1-Carbamoyl- and 1-Aminomethyl-1,4-dihydropyrrolo[3,4-*b*]indole Derivatives. Indole Formation by Fragmentation of Strain-Barrier Stabilized 2-Aminoindoline Derivatives[1a]

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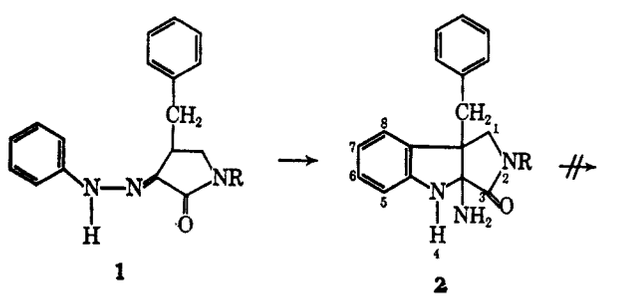
1-Substituted 4,5-dicarbethoxy-2,3-dioxopyrrolidines were prepared by addition of primary amines to diethyl maleate, followed by base-catalyzed condensation of the resulting N-substituted diethyl aspartates with ethyl oxalate. Base-catalyzed amide–ester interchange performed on the 1-cyclohexyl derivative with cyclohexylamine or benzylamine then afforded 1-cyclohexyl-4,5-bis(N-substituted carbamoyl)-2,3-dioxopyrrolidines. When treated with acids phenylhydrazones of the latter compounds underwent the initial transformations of the Fischer indole synthesis to yield 3a-amino-1,8b-bis(N-substituted carbamoyl)-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2H)-ones (**7**), which failed to undergo the normal spontaneous ammonia elimination, and therefore did not form the strained ring system of the corresponding indolenines. Instead, at elevated temperatures under acidic or basic conditions compounds of type **7** underwent a smooth fragmentation with elimination of both the 3a-amino and 8b-carbamoyl groups to yield 1-(N-substituted carbamoyl)-2-cyclohexyl-1,4-dihydropyrrolo[3,4-*b*]indol-3(2H)-ones (**11**). Lithium aluminum hydride reduction of the indole derivatives of type **11** under appropriate conditions yielded 1-(N-substituted carbamoyl)- or 1-(N-substituted aminomethyl)-1,4-dihydropyrrolo[3,4-*b*]indoles (**13** or **14**). The last-mentioned compounds (**14**) represent a new type of tryptamine analog.

When the Fischer indole synthesis was conducted with phenylhydrazones of 4-benzyl-2,3-dioxopyrrolidines (**1**), the expected spontaneous sequence of transformations was arrested at the deamination step, with the result that 2-aminoindolines (**2**) rather than indolenine derivatives (**3**) were obtained as the final products.[2] The survival of 2-aminoindolines, which had been postulated to be intermediates in the Fischer indole synthesis[3] but had not previously been demonstrated by isolation, was attributed to the significant increase in bond angle strain which would have attended formation of indolenines of type **3**. According to this view, a normally unstable structure was rendered isolable by a strain barrier against its usual mode of decomposition, which in the cases in question would generate a trigonal carbon atom at an unfavorable location in a fused system of two five-membered rings.[4] Such compounds could be characterized as "strain barrier stabilized."



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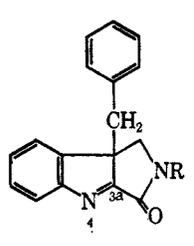

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Further investigation of this phenomenon has indicated that the strain barrier to the establishment of a double bond between the 4 nitrogen and the 3a-carbon atom as in the indolenine structure **3** is so effective that even severe reaction conditions fail to produce an indolenine, but may induce novel elimination reactions to form an indole instead. The indole-forming elimination reactions were encountered in work on compounds of structure **7** which contained N-substituted carboxamido groups at the angular 8b position in place of the benzyl group present in the series of compounds originally examined.[2]

The 1,8b-dicarboxamido derivatives **7** were obtained *via* the sequence of reactions outlined in Scheme I.[5] The 1-substituted 4,5-dicarbethoxy-2,3-dioxopyrrolidines (**6**) were prepared by an extension of a general method for the preparation of 4-carbethoxy-2,3-dioxopyrrolidines which had previously been based upon the use of acrylate esters, usually ethyl acrylate, as one starting material.[6] In the present investigation diethyl maleate (**4**) was substituted for ethyl acrylate. It was treated with primary amines to yield N-substituted diethyl aspartates (**5**), which were converted into the sodium enolates of 4,5-dicarbethoxy-2,3-dioxopyrrolidines when treated with ethyl oxalate and sodium ethoxide in absolute ethanol. The enolic 1-substituted 4,5-dicarbethoxy-2,3-dioxopyrrolidines (**6**) were subjected to ester–amide interchange by treatment with 2 mol of a primary amine (benzylamine or cyclohexylamine) in the presence of at least 1 mol of

(1) (a) Supported by Research Grant GM-04371 from the National Institutes of Health, U. S. Public Health Service. (b) This paper is taken in part from the thesis submitted by J. A. Vida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, Dec 1960. (c) Postdoctoral Research Associate, 1965–1966. (d) This paper is based principally on the thesis submitted by S. K. Lee in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, Nov 1964.

(2) P. L. Southwick, B. McGrew, R. R. Engel, G. E. Milliman, and R. J. Owellen, *J. Org. Chem.*, **28**, 3058 (1963).

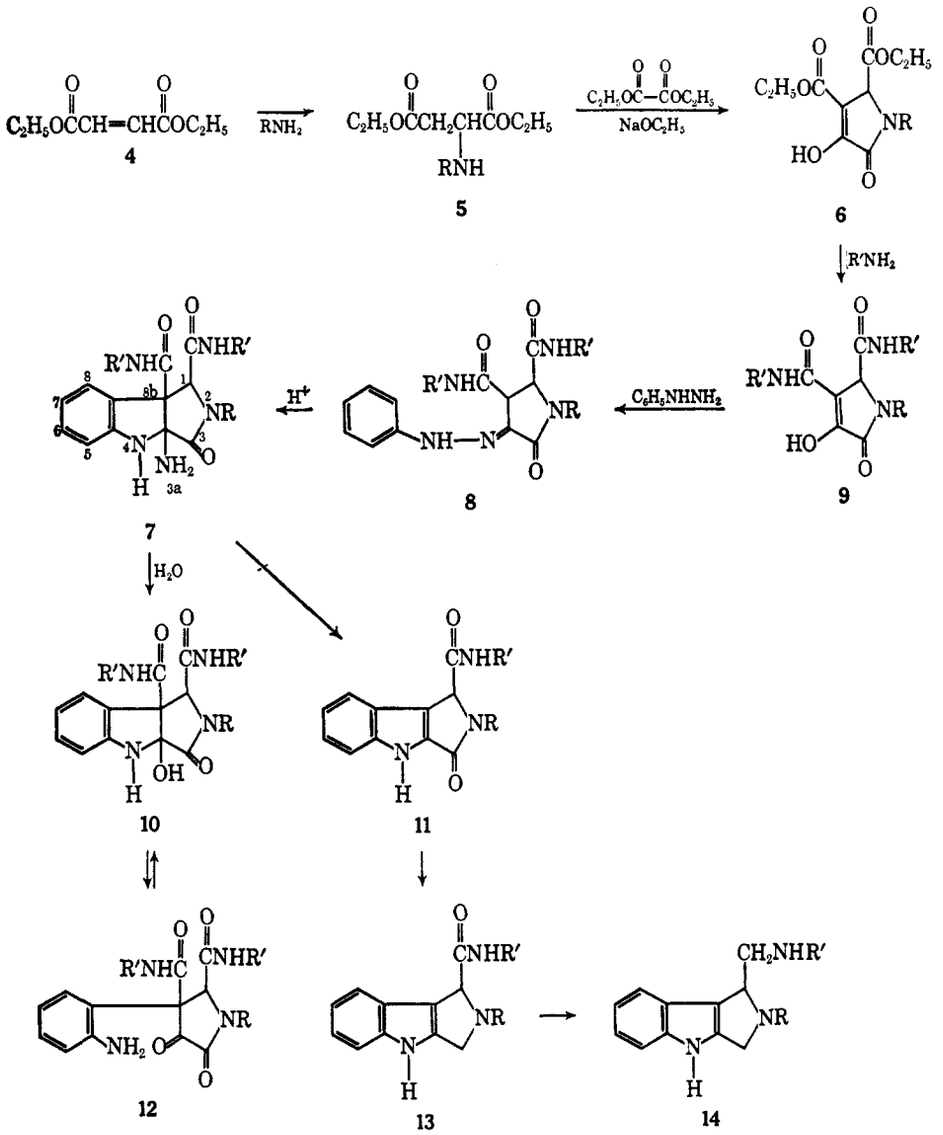
(3) See B. Robinson, *Chem. Rev.*, **63**, 373 (1963).

(4) For references to related observations in the literature, see footnote 8b of ref 2.

(5) The substituents R and R′ were benzyl or cyclohexyl in the compounds used in the experiments in which indole or indoline derivatives were prepared and studied. In the discussion and in the Experimental Section each individual compound will be identified with reference to the structures in Scheme I by giving the appropriate numeral from the scheme together with one or two appended letters (b for benzyl, c for cyclohexyl), the first designating the group R and the second the group R′.

(6) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

SCHEME I



sodium ethoxide in ethanol solution. Even in weakly basic solutions the compounds of type **6** exist in enolate form, and the delocalized negative charge in the enolate anion would be expected to reduce the reactivity of the 4-carbethoxy group toward nucleophilic agents such as amines. However, when catalysis by sodium ethoxide is provided,[7] the 4-carbethoxy group, as well as the more reactive 5-carbethoxy group, can be induced to undergo reaction with amines, and the N-substituted 4,5-dicarboxamido derivatives (**9**) can be obtained in satisfactory yield.

The phenylhydrazones of these compound underwent rearrangement readily when treated with solutions of hydrochloric acid in acetic acid to give products retaining all of the original nitrogen atoms. Ultraviolet spectra, which displayed maxima at *ca.* 300 mμ (ε 2150–2410) and shoulders at *ca.* 245 mμ (ε 2810–3470), indicated that these products were indoline derivatives.[2] Both the spectroscopic and chemical characterization of these compounds, did, in fact, establish their close resemblance to the previously studied compounds of structure **2**. Like the compounds of structure **2**, compound **7cc** underwent hydrolysis when refluxed with aqueous acetic acid with a change in composition corresponding to replacement of $-NH_2$ by $-OH$. The hydrolysis product showed infrared absorption at 2.89 μ, which could be attributed to a hydroxyl group, but none at *ca.* 5.7 μ, the position for the 3-keto group of a 2,3-dioxopyrrolidine. The ultraviolet spectrum of the hydrolysis product was very similar to those of the amino compounds (**7**) [λ_{max}^{EtOH} 298 mμ (ε 1808), shoulder at 243 mμ (ε 1808)] and again typical of indoline derivatives. It was evident, therefore, that mild acid treatment of the amino compound **7cc** had produced a 3a-hydroxy derivative (**10cc**), not an indolenine or the uncyclized ketonic tautomer (**12cc**).

The possibility remained that elimination of the elements of ammonia from compounds of type **7** to form indolenines might occur if more drastic reaction conditions were employed. As a matter of fact, decomposition with evolution of vapors was evident when hydrochlorides (**15**) of compounds of type **7** were held above their melting points. When these

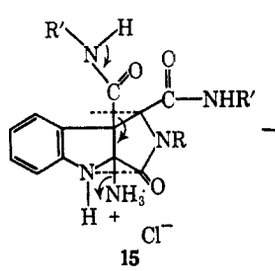
(7) See, for example, (a) R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1569 (1937); (b) P. B. Russell, *ibid.*, **72**, 1853 (1950); (c) P. J. Hawkins and D. S. Tarbell, *ibid.*, **75**, 2982 (1953); (d) R. Baltzly, I. M. Berger, and A. A. Rothstein, *ibid.*, **72**, 4149 (1950); (e) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).

hydrochlorides were heated in the absence of solvent at temperatures above about 220°, volatile products, including a crystalline substance, condensed on the cooler upper walls of the apparatus and the nonvolatile residues often resolidified after a time. These residues were found in many instances to consist almost entirely of a single compound.

The nonvolatile products of these thermal decompositions corresponded in composition and spectroscopic characteristics to the pyrrolo[3,4-*b*]indole structure (**11**). Their ultraviolet spectra, as well as their infrared spectra, showed a very close similarity to those of previously known compounds of this type.[8] Structure **11** also fully accounted for the nuclear magnetic resonance spectra of these products.[9] Unmistakable evidence for the presence of an indole nucleus was later seen in the spectra of the reduction products of these compounds which are described below. The volatile crystalline product from thermal decomposition of compound **7cc** proved to be N,N′-dicyclohexylurea, as demonstrated by comparison with an authentic sample.

The change in composition involved in conversion of compound **15cc** to the indole **11cc** by this fragmentation process is equivalent to elimination of the elements of ammonium chloride plus the elements of cyclohexyl isocyanate. It is apparent that the volatile decomposition product, N,N′-dicyclohexylurea, might arise from cyclohexyl isocyanate, although it is not known as yet how that conversion could occur under the conditions prevailing in the thermal decomposition.

As pictured in eq 1 below, the thermal decomposition would be analogous in form to various decarboxylation–elimination reactions which Grob has discussed as



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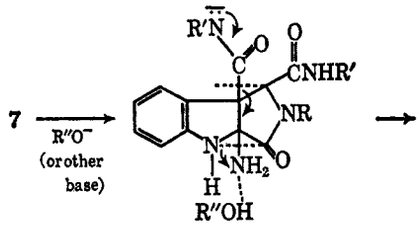
$$\longrightarrow \mathbf{11} + NH_4Cl + RN{=}C{=}O \quad (1)$$

examples of fragmentation processes.[10] In the formation of these indoles the release of alkyl isocyanate would replace the release of the carbon dioxide which occurred in the reactions considered by Grob.

Although no direct evidence has been obtained as yet to support it, this view of the mode of indole formation did lead to the discovery of a more convenient method for the conversion of compounds of type **7** into the indoles of type **11**. As an alternative to the promotion of fragmentation by protonation of the angular amino group to form the hydrochloride **15**, it seemed reasonable to attempt to initiate the process by removal of a proton from the angular carbamoyl function through the action of a strong base, as outlined in eq 2.



$$\mathbf{11} + NH_3 + RN{=}C{=}O \quad (2)$$

Although such a fragmentation was not realized by heating compounds of type **7** in ethanol containing sodium ethoxide, it did occur smoothly at 180° in ethylene glycol containing its sodium derivative. For the preparation of several grams of indoles of type **11** at one time, the base-catalyzed fragmentation in ethylene glycol was generally preferable to the thermal decomposition of the hydrochlorides **15**, from which wider variations in yield were observed. No search has been conducted as yet for the products derived from the eliminated angular substituents in the base-catalyzed fragmentation, although ammonia evolution was evident.

The results of one experiment in which a reduction with lithium aluminum hydride was sought in refluxing tetrahydrofuran demonstrated that with a sufficiently strong base (AlH_4^- ion) fragmentation of indolineamines of type **7** could be brought about under relatively mild conditions, since the reduction product obtained was of the type **13** and hence derived from a fragmentation product of type **11**. Thus the fragmentation had occurred at or below the boiling point of the solution, *ca.* 66°. Conceivably, such reactions may be favored by the geometry of the rather rigid structures **7**, in which the bonds to the angular groups being eliminated would be nearly coplanar, irrespective of whether the configuration of the system of fused five-membered rings is *cis* or *trans*. Grob[10a,b] has demonstrated that some types of fragmentation reactions are facilitated by an *anti*-periplanar[10c] conformation, as would be found in the *trans* isomer of **7**, but a *syn*-periplanar[10c] conformation, as found in the *cis* isomer, has apparently not been shown to produce this effect. Since the monocyclohexyl derivative of urea was not among the products isolated, there was no reason to assume that elimination was occurring *via* an intramolecular interaction of the 3a-amino group and the 8b-N-cyclohexylcarbamoyl group, such as might occur in the *cis* isomer of **7**.

The indole derivatives of type **11** were converted by reduction into compounds resembling many indole alkaloids with respect to incorporation of the tryptamine structure. Lithium aluminum hydride in tetrahydrofuran at room temperature removed the lactam carbonyl group of the pyrrolidine ring without reducing the side-chain amido function of compound **11cc**; the product **13cc** was produced in this manner in 76% yield. The conversion of the amide **13cc** into the N-substituted 1-aminomethyl derivative **14cc** was accomplished in 70% yield by the action of lithium aluminum hydride in refluxing dioxane. Under the latter conditions both carbonyl groups of the benzyl derivative **11cb** were removed to yield the 1-benzyl-

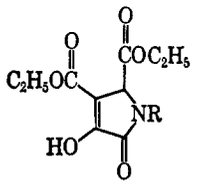
(8) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, **25**, 1133 (1960).

(9) The nmr spectrum of **11cc** in trifluoroacetic acid showed a singlet at τ 4.33 (proton at position 1 of the pyrrolo[3,4-*b*]indole system)and multiplets centered at *ca.* 8.3 (protons at unsubstituted positions of cyclohexyl groups), at *ca.* 5.9 (protons at 1 position of cyclohexyl groups), and at 2.5 (protons of indole structure).

(10) (a) C. A. Grob, "Theoretical Organic Chemistry," Report on the Kekulé Symposium, Butterworth and Co. Ltd., London, 1959, p 114; (b) C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkins, *Tetrahedron Lett.*, 2901 (1964); (c) W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

TABLE I

ENOLS OF 1-SUBSTITUTED 4,5-DICARBETHOXY-2,3-DIOXOPYRROLIDINES (6)



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R	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
c-C_6H_{11}–	125–127	75–80	$C_{16}H_{23}NO_6$	59.06	7.13	4.31	59.02	7.10	4.50
$C_6H_5CH_2$–	104–106[a]	47[b]	$C_{17}H_{19}NO_6$[c]	61.25	5.75	4.20	61.30	5.67	4.10
$C_6H_5CH_2CH_2$–	108–110[a]	48[b]	$C_{18}H_{21}NO_6$[d]	62.24	6.10	4.03	62.43	6.45	4.34
$(CH_3)_2CH$–	112–113[a]	55[b]	$C_{13}H_{19}NO_6$[e]	54.73	6.71	4.91	54.69	6.49	4.83
$CH_3(CH_2)_3$–	86–88[a]	46[b]	$C_{14}H_{21}NO_6$[f]	56.17	7.07	4.68	56.29	7.13	4.72

[a] Recrystallized from toluene. [b] Yield is of fully purified product. [c] Registry no: 16206-00-1. [d] 16206-01-2. [e] 16206-02-3. [f] 16206-03-4.

aminomethyl derivative **14cb** in 87% yield. The ultraviolet spectra of all of these reduction products (maxima at 269–274 mμ (ε 6000) with a shoulder at 286 mμ) corresponded closely to those of analogous indole derivatives such as 1,2,3,4-tetrahydrocarbazole.

Experimental Section[11]

1-Substituted 4,5-Dicarbethoxy-2,3-dioxopyrrolidines (6).—A number of slight variations of a single procedure were used in the preparation of these compounds. The procedure for the 1-cyclohexyl derivative which follows illustrates all of the significant details of the method. Results with other examples are given in Table I.

1-Cyclohexyl-4,5-dicarbethoxy-2,3-dioxopyrrolidine (6c).—Cyclohexylamine (99 g, 1.0 mol) was added to a solution of 172 g (1.0 mol) of diethyl maleate in 120 ml of absolute ethanol. The mixture was allowed to stand overnight at room temperature to complete the formation of diethyl N-cyclohexylaspartate. A solution of sodium ethoxide was prepared by dissolving 69 g (3.0 mol) of sodium in 1.5 l. of absolute ethanol. This solution was cooled to 10° or below, stirred, and maintained under a nitrogen atmosphere while 146 g (1.0 mol) of diethyl oxalate was added, followed by addition of the solution of diethyl N-cyclohexylaspartate described above. The mixture was allowed to warm to room temperature and was stirred overnight under a nitrogen atmosphere. Approximately one-half of the ethanol was then removed by distillation from a steam cone under reduced pressure. The residual solution was then stirred into *ca.* 6 l. of cold water and the mixture was acidified strongly with 20% hydrochloric acid to precipitate the product, which was collected by filtration, washed with water, and dried. Yields of crude product as high as 86% were obtained. Crystallization from aqueous ethanol, toluene, or benzene–petroleum ether (bp 60–110°) mixtures gave white needles, mp 125–126°. Typical yields of once-recrystallized product, mp 123–125°, were 55–65% using aqueous ethanol for recrystallization or 75–80% using the benzene–petroleum ether solvent mixture. Analytical samples, mp 125–127°, were obtained by crystallization from toluene or aqueous ethanol.

Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.02; H, 7.10; N, 4.50.

Preparation of 1-Cyclohexyl-4,5-bis-(N-substituted carbamoyl)-2,3-dioxopyrrolidines (9).—In an atmosphere of dry nitrogen, reagent grade benzylamine or freshly distilled cyclohexylamine (0.2 mol) was added dropwise to a stirred, concentrated solution of sodium ethoxide (prepared from 6.8 g (0.3 mol) of sodium and 160 ml of absolute ethanol, then concentrated by distillation of *ca.* 120 ml of ethanol). Under increased nitrogen pressure, 1-cyclohexyl-4,5-dicarbethoxy-2,3-dioxopyrrolidine (0.1 mol) was added in solid form to the above mixture, which was heated and stirred under reflux for 8–24 hr under an atmosphere of dry nitrogen. At the end of the heating period, the viscous bright red reaction mixture was poured into *ca.* 3 l. of distilled water and acidified with 20% hydrochloric acid to give an immediate precipitate of white solid. The mixture was allowed to stand at room temperature overnight. The solid product was collected by filtration, washed well with water, air dried, and recrystallized from methanol.

4,5-Bis-N-benzylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine (9cb).—A yield of 35.5 g (78.6%) of white needles, mp 239–240°, was obtained in a reaction period of 8 hr.

Anal. Calcd for $C_{26}H_{29}N_3O_4$: C, 69.78; H, 6.53; N, 9.39. Found: C, 69.53; H, 6.50; N, 9.32.

4,5-Bis-N-cyclohexylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine (9cc).—A yield of 31.25 g (72.4%) of white powder, mp 195–215°, was obtained in a reaction period of 24 hr. Recrystallization from methanol produced white needles, mp 246–247°.

Anal. Calcd for $C_{24}H_{37}N_3O_4$: C, 66.74; H, 8.64; N, 9.79. Found: C, 66.72; H, 8.60; N, 9.74.

Preparation of 1-Cyclohexyl-4,5-bis-(N-substituted carbamoyl)-2,3-dioxopyrrolidine Phenylhydrazones (8).—To a suspension of the 4,5-bis-(N-substituted carbamoyl)-1-cyclohexyl-2,3-dioxopyrrolidine in methanol (20 ml/g of compound) was added phenylhydrazine (1.5 mol/mol of compound) and glacial acetic acid (0.2 ml/g of compound) and the resulting slurry was heated at the boiling point for 30 min, then stirred at room temperature for 2 hr. The starting material gradually dissolved and the solution turned yellow. The product began to precipitate during the period of stirring at room temperature. (Samples withdrawn from the solution gave a red ferric chloride test until reaction was complete.) After evaporation of some of the methanol, the mixture was cooled, and the phenylhydrazone was collected by filtration, washed with ether, and air dried. The yields quoted are of the crystalline products obtained directly from the reaction mixture. In both cases the products were pure enough to be used in the subsequent reactions without further purification. Analytical samples, recrystallized from methanol, have the same melting points as the initial crystalline products.

4,5-Bis-N-benzylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine Phenylhydrazone (8cb).—A yield of 38.3 g (90%) of light yellow needles, mp 185–186°, was obtained from 35.40 g (0.079 mol) of 4,5-bis-N-benzylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine: ultraviolet spectrum (95% ethanol), λ_{max} 236 mμ (ε 8420), 296 (3860), 349 (16,870); $\lambda_{shoulder}$ 288 mμ (ε 3820); λ_{min} 226 mμ (ε 7430), 261 (2090), 303 (3290).

Anal. Calcd for $C_{32}H_{35}N_5O_3$: C, 71.48; H, 6.56; N, 13.03. Found: C, 71.69; H, 6.49; N, 12.72.

4,5-Bis-N-cyclohexylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine Phenylhydrazone (8cc).—A yield of 14.5 g (80%) of light yellow needles, mp 226–227°, was obtained from 15.0 g (0.035 mol) of 4,5-bis-N-cyclohexylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine.

Anal. Calcd for $C_{30}H_{43}N_5O_3$: C, 69.07; H, 8.31; N, 13.43. Found: C, 68.92; H, 8.27; N, 13.19.

(11) Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England; Galbraith Laboratories, Knoxville, Tenn.; Alfred Bernhardt, Mülheim, Germany; and Geller Laboratories, Saddle River, N. J. Ultraviolet spectra were obtained with a Cary Model 11 spectrophotometer, nuclear magnetic resonance spectra with a Varian A60 instrument. Infrared spectra were measured using potassium bromide pellets or Nujol mulls with a Perkin-Elmer Infracord spectrophotometer. Only those infrared bands characteristic of the particular structural type being examined are listed; figures indicate wavelength in microns; s, m, w, and sh indicate, respectively, strong, medium, weak, and shoulder.

Preparation of 1,8b-Bis-(N-substituted carbamoyl)-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-ones (7) and Their Hydrochlorides (15).—The 4,5-bis-(N-substituted carbamoyl)-1-cyclohexyl-2,3-dioxopyrrolidine phenylhydrazones were suspended in a solution of glacial acetic acid (10 ml/g of compound) and concentrated hydrochloric acid (3 ml/g of compound). The mixtures were heated on a hot plate until solution occurred (*ca.* 20 min), cooled to room temperature, and diluted with water (*ca.* 150 ml of water/g of phenylhydrazone) to give an immediate bright yellow precipitate. The reaction mixture was allowed to stand at room temperature for 30 min to complete the precipitation of the product, which was then collected by filtration, washed well with water, air dried, and recrystallized from methanol. In both cases the crude product was used in the subsequent step without recrystallization.

1,8b-Bis-N-cyclohexylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,-4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one (7cc) and Its Hydrochloride (15cc).—A yield of 9.75 g of yellow powder, mp 212–217°, was obtained from 9.8 g (0.0182 mol) of 1-cyclohexyl-4,5-bis-N-cyclohexylcarbamoyl-2,3-dioxopyrrolidine phenylhydrazone (**8cc**). After the powder melted, the melt solidified at 227° and remelted at *ca.* 290°. It consisted in part of the hydrochloride. The salt could be separated from the free base by fractional crystallization, but only with a great loss of material. The free 3a-amino compound was obtained in 75% yield as a relatively pure solid by making the original aqueous acid solution strongly basic with 40% sodium hydroxide solution while keeping the temperature below 30°. The resulting mixture was extracted with chloroform, and the chloroform extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to yield an orange oil which was crystallized from methanol to yield white needles: mp 250–255° (recrystallization from methanol narrowed the melting range to 252–254°; the melt did not solidify upon raising the bath temperature above 270°): ultraviolet spectrum (95% ethanol), λ_{max} 299 mμ (ε 2410); $\lambda_{shoulder}$ 245 mμ (ε 3470); λ_{min} 270 mμ (ε 535); infrared spectrum, 2.86 m, 2.98 m, 6.04 s, 6.41 s, 8.16 μ m.

Anal. Calcd for $C_{30}H_{43}N_5O_3$: C, 69.07; H, 8.31; N, 13.43. Found: C, 68.84; H, 8.26; N, 13.64.

The hydrochloride was prepared by dissolving 50 mg (0.096 mmol) of 1,8b-bis-N-cyclohexylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one in 15 ml of absolute ethanol and then saturating this solution with dry hydrogen chloride gas. Most of the ethanol was then removed by evaporation under reduced pressure, and ether was added to yield an immediate white precipitate. After cooling to complete the precipitation, the product was collected by filtration, washed with ether, and air dried. Recrystallization from a methanol–ethyl acetate solution afforded 48.8 mg (91%) of 1,8b-bis-N-cyclohexylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one hydrochloride (**15cc**), as white needles, mp 225–226°. The melt solidified immediately after melting and then remelted at *ca.* 310°. Upon basicification of an aqueous slurry of this hydrochloride and subsequent extraction with ether, the free 3a-amino compound could be recovered in quantitative yield: ultraviolet spectrum of **15 cc** (95% ethanol), λ_{max} 299 (ε 2150); $\lambda_{shoulder}$ 245 mμ (ε 3310); λ_{min} 271 mμ (ε 540); infrared spectrum, 3.01 s, 5.89 s, 6.00 s, 6.21 m, 6.49 s, 6.80 s, 13.41 μ m.

Anal. Calcd for $C_{30}H_{44}N_5O_3Cl$: C, 64.55; H, 7.95; N, 12.55; Cl, 6.35. Found: C, 64.34; H, 7.91; N, 12.78; Cl, 6.63.

1,8b-Bis-N-benzylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one (7cb) and Its Hydrochloride (15cb).—The yield was 36.6 g (96%) of yellow powder, mp 220–235°, from 38.3 g (0.71 mol) of 4,5-bis-N-benzylcarbamoyl-1-cyclohexyl-2,3-dioxopyrrolidine phenylhydrazone (**8cb**). Recrystallization from methanol produced off-white needles: mp 264–265°; ultraviolet spectrum (95% ethanol), λ_{max} 300 mμ (ε 2150); $\lambda_{shoulder}$ 245 mμ (ε 2760); λ_{min} 272 mμ (ε ~0); infrared spectrum, 2.90 m, 2.99 m, 6.05 s, 6.37 s, 8.15 μ m.

Anal. Calcd for $C_{32}H_{35}N_5O_3$: C, 71.48; H, 6.56; N, 13.02. Found: C, 71.66; H, 6.58; N, 12.90.

A suspension of 1,8b-benzylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one (**7cb**) (1.85 g, 3.44 mmol) in 400 ml of absolute ethanol was saturated with dry hydrogen chloride gas to produce a clear colorless solution. This solution was concentrated by removal of ethanol under reduced pressure and then anhydrous ether was added to the cloudy point. After cooling at 0° for 4 hr, the precipitate product was collected by filtration, washed well with ether, and air dried. Recrystallization from 2-propanol afforded 1.8 g (91%) of 1,8b-bis-N-benzylcarbamoyl-2-cyclohexyl-3a-amino-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indol-(2H)-one hydrochloride (**15cb**), as white needles, mp 181–183°. The melt solidified at 232° and remelted at 240–246°. Analytical results suggest that this hydrochloride, which was difficult to recrystallize, was not fully purified: ultraviolet spectrum (95% ethanol), λ_{max} 299 mμ (ε 2160); $\lambda_{shoulder}$ 246 mμ (ε 2810); λ_{min} 272 mμ (ε 777); infrared spectrum, 3.00 m, 5.88 s, 5.98 s, 6.23 m, 6.43 m, 6.76 m, 13.40 μ m.

Anal. Calcd for $C_{32}H_{38}N_5O_3Cl$: C, 66.94; H, 6.32; N, 12.20. Found: C, 65.26; H, 6.32; N, 11.81.

1,8b-Bis-N-cyclohexylcarbamoyl-2-cyclohexyl-3a-hydroxy-3a,4,8b-tetrahydropyrrolo[3,4-b]indol-3(2H)-one (10cc).—A yield of 0.57 g (71%) of the 3a-hydroxy compound as white needles, mp 249–251°, was obtained from 0.8 g (1.54 mmol) of compound **7cc** when it was refluxed for 1.5 hr with 40 ml of 60% aqueous acetic acid, and the mixture was diluted with water. Recrystallization from a benzene–methanol solution yielded the analytical sample: mp 293–294°; ultraviolet spectrum (95% ethanol), λ_{max} 298 mμ (ε 1808); $\lambda_{shoulder}$ 243 mμ (ε 1808); λ_{min} 269 mμ (ε ~0); infrared spectrum, 2.85 m, 3.05 m, 3.25 m, 5.90 s, 6.01 s, 6.22 s, 6.50 μ s.

Anal. Calcd for $C_{30}H_{42}N_4O_4$: C, 68.93; H, 8.10; N, 10.72. Found: C, 68.69; H, 8.05; N, 10.58.

Preparation of 1-(N-Substituted carbamoyl)-2-cyclohexyl-1,4-dihydropyrrolo[3,4-b]indol-3(2H)-ones (11). Procedure A. Thermal Decomposition of Hydrochlorides of Type 15.—The initial experiments were conducted in a vacuum sublimation apparatus equipped with a cold-finger condenser. The system was flushed with dry nitrogen and evacuated after the sample had been placed in the sublimation vessel. This vessel was then immersed to a depth of about 1 in. in an oil bath previously heated to a temperature just above the melting point of the sample. The temperature was held at this point until resolidification of the melt occurred, usually after a period of 30 min or less. Further heating at a somewhat higher temperature (usually 30–50° higher) then brought about removal of volatile products from the resolidified residue and removed a good deal of its original dark brown color. During the early part of the heating period solid or liquid decomposition products collected on the cold finger, which remained at a temperature about 100° below that of the heating bath. Frequently heating of the evacuated sublimator was continued for 15–20 hr to complete the removal of the volatile products from the residue. Examination of the white crystalline condensate which had deposited on the cold finger during decomposition of the bis-N-cyclohexylcarbamoyl derivative **15cc** disclosed that it was N,N′-dicyclohexylurea, as demonstrated by comparison with an authentic sample. It was obtained as white needles, mp 227–228°, after crystallization from acetone. The residue in the sublimation vessel represented the indole derivatives formed, and these were purified by recrystallization from ethanol.

Subsequent experiments showed that a very simple procedure would suffice for thermal conversion of the aminoindoline hydrochlorides of type **15** to indole derivatives of type **11**. A test tube containing the aminoindoline hydrochloride (**15**) was immersed in an oil bath already raised to a temperature slightly above the melting point of the compound, and heating was continued at that temperature for *ca.* 5 min. During this period the melt usually resolidified. By then raising the temperature by *ca.* 20° and continuing the heating for 20 min the N,N′-disubstituted urea which had been formed was caused to sublime and condense on the cooler upper walls of the tube, while the color of the residue at the bottom of the tube faded from dark brown to light tan. After the tube had been cooled acetone was added with a dropper to the residue in the bottom and the resulting acetone suspension was removed in the dropper and filtered to collect the indole derivative, which was usually nearly white and quite free from impurities.

Procedure B. Base-Catalyzed Fragmentation of the Aminoindolines 7.—A stirred solution prepared by dissolving sodium (3 mol/mol of **7**) in ethylene glycol (40 ml/g of **7**) was held at room temperature while the aminoindoline derivative (**7**) was added in solid form. Stirring was continued while the temperature was raised to *ca.* 180° and all of the solid had dissolved. The indole derivative (**11**) was precipitated by pouring the hot solution onto ice. After the resulting mixture was acidified and the ice had melted the product was collected by filtration, washed

with water, and air dried. The products so obtained were nearly white and pure enough for use in subsequent reactions without purification.

1-N-Benzylcarbamoyl-2-cyclohexyl-1,4-dihydropyrrolo[3,4-*b*]-indol-3-(2H)-one (11cb). From Procedure A.—Compound **11cb** was obtained in a yield of 0.05 g (76%) of tan powder, mp 273–274°, from 0.1 g (0.174 mmol) of the hydrochloride **15cb**. The fragmentation reaction was rapid at the melting point of **15cb** and the melt resolidified almost immediately.

From Procedure B.—Compound **11cb** was obtained in a yield of 2.8 g (78%) of light tan powder, mp 273–276°, from 5.0 g (9.25 mmol) of **7cb** (recrystallization from absolute ethanol gave the raised mp 279–280° dec): ultraviolet spectrum (95% ethanol), λ_{max} 299 mμ (ε 16,550); $\lambda_{shoulders}$ 225 mμ (ε 28,000), 308 (14,610); λ_{min} 263 mμ (ε 2550); infrared spectrum, 2.99 m, 3.10 m, 5.98 s, 6.02 s, 6.52 m, 7.50 m, 8.28 m, 13.60 μ s.

Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.85. Found: C, 74.17; H, 6.65; N, 10.64.

1-N-Cyclohexylcarbamoyl-2-cyclohexyl-1,4-dihydropyrrolo-[3,4-*b*]indol-3(2H)-one (11cc). From Procedure A.—Compound **11cc** was obtained in a yield of 0.15 g (80%) of an off-white crystalline solid, mp 315–317°, from 0.25 g (0.48 mmol) of the hydrochloride **15cc**.

From Procedure B.—Compound **11cc** was obtained in a yield of 7.70 g (*ca.* 80%) of white needles, mp 316–318°, from 13.5 g (*ca.* 0.025 mol) of a mixture of **7cc** and its hydrochloride **15cc** (recrystallization from absolute ethanol raised the melting point to 317–319°): ultraviolet spectrum (95% ethanol), λ_{max} 222 mμ (ε 24,140), 298 (16,120); $\lambda_{shoulders}$ 306 mμ (ε 14,310), 253 (3710); λ_{min} 261 mμ (ε 1570); infrared spectrum, 2.99 m, 3.10 m, 5.99 s, 6.02 s sh, 6.54 m, 7.49 m, 8.30 m, 13.70 μ s.

Anal. Calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.73; H, 7.73; N, 11.06.

1-N-Cyclohexylcarbamoyl-2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole Hydrochloride (13cc).—The lithium aluminum hydride reductions to be described under this and the next two headings were carried out by adding the solid indole derivative of types **11** or **13** to a stirred slurry of lithium aluminum hydride in purified tetrahydrofuran (distilled from lithium aluminum hydride, stored over calcium hydride) or dioxane (chromatographed over alumina) in a dry nitrogen atmosphere. The reaction mixtures were refluxed for several hours, then cooled in an ice bath, and worked up by one of several alternative procedures, as described below. A mixture of 3.79 g (0.01 mol) of compound **11cc** and 3.8 g of lithium aluminum hydride in 80 ml of tetrahydrofuran was refluxed for 13 hr and decomposed by cautious addition of water. After the excess hydride was destroyed, enough 20% hydrochloric acid was added to dissolve the precipitated salts, and the solution was evaporated to dryness under reduced pressure. The residual oily solid was extracted into hot methanol. The product crystallized from the methanol solution when it was cooled overnight in a refrigerator; filtration afforded 3.05 g (76%) of the hydrochloride of **13cc**, mp 201–204°. Recrystallization from methanol yielded the pure hydrochloride: mp 205–206°; ultraviolet spectrum (95% ethanol), λ_{max} 218 mμ (ε 23,650), 269 (6080), 286 (3840); $\lambda_{shoulders}$ 276 mμ (ε 5690), 279 (5590); λ_{min} 240 mμ (ε 1300), 283 (3630); infrared spectrum, 2.95 m, 315 s, 3.28 s, 6.01 s, 6.40 m, 13.12 μ s.

Anal. Calcd for $C_{23}H_{31}N_3O \cdot HCl$: C, 68.72; H, 8.02; N, 10.45. Found: C, 68.69; H, 8.09; N, 10.28.

1-N-Cyclohexylaminomethyl-2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (14cc).—The reaction mixture containing 1.90 g (0.0047 mol) of 1-N-cyclohexylcarbamoyl-2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole hydrochloride **13cc** and 1.90 g of lithium aluminum hydride in 40 ml of dioxane was refluxed for 7 hr. Saturated sodium sulfate solution, sufficient to decompose the lithium and aluminum salts, was added after the solution had cooled. The resulting mixture was filtered and the residue was washed well with ether. The organic solution was evaporated to dryness under reduced pressure to yield a light brown oil which was crystallized from methanol solution. Recrystallization from a methanol–ether solution afforded 1.15 g (70%) of the free amine: mp 151–152°; ultraviolet spectrum (95% ethanol), λ_{max} 273 mμ (ε 6000); $\lambda_{shoulder}$ 287 mμ (ε 4220); λ_{min} 244 mμ (ε 778); infrared spectrum, 3.22 s, 3.61 s, 6.18 w, 6.30 w, 8.91 m, 9.15 m, 13.69 μ s.

Anal. Calcd for $C_{23}H_{33}N_3$: C, 78.58; H, 9.46; N, 11.95. Found: C, 78.62; H, 9.60; N, 11.88.

1-N-Benzylaminomethyl-2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (14cb) and its Dihydrochloride.—The reaction mixture containing 3.87 g (0.01 mol) of compound **11cb** and 3.9 g of lithium aluminum hydride in 80 ml of dioxane was refluxed for 8 hr, decomposed with saturated sodium sulfate (20 ml), filtered, and evaporated to dryness under reduced pressure. The residue was taken up in anhydrous ether and the resulting solution was saturated with dry hydrogen chloride gas. The precipitated solid was collected by filtration, washed with ether, air dried, and recrystallized from an absolute ethanol–ether mixture to yield 3.75 g (87%) of the dihydrochloride: mp 163–164°; ultraviolet spectrum (95%) ethanol), λ_{max} 269 mμ (ε 6390); $\lambda_{shoulder}$ 286 mμ (ε 4190); λ_{min} 241 mμ (ε 2180).

Anal. Calcd for $C_{24}H_{29}N_3 \cdot 2HCl$: C, 66.66; H, 7.23; N, 9.72. Found: C, 66.50; H, 7.25; N, 9.66.

The free base, 1-N-benzylaminomethyl-2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole, mp 107–108°, could be obtained in quantitative yield by treating an aqueous slurry of the dihydrochloride with base, followed by extraction with ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to yield an orange oil, which afforded white crystals from an ether–Skellysolve B mixture: ultraviolet spectrum (95% ethanol), λ_{max} 274 mμ (ε 6500); $\lambda_{shoulder}$ 287 mμ (ε 4700); λ_{min} 243 (ε 1150); infrared spectrum, 3.23 s, 3.60 m, 6.20 w, 6.31 w, 8.92 s, 9.17 m, 13.80 μ s.

Anal. Calcd for $C_{24}H_{29}N_3$: C, 80.18; H, 8.13; N, 11.69. Found: C, 80.37; H, 7.95; N, 11.70.

Registry No.—**6c**, 16206-17-0; **7cc**, 16206-04-5; **7cb**, 16206-05-6; **8cc**, 16223-86-0; **8cb**, 16206-06-7; **9cc**, 16206-07-8; **9cb**, 16206-08-9; **10cc**, 16223-69-1; **11cc**, 16206-09-0; **11cb**, 16206-10-3; **13cc**, 16206-11-4; **14cc**, 16206-12-5; **14cb**, 16206-13-6; **14cb** 2HCl, 16206-14-7; **15cc**, 16206-15-8; **15cb**, 16206-16-9; indole, 120-72-9.