# REMARKS ON THE SYNTHESIS OF SUBSTITUTED STILBENES AND DIPHENYLBUTADIENES

# FELIX BERGMANN AND (MISS) ZIPORAH WEINBERG

## Received September 16, 1940

The synthesis of substituted stilbenes has recently become an interesting field of chemotherapeutical research, as members of this series have proved to be active as oestrogenic (1) or trypanocidal (2) agents. For some time, we have been occupied with the synthesis of lipophilic chemotherapeuticals (3), which are supposed to penetrate the waxy wall of the cells of certain bacteria. The substances in the group to be described here are all based on the same principle, *i.e.* the combination of an aromatically substituted unsaturated chain and a polar group, especially the amino group. Our results are, however, only preliminary and are published because this work can not be continued for the time being.

Of the many reactions which permit the synthesis of stilbene, only the method of Perkin can be generally applied. When  $\alpha$ -naphthaldehyde was condensed with *p*-nitrophenylacetic acid by means of piperidine, only a 13% yield of  $\alpha$ -(p-nitrophenyl)- $\beta$ -(1-naphthyl)ethylene (I) was obtained, whereas the modification of Kuhn (4), who uses the lead salt of the acid, gave a 20% yield of I and at the same time 25% of  $\alpha$ -(p-nitrophenyl)- $\beta$ -(1-naphthyl)acrylic acid (II). As is known from the work of Ruggli (5) and Taylor (6), the structure of these acrylic acids corresponds to the *cis* form of the ethylene. One may therefore conclude that first the two cis and trans acids are formed, but that the trans form is much more easily decarboxylated than the *cis* isomer. As there is no sure example of the different behavior of such isomeric acids in decarboxylation, another explanation seems to us more acceptable: First, the two stereoisomeric hydroxy acids A and B are formed, usually in unequal amounts. There are now two possibilities for elimination of the hydroxyl group, (a) by splitting off water with an adjacent hydrogen atom, or, (b) with the carboxyl group. Assuming now, that the aromatic nuclei are held at maximal distance from each other, one must conclude that in form A the hydroxyl is eliminated together with the neighboring hydrogen because these two are trans to each other, whereas in form B, for the same reason, lactonization with the carboxyl trans to the hydroxyl is the favored reaction. Such a mechanism would parallel the known behavior of the stilbene dibromides (7): Only the bromination-product of *cis*-stilbene readily loses hydrogen bromide to yield the corresponding bromoethylene, whereas the *trans* addition-product is very stable and occasionally regenerates the *trans*-stilbene.



1-Styryl-4-nitronaphthalene (III) was obtained by the method of Meerwein (8), through diazo coupling of cinnamic acid with 4-nitro-1-naphthylamine. Only the ethylene derivative was obtained (in 12% yield), and no trace of an isomer of II. The trans structure of III, in spite of the low melting point, 94°, is shown by the stability of the dibromide, which is not changed in boiling pyridine. 1-p-Nitrophenyl-4-phenyl-1,3-butadiene (IV) was synthesized by the two methods mentioned:



(a) The Perkin reaction between cinnamic aldehyde and p-nitrophenylacetic acid yielded about equal parts of IV (11%) and of the acid (V) (9%). The structure of IV is proved by the ready condensation with maleic anhydride, which gives, in quantitative yield 3-phenyl-6-p-nitrophenyl-1,2,3,6-tetrahydrophthalic anhydride (VI), and by the addition of four bromine atoms. On the other hand, the acid V, like  $\alpha$ -phenylcinnamic acid (9), does not react with bromine, although the second double bond is not sterically hindered by a carboxyl group. After esterification of the acid, two bromine atoms are added.

(b) The diazo coupling between *p*-nitroaniline and cinnamylideneacrylic acid gave also exclusively the ethylene (IV) in 25% yield. No trace of V could be detected. This means, on the basis of the above developed theory, that the diazo reaction yields solely the lactone (VII), which spontaneously splits off CO<sub>2</sub>. This assumption also is in accordance with the reaction-mechanism of Meerwein (8).



Reduction of the described nitro compounds was best effected by the method of Stoermer (10), although they are only sparingly soluble in alcohol. The amines are all brownish-yellow and difficult to purify. On the other hand, the nitro acids are easily reduced in water solution by ammonia and ferrous sulfate, and best precipitated as their hydrochlorides.

#### EXPERIMENTAL

1-(p-Nitrophenyl)-2-( $\alpha$ -naphthyl)ethylene (I). (a)  $\alpha$ -Naphthaldehyde (11 g.) (11) and p-nitrophenylacetic acid (13 g.) were heated with 1 cc. of piperidine for two hours at 160°, the syrupy mass triturated with glacial acetic acid, and the brown crystals separated by filtration. After repeated recrystallizations from glacial acetic acid and butyl acetate, long brownish needles were obtained, m.p. 183°, yield, 3 g. Anal. Cale'd for C<sub>18</sub>H<sub>18</sub>NO<sub>2</sub>: C, 78.55; H, 4.7. Found: C, 78.1; H, 4.9.

The dibromide was prepared in carbon tetrachloride, and crystallized from highboiling petroleum ether in beautiful plates, m.p. 183°.

Anal. Calc'd for C<sub>18</sub>H<sub>18</sub>Br<sub>2</sub>NO: C, 49.7; H, 3.0.

Found: C, 49.9; H, 2.9.

Reduction of the nitro group with stannous chloride in glacial acetic acid or with iron dust and hydrochloric acid in alcohol failed. Only the following method proved successful: Ten grams of the nitro compound was suspended in 250 cc. of boiling ethanol and a solution of 80 g. of ferrous sulfate and 400 cc. of concentrated ammonia in 400 cc. of water was added. The mixture was stirred and boiled for two hours. After twelve hours, the black precipitate was filtered, dried, and extracted with benzene. From this solution, after evaporation, 5 g. of the amino compound was obtained. On recrystallization from ethanol, yellow needles, m.p. 114°, were obtained.

Anal. Calc'd for C18H15N: N, 5.7. Found: N, 5.5.

(b) Fourteen grams of the aldehyde and 16.2 g. of *p*-nitrophenylacetic acid were added to a solution of lead oxide (10 g.) in acetic anhydride (18 g.), and the mixture heated at 140° for four hours. Crystallization set in spontaneously. The solid part was filtered and recrystallized once from glacial acetic acid, then from highboiling petroleum ether with some benzene; m.p. and mixed m.p. 183°, yield, 5 g.

The filtrate from the ethylene derivative, on standing, deposited a yellow substance, which, after recrystallization from xylene, melted at  $201^{\circ}$  (II), yield, 7 g. The substance did not add bromine.

Anal. Calc'd for C19H13NO4: C, 71.5; H, 4.1; N, 4.4.

Found: C, 71.0; H, 4.1; N, 4.4.

The acid (II) was esterified with diazomethane. The methyl ester was twice recrystallized from high-boiling petroleum ether, and melted then at 140°. It formed yellow blocks.

Anal. Calc'd for C20H15NO4: C, 72.1; H, 4.5.

Found: C, 71.9; H, 4.5.

Reduction of the nitro acid was accomplished by dissolving the acid (2 g.) in an excess of concentrated ammonia and adding ferrous sulfate (10 g.) in the same solvent. After short boiling, the mixture was cooled and acidified with hydrochloric acid. The amino acid was purified by dissolving in hot ammonia and reprecipitating with hydrochloric acid. In this way, the pure hydrochloride was obtained in the form of silky, yellow needles, m.p. 254°.

Anal. Calc'd for C<sub>19</sub>H<sub>16</sub>ClNO<sub>2</sub>: C, 70.2; H, 4.9.

Found: C, 70.8; H, 5.1.

1-Styryl-4-nitronaphthalene (III). 4-Nitro-1-naphthylamine (12) (24 g.) was suspended in 12% hydrochloric acid (100 cc.) and diazotized at 0° with 9 g. of sodium nitrite in 20 cc. of water. The diazo solution was added dropwise to cinnamic acid. Then cupric chloride (5.3 g.) and sodium acetate (27.5 g.) in water (25 cc.) were added; nitrogen was evolved at once. After stirring for one hour at 15°, the reactionmixture was distilled with steam until the distillate became clear. The non-volatile residue formed a black tar, containing the desired nitro compound and some unreacted cinnamic acid. The mass was dissolved in ether, dried, and distilled *in* vacuo, b.p. 240-260° at 9 mm. The brown distillate, on trituration with acetonepetroleum ether, gave a yellow powder. This was recrystallized first from glacial acetic acid, then from petroleum ether. Strong, yellow lancets were obtained, m.p. 94°, yield, 3.5 g. Concentrated sulfuric acid gives first a blue, then a blue-violet color. Anal. Calc'd for C<sub>18</sub>H<sub>18</sub>NO<sub>2</sub>: C, 78.55; H, 4.7. Found: C, 78.5; H, 5.0.

The dibromide, prepared as above, crystallized from high-boiling petroleum ether, m.p. 182°. It was recovered unchanged after four hours boiling in pyridine. *Anal.* Calc'd for C<sub>18</sub>H<sub>18</sub>Br<sub>2</sub>NO<sub>2</sub>: C, 49.7; H, 3.0; N, 3.2.

Found: C, 49.2; H, 3.1; N, 3.1.

p-Nitrophenylphenylbutadiene (IV). (a) p-Nitrophenylacetic acid (18 g.), cinnamic aldehyde (13 g.), lead oxide (11 g.), and acetic anhydride (20 g.) were boiled together for five hours. The crude product was separated into a soda-soluble and a neutral part. The neutral substance (IV), after recrystallization from toluene, melted at 172°, yield, 2.7 g. With concentrated sulfuric acid, a red-brown color reaction was noted.

Anal. Calc'd for C16H13NO2: C, 76.5; H, 5.2; N, 5.6.

Found: C, 76.1, 76.2; H, 5.2, 5.1; N, 6.0.

The acid (V) is insoluble in toluene and may be separated from IV also by means of that solvent. From butanol it crystallized in thin yellow needles, m.p. 256°, yield, 2.5. g. The acid did not react with bromine.

Anal. Calc'd for C<sub>17</sub>H<sub>12</sub>NO<sub>4</sub>: C, 69.2; H, 4.4; N, 4.7.

Found: C, 69.4; H, 4.7; N, 5.0.

(b) Diazo coupling between *p*-nitroaniline (18 g.) and cinnamylideneacrylic acid (22 g.)  $(13)^1$  in acetone (350 cc.), as described above, yielded, after steam distillation, brown crystals, which were purified with butyl acetate and high-boiling petroleum ether, m.p. and mixed m.p. 171-172°, yield, 8.0 g.

Reactions of p-nitrophenylphenylbutadiene. (a) With maleic anhydride: Two grams of the anhydride (6 equiv.) was melted on a water-bath with 0.8 g. of the diene, and afterwards heated for two hours to 110°. The melt was mixed with water and filtered. The product (VI) crystallized from acetic anhydride in nearly colorless prismatic rods, m.p. 213°, yield quantitative.

Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>NO<sub>5</sub>: C, 68.8; H, 4.3; N, 4.0.

Found: C, 69.0; H, 4.6; N, 4.3.

(b) With bromine: When excess bromine in carbon tetrachloride was added, a clear solution was first obtained, but immediately afterwards a red-brown precipitate appeared. The addition-product was recrystallized from a mixture of xylene and high-boiling petroleum ether (1:2), and formed clusters of colorless needles, m.p. 245-246°.

Anal. Calc'd for C16H13Br4NO2: C, 33.6; H, 2.3.

Found:

C, 34.3; H, 2.7.

(c) Reduction to 1-p-aminophenyl-4-phenyl-1,3-butadiene: By the same method described for (I), 10 g. of the nitro compound yielded 8 g. of the amino product. From toluene, glistening needles, m.p. 167°, were obtained. The brown color changes to yellow in contact with hydrochloric acid. It proved rather difficult to obtain a pure sample for analysis.

Anal. Calc'd for C<sub>16</sub>H<sub>15</sub>N: N, 6.3. Found: N, 6.3; 6.0.

For characterization, the amino compound was acylated with trichloroacetyl chloride in toluene-pyridine solution. The derivative melts at 177-178° and forms bright yellow rods from butanol.

Anal. Calc'd for C<sub>18</sub>H<sub>15</sub>Cl<sub>3</sub>NO: C, 59.0; H, 3.8; N, 5.9.

Found: C, 59.3; H, 4.0; N, 6.2.

Reactions of 1-p-nitrophenyl-4-phenyl-1,3-butadiene-1-carboxylic acid (V). The

<sup>1</sup> The acid is best recrystallized from glacial acetic acid.

methyl ester, which was prepared with diazomethane, formed soft, yellow needles, which, after recrystallization from high-boiling petroleum ether, melted at 134°.

Anal. Calc'd for C<sub>18</sub>H<sub>15</sub>NO<sub>4</sub>: C, 69.9; H, 4.85.

Found: C, 69.6; H, 4.7.

The ester was warmed with excess bromine in carbon tetrachloride. The syrupy residue which was left after evaporation of the solvent crystallized on trituration with methanol. From glacial acetic acid, beautiful colorless crystals of the tetragonal system, m.p. 248-249° were obtained.

Anal. Calc'd for C<sub>18</sub>H<sub>15</sub>Br<sub>2</sub>NO<sub>4</sub>: C, 46.05; H, 3.2.

Found: C, 45.7; H, 3.0.

Reduction of the acid was accomplished as described above for (II). The amino acid, which was first precipitated as hydrochloride, was recrystallized from diluted pyridine, m.p.  $258^{\circ}$ .

Anal. Calc'd for  $C_{17}H_{16}NO_2$ : C, 77.0; H, 5.7. Found: C, 77.1; H, 6.1.

### SUMMARY

The synthesis of some substituted stilbenes and diphenylbutadienes by the methods of Perkin and of Meerwein is described and the possible stereochemical mechanism is discussed.

REHOVOTH, PALESTINE.

### REFERENCES

- (1) DODDS AND CO-WORKERS, Nature, 141, 247 (1938); 142, 34 (1938).
- (2) LOURIE AND YORKE, Ann. trop. Med. Paras., 33, 289 (1939).
- (3) E. BERGMANN AND HASKELBERG, J. Chem. Soc., 1939, 1; ADLER, HASKELBERG, AND F. BERGMANN, J. Chem. Soc., 1940, 576.
- (4) KUHN AND WINTERSTEIN, Helv. chim. Acta, 11, 87 (1928).
- (5) RUGGLI AND STAUB, Helv. chim. Acta, 19, 1288 (1936); 20, 37 (1937).
- (6) TAYLOR AND HOBSON, J. Chem. Soc., 1936, 181.
- (7) PFEIFFER, Ber., 45, 1810 (1912).
- (8) MEERWEIN AND CO-WORKERS, J. prakt. Chem., 152, 237 (1939).
- (9) MÜLLER, Ber., 26, 659 (1893).
- (10) STOERMER AND OEHLERT, Ber., 55, 1232 (1922).
- (11) SCHLENK AND BERGMANN, Ann., 479, 42 (1930).
- (12) SAUNDERS AND HAMILTON, J. Am. Chem. Soc., 54, 636 (1932).
- (13) DOEBNER, Ber., 35, 2137 (1902).