Structure Elucidation of a Condensation Product of 4-Aminopyrrole Derivatives and Dicyclohexylcarbodiimide

Meir Bialer (1), Boris Yagen and Raphael Mechoulam*

Department of Natural Products, Hebrew University, Pharmacy School, Jerusalem, Israel

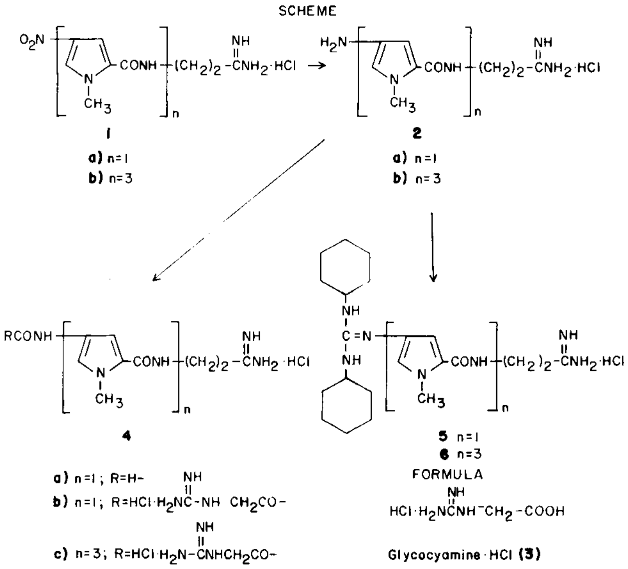
Received April 22, 1980

The chemical structure of the two condensation products of dicyclohexylcarbodiimide (DCC) with the precursors of the mono-pyrrole homologues of distamycin and with the mono and tri-pyrrole homologues of congocidine were established. The two products isolated were proven to be condensation products between 4-aminopyrrole derivatives and dicyclohexylcarbodiimide (DCC).

J. Heterocyclic Chem., **17**, 1797 (1980).

Dicyclohexylcarbodiimide (DCC) was proposed as a coupling reagent for peptide synthesis by Sheehan and Hess in 1955 (2,3) and it is still one of the most used reagents in this field. The reaction mechanisms were first discussed by Khorana, *et al.* (4-6), and later thoroughly reinvestigated by DeTar, *et al.* (7-9). The first step involves addition of the carboxylic acid to DCC to form a reactive intermediate *O*-acylurea (10). Direct attack of the amino component on the *O*-acylurea produces an amide or a peptide. The *O*-acylurea with an additional molecule of an acid can form an anhydride which reacts further with an amine. Dicyclohexylurea (DCU) is formed as a by-product during the coupling. An additional by-product frequently isolated from the reaction mixture is *N*-acylurea, which is formed by an O → N acyl migration (10,11).

During recent investigations of the structure activity relationship of pyrrole amidine antiviral antibiotics, DCC was used as a catalyst for the amide bond formation in the last step of the synthesis of distamycin and congocidine analogues (12-14). The present report deals with the chemical identification of the competing products obtained during these condensations. These new compounds are a result of the novel condensation of DCC with 4-aminopyrrole derivatives.



In the described route for the synthesis of distamycin A (12,13) and congocidine derivatives (14), the known compound *N*-methyl-4-nitropyrrole-2-carboxamido-β-propionamidine hydrochloride (**1a**) was catalytically reduced with hydrogen over palladium on charcoal to give the free amine *N*-methyl-4-amino pyrrole-2-carboxamido-β-propionamidine hydrochloride (**2a**). The amine **2a** was further converted, without isolation, to the desired amide by amidation with formic acid (16) or glycocyamine hydrochloride (**3**) (17), respectively, in the presence of DCC (Scheme). The products *N*-methyl-4-formamidopyrrole-2-carboxamido-β-propionamidine hydrochloride (**4a**) and *N*-methyl-4-guanidinoacetylpyrrole-2-carboxamido-β-propionamidine hydrochloride (**4b**) were formed, respectively, along with an additional compound. An unexpected reaction competing with the amide formation resulted in a new identical product from both reactions. This product (crystals, m.p. 223-226°) was obtained in about 8% yield. The mass spectrum of **5** had M^+ at m/e 415 and showed a strong peak at m/e 398 indicative of the loss of NH_3. The high resolution mass spectrum established the formulae ($C_{22}H_{37}N_7O$) for **5**. The ir spectrum contained bonds attributable to amino, carbonyl, amidine and guanidine groups. The ^{1}H nmr spectrum showed a wide multiplet at 1.2-2.3 ppm (20H, CH_2 of cyclohexane), 2.77 (C-CH_2), 3.89 (N-CH_3), 6.81, 7.1 (2H-aromatic), 7.1, 7.26, 8.73 and 8.78 (amide, amidine, and guanidine protons). Thus, the structure of **5** was established as *N*-methyl-4-(*N'N'*-dicyclohexylguanilyl)pyrrole-2-carboxamido-β-propionamidine.

Compound **5** was not obtained when DCU was allowed to react with the amine **2a** in the presence of formic acid or glycocyamine hydrochloride, emphasizing that DCU is not a precursor of **5**.

In a route similar to the formation of **5**, compound **6** was obtained in 9% yield from the free amine **2b** and DCC during the synthesis of the tripyrrole homologue of congocidine **4c**. The ir spectrum of **6** was similar to the spectrum of **5**, and the microanalysis confirmed the formulae $C_{34}H_{49}N_{11}O_3$·HCl. The ^{1}H nmr spectrum showed a

0022-152X/80/081797-02$02.25

multiplet at 1.16-1.83 ppm (methylene of cyclohexane rings), peaks indicative of 3-N-CH_3 groups and 6-aromatic protons as well as signals belonging to amide, amidine, and guanidine protons. The compounds **5** and **6** were less polar in the systems used for the analysis than the relevant distamycin or congocidine homologues. During the condensation of 5-aminopyrrole isomers of compounds **2a** and **2b** (18) with formic acid or glycocyamine hydrochloride in the presence of DCC, the formation of the by-products *N*-methyl-5-(*N'N'*-dicyclohexylguanilyl)pyrrole derivatives were not observed.

EXPERIMENTAL

Unless otherwise stated, the following apply. Uv measurements were made for solutions in ethanol. Ir spectra were taken in potassium bromide pellets. ^{1}H nmr data were determined in DMSO-d_6 with 3'-(trimethylsilyl)tetradeutero sodium propionate as an external standard. Tlc was performed on 0.3 mm silica gel plates, which were developed with Ehrlich reagent (2% *N*-dimethylaminobenzaldehyde in 6*N* hydrochloric acid or by irradiation at 254 nm. The eluent was methanol:isopropyl alcohol:acetic acid:water (50:20:10:5). Column chromatography was performed on Woelm Neutral Alumina. Mass spectra were obtained by direct inlet at 70 eV; in several cases the technique of field desorption (F.D.) was used.

N-Methyl-4-(*N'N'*-dicyclohexylguanilyl)pyrrole-2-carboxamido-*β*-propionamidine Hydrochloride (**5**).

The amidine **1a** (1.8 g., 6.5 mmoles) was dissolved in DMF and was reduced at atmospheric pressure with palladium on charcoal (0.5 g.) as a catalyst. The mixture was filtered. The intermediate amine **2a** presumably obtained was not purified due to instability. Glycocyamine hydrochloride (**3**) (1.3 g., 6.5 mmoles) in DMF was gradually added under nitrogen to the solution of **2a** kept at 0°. The solution was first stirred at this temperature for 1 hour, followed by stirring at room temperature overnight. The mixture was filtered and the filtrate evaporated. The crude product was purified by chromatography on an alumina (activity I) column (138 g.), using methanol as the eluent. Compound **4a** (240 mg., 9.7%) and **5** (145 mg., 8.1%), m.p. 223-226° were observed; ^{1}H nmr (DMSO-d_6): 1.1-2.3 (20 methylenic H's), 2.77 (C-CH_2), 3.89 (N-CH_3), 6.81, 7.1 (2-aromatic H's), 7.1, 7.26, 8.73, 8.78 (amide, amidines and guanidine H's); uv (ethanol): λ max 266 nm (ϵ, 6,700); ir (potassium bromide): 3300-3040, 2930, 2850, 1689, 1620, 1520, 1440, 1270, 1220, 1060, 890 cm^{-1}; ms: m/e 415 (M-100%), 398 (M-NH_3-100%), 345 (76%), m/e (field desorption) 415, 398; high resolution ms for m/e 398 for $C_{22}H_{34}N_6O$; found: 398.279410; requires: 398.279395.

Anal. Calcd. for $C_{22}H_{37}N_7O$ HCl: C, 58.47; H, 8.41; N, 21.71; Cl, 7.86. Found: C, 58.09; H, 8.75; N, 21.55; Cl, 8.07.

N-Methyl-4-*N*-methyl-4-[*N*-methyl-4-(*N'N'*-dicyclohexylguanilyl)pyrrole-2-carboxyamido]pyrrole-2-carboxamidopyrrole-2-carboxamido-*β*-propionamidine Hydrochloride (**6**).

Compound **6** was obtained from compound **2b** and DCC during the condensation of **2b** with formic acid under the above described conditions (yield 9%), m.p. 230-234°; ^{1}H nmr (DMSO-d_6): 1.16-1.83 (20 methylene H's), 2.8 (C-CH_2), 3.83, 3.86, 3.89 (3 N-CH_3 groups), 7.02, 7.16, 7.30 (6 aromatic H's), 8.2, 9.94, 10.6 (3 amide H's) 9.02 (amidine and guanidine H's); uv (ethanol): λ max 238, 304 nm (ϵ, 19,500, 25,000); ir (potassium bromide): 3340-3180, 2940, 2930, 2850, 1630, 1540, 1430, 1400, 1260, 1210, 1110 cm^{-1}

Anal. Calcd. for $C_{34}H_{49}N_{11}O_3 \cdot HCl$: C, 58.66; H, 7.18. Found: C, 58.36; H, 7.44.

Acknowledgement.

We thank the National Council for Research and Development and the Mif'al Hapai's (National Rotary) for partial support of this work.

REFERENCES AND NOTES

(1) Pharmacy Department, School of Pharmacy, Hebrew University, P.O. Box 12065, Jerusalem, Israel.

(2) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(3) J. C. Sheehan and M. Goodman and G. P. Hess, *ibid.*, **78**, 1367 (1956).

(4) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(5) H. G. Khorana, *Chem. Ind.*, 1087 (1955).

(6) M. Smith, J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

(7) D. F. DeTar and R. Silverstein, *ibid.*, **88**, 1013 (1966).

(8) D. F. DeTar and R. Silverstein, *ibid.*, **88**, 1020 (1966).

(9) D. F. DeTar, R. Silverstein and F. F. Rogers, *ibid.*, **88**, 1024 (1966).

(10) M. Rothe and F. W. Kunitz, *Ann. Chem.*, **609**, 88 (1957).

(11) Y. S. Klausner and N. Bodansky, *Synthesis*, 453 (1972).

(12) M. Bialer, B. Yagen and R. Mechoulam, *Tetrahedron*, **34**, 2389 (1978).

(13) M. Bialer, B. Yagen, R. Mechoulam and Y. Becker, *J. Med. Chem.*, **22**, 1296 (1979).

(14) M. Bialer, B. Yagen, R. Mechoulam and Y. Becker, "S.A.R. of Pyrrole Amidine Antiviral Antibiotics. Part 2. Preparation of Mono- and Tri-Pyrrole Derivatives of Congocidine", *J. Med. Chem.*

(15) F. Arcamone, V. Nicollela, S. Penco and S. Radaelli, *Gazz. Chim. Ital.*, **99**, 632 (1969).

(16) J. O. Thomas, *Tetrahedron Letters*, 335 (1967).

(17) M. Julia and N. Preau-Joseph, *Bull. Soc. Chim. France*, 4348 (1967).

(18) M. Bialer, B. Yagen, R. Mechoulam and Y. Becker, "S.A.R. of Pyrrole Amidine Antiviral Antibiotics, Part 3. Properties of 2,5-Disubstituted Analogs of Distamycin and Congocidine", *J. Pharm. Sci.* in Press (1980).