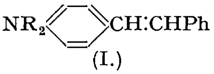
56. *4-Styrylbenzylamine and 4-Styrylbenzyldimethylamine.*

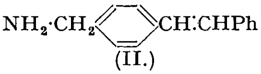
By George A. R. Kon.

The *bases* (II) and (III) have been prepared in order to compare their growth- and tumour-inhibiting activity with that of basically substituted stilbenes such as (I). In the course of preparation of (II) an abnormal Hofmann degradation, leading to the formation of an amide, has been noted.

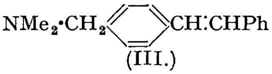
Certain stilbenes with a basic substituent in one of the para-positions such as 4-dimethylaminostilbene (I, R = Me) are carcinogenic and have a marked power of inhibiting the growth of transplanted tumours in the rat (Haddow, Harris, and Kon, *Biochem. J.*, 1945, **39**, ii). A description of a number of such compounds will be published shortly; in the meantime it appeared of interest to prepare the compounds (II) and (III) for comparison with those of type (I) as regards their biological properties, and more especially to ascertain whether the activity of such compounds could be connected with their ability to assume a quinonoid form. The compounds (II) and (III) are related to those of type (I) in the same way as "Marfanil" is related to sulphanilamide.



(I.)

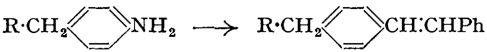


(II.)

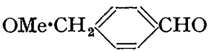


(III.)

A number of routes to the compounds (II) and (III) were explored. The most direct, reduction of 4-cyanostilbene (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103), was unsuccessful. It seemed probable that stilbene with a suitable substituent for conversion into (II) or (III) might be formed by diazotising a derivative of *p*-aminobenzyl alcohol and coupling it with cinnamic acid by the general method of Meerwein, Büchner, and van Emster (*J. pr. Chem.*, 1939, **152**, 237) :



(IV.) (V.)



(VI.)

Thus, the *ether* (V, R = OMe) should have been formed from *p*-aminobenzyl methyl ether, but no stilbene was produced when the Meerwein reaction was applied to this compound or to *p*-aminobenzyl cyanide, *p*-aminophenylacetic acid, and ethyl *p*-aminophenylacetate. An alternative method of preparing the same ether is by treatment of *p*-(ω-methoxymethyl)benzaldehyde (VI) (Quélet, *Bull. Soc. chim.*, 1933, **53**, 222) with benzylmagnesium chloride. A good yield of the required carbinol was produced, but dehydration of this presented unexpected difficulties and the yield of required ether was very small. The corresponding *alcohol* (V, R = OH) was prepared by treating the Grignard reagent from 4-bromostilbene (Anschütz, *Ber.*, 1927, **60**, 1322) with paraformaldehyde, but again the yield was very poor.

The method finally adopted was the degradation of 4-*styrylphenylacetic acid* or its *amide*. The acid could be prepared by two alternative routes : in the first, *p*-aminoacetophenone was converted by the Meerwein reaction into 4-*styrylphenyl methyl ketone*, $CHPh\colon CH\cdot C_6H_4\cdot COMe$(*p*). This was subjected to the Willgerodt reaction, but the yield of the *amide* (V, R = $CO\cdot NH_2$) was very low and the separation of it from sulphur difficult; however, the Kindler modification of the reaction afforded a good yield of the corresponding *thiomorpholide*, which gave styrylphenylacetic acid on hydrolysis. In the alternative process, *p*-aminobenzoic acid was converted by the Meerwein reaction into *stilbene*-4-*carboxylic acid*, the methyl and ethyl esters of which had already been obtained from the corresponding aminobenzoic esters by Fuson and Cooke (*J. Amer. Chem. Soc.*, 1940, **62**, 1180). In agreement with their observation, the Meerwein reaction proceeds satisfactorily with amines carrying a negative substituent in the para-position, as in this instance. The acid was converted through its chloride into the crystalline *diazo-ketone*, and this subjected to the Wolff rearrangement to give a good yield of 4-styrylphenylacetamide, which could be hydrolysed to the acid if required.

The Hofmann degradation of this amide, which should have given the amine (II), gave an unexpected result: the products were 4-cyanostilbene and *stilbene*-4-*carboxyamide*, the latter being the principal product, whilst no trace of amine was isolated. The formation of nitriles by oxidation of the amines initially formed in the Hofmann reaction has already been recorded, notably in acetylenic derivatives (Rinkes, *Rec. Trav. chim.*, 1920, **39**, 704; compare " Organic Reactions ", Vol. III, 276, New York, John Wiley and Sons Inc.), but the production of the next lower homologue of the amide appears to be novel.

Styrylphenylacetic acid was converted by way of the chloride into the azide, which on treatment with alcohol passed smoothly into *ethyl* 4-*styrylbenzylcarbamate* (V, R = $NH\cdot CO_2Et$). This was exceptionally resistant to hydrolysis with acids, but gave the desired *amine* (II) on alkaline hydrolysis.

For the preparation of the amine (III) 4-methylstilbene was brominated in the side chain by means of *N*-bromosuccinimide (Schmid and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573) and the *bromide* treated with excess of dimethylamine; the amine (II) could also be obtained from the bromide by the action of alcoholic ammonia.

EXPERIMENTAL.

4-*Styrylbenzylmethyl Ether*.—7·5 G. of *p*-(ω-methoxymethyl)benzaldehyde in dry ether were gradually added to a rapidly stirred Grignard reagent prepared from 7·9 g. of benzyl chloride (20% excess). The reaction product was decomposed with ammonium chloride solution, and the dried ethereal layer evaporated. The residue was dissolved in 50 c.c. of benzene and boiled with 25 g. of phosphoric oxide for ½ hour. The solution was then diluted with light petroleum and percolated through a short column of activated alumina (Spence, type H), evaporated, and the residue distilled, the greater part boiling at 190—230°/1 mm. (5·8 g.). The colourless distillate partly solidified, and the *ether* was freed from oil by rubbing with light petroleum (b. p. 40—60°) and crystallised from methyl alcohol in plates, m. p. 78° (Found: C, 85·5; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%). The petroleum washings contained another compound, evidently a hydrocarbon, which crystallised from methyl alcohol in plates, m. p. 108° (Found: C, 92·4; H, 7·6%). In a second preparation the *carbinol* first formed was isolated and boiled at 190—192°/2·5 mm. (7·8 g. from 9·1 g. of aldehyde) (Found: C, 79·5; H, 7·6. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%). On dehydration this gave the hydrocarbon as sole product.

4-*Styrylbenzyl Alcohol*.—10 G. of *p*-bromostilbene (conveniently prepared from *p*-bromoaniline by the Meerwein process) were boiled under reflux with 1 g. of magnesium turnings, activated by heating with iodine, and 50 c.c. of dry ether for 2 hours; only a small part of the metal dissolved. 5 G. of carefully dried paraformaldehyde were added, and the refluxing continued overnight. The reaction mixture was decomposed with dilute sulphuric acid, the ether layer dried and evaporated, and the residue taken up in light petroleum (b. p. 60—80°) and percolated through a column of activated alumina, the column being washed with the same solvent. Unchanged bromostilbene was recovered from the percolate. On stripping the column with ether containing methanol, a semi-solid mass was recovered which did not crystallise easily and was therefore re-chromatographed in benzene solution. On stripping the column, 0·6 g. of the *alcohol* was recovered, and crystallised from benzene in plates, m. p. 160—161° (Found: C, 85·9; H, 7·0. $C_{15}H_{14}O$ requires C, 85·5; H, 6·7%).

4-*Styrylphenyl Methyl Ketone*.—An ice-cold solution of 50 g. of *p*-aminoacetophenone in 100 c.c. of concentrated hydrochloric acid and 100 g. of ice was stirred and diazotised with 25·5 g. of sodium nitrite in the minimum of water. To this solution was added an ice-cold solution of 55 g. of cinnamic acid in 350 c.c. of acetone, followed by 70 g. of sodium acetate and 15·5 g. of cupric chloride in 45 c.c. of water. A slight rise in temperature soon occurred. The mixture was left overnight, then distilled in steam to remove acetone and volatile by-products of the reaction. After cooling, a brown solid was collected, which was dissolved in benzene, freed from cinnamic acid by extraction with alkali, and then washed, dried, and percolated through a column of activated alumina, the column being repeatedly developed with more benzene. On removal of the solvent, 36·7 g. of the *ketone* were recovered and crystallised from alcohol, then from benzene–petroleum, forming plates, m. p. 141—142° (Found: C, 86·5; H, 6·1. $C_{16}H_{14}O$ requires C, 86·4; H, 6·3%).

4-*Styrylphenylacet-thiomorpholide*.—11·1 G. of the above ketone were gently boiled with 4 g. of sulphur and 8·7 g. of morpholine for 2 hours (oil-bath), the contents of the flask dissolved in chloroform, and the solution well washed with water, dried, and evaporated, yielding 7·5 g. of the *thiomorpholide* after crystallisation from ethyl acetate; it formed lemon-yellow leaflets, m. p. 177—178° (Found: C, 74·3; H, 6·4. $C_{20}H_{21}ONS$ requires C, 74·3; H, 6·6%). The compound is very resistant to alkaline hydrolysis.

4-*Styrylphenylacetic Acid.*—5·4 G. of the thiomorpholide were boiled over-night with 200 c.c. of acetic acid and 80 c.c. of hydrochloric acid, and the solution cooled and diluted with water, precipitating the *acid*. This was crystallised from acetic acid, then from methyl alcohol containing a little water, and melted at 186—187° (Found: C, 80·4; H, 6·0. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%). The *anilide* crystallised from alcohol in small needles, m. p. 195—196° (Found: C, 84·1; H, 6·1. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1%).

Stilbene-4-*carboxylic Acid.*—66 G. of *p*-aminobenzoic acid were diazotised and treated with cinnamic acid exactly as described on p. 225. The precipitated acid was extracted with hot water to remove cinnamic acid, and the residue crystallised from acetic acid, the first crop weighing 48 g.; more was obtained from the mother-liquors. The *acid* crystallised from acetic acid or from alcohol in plates, m. p. 243—244° (Found: C, 80·4; H, 5·7. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·4%). On treatment with ethereal diazomethane it formed the methyl ester, m. p. 157° (Fuson and Cooke, *loc. cit.*, give 158—159°). The *anilide* crystallised from alcohol in small needles, m. p. 204—205° (Found: C, 84·1; H, 5·7. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%).

4-*Styrylphenylacetamide.*—The crude chloride prepared by warming the above acid with thionyl chloride had m. p. 125—126°. A dry ethereal solution of this (from 7 g. of acid) was added to dry ethereal diazomethane (0·1 mol.). After an hour the *diazo-ketone* began to separate, the process being completed over-night (yield 3·8 g.; in another run 11 g. of acid gave 7·8 g. of diazo-ketone). It crystallised from benzene–petroleum in fern-like aggregates of buff needles, m. p. 150—152° (Found: C, 77·4; H, 5·0. $C_{16}H_{13}ON$ requires C, 77·1; H, 5·3%). 2·2 G. of the ketone in 20 c.c. of dioxan were boiled under reflux with 16·5 c.c. of ammonia (*d* 0·88) and 3·3 c.c. of 10% aqueous silver nitrate for 2 hours. Water was then added, and the *amide*, formed in almost quantitative yield, was filtered off and crystallised from dioxan–water or from acetic acid (charcoal). It formed silvery plates, m. p. 258° (Found: C, 80·7; H, 6·4. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3%). An attempt to convert the diazo-ketone directly into styrylphenylacetic acid by treating it with silver oxide in presence of sodium carbonate and sodium thiosulphate in aqueous solution was unsuccessful, most of the ketone being recovered unchanged. The acid (1·6 g.) was readily obtained when 2 g. of amide were boiled for 3 hours with 50 c.c. of acetic acid and 50 c.c. of hydrochloric acid, and the solution diluted. The amide was also obtained, though in very poor yield, on heating styrylphenyl methyl ketone with ammonium polysulphide in a sealed tube.

Hofmann Degradation.—10·8 G. of bromine were gradually added to an ice-cold solution of 10·2 g. of potassium hydroxide in 100 c.c. of water, and the solution added to 11 g. of finely powdered styrylphenylacetamide with rapid mechanical stirring. 14·4 G. of potassium hydroxide in 25 c.c. of water were added, and the mixture kept rapidly stirred at 80° for 1½ hours. It was cooled and diluted, and the solid filtered off and crystallised from alcohol. The first two crops of crystals were recrystallised from acetic acid, giving 4 g. of the *amide*, which separated from benzene–petroleum in large plates, m. p. 157° (Found: C, 80·9, 80·9; H, 5·9, 6·1. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%); on hydrolysis with acetic–hydrochloric acid it gave stilbenecarboxylic acid, m. p. and mixed m. p. 243°. The mother-liquors from which the amide had separated were diluted, a more fusible substance separating. As it did not crystallise readily, it was twice chromatographed in petroleum solution, then crystallised from this solvent; several crops of crystals, m. p. 115—116°, were obtained and identified as 4-cyanostilbene (mixed m. p.) (Found: C, 88·1; H, 5·2. Calc.: C, 87·8; H, 5·4%). The substance for comparison had been prepared in good yield from *p*-aminobenzonitrile by the Meerwein method, which is preferable to the method used by Ashley *et al.* (*loc. cit.*) (unpublished observation by Dr. R. J. C. Harris).

Modified Hofmann Degradation.—0·7 G. of the amide in 9 c.c. of methyl alcohol were mixed with a solution of 0·25 g. of sodium in 7·5 c.c. of methyl alcohol, and the ice-cold solution treated with 0·2 c.c. of bromine. After an hour at room temperature the mixture was warmed for 10 minutes on the steam-bath, cooled, the unchanged amide filtered off, and the solution evaporated. The small amount of solid obtained crystallised from methyl alcohol, m. p. 165°, and was evidently *methyl* 4-*styrylphenylmethylcarbamate* (Found: C, 76·9; H, 6·3. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4%).

Curtius Degradation.—1·6 G. of styrylphenylacetic acid were converted into the chloride by warming with excess of thionyl chloride, which was then distilled off and the last traces removed by repeated evaporation with chloroform under reduced pressure. The chloride in 30 c.c. of acetone was treated with 0·56 g. of sodium azide in the minimum of water with ice-cooling. After 15 minutes the solution was diluted with water, precipitating the azide in almost quantitative yield. It was comparatively stable and could be recrystallised from benzene; it melted at 260—265° (decomp.). The crude azide was warmed for 5 minutes with 10 vols. of alcohol; solution took place and there was a steady evolution of gas. The solution was concentrated and diluted with water, precipitating *ethyl* 4-*styrylbenzylcarbamate* in good yield. It crystallised from dilute methyl or ethyl alcohol in needles, m. p. 146—147° (Found: C, 77·0; H, 6·9. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8%).

4-*Styrylbenzylamine.*—The above urethane was not hydrolysed by heating for 24 hours with concentrated hydrochloric acid in a sealed tube at 170—180°. 1·8 G. were boiled with 20 c.c. of alcohol and 5 g. of potassium hydroxide in 10 c.c. of water under reflux for 1½ hours. Some alcohol was distilled off, and hot water gradually added; as this caused a precipitate, 20 c.c. of alcohol were added and the boiling continued for a further 2½ hours. The solution was diluted, and strongly acidified with hydrochloric acid to ensure the elimination of carbon dioxide. Some solid, evidently the hydrochloride of the amine, was precipitated and was filtered off, the liquid and solid being separately basified and extracted with ether. After removal of the solvent the *base* (0·45 g.) was crystallised from benzene–petroleum or from *cyclo*hexane, forming plates, m. p. 130° (Found: C, 86·2; H, 7·1. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%). The hydrochloride crystallised from acetic acid in silvery leaflets, m. p. 300—305° (decomp.). The *benzoyl* derivative crystallised from alcohol in lustrous plates, m. p. 205—206° (Found: C, 84·1; H, 6·2. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1%).

4-*Bromomethylstilbene.*—8·4 G. of *p*-methylstilbene, 7·8 g. of *N*-bromosuccinimide, 50 mg. of benzoyl peroxide, and 30 c.c. of carbon tetrachloride were boiled under reflux for 3 hours. After the precipitated succinimide had been filtered off, the solution was washed with water, dried, and evaporated. The residue was crystallised from alcohol, then from petroleum, forming small needles (5·8 g.), m. p. 117—118° depressed by the starting material, which had the same m. p. The analytical figures suggest a slight contamination with a hydrocarbon (Found : C, 66·7; H, 4·9; Br, 28·6. $C_{15}H_{13}Br$ requires C, 65·9; H, 4·8; Br, 29·3%).

The bromide is evidently easily hydrolysed to the alcohol : a specimen prepared in a pilot experiment and containing much unchanged methylstilbene was chromatographed in light petroleum. The stilbene was recovered from the percolate, and on eluting the column with ether–methanol pure hydroxymethylstilbene was recovered, m. p. and mixed m. p. 160—161° (Found : C, 85·7; H, 6·7. Calc. : C, 85·5; H, 6·7%) ; no trace of the bromide was recovered.

4-*Styrylbenzyldimethylamine.*—5 G. of the above bromide were kept for 3 days with 200 c.c. of alcohol and 8 c.c. of dimethylamine, a clear solution being formed. The alcohol was then evaporated off, the diluted residue treated with hydrochloric acid, extracted with ether to remove non-basic material, then strongly basified, and the *base* extracted with ether. The dried ethereal solution was evaporated, and the residue dissolved in petroleum and percolated through a column of alumina. The base, recovered in good yield, was very soluble but could be crystallised from petroleum (b. p. 30—40°) or very little methanol, forming large plates, m. p. 86—87° (Found : C, 86·1; H, 8·2. $C_{17}H_{19}N$ requires C, 86·0; H, 8·1%). The *picrate* formed yellow plates from alcohol, m. p. 146° (decomp.) (Found : C, 59·2; H, 4·8. $C_{23}H_{22}O_7N_4$ requires C, 59·2; H, 4·8%).

The author wishes to thank Mr. J. L. Everett for assistance, Mr. F. Goulden for the analyses, and the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, and the Anna Fuller Fund for grants made to the Royal Cancer Hospital (Free) in aid of this work.

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[*Received, April 9th,* 1947.]