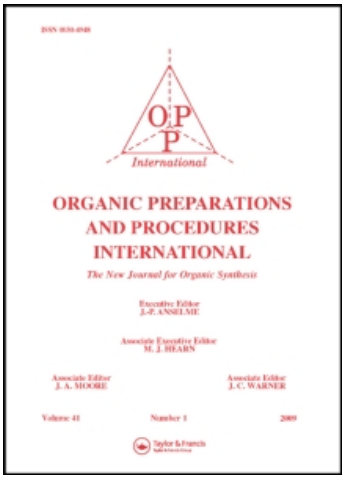

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ETHYL 2-(4-AMINOPHENYL) PROPIONATE

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ETHYL 2-(4-AMINOPHENYL)PROPIONATE

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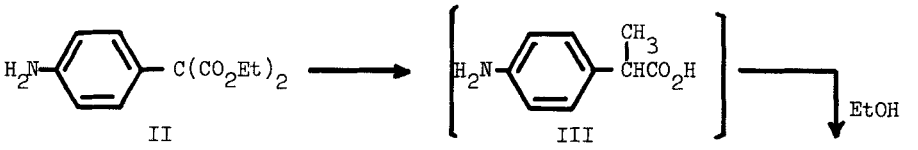
Ethyl 2-(4-aminophenyl)propionate(IV), a useful intermediate in the preparation of pharmaceutical drugs has been obtained as shown below.[1]

The corresponding acid III is well known[2] and an alternate route to IV has

I



II III

IV

been described.[3]

EXPERIMENTAL

Diethyl(4-nitrophenyl)methylmalonate.- To a stirred mixture of 60 g (2.5 moles) of sodium hydride and 235 ml of DMF, under a slight flow of nitrogen, was added dropwise a solution of 480 g (2.75 moles) of diethyl methylmalonate in 250 ml of DMF over a period of 1 hr. The mixture was stirred vigorously for 3 hrs to give a solution which was heated to 85° for 20 minutes. Then a solution of 394 g (2.33 moles) of p-chloronitrobenzene in 375 ml of DMF was rapidly added. The N_2 flow was stopped and the mixture was stirred at 80° for 16 hrs. The solvent was removed under reduced pressure, and the residue was treated with 1.25 ℓ water and extracted four times, first with 500 ml and then with 200 ml portions of ether. The combined ethereal extracts were washed with 500 ml of water, the solvent was removed to give 700 g of a dark brown oil which was distilled to give 556 g (75%) of I, bp. 179-182°/1 mm.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.98; H, 5.76; N, 4.74.

Found: C, 56.84; H, 5.83; N, 4.85.

TLC: R_f 0,45 on silica gel (Merck 60 F_{254}); eluent: hexane/acetone 3/1; I_2.

IR: 1730 cm^{-1} (CO); 1520 and 1350 cm^{-1} (NO_2); 850 cm^{-1} (p-disubstituted benzene).

NMR ($CDCl_3$): 8.08 δ (2H, d, Ar, H-3, H-5); 7.5 δ (2H, d, Ar, H-2); 4.15 δ (4H, q, $-CH_2-$); 1.8 δ (3H, s, $CH_3-\overset{|}{C}-$); 1.18 δ (6H, t, $\underline{CH_3}-CH_2-$).

Dimethyl(4-aminophenyl)methylmalonate. In a 5 ℓ round-bottomed flask fitted with a mechanical stirrer were placed 556 g (1.88 mole) of I, 1850 ml of ethanol, 317 g (5.60 moles) of iron powder and 185 ml of water. The mixture was heated to boiling and treated with a solution of 56.5 ml of conc. HCl in 750 ml of 1/1 water:ethanol. The mixture was boiled for 6 hrs and, after cooling, the inorganic compounds were removed by suction filtration and washed with two 50 ml portions of ethanol. The combined ethanol-water solution was distilled to remove the ethanol, cooled and the residue treated with 1.5 ℓ water. The mixture was extracted with 500 ml of freshly distilled ether and then three times with 100 ml portions. The combined ethereal extracts were washed five times with 100 ml portions of 4 N HCl. The acid solution was neutralized with 5 N NaOH and further extracted three times with freshly distilled ether, first with 500 ml and then twice with 200 ml portions. The combined ethereal extracts were subsequently washed with 300 ml water and the ether then removed by distillation to yield 480 g (96%) of a pale yellow oil.

TLC: R_f, 0.33 on silica gel plate (Merck 60 F_{254}); eluent:hexane/acetone 2/1; I_2.

IR: Bands at 3460 and 3380 cm^{-1} (NH_2); 1725 cm^{-1} (CO).

NMR ($CDCl_3$): 7.1 δ (2H, d, Ar, H-3); 6.55 δ (2H, d, Ar, H-3, H-5); 4.18 δ (4H, q, $-CH_2-$); 3.4-4.9 δ (2H, NH_2); 1.8 δ (3H, s, $CH_3-\overset{|}{C}-$); 1.2 δ (6H, t, $\underline{CH_3}-CH_2-$).

Ethyl 2-(4-aminophenyl)propionate (IV).- A mixture of 480 g (1.81 mole) of II, 5.8 ℓ of 0.5 N NaOH and 1.9 ℓ of ethanol was heated to boiling for 16 hrs. The hot mixture was acidified to about pH 4 with 850 ml of 4 N HCl and allowed to boil for two hours more. Ethanol and water were evaporated to give a solid residue (III + inorganics) which was dried over P_2O_5 overnight under reduced pressure. The solid was treated with 4.8 ℓ of anhydrous ethanol and 120 ml of 98% sulfuric acid and placed in a flask fitted with a condenser and a mechanical stirrer. The mixture was heated to boiling for 8 hrs, then after addition of about 2 kg of crushed ice, it was neutralized slowly to pH 8-8.5 with a 10% solution of Na_2CO_3. The ethanol was distilled under reduced pressure and the residue was extracted three times with freshly distilled ether, first with 500 ml and then with two 200 ml portions. The ethereal extracts were washed twice with 200 ml portions of water, dried and distilled to remove the ether. Distillation of the resulting oil under reduced pressure gave 292 g (96%) of IV, bp. 120-122°/0.8 mm.

TLC: R_f 0.38 on silical gel plate (Merck 60 F_{254}), 2/1 hexane/acetone; I_2.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25.
Found: C, 68.53; H, 7.84; N, 7.11.

IR: Bands at 3460 and 3380 cm^{-1} (NH_2); 1725 cm^{-1} (CO).

NMR ($CDCl_3$): 7.05 δ (2H, d, Ar, H-2); 6.54 δ (2H, d, Ar, H-3, H-5); 4.06 δ (2H, q, $-CH_2-$); 3.63 δ (2H, s, NH_2); 3.55 δ (1H, q, -CH-); 1.45 δ (3H, d, CH_3-C-); 1.18 δ (3H, t, $\underline{CH_3}-CH_2-$).

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