2-Amino-2-oxazolines, IV:

Kurzmitteilung:

Reactions with Bromo Esters, Synthesis of Some 3-Carboxyalkyl-2-imino-oxazolidines

2-Amino-2-oxazoline, 4. Mitt.: Reaktionen mit Bromestern, Synthese einiger 3-Carboxyalkyl-2-imino-oxazolidine

Christian Jarry and Catherine Misiaszek

Laboratoire de Chimie Physique, Faculté des Sciences Pharmaceutiques, Université de Bordeaux II, 3 Place de la Victoire, 33076 Bordeaux, France.

Received March 1, 1990

Heterocyclic systems having a five membered ring fused with another ring including a bridgehead N are widely described for their pharmacological activity [1-5]. A common method for the synthesis of these fused heterocyclic systems is the alkylation of heterocyclic amines having an amino group at the α-position in respect to the ring N-atom with α-halo carbonyl compounds[6,7]. In continuing our study on the reactivity of 2-amino-2-oxazolines[8], we describe here the synthesis of 3-carboxyalkyl-2-imino-oxazolidines **3** by treatment of 5-substituted-2-amino-2-oxazolines **1** with the bromo esters **2**.

The two N-atoms of 2-amino-2-oxazolines are potent nucleophilic centers. Depending on the experimental conditions, substitutive reactions take place either on the endo or on the exo N of the amidine system. As we have noticed[9], in the 2-amino-2-oxazoline form the endo N is more reactive than the exo one. At ambient temp. nucleophilic substitution preferably occurs on the endo N-atom. Substitutions on position 5 of the heterocycle are without effect on the reactivity indices calculated for the two nitrogens. The condensation of **1** with ethyl bromoacetate or ethyl 4-bromocrotonate in acetone at 0°C led to 3-carbethoxyalkyl-2-imino-oxazolidines as hydrobromine salts, with a small quantity of corresponding acid. HPLC analysis on a C18 reversed phase column (mobile phase: methanol-phosphate buffer M/30 pH 5.4) gave an integral ratio of 99/1. The alkylation reaction is generally believed to proceed by initial displacement of the bromine atom by the oxazoline ring nitrogen atom followed by rearrangement of the resonance stabilized oxazolinium salt[10]. An attempt to convert the 5-substituted-3-carboxymethyl-2-imino-oxazolidines to the corresponding imidazo[2,1-*b*]oxazoline by $POCl_3$ was performed according to lit.[2,11]: no cyclization occurred. A similar resistance to ring closure was observed with 3-phenacyl-2-imino-oxazolidines[12].

The hydrolysis of reaction compounds can be performed in acidic or in basic conditions. With an excess of NaOH in boiling water, we observed the opening of the oxazolidine ring in **3a** leading to the N-substituted glycine **4a** after neutralization. This reaction might proceed via the corresponding 2-oxazolidinone [13]. In acidic conditions (excess of HCl in boiling water), only **3a** and **3b**, respectively, were isolated as hydrochloride salts. **3c** was obtained as sodium salt after treatment with Na_2CO_3.

The structures of all new synthesized products were investigated by spectral analyses. In ^{1}H-NMR spectra of **3** as hydrochlorides, an exchangeable singlet assigned to the N^+H_2 was found near 9.8 ppm. The imine function (free bases obtained at ambient temp. after treatment with NH_3) was assigned on the basis of IR-data (sharp peak at 3340 cm^{-1}: ν NH) and ^{1}H-NMR (δ = 5.5 ppm for NH). As it was described [9,12], in 2-iminooxazolidines C-5-H and C-4-H of the heterocycle from an ABX system. In compounds **3**, C-5-H appeared as a complex multiplet near 5.5 ppm. In ^{13}C-NMR spectra, C-2 of the oxazolidine ring was found at 158.5 ppm. This value is comparable to the one of a 2-imino-oxazolidine whose structure was established by X-ray crystallography [9].

  0365-6233/90/1111-0943 $ 3.50 + .25/0

The compounds **3a-c** were evaluated for their local anaesthetic activity on male guinea pigs using a standard procedure[14] at the concentrations of 0.5 and 5%. No local anaesthetic activity was observed even at higher concentration.

Experimental Part

General procedure for the synthesis of the 5-substituted- 3-carboxyalkyl-2-imino-oxazolidines **3**

0.1 Mole of bromo ester in 50 ml of acetone was added at 0°C to 0.1 mole of 5-substituted-2-amino-2-oxazoline in suspension in 250 ml of acetone. The mixture was stirred 8 h at 0°C, then at ambient temp. until the consumption of the oxazoline controlled by TLC. The mixture was concentrated and the collected solid was washed twice with acetone.

5-Phenoxymethyl-3-carbethoxymethyl-2-imino-oxazolidine, HBr

Mp. 204°C (heptane). - IR (KBr): 1735 (C=O), 1685 (C=N) cm^{-1}. - ^{1}H-NMR (DMSO-D_6), δ (ppm) = 9-8.5 (N^+H_2), 7.5-6.8 (m, 5H, phenyl), 5.7-5.4 (m, 1H, C-5-H), 4.8 (s, 2H, NCH_2), 4.4-3.6 (m, 6H, CH_2), 1,2 (t, 3H, CH_3). After 3 recrystallizations in heptane, HPLC analysis (C18 μ Bondapack column 30 cm x 3.9 mm I.D., 10 μ particle size - UV detection 270 nm) indicated the presence of 1.6 % of the corresponding acid (retention times 2.60 min for acid and 4.36 min for ester).

An equivalent of 0.01 mole of the precedent solid in 100 ml of water was heated 3 h with 0.03 mole of HCl. The homogenized mixture was concentrated under reduced pressure and a solid crystallized after trituration with acetone.

5-Phenoxymethyl-3-carboxymethyl-2-imino-oxazolidine, HCl (**3a**)

Yield 31 %; mp. 178°C (acetone). - IR (KBr): 1735 (C=O), 1695 (C=N) cm^{-1}. - ^{1}H-NMR (DMSO-D_6) δ (ppm) = 13.9-11.9 (COOH), 9.8 (s, 2H, N^+H_2), 7.6-6.9 (m, 5H, phenyl), 5.8-5.3 (m, 1H, C-5-H), 4.8-3.6 (m, 6H, CH_2). - ^{13}C-NMR (DMSO-D_6), δ (ppm) = COOH 172.2, C-2 158.5, phenyl 157, 129.5, 120.6, 114.5, C-4 51.9, C-5 67, OCH_2 69.9, NCH_2 45.2.

5-Phenoxymethyl-3-(1-carboxy-1-propenyl)-2-imino-oxazolidine, HCl (3b)

Yield 21 %; mp. 201°C (chloroform). - IR (KBr): 1690 (C=O), 1665 (C=N) cm^{-1}. - ^{1}H-NMR (DMSO-D_6), δ (ppm) = 12.8-10.8 (COOH), 9.6 (s, 2H, N^+H_2), 7.5-6.6 (m, 6H, phenyl and =CH), 6.15 (d, 1H, =CH, J = 16 Hz), 5.7-5.3 (m, 1H, C-5-H), 4.5-3.6 (m, 6H, CH_2).

3c was obtained as a Na-salt in water by addition of Na_2CO_3 until pH 8.

5-(1-Phenyl-4-piperazino)methyl-3-carboxymethyl-2-imino-oxazolidine (**3c**)

Yield 23 %; mp. > 250°C. - IR (KBr): 1660 (C=O), 1610 (C=O) cm^{-1}. - ^{1}H-NMR (D_2O), δ (ppm) = 7.4-6.8 (m, 5H, phenyl), 5-4.4 (m, 1H, C-5-H), 3.9-2.4 (m, 14H, CH_2).

1-Carboxymethylamino-3-phenoxy-propane-2-ol (**4a**)

2.87 g (0.01 mole) of **3a** in 50 ml of water were heated 3 h with 0.04 mole of NaOH in 10 ml of water. After cooling the mixture was neutralized by HCl until pH 6. The solid collected was recrystallized from C_2HCl_3 to yield 1.2 g of **4a** (53 %); mp. 140°C. - IR (KBr): 3490 (NH), 3160 (OH), 1710 (CO) cm^{-1}. - ^{1}H-NMR (DMSO-D_6), δ (ppm) = 10.6 (s, 1H, COOH), 7.5-6.8 (m, 5H, phenyl), 5.3 (OH), 4.3-3.8 (m, 6H, NH, 2 CH_2 and CH), 3.5-3.1 (d, 2H, NCH_2, J = 4.8 Hz).

References

1 A.H.M. Raeymaekers, F.T.N. Allewijn, J. Vanderberk, P.J.A. Demoen, T. Van Offenwert, and P.A.J. Janssen, J. Med. Chem. *9*, 545 (1966).
2 J.P. Paolini and L.T. Lendvay, J. Med. Chem. *12*, 1031 (1969).
3 H. Böhme and K.H. Weisel, Arch. Pharm. (Weinheim) *309*, 959 (1976).
4 R.N. Hanson, R.W. Giese, M.A. Davis, and S.M. Costello, J. Med. Chem. *21*, 496 (1978).
5 A. Andreani, M. Rambaldi, D. Bonnazzi, G. Lelli, R. Bossa, and I. Galatulas, Eur. J. Med. Chem. *19*, 219 (1984).
6 J.P. Paolini, "Special topics in heterocyclic chemistry", 1-115, A. Weissberger and E.C. Tayler eds., J. Wiley and Sons, New York, 1977.
7 K.C. Liu, H.S. Huang, and S.M. Lin, Arch. Pharm. (Weinheim), *323*, 61 (1990).
8 I. Forfar, C. Jarry, A. Carpy, and J.M. Léger, Arch. Pharm. (Weinheim) *323*, 905 (1990).
9 J.J. Bosc, I. Forfar, C. Jarry, J. Ouhabi, J.M. Léger, and A. Carpy, Arch. Pharm. (Weinheim) *323*, 561 (1990).
10 E.S. Hand and W.W. Paudler, Tetrahedron *38*, 49 (1982).
11 J. Parrick and K. Pearson, Chem. Ind. *1970*, 1261.
12 C. Misiaszek, C. Jarry, E. Panconi, and A. Carpy, Eur. J. Med. Chem, 1990, in press.
13 G. Fodor and K. Koczka, J. Chem. Soc. *1952*, 850.
14 J. Régnier, C.R. Acad. Sci. 177, 558 (1923). [KPh533]

Verantwortlich für die Redaktion: Prof. Dr. W. Wiegrebe. Pharmazeutisches Institut der Universität Regensburg, Universitätsstraße 31, Postfach 397, D-8400 Regensburg. – Anzeigenleitung: R.J. Roth, D-6940 Weinheim – VCH Verlagsgesellschaft mbH (Geschäftsführer: Hans Dirk Köhler), Postfach 101161, D-6940 Weinheim – Alle Rechte, insbesondere die der Übersetzung in fremde Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form – durch Photokopie, Mikrofilm oder irgendein anderes Verfahren – reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden. – All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers. – Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen und sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. Der Inhalt dieses Heftes wurde sorgfältig erarbeitet. Dennoch übernehmen Autoren, Herausgeber, Redaktion und Verlag für die Richtigkeit von Angaben, Hinweisen und Ratschlägen sowie für eventuelle Druckfehler keine Haftung. This journal was carefully produced in all its parts. Nevertheless, authors, editors and publishers do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate. – Die Wiedergabe von Gebrauchsnamen, Handelsnamen, Warenbezeichnungen u. dgl. in dieser Zeitschrift berechtigt nicht zu der Annahme, daß solche Namen ohne weiteres von jedermann benutzt werden dürfen. Es handelt sich häufig um gesetzlich eingetragene Warenzeichen, auch wenn sie in dieser Zeitschrift nicht als solche gekennzeichnet sind. Texterfassung und EDV-Bearbeitung: Fa. Hellinger, D-6901 Heiligkreuzsteinach; Druck und Buchbinder: Rheinhessische Druckwerkstätte, D-6508 Alzey. – Unverlangt zur Rezension eingehende Bücher werden nicht zurückgesandt.

Valid for users in the USA: The appearance of the code at the bottom of the first page of an article in this journal (serial) indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that copier pay the stated per-copy fee through the Copyright Clearance Center, Inc., for copying beyond that permitted by Sections 107 for 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective work, or for resale. For copying from back volumes of this journal see »Permissions to Photo-Copy: Publisher's Fee List« of the CCC.

Printed on acid-free paper/Gedruckt auf säurefreiem Papier