Tetrahedron Letters No. 16, pp. 701-707, 1962. Pergamon Press Ltd. Printed in Great Britain.

CYCLOL FORMATION IN PEPTIDE SYSTEMS

TAUTOMERISM OF N-(α-HYDROXYACYL)-AMIDES

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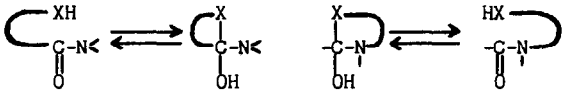
(Received 15 June 1962)

INTRAMOLECULAR interaction of amide groups with various functional groups (OH, SH, NH_2) has been repeatedly advanced as the underlying cause for the specific properties of peptides or related compound such as ergot alkaloids,[1] the antibiotics bacitracin A[2] and polymyxin M,[3] peptides containing cysteine, serine and threonine residues,[4,5] esterases[6] etc. In all cases the formation of unstable intermediates (cyclols) has been postulated. However,



X = O, S, NH

this assumption had no experimental backing, being based only on indirect evidence; namely, enhanced reactivity of the amide group or formation of unexpected reaction products. Investigation of this problem on examples wherein the cyclols formed were more or less stable would therefore be of considerable theoretical interest.

[1] A. Stoll, Progr. Chem. Org. Nat. Prod. 9, 114 (1952).

[2] D. Wrinch, Nature, Lond. 179, 536 (1957).

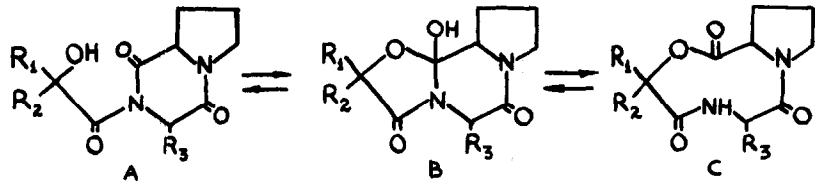
[3] A.B. Silaev, G.S. Katrukha, L.I. Andreeva and L.V. Kozlova, IV European Symposium on Peptides Moscow (1961).

[4] L. Cohen and B. Witkop, Angew. Chem. 73, 253 (1961).

[5] H. Brenner, CIBA Foundation Symposium on Amino Acids and Peptides with Antimetabolic Acitivity p. 157. London (1958).

[6] S. Bernhard, J. Cell. Comp. Physiol. 54, suppl. 1, 252 (1959).

One should expect that N-(α-hydroxyacyl)-amides, possessing greatly diminished electron density at the carbonyl C-atoms, would give rise to cyclols of sufficient stability and it was with glycolyl diketopiperazines and glycolyl lactams that we began this series of studies. These compounds are of interest primarily because they may be regarded as models of the peptide moiety of ergot alkaloids, for which a cyclol structure (Formula IB for ergotamine) has been proposed by Stoll[1]. At the same time we have expressed the opinion that ergot alkaloids and their analogues can undergo intraconversions of the type A ⇄ B ⇄ C.[7]



A B C

Ergotamine (I), R_1= lysergyl-NH, R_2= CH_3, R_3= CH_2Ph
Ergotamine analog (II), R_1= H, R_2= CH_3, R_3= CH_2Ph

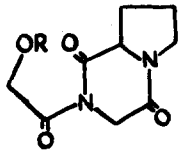
The present investigation carried out with compounds III-XIV (Tables 1 and 2) has shown for the first time the existence of a tautomeric equilibrium between A and B type structures - in the case of relatively simple N-(α-hydroxyacyl)-amides - and has also provided unequivocal proof of the cyclol structure of these compounds as well as of ergotamine.*

Benzyloxyacetyl derivatives III, V, VII and IX were prepared by refluxing toluene solutions of diketopiperazines and lactams with $C_6H_5CH_2OCH_2COCl$. The I.R. spectra of these compounds exhibit an absorption

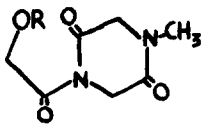
* In the course of this study Hofmann et al. [A. Hofmann, A.J. Frey and H. Ott, Experientia 17, 206 (1961); A. Hofmann, A.J. Frey, H. Ott and J. Rutschmann, IV European Symposium on Peptides Moscow (1961)] published preliminary reports on the synthesis of ergotamine and its II-analogue, without, however, presenting experimental evidence for the formulation of ergotamine as a cyclol; their results could therefore, regrettably not be used in further study of cyclol chemistry.

7 V.K. Antonov, G.A. Ravdel and M.M. Shemyakin, Chimia 14, 374 (1960); G.A. Ravdel, N.A. Krit, L.A. Shchukina and M.M. Shemyakin, Dokl. Akad. Nauk SSSR 137, 1377 (1961).

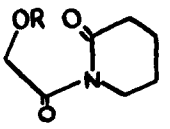
band in the region 1710-1740 cm^{-1} characteristic of the -CO-N-CO- grouping.[8,9]



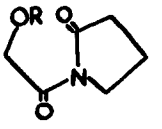
III, R= CH_2Ph
IV, R= H



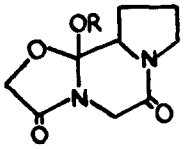
V, R= CH_2Ph
VI, R= H



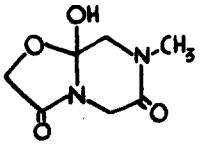
VII, R= CH_2Ph
VIII, R= H



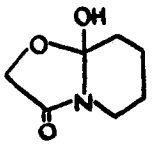
IX, R= CH_2Ph
X, R= H



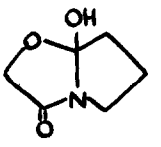
XI, R= H
XII, R= CH_3



XIII



XIV



XV

Compounds III and V also display a 1693 cm^{-1} band belonging to the glycyl CO. Hydrogenolysis with Pd-black of III, V, VII and IX in abs. THF led to glycolyl derivatives IV, VI, VIII and X which (excepting X) immediately, or gradually, cyclolize to XI, XIII and XIV, respectively. Thus in the spectrum of the solution of IV, obtained on hydrogenolysis of III one initially observes bands at 1730 and 1693 cm^{-1}, but by 10-15 days the 1693 cm^{-1} band has faded considerably, whereas a strong band has appeared at 1672 cm^{-1}. The cause of these spectral changes is the formation of a new substance, which was isolated in the crystalline state. This compound, isomeric to IV, exhibited a spectrum lacking the 1693 cm^{-1} band characteristic of the diketopiperazines III-V and displaying a band at 1672 cm^{-1}. Treatment of this compound with $CH_3J + Ag_2O$ yielded the methyl derivative XII, a cyclol structure for which followed from the presence among its total hydrolysis products of glycolic acid and the absence of methoxyacetic acid and sarcosine (i.e. structure of type B and not A or C). Since the position of the

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[8] J.C. Sheehan and E.J. Corey, J. Amer. Chem. Soc. 74, 4556 (1952).
[9] C.A. Grob and W. Meyer, Helv. Chim. Acta 39, 776 (1956).

TABLE 1

Constants and Analytical and I.R. Data

Comp.	M.p. °C	$[\alpha]_D^{20°}$ c=1 THF	Found (%)			Calculated (%)			Position of CO-band cm^{-1} [a]
			C	H	N	C	H	N	
IB									1736, 1669
IIB									1732, 1664
III	150	-43.6	63.62	6.03	9.35	63.56	6.00	9.27	1725, 1694
IV [b]		-53.2							1730, 1693
V	133		61.14	5.83	9.89	60.86	5.84	10.14	1723, 1693
VI	120		45.14	5.33	14.72	45.16	5.41	15.05	1730, 1693
VII	41		67.90	7.07	6.06	67.99	6.93	5.66	1708
IX	108		67.01	6.49	6.04	66.93	6.48	6.01	1738, 1711
X	69		50.42	6.35	9.69	50.34	6.34	9.79	1745, 1700
XI	148		50.80	5.67	13.04	50.94	5.70	13.20	1730, 1672
XII	172-174		53.52	6.27	12.31	53.09	6.24	12.38	1737, 1678
XIV	97		53.21	7.09	8.98	53.49	7.05	8.91	1719

[a] All I.R. spectra were obtained on a Zeiss UR-10 spectrophotometer in THF solution with a 0.2-1 mm cell and c = 0.05-0.5%.

[b] Due to its glass-like nature this substance was difficult to obtain in an analytical pure state.

TABLE 2

U.V. Spectra of Dioxane Solutions [a]

Compounds	$\lambda_{max}^{init.}$	$\varepsilon_{init.}$	$\lambda_{max}^{fin.}$	$\varepsilon_{fin.}$	Time of observ. (hr)
N-acetyl-pyrrolidone [11]	218	11300			
N-acetyl-piperidone [11]	216	8900			
VI	216	7500	214	5650	24
X	220	7250			2
XI	214	3300	215	4200	24
XII	220	1150			2
XIV	221	300	222	1600	24

[a] Spectra obtained on Zeiss VSU-1 and Hitachi EPS-2 spectrophotometers with 0.5-1 cm cells.

CO bands in its I.R. spectrum is similar to that of the non-methylated compound the latter must also possess a cyclol structure, namely, XI. Apparently the absorption band in the 1730-1740 cm^{-1} region of the spectra of these cyclols belongs to the CO group of the oxazolidinone ring (cf.[10]). The superposition of this band on the -CO-N-CO- band does not allow one to use their alterations in judging of the occurrence of cyclolization. For this purpose use may be made of the 1672-1678 cm^{-1} band, belonging to the glycyl CO group.

Further, shortly after dissolution of XI in THF or dioxane, formation of IV could be observed by the appearance of the 1693 cm^{-1} band and weakening of the 1672 cm^{-1} band. The conversion is also accompanied by increase in absorption at 215 mμ. At about 30°C equilibrium is established within 4-5 hr. The rate of equilibration is considerably accelerated in the presence of water (D_2O). After equilibrium in the intraconversions XI → IV and IV → XI has set in the spectra of both solutions become very similar to each other in the CO frequencies region, with the cyclol form of the compound predominant. The reversibility of these transitions is thus quite apparent.

Both ergotamine and its analogue II, synthesis of the latter of which was reproduced in our laboratory by K.P. Butin, possess CO bands very similar to those of XI and XII (see Table 1), bearing evidence of the cyclol structure - IB and IIB. However, under the above described conditions these compounds do not undergo tautomeric transformations.

A crystalline compound was isolated from the solution obtained after hydrogenolysis of V. On the basis of its I.R. spectrum it was assigned the structure VI. Like IV it undergoes partial conversion in THF to the cyclol form XIII the presence of which is manifested by the appearance of a band at 1676 cm^{-1}. Simultaneously there is diminishing of extinction in

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[10] K. Eichenberger, E. Ganz and J. Druey, Helv. Chim. Acta 38, 284 (1955).

the region of 216 mμ. In contrast to the IV⇌XI equilibrium, that of VI⇌XIII is shifted in the direction of the glycolyl diketopiperazine form.

The attack of the hydroxyl group on the carbonyl in N-(α-hydroxyacyl)-amides may also take place intermolecularly. Thus, alongside the transition IV→XI, a certain amount of glycolide is formed, identified spectroscopically and chromatographically. Prolonged heating of the THF solution of XI also leads to the formation of glycolide in addition to increasing content of IV.

The glycolyl derivatives of lactams are without the amide group which served as the unique label for tracking the tautomeric conversions of the glycolyl diketopiperazines IV and VI. However, the decrease in their content is also manifested in a decrease of extinction in the 215 mμ region where the N-acyl lactam band is found.[11] This circumstance we made use of in ascertaining the structure of glycolyl lactams formed in the hydrogenolysis of VII and IX. An examination of the U.V. spectrum of glycolyl pyrrolidone in dioxane solution showed that it possesses considerable extinction, similar to that of N-acetylpyrrolidone, allowing it to be assigned the structure X. At the same time the crystalline glycolyl derivative of piperidone possessing very little extinction when first dissolved in dioxane, acquires this property rapidly, a maximum value being reached on an average within an hour. A spectrophotometric study of the reaction reflected by the changes in extinction showed it to be of the first order. The results are readily explained if one assumes that the crystalline compound is the cyclol XIV, which in solution establishes an equilibrium with the glycolyl lactam VIII. The absence of changes in extinction of solutions of X shows that the conversion of X to XV apparently does not take place.

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[11] C.M. Lee and W.D. Kumler, J. Amer. Chem. Soc. 83, 4593 (1961).

Highly noteworthy is the racemization of the proline residue accompanying the conversion IV ⟶ XI. We were able to isolate only racemic XI in crystalline state, since the specific rotation of solutions of IV, obtained by hydrogenolysis of III falls at a rate comparable to that of the spectral changes (the specific rotation of III in THF remains unchanged). The racemization of the proline residue is confirmed by the absence of optical activity in the products of total hydrolysis of XI. We are at present investigating the nature of this phenomenon.

It is possible that the ring-chain tautomerism and tendency to racemization of the cyclols will provide a new approach to the various reactions of ergot alkaloids.

Since the cyclolization is of quite general character we are now engaged in a systematic study of the chemical properties of various types of cyclols and of conditions for their formation.

Acknowledgements - We are indebted to Dr. M. Semonsky for generous gift of a sample of ergotamine and G.Yu. Peck for translating this paper.