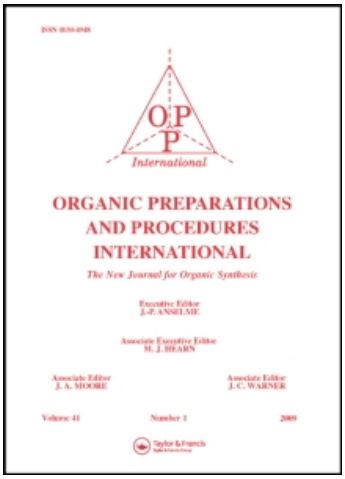

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A MODIFIED METHOD FOR PREPARING 2-(2-PHENETHYL)PHENYLACETIC ACID

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A MODIFIED METHOD FOR PREPARING 2-(2-PHENETHYL)PHENYLACETIC ACID

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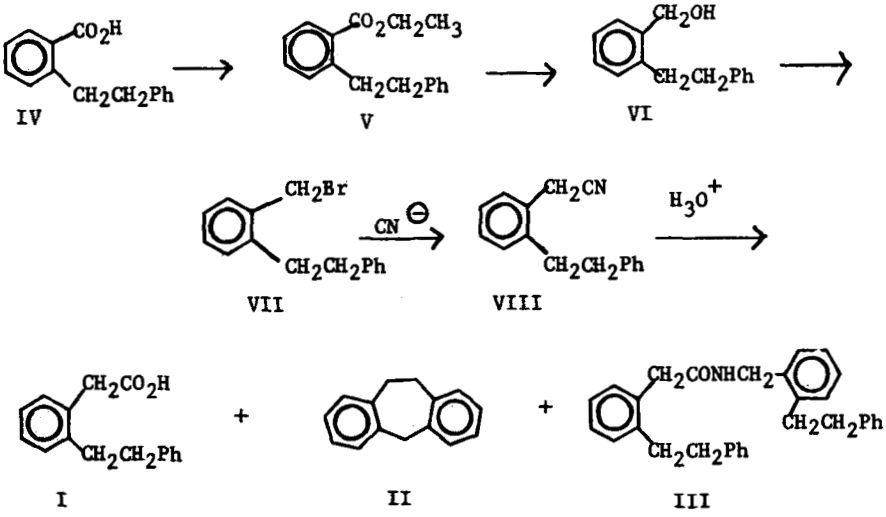
In connection with another study, 2-(2-phenethyl)phenylacetic acid (I) was required in quantity. When a multi-step literature[1] method was employed for the synthesis of I from 2-(2-phenethyl)benzoic acid (IV), a side-reaction predominated to give the previously undetected hydrocarbon II and only minor amounts (28%) of the desired acid I. A second side-product, the amide III, was also detected. The reaction sequence has now been studied and modifications made at various points so as to give much improved yields of the desired acid I.



After preparing the ester V according to a reported[2] method, the following modifications were made:

a) More convenient reduction to the carbinol VI was accomplished in benzene solution using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich Chemical Co.) for 35 mins at reflux. After hydrolyzing the reaction, the C_6H_6 layer yielded pure carbinol VI in 90% yield (mp 58-60°, lit.[1] mp 58-59°).

b) The preparation of bromide VII using PBr_3-pyridine at 0° gave almost pure product which was then converted to nitrile VIII. This latter compound was shown to be free of hydrocarbon II by NMR analysis (no peak near 5.91 τ). Crude VIII, on acid hydrolysis, gave 51% of the desired acid I, 17% of hydrocarbon II and 2% of the amide III. The overall yield of I in four steps from the ester V, without purifying intermediates, was 40%.[3]

It would appear that from the formation of the intermediate 2-(2-phenethyl)benzyl carbonium ion in the bromination of the alcohol VI in hot aqueous HBr as well as in the vigorous acid hydrolysis of the nitrile VIII might explain the formation of compounds II and III.

EXPERIMENTAL

2-(2-Phenethyl)phenylacetic acid (I). To a solution of 138 g (0.51 mole) of PBr_3 in 142 ml of dry benzene at 0° was slowly added 18.6 g of dry pyridine, following by the dropwise addition of a solution of 404 g (1.91 mole) of 2-(2-phenethyl)benzyl alcohol[1] in 400 ml of benzene containing 9.3 g of dry pyridine. After complete addition and 1 hr at 0°, the resulting solution was allowed to stand at room temperature for

24 hrs. After adding 800 ml of water to the solution, repeated ether extractions yielded 460 g (85%) of 2-(2-phenethyl)benzylbromide (VII) which was homogeneous on thin-layer chromatographic examination. Nmr (deuteriochloroform): τ 2.68 (s, 4, aromatic ring), 2.79 (s, 5, phenyl), 5.57 (s, 2, CH_2Br) 7.02 ppm (s, 4, CH_2CH_2).

All of the above bromide (1.67 moles) was refluxed in a solution of 900 ml of ethanol containing 136 g (2.09 moles) of KCN for 0.5 hr. The resulting suspension was poured into H_2O and extracted repeatedly with Et_2O. Evaporation of the ether extracts yielded 337 g (91%) of 2-(2-phenethyl)benzyl cyanide (VIII) as a tan oil which slowly crystallized. Nmr (deuteriochloroform):τ 2.82 (m, 9, aromatic), 6.60 (s, 2, CH_2CN), 7.15 (s, 4, CH_2CH_2); mass spectrum (70 e/v) m/e (rel intensity) (calc m^+ 221) 221 (2), 194 (5), 193 (28), 192 (16), 179, 178, 177.

All of the above nitrile (1.5 moles) in a mixture of 400 ml of water, 400 ml of H_2SO_4 and 675 ml of glacial acetic acid was refluxed for 3 hrs. The resulting solution was poured into 2 l of ice-H_2O to produce a pale yellow wax which was filtered. Partitioning the wax between ether-10% NaOH gave: a) from the acidified basic aqueous layer, 185 g (51%) of 2-(2-phenethyl)phenylacetic acid (I), mp 88-90°, lit.[1] mp. 92-93°; b) from the ethereal layer, on evaporation and recrystallization of the residue from ether-hexane, 7.5 g (2%) of N-[2-(2-phenethyl)benzyl]-2'-(2-phenethyl)phenylacetamide (III), mp. 99-102°. IR (KBr): 3.05 (NH), 6.09 μ (C=O); nmr (D_6-DMSO)τ 2.78 (m, 18, aromatic protons), 5.68 (d, 2, J = 6Hz, CH_2N), 6.41 (s, 2, CH_2-C), 6.7 (broad, 1, exchanges D_2O, NH), 7.17 ppm (s, 8, CH_2CH_2).

Anal. Calcd, $C_{31}H_{31}NO$: C, 85.87; H, 7.21; N, 3.23. Found: C, 86.30; H, 7.24; N, 3.09;

and c) by evaporation of the ether-hexane filtrate from b) above, 50 g (17%) of dibenzo(a,d)cyclohepta(1,4)diene (II), which, after recrystallization from ethanol-H_2O, had mp. 75-77°, lit.[4] mp. 78-79°. Insoluble NaOH; IR (KBr): no C=O peaks near 5-6 μ; nmr (deuteriochloroform) τ 2.91 (s, 8H, aromatic protons), 5.91 (s, 2H, CH_2) 6.88 ppm (s, 4, CH_2CH_2).

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.49; H, 7.28.

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2. S. Natelson and S. P. Gottfried, ibid, 58, 1432 (1936).
3. When carbinol VI was treated with HBr according to Leonard et al.,[1] the resulting crude bromide (VII) after treatment with KCN, gave a semisolid nitrile (VIII) containing only one-third (2.23%) of the theoretical N (6.35%) suggesting a mixture of II and VIII. An NMR spectrum of the mixture indicated a 4:3 ratio of area under the peaks for the $-CH_2-$ of hydrocarbon II (5.91 τ) and the $-CH_2-$ of nitrile VIII (6.6 τ). When this nitrile was hydrolyzed according to Leonard et al.[1], hydrocarbon II was formed in 60% yield and the desired acid I obtained in only 28% yield. No mention has previously been made of the presence of hydrocarbon II in this reaction.
4. W. Treibs and H. J. Klinkhammer, Chem. Ber., 84, 671 (1951).

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