141.3	63	s	C-5a
138.1	55	s	C-1′
136.1	65	s	C-2′
134.1	50	s	C-6′
131.1	158	d	C-4′
130.5	114	s	C-9a
130.1	171		C-3′
129.3	169		C-5′
128.5	163		C-7
124.9	176		C-9
123.7	182	d	C-8
116.9	142	d	C-6
79.7	174	d	C-10a
50.1	220	d	C-10
41.7	168	t	C-2
31.7	190	t	C-3

J = 6 Hz, $CHCH_3$), 1.4–2.6 (m, 7), 3.0–4.0 (m, 4), 6.00 (s, 2, maleic acid), 6.3–7.3 (m, 4, C_6H_4); ir (Nujol) 2300–3500 (NH), 1618, 1585 cm^{-1}; uv 248 nm (ϵ 11 700), 303 (2500). Anal. Calcd for $C_{15}H_{20}N_2 \cdot C_4H_4O_4$ (344.3): C, 66.3; H, 7.0; N, 8.1. Found: C, 66.0; H, 7.0; N, 7.9.

1-[2-(2,6-Dichlorophenyl)-1-hydroxyethyl]-2-phenyl-3-pyrazolidinone (10). A mixture of 1.6 g (0.01 mol) of 1-phenyl-5-pyrazolidinone[8] and 1.9 g (0.01 mol) of 2,6-dichlorophenylacetaldehyde[14] was warmed in 50 ml of toluene until a clear solution was obtained. Upon cooling the product precipitated as a white solid, mp 119–120 °C, yield 2.6 g (74%). A small sample was recrystallized from ethanol: mp 128–130 °C; m/e 332 ($M^+ - 18$); NMR ($CDCl_3$) δ 2.67 (t, J = 7.5 Hz), 3.1–4.0 (m), 4.11[19] (d, J = 1.5 Hz), 4.5–5.1 (m), 6.9–7.6 (m), 7.7–8.0 (m), 9.7 (t, J = 3 Hz); ir (CH_2Cl_2) 3580 (NH or OH), 1720, 1690, 1590 cm^{-1}. Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_2$ (351.25): C, 58.1; H, 4.6; N, 8.0; Cl, 20.2. Found: C, 58.1; H, 4.6; N, 8.1; Cl, 20.1.

1-(*trans*-2,6-Dichlorostyryl)-2-phenyl-3-pyrazolidinone (11). When the crude compound **10** was recrystallized from hot ethanol/water the product precipitated as a white solid: mp 133–134 °C; m/e 332 (M^+); NMR ($CDCl_3$) δ 2.82 (t, 2, J = 7.0 Hz, $COCH_2$), 3.80 (t, 2, J = 7.0 Hz, NCH_2), 5.60 (d, 1, J = 14 Hz, vinyl H), 6.73 (d, 1, J = 14 Hz, vinyl H), 6.8–7.7 (m, 6, aromatic), 7.7–8.1 (m, 2, 2,6-C_6H_2); ir (CH_2Cl_2) 1710 (C=O), 1645, 1594 cm^{-1}; uv 273 nm (ϵ 16 500). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$ (333.2): C, 61.3; H, 4.2; N, 8.4; Cl, 21.3. Found: C, 61.2; H, 4.3; N, 8.2; Cl, 20.9.

10-(2,6-Dichlorophenyl)-1,2,10,10a-tetrahydropyrimido-[1,2-*a*]indol-4(3*H*)-one (12). A solution of 4.0 g (0.012 mol) of **11** in 50 ml of *o*-dichlorobenzene was heated to reflux under an atmosphere of nitrogen during 12 h. The solvent was evaporated under reduced pressure. The product solidified upon the addition of ether, mp 201–203 °C, yield 3.6 g (90%). A sample was recrystallized from methylene chloride/hexane: mp 203–205 °C; m/e 332 (M^+); ^{13}C NMR see Table VIII; NMR ($CDCl_3$) δ 1.90 (broad singlet, 1, exchangeable[17] with D_2O, NH), 2.3–2.8 (m, 2, $COCH_2$), 2.8–3.7 (m, 2, $NHCH_2$), 5.44 (q, 2, J = 9 Hz, $\Delta\nu$ = 6.4 Hz, 2 CH), 6.6–7.6 (m, 6, 2 C_6H_3), 7.9–8.3 (m, 1, C_6H); ir (CH_2Cl_2) 3300 (NH), 1655 (C=O), 1600, 1580, 1560 cm^{-1}; uv 265 nm (ϵ 14 500), 301 (3260). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$ (333.2): C, 61.3; H, 4.2; N, 8.4; Cl, 21.3. Found: C, 60.9; H, 4.5; N, 8.3; Cl, 21.3.

The hydrochloride of **12** was prepared following the usual procedures: mp 258–261 °C (ethanol/ether); NMR ($CDCl_3$ + Me_2SO) δ 2.88 (t,[20] 2, J = 6.7 Hz, $COCH_2$), 3.55 (t,[20] 2, J = 6.7 Hz, NCH_2), 5.96 (q, 2, J = 9 Hz, $\Delta\nu$ = 4.1 Hz, 2 CH), 6.7–7.7 (m, 6, 2 C_6H_3), 7.9–8.2 (m, 1, C_6H), below 8.5 (broad, 2, NH_2); ir (Nujol) 3450 (NH), 1670 cm^{-1} (C=O); uv 249 nm (ϵ 13 700), 279 (3200), 288 (2740). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O \cdot HCl$ (369.69): C, 55.2; H, 4.1; N, 7.6. Found: C, 54.9; H, 4.2; N, 7.6.

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Registry No—**4a,** 60260-53-9; **4a** free base, 16860-34-7; **4b,** 13292-56-3; **5a,** 60260-54-0; **5a** free base, 60260-55-1; **5b,** 60260-56-2; **5c,** 60260-57-3; **5d,** 60260-58-4; **5e,** 60260-59-5; **5f,** 60260-60-8; **5f** free base, 60260-61-9; **5g,** 60260-62-0; **7c** HCl, 60260-63-1; **7d** maleate, 52987-43-6; **8a,** 60260-64-2; **8a** HCl, 60260-65-3; **8b,** 60260-66-4; **8b** HCl, 60260-67-5; **9** maleate, 60260-69-7; **10,** 60260-70-0; **11,** 60260-71-1; **12,** 60260-72-7; **12** HCl, 60260-73-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7; cyclopentanone, 120-92-3; 2,6-dichlorophenylacetaldehyde, 20973-90-4.

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