Tetrahedron Letters No. 49, pp 4347 - 4350, 1975. Pergamon Press. Printed in Great Britain.

SYNTHETIC ROUTE TO NEUROTOXINS IN THE 2,7-EPI-HISTRIONICOTOXIN SERIES

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(Received in USA 18 September 1975; received in UK for publication 28 October 1975)

Recent studies[1] have resulted in a number of synthetic pathways to the useful neurotoxin (+)-perhydrohistrionicotoxin.[2] We describe here a new entry into the histrionicotoxin ring system using a Mannich-type spiro cyclization which eventually led to the synthesis of two new biologically interesting substances 2,7-epi-perhydrohistrionicotoxin (XVIII) and its dioxa analog (XXI).

Δ^1-Cyclopentenylacetonitrile (I) was converted by standard procedures to the bromide V[3] (bp 67-69°/10 mm) in 59% overall yield via intermediates II-IV. Reaction of V with the dianion of methyl acetoacetate[4] (2.0 equiv) in 15% hexamethylphosphoricamide (HMPA) in tetrahydrofuran (THF) afforded VI (77%) which was converted by heating at reflux with pyrrolidine (6 equiv) and acetic acid (0.5 equiv) in benzene (3 hr) to enamine-ester VII, isolated as a crystalline solid (86%) mp 37-39° after rapid passage in benzene-ether (1:1) through a chilled (5°) Florisil column. Hydroxylation of VII with osmium tetroxide (0.98 equiv, -40 to -15°, 50 min) in pyridine-ether followed by hydrolysis with aq sodium bisulfite[5] (5 equiv. -10 to 0°, 30 min) to form diol VIII, mp 66-67.5° (86%), followed by oxidation using silver carbonate on Celite[6] in boiling benzene gave the ketoaldehyde (IX) (65-75%). Crude IX was converted to the E unsaturated ester (X) using the anion of triethyl phosphonoacetate (1 equiv) in THF at -20 to -30°. Although pure X could be isolated by column chromatography using acetylated polyamide[7] with 15% benzene-heptane for elution, unpurified X was satisfactory for the next step. Reaction of crude X with liquid ammonia in a sealed tube at room temperature for 24 hr, and filtration (using methylene chloride-ether (1:1)) through a short column packed from the bottom with Florisil, charcoal and magnesium sulfate gave essentially pure imine XI.

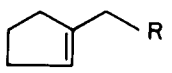
A solution of the imine (XI) in dry methylene chloride (20 mg/ml) was treated at 0° with p-toluenesulfonic acid monohydrate (1.8 equiv) in two equal portions with a 15 min interval. After stirring for a total of 60 min the resultant homogeneous solution was diluted with ether (2 volumes) and shaken thoroughly with cold sat. aq sodium bicarbonate solution for 2-3 min. The product obtained from the organic layer (XII) was immediately treated with sodium borohydride (4 mol equiv, 1.0 wt% KOH) in absolute ethanol at -20° for 1.5 hr to give after extractive workup with methylene chloride an oily mixture containing XIII. Phosgene gas was briefly bubbled through a solution of crude XIII in methylene

chloride at 0°. After 30 min excess phosgene was purged and a portion of dry pyridine was added. Extractive workup after 20 hr with methylene chloride-ether followed by chromatography on a silica gel column afforded the urethane-diester intermediate XIV (16.5% overall yield from VIII) as a crystalline solid. which was further recrystallized from methylene chloride-ether to furnish an analytical sample mp 126-126.5°. The structure and stereochemistry of XIV were ascertained by a single-crystal, 3-dimensional X-ray diffraction study.[8]

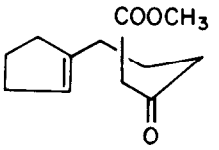
Selective reduction of the diester (XIV) with diisobutylaluminum hydride (2.5 equiv, -78°) in methylene chloride to the corresponding dialdehyde XV followed by the Wittig olefination using allyldimethylphenylphosphonium bromide[9] (5 equiv, 0°, 45 min, potassium methylsulfinylmethylide[10] as the base) in THF-DMSO afforded bisdiene XVI after chromatographic separation on silica gel. Hydrogenation of XVI proceeded smoothly with Pd-C catalyst (10%) in dry THF to form XVII. Cleavage of the urethane group was effected with excess lithium in monomethylamine at -78° for 90 min to afford after chromatography 2.7-epi-(±)-perhydrohistrionicotoxin (XVIII) (11.3% overall from diester XIV) as a colorless oil.

The diester XIV was also selectively reduced to the corresponding diol (XIX)(73%), mp 142-142.5°. with lithium borohydride (10 mol equiv, 23°, 20 hr) in dry THF. Etherification of XIX with potassium hydride (5 equiv) and ethyl iodide (16 equiv) in hexamethylphosphoricamide quantitatively furnished the ether XX. which was converted (57%) to dioxa 2,7-epi-(±)-perhydrohistrionicotoxin XXI as described above for XVII → XVIII.

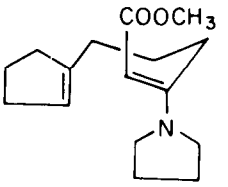
Interestingly. the dioxa analog was found to possess ca. one fourth the biological activity of naturally derived perhydrohistrionicotoxin. No biological data have been obtained as yet for 2.7-epi-(±)-perhydrohistrionicotoxin.[12]



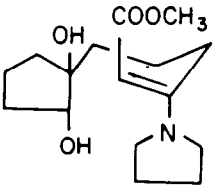
I, R = CN
II, R = COOH
III, R = CH_2OH
IV, R = CH_2OTs
V, R = CH_2Br



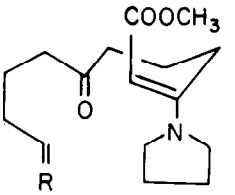
VI



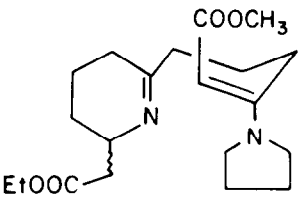
VII



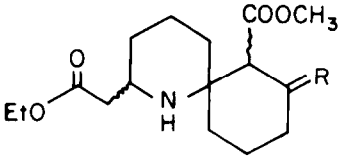
VIII

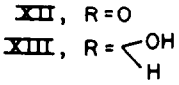


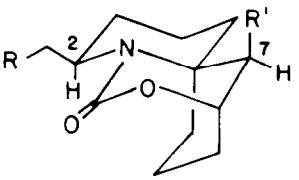
IX, R = O
X, R = CHCOOEt



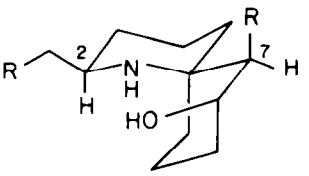
XI



XII, R = O
XIII, R = 



XIV, R = COOEt, R' = $COOCH_3$
XV, R = R' = CHO
XVI, R = R' = $-CH=CH-CH=CH_2$
XVII, R = R' = $n-C_4H_9$
XIX, R = R' = CH_2OH
XX, R = R' = CH_2OEt



XVIII, R = $n-C_4H_9$
XXI, R = CH_2OEt

References

1. See (a) E. J. Corey, J. F. Arnett and G. N. Widiger, J. Amer. Chem. Soc., 97, 430(1975); (b) M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inoue, J. Org. Chem., 40, 2009 (1975); (c) T. Fukuyama, L.V. Dunkerton, M.Aratani and Y. Kishi, J. Org. Chem. 40, 2011(1975); (d) E. Gössinger, R. Imhof and H. Wehrli, Helv. Chim. Acta, 58, 96(1975); (e) E. J. Corey, M. Petrzilka and Y. Ueda, accompanying paper.
2. See T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly and B. Witkop, Helv. Chim. Acta, 57, 2597 (1974), and references cited therein.
3. Satisfactory infrared. nuclear magnetic resonance, and mass spectral data were obtained for all isolable intermediates using purified, chromatographically homogeneous samples.
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8. Kindly performed by Prof. Jon Bordner, Department of Chemistry, North Carolina State University, Raleigh, N. C. Details of the X-ray analysis will be published in Crystal Structure Communications.
9. Prepared from phenyldichlorophosphine and methyllithium followed by quaternization with allyl bromide, mp 117-118°.
10. C. A. Brown, J. Amer. Chem. Soc., 95, 982 (1973).
11. Tests made using murine nerve/diaphram preparation by Dr. E. X. Albuquerque and associates.
12. This work was assisted in part by a grant from the National Science Foundation.