Intramolecular Reactions of *ortho*-Substituted *N*-Phenethylamides

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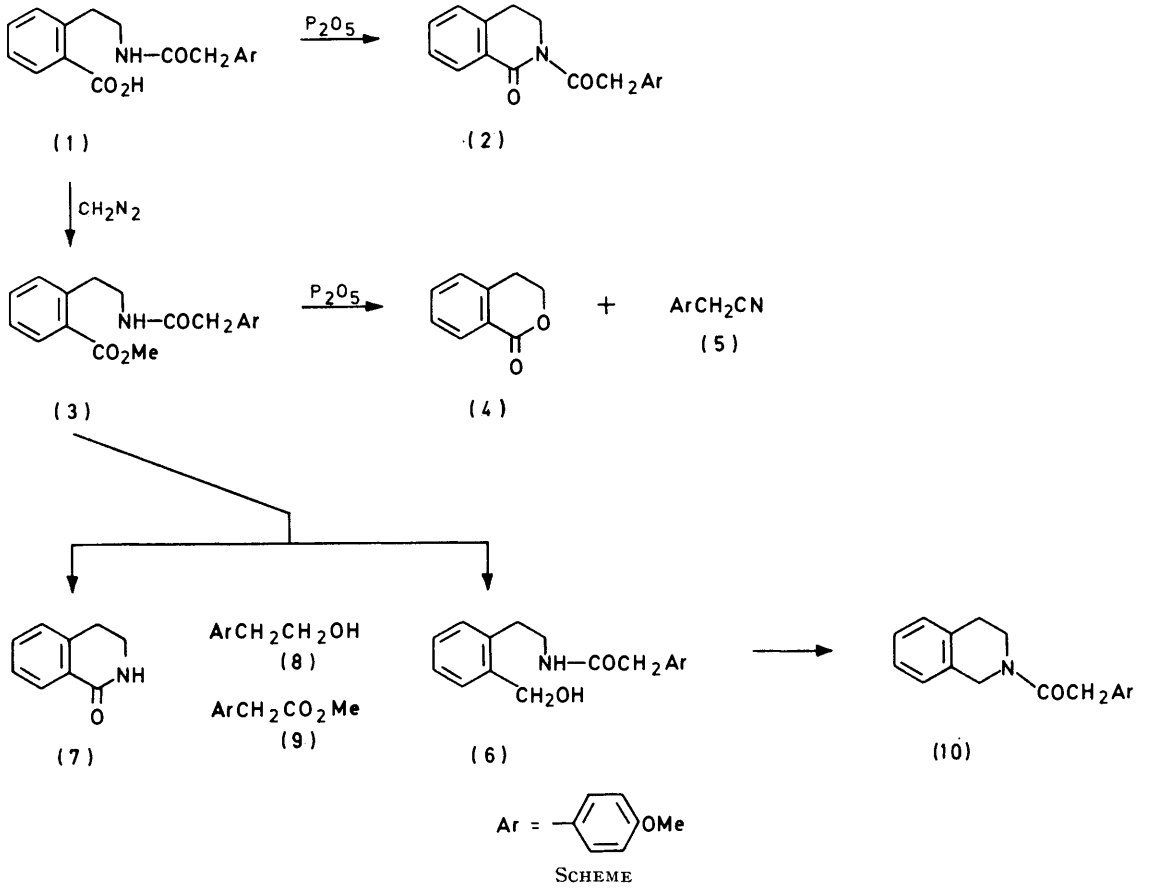
Under conditions for the Bischler–Napieralski synthesis of isoquinolines, 2-[2-(*p*-methoxyphenylacetamido)ethyl]-benzoic acid (1), its methyl ester (3), and the corresponding benzyl alcohol derivative (6) undergo alternative cyclisations.

ATTEMPTS to effect the Bischler–Napieralski reaction on the compound (1; Ar = *p*-methoxyphenyl throughout), in order to form the corresponding 1,5-disubstituted isoquinolines, have revealed several intramolecular reactions leading to other types of product. The amido-acid (1) was readily obtained from indan-1-one by the Schmidt reaction [1] followed by vigorous alkaline hydrolysis of the lactam and treatment with *p*-methoxyphenylacetyl chloride.

Under typical Bischler–Napieralski conditions (P_2O_5 in refluxing toluene), compound (1) formed the imide (2). We infer that (1) forms its acid anhydride, or the mixed anhydride, and that this undergoes intramolecular displacement even by the weakly nucleophilic amidic nitrogen.

To circumvent this, the amido-acid (1) was converted into its methyl ester (3).† However, under Bischler–Napieralski conditions this yielded products (4) and (5), from which we infer that the ester group is a more effective nucleophile than the 3-position of the benzenoid ring towards the P_2O_5-activated amide function [*e.g.* reaction (i)].

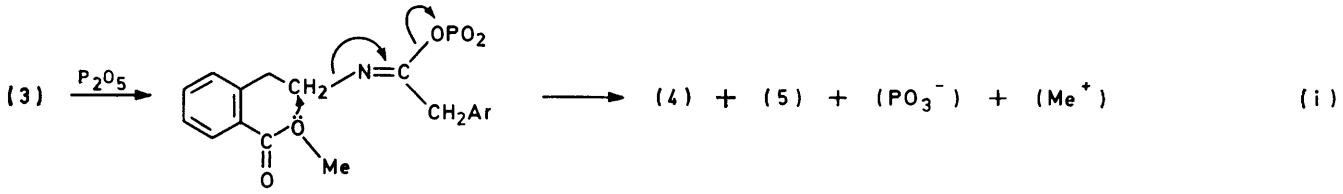


SCHEME

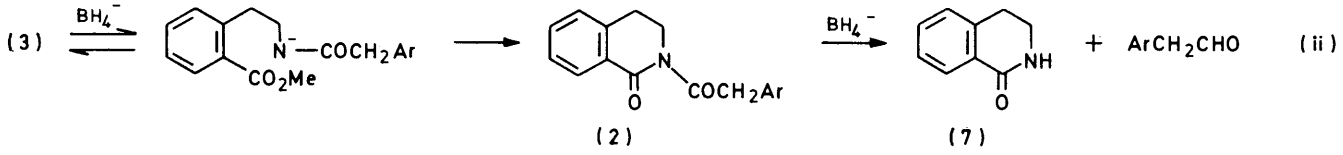
In order to reduce the nucleophilic character associated with the oxygen atom of the ester, we decided to reduce the ester group to the alcohol since, under

† Attempts to make the ethyl ester with either toluene-4-sulphonyl chloride in pyridine with ethanol [2] or 2-bromo-1-methylpyridinium iodide in dichloromethane with ethanol [3] again gave the imide (2). Evidently the amidic nitrogen is once more the effective nucleophile for reaction at the activated acid group, this time in competition with ethanol.

Bischler–Napieralski conditions, this should be phosphorylated (or trifluoroacetoxylated, if reaction were in trifluoroacetic acid); moreover, this modified substituent should have less deactivating influence than methoxycarbonyl on the required electrophilic substitution at the aromatic 3-position.

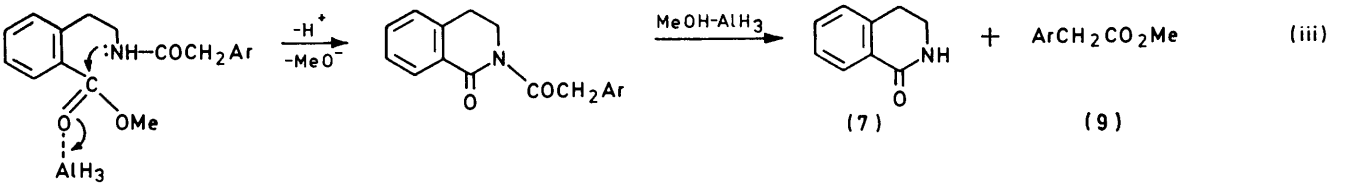


Reduction with lithium borohydride (which is specific to carboxylic esters in the presence of amides [4]) gave an erratic and low yield of the alcohol (6), and sodium borohydride gave a maximum yield of (6) of 35%. In each case products (7) and (8) were formed in *ca.* 75% yield together with a small quantity of the ester (9). It seems likely that (7), (8), and (9) arise by way of the imide (2); thus, methanolysis of (2) could yield (7) and (9), further reduction of which could give (8), or reductive cleavage of (2) could yield (7) and $ArCH_2CHO$ [thence (8)] as in reaction (ii). In accord with this, products (7)



and (8) were formed when the imide (2) was reduced in the same way. However, the alcohol (6) was not then formed, so that it evidently results from the direct reduction of the ester rather than from the alternative mode of reductive cleavage of the imide.

A non-basic reducing agent should eliminate reduction of the ester (3) as in reaction (ii) and thereby favour formation of the required alcohol. We chose aluminium hydride, since this reacts faster with esters than with secondary amides,[4] but this yielded the products (7) and



(9). It seems probable that the reducing agent, as a Lewis acid, facilitates cyclisation and methanolysis as in reaction (iii); in accord with this, these products were formed when aluminium trichloride was used instead of the hydride.

Treatment of the amido-alcohol (6) with trifluoroacetic acid under reflux gave the product (10); with polyphosphoric acid at 120 °C both (10) and other unidentified products were obtained. Evidently the acid reagent activates the alcoholic function so that once again intramolecular nucleophilic substitution by amidic nitrogen occurs.

EXPERIMENTAL

I.r. spectra (liquid film or Nujol mull) were recorded on Pye Unicam SP200 and SP1025 spectrometers. ^1H N.m.r spectra for solutions in deuteriochloroform were obtained with Varian A-60A or JEOL JNM 100 MHz spectrometers and ^{13}C n.m.r. spectra with a JEOL JNM-FX60 F.T. spectrometer. Tetramethylsilane was used as internal standard. Routine low-resolution mass spectra were measured on A.E.I. MS9, MS12, and MS30 spectrometers. Elemental analyses were carried out by Butterworths Microanalytical Consultancy Ltd. T.l.c. was carried out on silica gel GF_{254} (Merck) and column chromatography employed 80—200 mesh silica gel (Fisons Scientific Apparatus Ltd.). G.l.c. used a Pye Series 104 gas chromatograph with an F.I.D. detector and a glass column (0.4 cm i.d. × 150 cm) packed with 10% silicone oil (M.S. 550) on 80—120 mesh Celite (B.D.H. Ltd.).

Materials.—All the commercial materials were reagent grade and obtained from Aldrich Chemical Co. Ltd., B.D.H. Ltd., Koch–Light Ltd., or Fisons Scientific Apparatus Ltd. Nitrogen (British Oxygen white spot grade) was dried by passing it successively through concentrated sulphuric acid, potassium hydroxide pellets, and silica gel.

2-[2-(p-*Methoxyphenylacetamido)ethyl*]*benzoic Acid* (1).—3,4-Dihydroisoquinolin-1(2*H*)-one [1] (3.52 g) was added to 6M-aqueous sodium hydroxide (175 cm^3) and stirred at 100 °C. After 1 h the homogeneous solution was cooled (salt–ice) and *p*-methoxyphenylacetyl chloride (7.3 g) was added with stirring. The solution was then left to stir at room temperature for 1 h before it was acidified with 6M-hydrochloric acid (180 cm^3). Extraction with dichloromethane followed by evaporation gave the *amide* (1) (4.7 g, 63%), m.p. 150—152 °C (MeOH–H_2O with active carbon) (Found: C, 69.1; H, 6.3; N, 4.45. $C_{18}H_{19}NO_4$ requires C, 69.01; H, 6.07; N, 4.47%); $\nu_{max.}$ 3 300 (NH), 3 000br (OH), 1 690, 1 670 (acid C=O), and 1 640 and 1 610 cm^{-1} (amide I and II bands); τ −3.5 (1 H, br, CO_2H), 1.9 (1 H,

br, NH), 1.9—3.4 (8 H, m, ArH), 6.3 (3 H, s, OMe), and 6.5—7.2 (6 H, m, CH_2); *m/e* 313 (M^+, 0.3%) and 121 (100).

3,4-*Dihydro*-2-(p-*methoxyphenylacetyl*)*isoquinolin*-1(2H)-*one* (2).—The imide (2) was prepared in low yield (0.013 g, 10%) by the method of Hurd and Prapas [5] from 3,4-dihydroisoquinolin-1(2*H*)-one (0.062 g) and *p*-methoxyphenylacetyl chloride (0.078 g) and was purified by column chromatography (ethyl acetate). It had $\nu_{max.}$ 1 690 (CO–N–CO stretch) cm^{-1}; τ 1.8—3.4 (8 H, m, ArH), 5.7 (2 H, s, $COCH_2Ar$), 5.94 (2 H, t, CH_2N), 6.28 (3 H, s, OMe), and 7.1 (2 H, t, $ArCH_2CH_2$).

Methyl 2-[2-(p-*Methoxyphenylacetamido*)*ethyl*]*benzoate* (3).—A solution of diazomethane [6] in ethanolic ether was added dropwise to the amido-acid (1) in ethanol until reaction was complete. Removal of the solvent gave the *ester* (3) (96%), m.p. 95—95.5 °C (Found: C, 69.55; H, 6.5; N, 4.2. $C_{19}H_{21}NO_4$ requires C, 69.72; H, 6.42; N, 4.28%); $\nu_{max.}$ 3 350 (NH), 1 705 (C=O ester), and 1 645 and 1 610 (amide I and II bands) cm^{-1}; τ 2.2—3.5 (8 H, m, ArH), 3.6—4.0 (1 H, m, NH), 6.25 (3 H, s, CO_2Me), 6.31 (3 H, s, OMe), and 6.4—7.2 (6 H, m, CH_2); δ_C 171.6 (NHCO), 168.0 (CO_2CH_3), 158.6—114.2 (12 C_{Ar}), 55.2 ($ArOCH_3$), 52.1 (CO_2CH_3), 42.9 (CH_2NHCO), 41.1 ($ArCH_2CONH$), and 33.0 ($ArCH_2CH_2$) (all resonances gave the expected couplings in the off-resonance spectrum); *m/e* 327 (M^+, 16%) and 121 (100).

4-*Methoxybenzyl Cyanide* (5).—To phosphorus pentaoxide (0.2 g) in dry toluene (5 cm^3) was added 4-methoxyphenylacetamide (0.1 g) and the mixture was refluxed. After 10 min water was added to the cooled solution and extraction with ether gave the cyanide (0.06 g, 67%); $\nu_{max.}$ 2 285 (CN); τ 2.7—3.4 (4 H, m, ArH), 6.36 (3 H, s, OMe), and 6.5 (2 H, s, CH_2CN).

1,2,3,4-*Tetrahydro*-2-(p-*methoxyphenylacetyl*)*isoquinoline* (10).—A slight excess of *p*-methoxyphenylacetyl chloride was added to 1,2,3,4-tetrahydroisoquinoline under nitrogen. After warming for 1 h water was added and the *tetrahydroisoquinoline* (10) was recrystallised (methanol–water), m.p. 73—74 °C (Found: C, 76.95; H, 6.85; N, 5.0. $C_{18}H_{19}NO_2$ requires C, 76.84; H, 6.81; N, 4.98%); τ 2.8—3.4 (8 H, m, ArH), 5.4 (2 H, d, $ArCH_2NCO$), 6.2—6.6 (7 H, m, OMe, $ArCH_2CO$, $ArCH_2CH_2NCO$), and 7.3 (2 H, m, $ArCH_2CH_2NCO$).

Attempted Syntheses of Ethyl 2-[2-(p-*Methoxyphenylacetamido*)*ethyl*]*benzoate*.—The amido-acid (1) (0.1 g) was treated with toluene-4-sulphonyl chloride and pyridine in ethanol following the method of Hennion and Barrett.[7] The reaction mixture was poured into water, and the dichloromethane extract was washed with dilute hydrochloric acid, dried (Na_2SO_4), and evaporated to give crude product (0.1 g). Column chromatography (ethyl acetate) gave the imide (2) (0.046 g, 44%).

The attempted esterification of the amido-acid (1) (0.151 g) with 2-bromo-1-methylpyridinium iodide and ethanol following the method of Mukaiyama *et al.*[3] gave the imide (2) (0.04 g, 28%) after column chromatography (ethyl acetate).

Both the esterification procedures gave the imide (2) when ethanol was omitted from the reaction mixture.

Reduction of Amido-ester (3).—(i) A 1M-solution of lithium borohydride in ether–tetrahydrofuran (17 cm^3) was added with stirring to the amido-ester (3) (1 g) in tetrahydrofuran (30 cm^3). After 4 h the mixture was added cautiously to dilute hydrochloric acid (20 cm^3) and neutralised ($NaHCO_3$) before it was extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporation gave a residue (1.03 g). Recrystallisation (EtOH–H_2O) gave *N*-(2-*hydroxymethylphenethyl*)-p-*methoxyphenylacetamide* (6) (0.2 g, 23%), m.p. 101—102 °C (Found: C, 72.0; H, 7.15; N, 4.5. $C_{18}H_{21}NO_3$ requires C, 72.24; H, 7.02; N, 4.68%); $\nu_{max.}$ 3 250 (OH), and 1 640 and 1 608 cm^{-1} (amide I and II bands); τ 2.7—3.4 (8 H, m, ArH), 3.8 (1 H, br, NH), 5.45 (2 H, d, $ArCH_2OH$), 6.3 (3 H, s, OMe), 6.4—6.9 (5 H, m, CH_2NH, CH_2OH, and $COCH_2Ar$), and 7.22 (2 H, t, $ArCH_2CH_2$); *m/e* 299 (M^+, 8.5%), 281 (12), and 121 (100).

Extraction of the mother liquor (CH_2Cl_2) from the above recrystallisation gave a mixture which was shown by g.l.c.–mass spectrometry to contain compounds (7), (8), and (9). Column chromatography (ethyl acetate) gave 3,4-dihydroisoquinolin-1(2*H*)-one (7) (0.36 g, 77%), with n.m.r. and mass spectra identical to those of authentic material, and a mixture of *p*-methoxyphenethyl alcohol (8) and methyl *p*-methoxyphenylacetate (9).

(ii) The reduction was repeated by adding sodium borohydride (0.05 g) to a solution of the amido-ester (3) (0.025 g) in ethanol (1 cm^3). Water was added to the mixture after 3 days stirring and the solution was acidified and extracted with dichloromethane. Column chromatography (ethyl acetate) gave low yields (20—35%) of the amido-alcohol (6).

(iii) A solution of aluminium hydride [8] (7.8×10^{-3} g) in dry ether was added dropwise to a stirred solution of the amido-ester (3) (0.2 g) in dry ether under nitrogen. When reaction was complete (t.l.c.), water was added, and the ether extract was dried ($MgSO_4$) and evaporated to give a yellow oil. Column chromatography (ethyl acetate) gave the reduced isoquinolone (7) and the ester (9).

Reduction of Imide (2).—1M-Lithium borohydride in ether–tetrahydrofuran (1 cm^3) was added with stirring to the imide (2) (0.066 g) in dry tetrahydrofuran (1 cm^3). After 4 h the solution was worked up, as described for the reduction of (3), to give a mixture of the reduced isoquinolone (7) and *p*-methoxyphenethyl alcohol (8). The identities of the components of the mixture were confirmed by t.l.c., g.l.c., and n.m.r. spectroscopy.

Reaction of Amido-ester (3) *with Aluminium Trichloride*.—When the ester and aluminium trichloride were mixed in tetrahydrofuran the reduced isoquinolone (7) and methyl *p*-methoxyphenylacetate (9) were formed almost immediately (g.l.c.).

Attempted Bischler–Napieralski Reactions.—(i) The amido-acid (1) (0.02 g) was added to phosphorus pentaoxide (0.08 g) in a refluxing dry hydrocarbon solvent [toluene, xylene, or tetralin (1—2 cm^3)]. The mixture was cooled after 10 min, and water was added. Neutralisation ($NaHCO_3$), extraction with dichloromethane, followed by drying ($MgSO_4$) and evaporation gave a brown oil (0.03 g). Column chromatography (methanol) gave the imide (2).

(ii) The amido-ester (3) (0.02 g) was treated as above in dry toluene. After the addition of water, the ether was dried ($MgSO_4$) and evaporated off to give a residue (0.015 g). Basification of the aqueous reaction mixture after extraction with ether followed by a further extraction with ether gave no basic organic products. The residue above was analysed by g.l.c.–mass spectrometry and shown to contain isocoumarin (4) and 4-methoxybenzyl cyanide (5). I.r. and n.m.r. spectroscopy of the reaction mixture confirmed the presence of (4) and (5) in the reaction mixture.

(iii) The amido-alcohol (6) (0.1 g) was dissolved in tri-

fluoroacetic acid (2 cm^3) and refluxed for 15 h before it was poured into water (25 cm^3). The solution was basified ($NaHCO_3$) and the dichloromethane extract was dried (Na_2SO_4) and evaporated to give an oil (0.093 g). The residue contained the tetrahydroisoquinoline (10) as the only major component (t.l.c., i.r., n.m.r.).

(iv) When the amido-alcohol (6) (0.089) was added to stirred polyphosphoric acid (2 cm^3) under nitrogen at 120 °C and poured into water after 4 h, basification and extraction with chloroform gave an oil (0.069 g). T.l.c. (ethyl acetate) showed this contained several products; the predominant material was the tetrahydroisoquinoline (10).

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