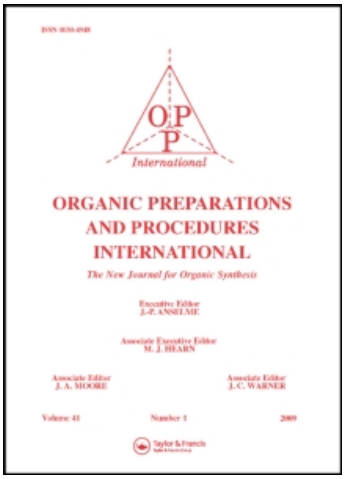

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SYNTHESIS OF THE PRECURSORS OF PHENANTHROINDOLIZIDINE ALKALOID ANALOGUES

Tai-Shun Lin[a]; Robert E. Harmon[a]; Wayne Pierantoni[a]; Joseph C. W. Su[a]
[a] Department of Chemistry, Western Michigan University, Kalamazoo, Michigan

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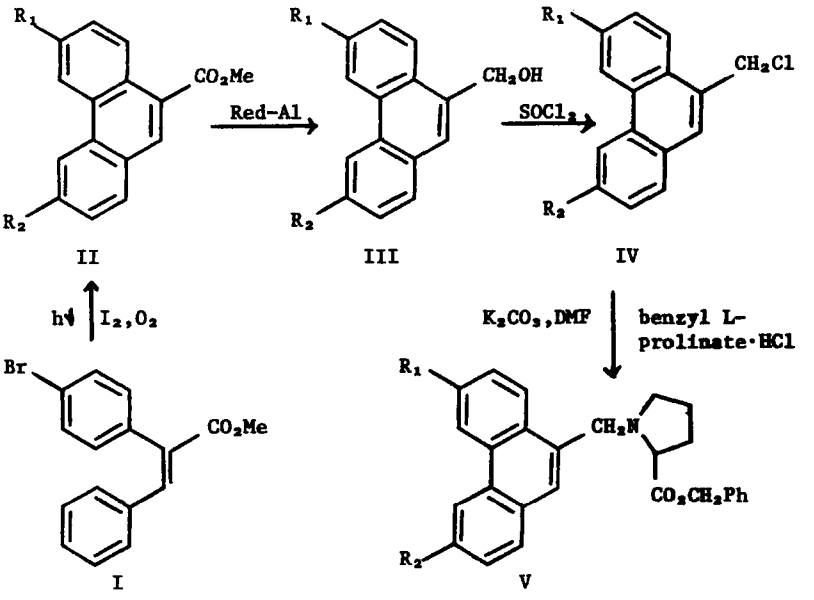
SYNTHESIS OF THE PRECURSORS OF PHENANTHROINDOLIZIDINE ALKALOID ANALOGUES

Tai-shun Lin, Robert E. Harmon*,
Wayne Pierantoni and Joseph C.W. Su

Department of Chemistry, Western Michigan University
Kalamazoo, Michigan 49001

Benzyl N-[3,6-bis(trifluoromethyl)phenanthr-9-ylmethyl]-L-prolinate (Va) and benzyl N-(6-bromophenanthr-9-ylmethyl)-L-prolinate (Vb) are key intermediates for the synthesis of phenanthroindolizidine alkaloid analogues,[1-3] which show high activity against lymphoid leukemia L1210 in mice.[4] In addition, these alkaloids possess cytotoxic activity against Hela cells grown in culture.[5] We now report syntheses of Va and of Vb.



a) $R_1 = R_2 = CF_3$ b) $R_1 = Br$; $R_2 = H$

trans-α-(p-bromophenyl)cinnamic acid,[6] obtained by the condensation of benzaldehyde with p-bromophenyl acetic acid, was converted to its methyl ester (I) with thionyl chloride and methanol. Photochemical cyclization of I gave 6-bromophenanthrene-9-carboxylate (IIb).[7] The methyl ester of 3,6-bis(trifluoromethyl)-phenanthrene-9-carboxylic acid (IIa) was obtained from reaction of the acid[8] with thionyl chloride and methanol. IIa and IIb were reduced to the corresponding alcohols IIIa and IIIb with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in anhydrous ether. The alcohols IIIa and IIIb were converted to chlorides IVa and IVb which on treatment with benzyl L-prolinate hydrochloride[9] in the presence of anhydrous potassium carbonate in N,N-dimethylformamide gave the desired products Va and Vb.[2]

EXPERIMENTAL[10]

trans-α-(p-Bromophenyl)cinnamic Acid. - A mixture of p-bromophenyl acetic acid (215 g, 0.5 mol), benzaldehyde (53 g, 0.5 mol), triethylamine (50 g, 0.5 mol) and 250 ml of acetic anhydride was refluxed for 30 min. The solution was cooled to 90° and 500 ml of cold water was added at such a rate that the temperature remained above 90°. The solution was then cooled to room temperature and the precipitate was filtered and washed with 300 ml of 50% acetic acid and water. Recrystallization from benzene gave trans-α-(p-bromophenyl)cinnamic acid (197.6 g, 73%) as white crystals, mp 191-194°; ir (Nujol), 1675 (C=O), 1620 cm^{-1} (C=C); nmr (DMSO-d_6), δ 7.80 (S, 1, C=CH-Ø), 6.95-7.70 (m, 9, Ar).

Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66; Br, 26.36. Found: C, 59.22; H, 3.72; Br, 26.14.

Methyl trans-α-(p-bromophenyl) cinnamate (I)- To a solution of trans-α-(p-bromophenyl)cinnamic acid (197.6 g, 0.65 mol) in 2 l of methanol was slowly added 147 ml of thionyl chloride (238 g, 2 mol). The mixture

was refluxed for 2 hr. The pale yellow crystals obtained upon cooling to room temperature was separated by filtration. The mother liquor was condensed to 500 ml under reduced pressure and a second crop of crystals were collected. The product was recrystallized twice from methanol giving a combined yield of 152.7 g (75%) of I as white crystals, mp 74-75°; ir (Nujol), 1710 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$), δ 7.87 (S, 1, C=CH=Ø), 7.63-6.90 (m, 9, Ar), 3.79 (S, 3, OCH_3).

Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13; Br, 25.19. Found: C, 60.34; H, 4.40; Br, 25.18.

Methyl 6-bromophenanthrene-9-carboxylate (IIb). - To a solution of I (9.48 g, 0.03 mol) in 3.5 l of cyclohexane contained in a 5 l three-necked round bottom Pyrex flask equipped with a long condenser and a magnetic stirrer was added 0.38 g of iodine. With the solution stirred and a slow stream of oxygen bubbling through it, the solution was photolysed for 48 hr (a 450 watt Hanovia uv lamp placed five inches from the flask). At the end of the photolysis, the solvent was removed under reduced pressure. The reddish residue was dissolved in chloroform and passed through a 1 cm x 10 cm alumina column. The solvent was stripped off and the solid residue was crystallized from methanol to give 4.1 g (44%) of white needles, mp 131-132°; ir (Nujol), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 8.88-8.27 (m, 4, Ar), 7.92-7.37 (m, 4, Ar), 4.0 (S, 3, OCH_3).

Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52; Br, 25.35. Found: C, 60.83; H, 3.63; Br, 25.33.

Methyl 3,6-bis(trifluoromethyl)phenanthrene-9-carboxylate (IIa). - A mixture of 3,6-bis(trifluoromethyl)phenanthrene-9-carboxylic acid[8] (12.5 g, 0.035 mol) in 200 ml of methanol and 7.6 ml of thionyl chloride (12.5 g, 0.105 mol) was refluxed for 3 hr. Upon cooling, a white precipitate separated from the solution and was recrystallized from methanol to give

10.8 g (83%) of IIa, mp 147-150°; ir (Nujol), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{10}F_6O_2$: C, 58.08; H, 2.71. Found: C, 58.19; H, 2.83.

9-Hydroxymethyl-3,6-bis(trifluoromethyl)phenanthrene (IIIa). - To the methyl ester IIa (10 g, 0.027 mol) in 100 ml of anhydrous ether was added 0.027 mol of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al) in 30 ml of ether at 0° over a 15 min period. The solution was allowed to stir at this temperature for an additional 2 hr, after which 30 ml of methanol was added to decompose the excess Red-Al. The solution was then poured over 300 ml of ice containing 25 ml of conc. hydrochloric acid. The ethereal layer was separated and the aqueous layer was extracted with ether (3x50 ml). The combined ethereal phase was washed with water (2x50 ml), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting pale yellow solid was recrystallized from ether affording 6.5 g (70%) of compound IIIa as white crystals, mp 219-220°; ir (Nujol), 3460 (OH), 1620 cm^{-1} (C=C); nmr (DMSO-d_6), δ 9.33-9.00 (m, 2, Ar), 8.40-7.70 (m, 5, Ar), 5.02 (S, 2, $-CH_2OH$).

Anal. Calcd for $C_{17}H_{10}F_6O$: C, 59.31; H, 2.93. Found: C, 59.60; H, 2.67.

9-Hydroxymethyl-6-bromophenanthrene (IIIb) was prepared in the same manner as described in the synthesis of compound IIIa from IIb (2 g, 0.0064 mol) and Red-Al (3.5 ml) in 150 ml of ethyl ether. It was isolated in 70% as white needles, mp 157-159° from ether; ir (Nujol), 3200 (OH), 1600 cm^{-1} (C=C); nmr (DMSO-d_6), δ 9.10-8.57 (m, 2, Ar), 8.30-7.33 (m, 6, Ar), 5.05 (S, 2, $-CH_2OH$).

Anal. Calcd for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86; Br, 27.83. Found: C, 62.48; H, 3.92; Br, 27.66.

9-Chloromethyl-3,6-bis(trifluoromethyl)phenanthrene (IVa). - To a solution of the Alcohol IIIa (4.7 g, 0.014 mol) in 150 ml of chloroform containing 2.5 ml of pyridine was added 2 ml of thionyl chloride (0.028 mol)

at 0°. The reaction mixture was heated at 50-60° with stirring for 1 hr and then poured on ice. The chloroform layer was separated, washed with dilute sodium bicarbonate solution, then with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the yellow residue crystallized from chloroform-pet ether (60-120°), giving 4.46 g (88%) of pale yellow crystals, mp 167-169°; nmr (DMSO-d_6), δ 9.50-9.10 (m, 2, Ar), 8.70-7.73 (m, 5, Ar), 5.27 (S, 2, -$\underline{CH_2}$Cl).

<u>Anal</u>. Calcd for $C_{17}H_9ClF_6$: C, 56.30; H, 2.49. Found: C, 56.57; H, 2.68.

<u>9-Chloromethyl-6-bromophenanthrene (IVb)</u>. - This compound was prepared by the same method as described above from alcohol IIIb (8 g, 0.028 mol) and with thionyl chloride (4.0 ml) in the presence of pyridine (4.8 ml) to give 7.3 g (86%) of white needles, mp 130-132°; nmr ($CDCl_3$), δ 8.83-8.30 (M, 2, Ar), 8.09-7.45 (M, 6, Ar), 4.96 (S, 2, -$\underline{CH_2}$Cl).

<u>Anal</u>. Calcd for $C_{15}H_{10}BrCl$: C, 58.95; H, 3.30; Br, 26.15; Cl, 11.60. Found: C, 58.78; H, 3.46; Br, 25.92; Cl, 11.43.

<u>Benzyl N-[3,6-bis(trifluoromethyl)phenanthr-9-ylmethyl]-L-prolinate (Va)</u>.

A mixture of the chloride IVa (7.47 g, 0.021 mol), benzyl L-prolinate hydrochloride (5.55 g, 0.023 mol) and anhydrous potassium carbonate (3.45 g, 0.025 mol) in dry N,N-dimethylformamide (50 ml) was protected from moisture and stirred overnight at 60-80°. The solvent was removed under reduced pressure at 70°. The residue was extracted with 200 ml of methylene chloride, washed with water and dried ($MgSO_4$). The methylene chloride solution was evaporated to dryness leaving a residue which was taken up in benzene (50 ml). The benzene solution was then eluted through a short column of neutral alumina (50 g). The eluate was evaporated again to dryness and the residue was recrystallized from ether-<u>n</u>-hexane to afford 2.11 g (88%) of Va, mp 75-78°; ir (Nujol), 1750 (C=O), 1630 cm^{-1} (C=C); nmr ($CDCl_3$), δ 9.00-7.00 (m, 12, Ar), 5.10 (S, 2, -$\underline{CH_2}\phi$), 4.64-

1.40 (m, 9, aliphatic).

Anal. Calcd for $C_{29}H_{23}F_6NO_2$: C, 65.54; H, 4.36; N, 2.64. Found: C, 65.75; H, 4.35; N, 2.57.

Benzyl N-(6-bromophenanthr-9-ylmethyl)-L-prolinate (Vb). - The title compound was synthesized in the same manner as described in the preparation of Va. The chloride IVb (1.53 g, 0.005 mol) was treated with benzyl L-prolinate hydrochloride (1.33 g, 0.0055 mol) in the presence of anhydrous potassium carbonate (1.38 g, 0.01 mol) using DMF as solvent to afford 1.25 g (53%) of product, mp 91-93° (from EtOH-CH_2Cl_2); ir (Nujol), 1740 (C=O), 1600 cm^{-1} (C=C); nmr ($CDCl_3$), δ 9.00-7.00 (m, 13, Ar), 5.10 (S, 2, $-CH_2\emptyset$), 4.64-1.40 (m, 9, aliphatic).

Anal. Calcd for $C_{27}H_{24}BrNO_2$: C, 68.36; H, 5.10; N, 2.95; Br, 16.84. Found: C, 67.85; H, 5.01; N, 2.89; Br, 17.10.

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REFERENCES

1. T.R. Govindachari in ''The Alkaloids,'' Vol. 9, p. 517, R.H.F. Manske, Ed., Academic Press, New York, N.Y., 1967.
2. B. Chauncy and E. Gellert, Aust. J. Chem., 23, 2503 (1970).
3. P. Marchini and B. Belleau, Can. J. Chem., 36, 581 (1958).
4. E. Gellert and R. Rudzats, J. Med. Chem., 7, 361 (1964).
5. M. R. Atkinson, G. R. Donaldson, and A. W. Murray, Biochem. Biophys. Res. Commun., 31, 104 (1968).
6. D. F. Detar, Org. Syn. Coll. Vol. 4, 730 (1963).
7. C. S. Wood and F. B. Mallory, J. Org. Chem., 29, 3373 (1964).
8. A generous sample was supplied by Walter Reed Army Medical Center, Washington, D.C. 20012.

9. R. E. Neuman and E. L. Smith, J. Biol. Chem., 193, 97 (1951).

10. Melting points were taken on a Thomas-Hoover Unimelt apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The nmr spectra were obtained on a Varian A-60 spectrophotometer using Me_4Si as internal standard. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

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