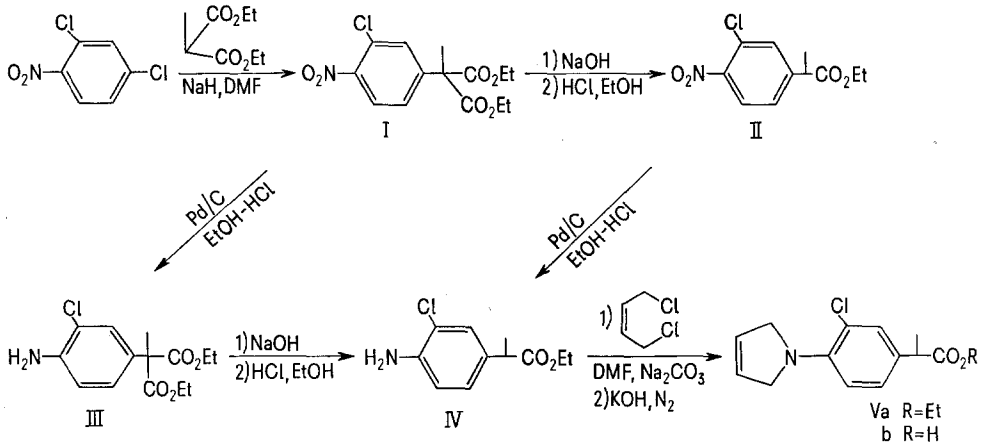
A Potent Non-Steroidal Anti-Inflammatory Agent: 2-[3-Chloro-4 (3-pyrrolinyl) phenyl] propionic Acid

The search for an effective non-steroidal anti-inflammatory agent has increased over the past decade[1]. In 1967 our attention was drawn to the potent activity (carrageenin edema-ED_{50} of 0.3 mg/kg p.o.) of 3-chloro-4-cyclohexylphenyl-2-propionic acid[2]. A number of arylalkanoic acids have been prepared since that time and screened in the various animal tests. The clinical evaluation of some of these substances has been noted[3]. Our interest was based on the assumption that while anti-inflammatory activity was found in these acids, we thought the various side-effects might be attributed to the acidic nature of these compounds. It is the purpose of this communication to outline the synthesis and biological activity of an aminoacid, 2-[3-chloro-4(3-pyrrolinyl)phenyl]propionic acid (Vb).



A number of pathways for the synthesis of Vb were envisioned, however when the versatility and simplicity of these processes were considered the selection was considerably narrowed. The scheme illustrates the route used to prepare Vb.

The alkylation of 2,4-dichloronitrobenzene with sodiodiethyl-methyl malonate in DMF at 100° for 15 h gave a 63% yield of I: b.p. 147-8/0.25 mm; analysis for $C_{14}H_{16}ClNO_6$, Calc: C, 50.98; H, 4.89; N, 4.25; Found: C, 50.90; H, 4.84; N, 4.15. The preparation of IV could be carried out in two ways: Hydrolysis and decarboxylation of I with 6N HCl followed by esterification with ethanol-HCl gave II: b.p. 138–142/0.25 mm; analysis for $C_{11}H_{12}ClNO_4$, Calc: C, 51.27; H, 4.70; N, 5.44. Found: C, 51.22; H, 4.55; N, 5.40. Hydrogenation of an anhydrous saturated HCl-ethanol solution of II over 10% Pd-C gave IV (with no loss of the chlorine): HCl salt, m.p. 165–7°; analysis for $C_{11}H_{14}ClNO_2$, Calc: C, 49.98; H, 5.73; N, 5.31: Found: C, 49.83; H, 5.58; N, 5.22.

IV could also be prepared by hydrogenation of I dissolved in anhydrous saturated HCl-ethanol solution over 10% Pd-C to give III: b.p. 180–185/0.25 mm; analysis for $C_{14}H_{18}ClNO_4$, Calc: C, 56.09; H, 6.06, N, 4.67: Found: C, 56.17; H, 5.98; N, 4.62. Base (25% NaOH) hydrolysis and subsequent work-up with EtOH-HCl gave IV identical with the above.

The reaction of *cis* 1,4-dichloro-2-butene[4] with IV in DMF and Na_2CO_3 gave after refluxing for 10 h 81% of Va: b.p. 128–133/0.25 mm; analysis for $C_{15}H_{18}ClNO_2$, Calc: C, 64.39; H, 6.49; N, 5.01: Found: C, 64.31; H, 6.39; N, 5.00; ir (Nujol) 1700 cm^{-1} (s, acid); pmr δ 1.48 (d, 3, c-Me), 3.61 (q, 1, –CH), 4.34 (s, 4, CH_2), 5.88 (s, 2, –CH), 6.7–74 (m, 3, Ar), 9.28 (s, 1, CO_2H). Hydrolysis of Va with EtOH-KOH at reflux for 6 h under N_2, followed by removal of EtOH and adjustment of the pH to 5.5, gave on extraction with Et_2O, Vb (61%): m.p. 98–100/benzene-hexane, analysis for $C_{13}H_{14}ClNO_2$, Calc: C, 62.03; H, 5.60; N, 5.56; Found: C, 62.12; H, 5.87; N, 5.60.

Resolution of Vb by the use of dexorotatory and levorotatory α-[1-naphthyl]ethylamine gave the dexo-isomer of the amino acid Vb: b.p. ~ 255; $[\alpha]_D^{25}$ + 38.08/EtOH; Na salt, m.p. 214–6°/EtOH-Et_2O; $[\alpha]_D^{25}$ −17.38, and the levo-isomer of the amino acid Vb: b.p. ~ 225°; $[\alpha]_D^{25}$ −38.44/EtOH; Na salt, m.p. 205–8/EtOH-Et_2O; $[\alpha]_D^{25}$ + 17.38/EtOH.

A structure-activity relationship study of this series has led to other derivatives which will be reported in more detail in a subsequent paper.

Biological activity. The anti-inflammatory activity of Vb (little difference in activity was found between the dexorotatory and levorotatory isomers) is quite comparable to that of Indomethacin. However, it is considerably less toxic than the reference drug. In the anti-carrageenin screen Vb is 1.56 times more potent with a therapeutic ratio of approximately 30 times that of Indomethacin. Good activity was also found in the cotton pellet test as well as the adjuvant arthritis screen. Due to this good activity and the safety advantage Vb is presently undergoing clinical study.

Zusammenfassung. Die Synthese und biologische Prüfung von 2-[3-Chlor-4(3-pyrrolinyl)phenyl]-propionsäure als neuer entzündungshemmender Stoff wird beschrieben.

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