1008. *The Diphenylmethylation of Amides and of Salicylic Acid and its Derivatives: the Acid-catalysed Rearrangement of* N-*Diphenylmethylsalicylamide.*

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The *N*-diphenylmethylation of amides with diphenylmethanol and toluene-*p*-sulphonic acid is discussed, and evidence is presented that diphenylmethyl toluene-*p*-sulphonate is an intermediate. This procedure was also used for the *C*-diphenylmethylation of salicylic acid and its derivatives. Treatment of *N*-diphenylmethylsalicylamide with toluene-*p*-sulphonic acid causes rearrangement to 5-diphenylmethyl-2-hydroxybenzamide.

Diphenylmethylation of primary amides can be carried out conveniently by treatment in boiling acetic acid with an approximately equimolecular mixture of diphenylmethanol and toluene-*p*-sulphonic acid.[1] An equimolecular proportion of toluene-*p*-sulphonic acid is used because in the presence of catalytic amounts of strong acid diphenylmethanol is very readily converted into bisdiphenylmethyl ether.[2] Diphenylmethyl toluene-*p*-sulphonate could function as an intermediate in these conditions and we therefore prepared the ester from diphenylmethyl chloride and silver toluene-*p*-sulphonate. Diphenylmethyl toluene-*p*-sulphonate has been described previously as an oil,[3] but our specimen readily crystallised from ethereal solution. It discoloured on exposure to light and was rapidly solvolysed in aqueous acetone at room temperature. Reaction of the ester in refluxing glacial acetic acid with propionamide and benzenesulphonamide gave the corresponding *N*-diphenylmethyl derivatives, and with sodium toluene-*p*-sulphinate in formic acid at room temperature gave the expected sulphone. This pattern of reactivity is typical of esters which undergo unimolecular alkyl–oxygen heterolysis.[4]

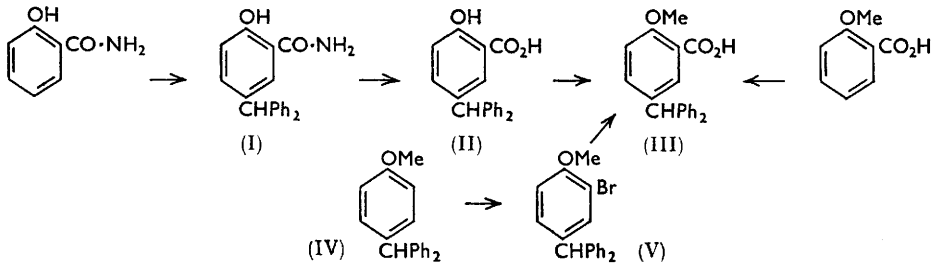
All the primary amides examined, with the exception of salicylamide, gave *N*-diphenylmethyl derivatives. This was indicated whenever possible by comparison with known compounds, by correlation of infrared spectra, and, in the case of the derivatives from *o*-toluamide and *o*- and *p*-methoxybenzamide, was confirmed by alternative synthesis from the appropriate acid chloride and diphenylmethylamine.

Salicylamide underwent *C*-diphenylmethylation, the powerfully activating hydroxyl group causing preferential ring substitution. The product is now shown to be 5-diphenylmethyl-2-hydroxybenzamide (I). Thus alkaline hydrolysis gave the acid (II) which on treatment with an excess of methyl iodide and silver oxide, and hydrolysis of the resulting methyl ester, gave 5-diphenylmethyl-2-methoxybenzoic acid (III). Direct diphenylmethylation of *o*-methoxybenzoic acid under our standard conditions also gave the acid (III), and from previous experiments with anisole [5] it seemed probable that substitution would occur in the *para*-position with respect to the methoxyl group rather than in the more hindered *ortho*-position. All attempts to decarboxylate the hydroxy- (II) or the methoxy-acid (III) failed, and indeed an analytically pure specimen of the methoxy-acid was obtained by sublimation at 200°/0·5 mm. Bromination of *p*-diphenylmethylanisole (IV) in glacial acetic acid gave the monobromo-derivative (V), and this on treatment with magnesium in the presence of 1,2-dibromoethane,[6] and then with carbon dioxide, gave 5-diphenylmethyl-2-methoxybenzoic acid (III).

[1] Cheeseman and Poller, *Analyst*, 1962, **87**, 366.
[2] Burton and Cheeseman, *J.*, 1953, 986.
[3] Hiroshige Ueda, Jap. P. 2311; *Chem. Abs.*, 1953, **47**, 4916.
[4] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.
[5] Burton and Cheeseman, *J.*, 1953, 832.
[6] Pearson, Cowan, and Becker, *J. Org. Chem.*, 1959, **24**, 504.

Diphenylmethylation of salicylic acid gave a monosubstituted acid, not identical with (II) and therefore presumably 3-diphenylmethyl-2-hydroxybenzoic acid; we were unable to isolate any *para*-monosubstituted derivative (II) even after careful chromatography of the crude product. Salicylic acid appears to be exceptional in undergoing *ortho*-substitution: in phenol,[5] anisole,[5] salicylamide, and *o*-methoxybenzoic acid monodiphenylmethylation occurred *para* to the hydroxyl or methoxyl group.

As we had been unable to prepare *N*-diphenylmethylsalicylamide by direct substitution, we prepared it by treating phenyl salicylate or salicyloyl chloride with diphenylmethylamine. Our product had m. p. 151—152°; it had the expected elemental composition and infrared absorption. On treatment with acetic anhydride it gave *N*-diphenylmethylacetamide, probably owing to diacetylation and subsequent hydrolysis. An indirect synthesis of *N*-diphenylmethylsalicylamide has been reported;[7] it furnished a product, m. p. 140°, which on similar treatment with acetic anhydride gave an *O*-acetyl derivative.



Reaction of *N*-diphenylmethylsalicylamide with toluene-*p*-sulphonic acid in glacial acetic acid gave the isomeric *C*-diphenylmethyl compound (I). Thus it is clear that any *N*-diphenylmethyl derivative formed during the direct substitution of salicylamide would rearrange to 5-diphenylmethyl-2-hydroxybenzamide (I). The rearrangement presumably involves protonation of the amide-nitrogen atom (facilitated by the electron-releasing properties of the diphenylmethyl group), heterolysis of the N–alkyl bond, and ring substitution.

While several aromatic electrophilic rearrangements involving migration from side-chain nitrogen to nuclear carbon are known, the rearrangement of *N*-diphenylmethylsalicylamide is unusual in that the migrating group is initially separated by two atoms from the benzene ring. Nevertheless this rearrangement bears some formal relation to the Hofmann–Martius rearrangement of the salts of *N*-alkyl- and *NN*-dialkyl-anilines to salts of ring-alkylated anilines. High temperatures are normally required to effect this rearrangement but that is a function of the migrating group. We propose to investigate further aspects of these reactions.

Experimental

Where appropriate, identity of samples was confirmed by comparison of infrared absorption spectra; the latter were measured, by the potassium bromide disc technique, with an Infracord model 137 spectrophotometer.

Diphenylmethyl Toluene-p-*sulphonate*.—Powdered silver toluene-*p*-sulphonate (2·79 g., 0·01 mole) was added to a solution of diphenylmethyl chloride (2·0 g., 0·01 mole) in dry ether (100 ml.). The mixture was heated under reflux for 1 hr. then filtered and concentrated under reduced pressure to 25 ml. On cooling to 0°, diphenylmethyl toluene-*p*-sulphonate (2·0 g., 59%), m. p. 63° (decomp.), separated. Complete solvolysis in aqueous acetone and titration of the liberated acid showed 100% purity. The product showed the expected [8] absorption maxima

[7] Mustafa and Hassan, *J. Amer. Chem. Soc.*, 1957, **79**, 3846.
[8] Tipson, *J. Amer. Chem. Soc.*, 1952, **74**, 1354.

at 1358 and 1170 cm.$^{-1}$ for a sulphonic ester; it coloured rapidly, even on storage in a desiccator (KOH). Treatment of the ester in boiling glacial acetic acid for 30 min. with propionamide and with benzenesulphonamide gave *N*-diphenylmethyl-propionamide,[1] m. p. and mixed m. p. 143—144°, and -benzenesulphonamide,[1] m. p. and mixed m. p. 185—186°, respectively. Reaction with sodium toluene-*p*-sulphinate at room temperature in formic acid gave diphenylmethyl *p*-tolyl sulphone,[9] m. p. and mixed m. p. 193—194°.

N-*Diphenylmethyl*-o-*methoxybenzamide*.—(*a*) A solution of *o*-methoxybenzamide (1·0 g.), diphenylmethanol (1·0 g.), and toluene-*p*-sulphonic acid monohydrate (1·0 g.) was boiled under reflux for 30 min. and then cooled and poured into water. Crystallisation of the product from 96% ethanol gave N-*diphenylmethyl*-o-*methoxybenzamide* (0·55 g., 25%), m. p. 133—134°. The m. p. was raised to 134—135° by further crystallisation from 96% ethanol or 1 : 2 benzene–light petroleum (b. p. 40—60°) (Found: C, 79·4; H, 6·1. $C_{21}H_{19}NO_2$ requires C, 79·4; H, 6·0%).

(*b*) Diphenylmethylamine (3·0 ml.) was added dropwise with stirring to *o*-methoxybenzoyl chloride (1·0 g.) at 0°, and then an excess of 2N-hydrochloric acid was added. Crystallisation of the precipitate from 96% ethanol gave needles of the amide (1·48 g., 79%), m. p. 133—134°. *N*-Diphenylmethyl-*p*-methoxybenzamide, m. p. 198—199°, and *N*-diphenylmethyl-*o*-toluamide, m. p. 181—182°, were prepared similarly.

5-*Diphenylmethyl*-2-*hydroxybenzamide* (I).—A solution of diphenylmethanol (20·0 g.), salicylamide (20·0 g.), and toluene-*p*-sulphonic acid monohydrate (20·0 g.) in glacial acetic acid (200 ml.) was boiled under reflux for 30 min. The mixture was then distilled until the volume had been reduced by 100 ml. and the resulting mixture was poured on crushed ice to give the crude product. Crystallisation from benzene gave 5-diphenylmethyl-2-hydroxybenzamide (17·8 g., 40%), m. p. 156·5—159°, raised by further crystallisation from benzene to 159·5—160° (lit.,[1] 159·5—160°).

5-*Diphenylmethyl*-2-*hydroxybenzoic Acid* (II).—A solution of 5-diphenylmethyl-2-hydroxybenzamide (13·1 g.) in 2N-sodium hydroxide (160 ml.) was boiled for 2·75 hr. Ammonia was evolved and acidification of the cooled solution gave the acid which was crystallised from 50% aqueous ethanol to give 5-*diphenylmethyl*-2-*hydroxybenzoic acid* (9·45 g., 72%), m. p. 159—163°. Further crystallisation from 1 : 1 benzene–light petroleum (b. p. 60—80°) gave the analytical specimen, m. p. 162—164° (Found: C, 79·2; H, 5·8. $C_{20}H_{16}O_3$ requires C, 78·9; H, 5·3%).

Methylation of 5-*Diphenylmethyl*-2-*hydroxybenzoic Acid*.—A mixture of the acid (5·0 g.), methyl iodide (9·4 g.), silver oxide (7·7 g.), and benzene (50 ml.) was heated under reflux for 6 hr. The inorganic matter was filtered off and the solution evaporated to give methyl 5-diphenylmethyl-2-methoxybenzoate which was hydrolysed without purification. Claisen's alkali [10] (50 ml.) was added and the mixture boiled under reflux for 4·5 hr. Acidification of the clear solution with 2N-sulphuric acid gave the crude product which was crystallised successively from carbon tetrachloride and absolute ethanol, to give 5-*diphenylmethyl*-2-*methoxybenzoic acid* (III) (1·74 g., 33%), m. p. 143—147°. Sublimation at 200°/0·5 mm. raised the m. p. to 147—148° (Found: C, 78·9; H, 5·7. $C_{21}H_{18}O_3$ requires C, 79·2; H, 5·7%).

2-*Bromo*-4-*diphenylmethylanisole* (V).—A 10% w/v solution of bromine in glacial acetic acid (65 ml.) was added to a solution of *p*-diphenylmethylanisole (9·0 g.) in glacial acetic acid (100 ml.), and the mixture was kept at 70° for 2 hr. and then at room temperature for 5 days. The crystalline product was filtered off and concentration of the mother-liquor gave a second crop of 2-*bromo*-4-*diphenylmethylanisole* (total yield 5·52 g., 48%), m. p. 93—95°. After one crystallisation from acetic acid the m. p. was 94—95° (Found: C, 68·3; H, 4·8. $C_{20}H_{17}BrO$ requires C, 68·0; H, 4·85%).

Bromination of *p*-diphenylmethylanisole in carbon tetrachloride solution gave a second, as yet unidentified, bromo-derivative, m. p. 118—118·5° (Found: C, 63·35; H, 4·8%).

5-*Diphenylmethyl*-2-*methoxybenzoic Acid* (III).—Magnesium (0·17 g.) was added to a solution of 2-bromo-4-diphenylmethylanisole (1·0 g.) in ether (25 ml.), and the mixture was boiled under reflux. During 5·5 hr. a solution of 1,2-dibromoethane [6] (0·54 g.) in ether (25 ml.) was added to the boiling mixture. The heating was continued for a further hour and the mixture was then poured on an excess of powdered solid carbon dioxide and left overnight. Trituration with a mixture of 2N-hydrochloric acid (20 ml.) and ether (20 ml.) gave a suspension, and

[9] Cheeseman, *J.*, 1957, 115.
[10] Fieser, " Experiments in Organic Chemistry," D. C. Heath and Co., Boston, 3rd edn., p. 310.

filtration gave 5-diphenylmethyl-2-methoxybenzoic acid (0·27 g.), m. p. 143—147°. Evaporation of the ether, extraction of the residue with ethanolic alkali, and acidification gave a further 0·23 g. of the acid, m. p. 135—142° (total yield 0·50 g., 56%).

Crystallisation from absolute ethanol gave the pure acid, m. p. 147—148°, identical with the products obtained (*a*) by methylation of 5-diphenylmethyl-2-hydroxybenzoic acid and (*b*) by diphenylmethylation of *o*-methoxybenzoic acid which gave the acid (III) in 49% yield.

3-Diphenylmethyl-2-hydroxybenzoic Acid.—A solution of salicylic acid (2·0 g.), diphenylmethanol (2·0 g.), and toluene-*p*-sulphonic acid monohydrate (2·0 g.) in glacial acetic acid (20 ml.) was boiled under reflux for 30 min. The mixture was poured into an excess of water, and the crude product crystallised from benzene to give *3-diphenylmethyl-2-hydroxybenzoic acid* (1·27 g.), m. p. 193—195°. Evaporation of the mother-liquor gave a further crop, m. p. 183—192° (total yield 1·48 g., 34%). The analytical specimen, crystallised from 1 : 1 benzene–light petroleum (b. p. 60—80°), had m. p. 194—195° (Found: C, 78·8; H, 5·35. $C_{20}H_{16}O_3$ requires C, 78·9; H, 5·3%).

Further evaporation of the original benzene mother-liquor gave a gummy solid from which, by chromatography on silica gel, additional small quantities of 3-diphenylmethyl-2-hydroxybenzoic acid were obtained. No evidence for the presence of 5-diphenylmethyl-2-hydroxybenzoic acid was obtained during the chromatographic experiments though traces of an additional product were isolated which gave a deep violet colour with ferric chloride in chloroform and had m. p. 173—174° (Found: C, 86·7; H, 5·8%).

N-Diphenylmethylsalicylamide.—(*a*) A mixture of phenyl salicylate (2·14 g., 0·01 mole) and diphenylmethylamine (4·0 g., 0·022 mole) was heated at 215—240° for 30 min., then cooled and dissolved in a mixture of benzene (25 ml.) and 2N-sodium hydroxide (25 ml.). The alkaline layer was separated, washed with benzene, and acidified. The crude product (2·6 g.) was filtered off and washed with water. Crystallisation from light petroleum (b. p. 100—120°; 120 ml.) gave *N-diphenylmethylsalicylamide* (2·2 g., 72%), m. p. 151—152° (Found: C, 79·4; H, 5·8; N, 4·8. $C_{20}H_{17}NO_2$ requires C, 79·2; H, 5·65; N, 4·6%).

A solution of the amide (1·0 g.) in acetic anhydride (20 ml.) was heated under reflux for 3 hr., then poured into water. Sodium carbonate was added to neutralise most of the acetic acid, and the product was filtered off and dried. Crystallisation from light petroleum (b. p. 100—120°) gave *N*-diphenylmethylacetamide,[1] m. p. and mixed m. p. 148—149° (Found: C, 80·3; H, 6·8; N, 6·4. Calc. for $C_{15}H_{15}NO$: C, 80·0; H, 6·7; N, 6·2%).

(*b*) Salicyloyl chloride [11] (from salicylic acid, 10 g.) was treated with diphenylmethylamine (27 g.) in benzene. After removal of the hydrochloride the filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of ether and 2N-sodium hydroxide, and the alkaline layer was separated and acidified. Successive crystallisation of the product (9·45 g., 43%), m. p. 149—150°, from 96% ethanol and from light petroleum (b. p. 100—120°) furnished the amide as needles m. p. 151—152°.

Rearrangement of N-*Diphenylmethylsalicylamide.*—A mixture of the amide (1·0 g.), toluene-*p*-sulphonic acid monohydrate (1·0 g.), and glacial acetic acid (10 ml.) was boiled under reflux for 30 min., then cooled and poured into ice-water. The product (0·85 g.) was filtered off, washed with water, and dried in a vacuum. Crystallisation from 2 : 1 benzene–light petroleum (b. p. 60—80°) gave 5-diphenylmethyl-2-hydroxybenzamide (0·45 g.), m. p. (mainly) 155—158°. After further crystallisation from benzene this material had m. p. and mixed m. p. 159—160°.

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[11] Kirpal, *Ber.*, 1930, **63**, 3190.