Tetrahedron Letters No.18, pp. 1741-1746, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE CYCLIZATION PHASE OF THE FISCHER INDOLE SYNTHESIS. THE STRUCTURE AND SIGNIFICANCE OF PLIENINGER'S INTERMEDIATE.*

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(Received 21 January 1967; in revised form 8 March 1967)

Plieninger (1) reported that the phenylhydrazone of α-keto-γ-butyrolactone (I), when subjected to the conditions appropriate for the Fischer indole synthesis (treatment with hydrogen chloride in glacial acetic acid at 90°), rearranged to form a product for which the structure II was suggested. The latter substance yielded the indole III when heated in a mixture of glacial acetic acid and concentrated hydrochloric acid; it was regarded by Plieninger as representing an intermediate of a type which had been postulated to intervene in the course of the Fischer synthesis (2), but had not previously been demonstrated by isolation.

In a more recent study (3), similar treatment of the phenylhydrazones of several 1-substituted-4-benzyl-2,3-dioxopyrrolidines (V) was found to lead to 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-b]indole-3(2H)-ones (VIII). It seemed quite possible, therefore, that Plieninger's intermediate might be similarly constituted (as in formula IV); no spectroscopic characterization supporting structure II had been reported.

In agreement with Plieninger's findings, we found that the action of hydrogen chloride in acetic acid on α-keto-γ-butyrolactone phenylhydrazone (I) (4) yielded a rearrangement product which retained both nitrogen atoms. (Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.30; N, 14.99.) Our sample, which was purified by recrystallization from

*Supported in part by a research grant (GM-04371) from the National Institutes of Health, U.S. Public Health Service.

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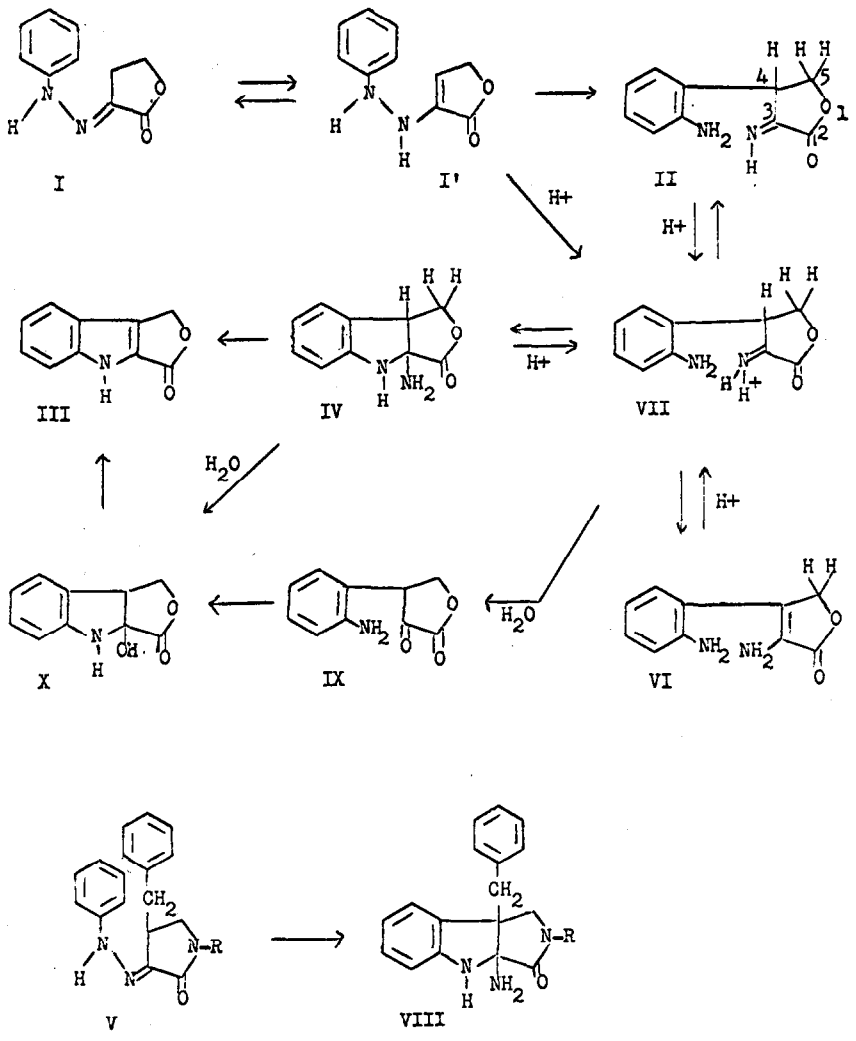
Chart I



absolute ethanol, showed a slightly higher melting point (99-101°) than that previously reported (86°), but the observations recorded below leave little doubt that we obtained the same substance. Perhaps our sample represents a second crystalline form.

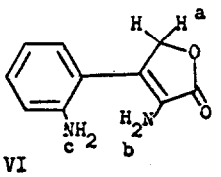
Ultraviolet and nuclear magnetic resonance data obtained in the present investigation appear to eliminate both II and IV as possible correct structures for Plieninger's intermediate, and to show that the compound is the lactone of 2-amino-3(o-aminophenyl)-4-hydroxy-2-butenoic acid (VI), a tautomer of II. The ultraviolet spectrum (Table I) is clearly not that of an indoline (3,5) of structure IV, which should have its long-wavelength maximum at ca. 300 mμ. Strong evidence in favor of structure VI is found in the extremely simple n.m.r. spectrum (6) of the Plieninger intermediate (Figure 1 and Table I), which consisted of a downfield multiplet from four aromatic protons, a broad four-proton signal at 5.96 τ removable by exchange with deuterium oxide, and a narrow signal at 5.18 τ from two non-exchangeable protons. The spectrum is consistent with structure VI (four protons on nitrogen, two like protons on carbon at position 5) but not with structures II or IV (three protons on nitrogen, three unlike protons on carbon at positions 4 and 5). No structure other than VI seems to provide an acceptable explanation for the conversion of the intermediate to the indole III and for the spectroscopic data (7).

As outlined in Chart II, a pyrrolidine analogue (XIV, 3-amino-4-(o-aminophenyl)-1-cyclohexyl-3-pyrrolin-2-one) of Plieninger's intermediate (VI) has now been synthesized. The ultraviolet and n.m.r. spectra of XIV closely resemble those of VI, as is evident from the data presented in Table I. Compound XIV was not converted to the corresponding indole (XVII) when heated in methanol, but was so converted when heated in methanol containing acetic acid or when allowed to stand in dilute hydrochloric acid at room temperature. The last observation appears to account for the failure (8) to obtain compound XIV as an intermediate in the Fischer reaction of XVIII. The methanolic acetic acid treatment failed to convert VI to the indole III.

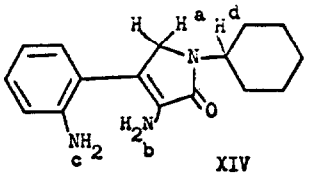
Formation of a compound with properties corresponding to the enol of a keto lactone (XIII) accompanied the preparation of the intermediate XII, and XIII could be obtained in satisfactory yield by substituting triethylamine for cyclohexylamine in the reaction mixture. Unfortunately, efforts to convert compound XIII to the corresponding enamine XVI produced no more than trace amounts of the latter substance. Except for XVI, all new compounds shown in Chart II were characterized by analysis and appropriate spectroscopic measurements.

TABLE I

Ultraviolet and Nuclear Magnetic Resonance Data



VI



XIV

Ultraviolet Spectra in 95% Ethanol

Plieninger's Intermediate (VI)				Compound XIV			
maxima		minima		maxima		minima	
λ (mμ)	log ε	λ(mμ)	log ε	λ(mμ)	log ε	λ(mμ)	log ε
235	4.09	222	4.02	230	4.23	220	4.18
284	4.00	262	3.84	285	3.98	265	3.79
322	3.82	310	3.79	314	3.87	302	3.85

NMR Signals in Deuteriochloroform(a)

Plieninger's Intermediate (VI)				Compound XIV			
	Signal				Signal		
Proton Position	τ Value	No. of H's	Type	Proton Position	τ Value	No. of H's	Type
a	5.18	2	single, narrow, no effect by D_2O	a	6.00	2	single, narrow after D_2O exchange
b, c	5.96	4	single, broad, removed by D_2O	b, c	6.00	4	single, broad, removed by D_2O
				d	6.00-6.30	1	broad, seen at base of the a signal after D_2O exchange

(a) Signals from aromatic ring and upfield signals from cyclohexyl not listed.

FIG. 1

NMR Spectrum of VI

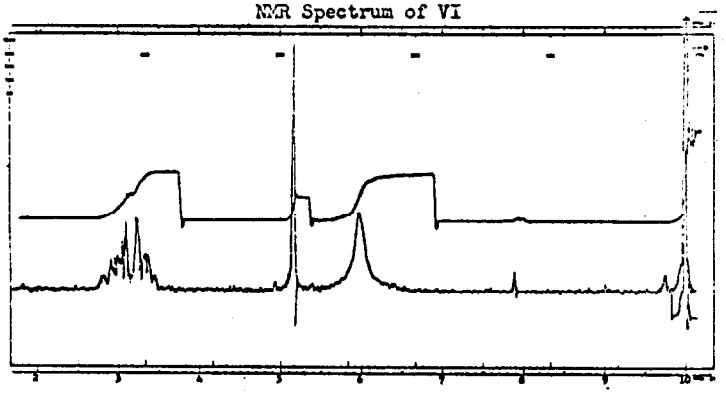
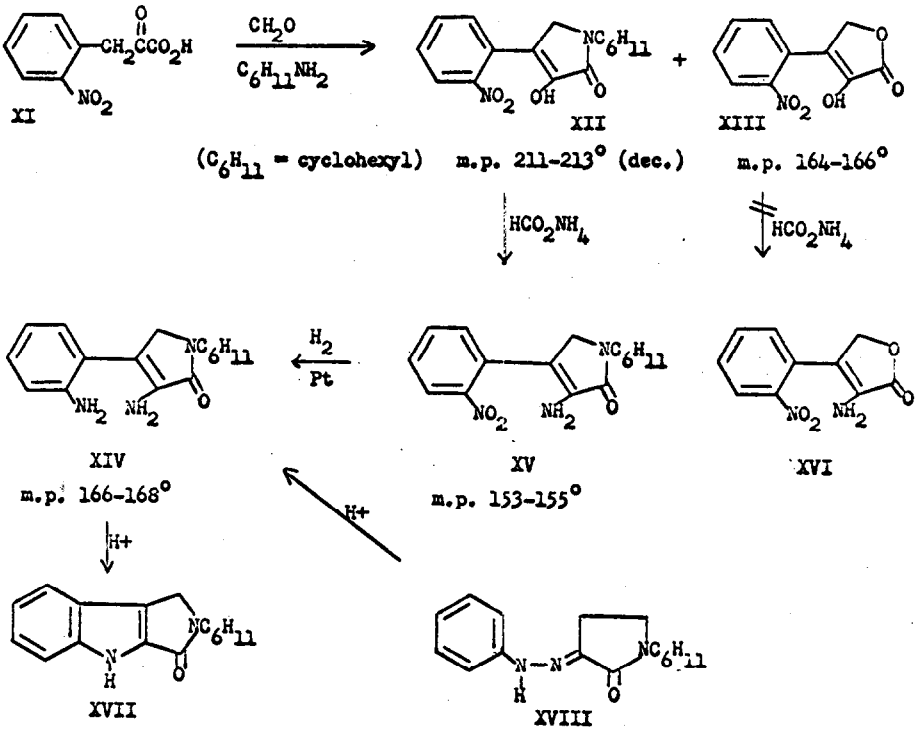


Chart II



The requirement for acid catalysis to effect indolization of either enamine VI or enamine XIV strongly suggests that imonium ions such as VII are normally involved in the final ring-closure stages of the Fischer indole synthesis. Such might be the case whether, in a particular instance, hydrolysis to a keto compound (such as IX) intervenes in the cyclization process or direct cyclization to a 2-aminoindoline (such as IV) represents the mode of cyclization. Imonium ions rather than imines (e.g., VII rather than II) may, in fact, very well be the initial products which follow the aromatic ring substitution which occurs in the first stages of the Fischer indole synthesis. The Plieninger enamine would result from deprotonation of such an imonium ion. The exceptional resistance of Plieninger's enamine VI to indolization seems to reflect a very low basicity of its enamine function (even lower than that of the lactam analogue XIV) and a consequent low concentration of VII in acid solutions. Monoprotonation of VI may occur almost exclusively at the aromatic amine group.

There have been other reports of acid-induced rearrangements of phenylhydrazones which occurred without spontaneous removal of the elements of ammonia to form an indole or indolenine (9a,b), but whether these products were enamines analogous to Plieninger's compound, 2-amino-indolines analogous to VIII, or still other types of isomers has not been determined.

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(6) The n.m.r. spectra were obtained with a Varian A-60 spectrometer provided by National Science Foundation Grant GP-3660.

(7) Professor Plieninger reports (private communication) that he reached the same conclusion on the basis of a less complete unpublished n.m.r. investigation conducted in 1964.

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