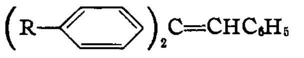
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

β,β-Diarylacrylic Acids. II. A New Synthesis of Triarylethylenes

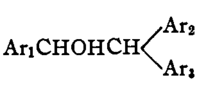
BY FELIX BERGMANN, ELCHANAN DIMANT AND HELENE JAPHE

Triphenylethylene (I) and its derivatives have acquired new interest since the discovery of Robson and Schönberg[1] that the hydrocarbon (I) itself, its dimethoxy derivative (II)[2] and their α-halogen derivatives are endowed with estrogenic activity of prolonged duration. The classical method of synthesis for derivatives of I is the Grignard reaction,[3] in which the carbinols of type III or IV are intermediates. When Ar_2 and Ar_3 represent different aryl groups, two geometrical isomers are possible. However, only very few cases are known where both forms have actually been isolated.[4] There exist also some other, less well known methods of formation of triphenylethylene, *e. g.*, rearrangement of β,β,β-triphenylethylammonium nitrite[5] or condensation of diphenylketene with substituted benzaldehydes[6] in quinoline (with elimination of carbon dioxide).

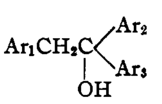
Triphenylethylene itself is unsuitable for direct substitution in a ring, because the common cationoid reagents first attack the central double bond.[7] We observed that 1,1,2-triphenylethanol (V), too, is converted by fuming nitric acid in acetic acid solution into 1,1,2-triphenyl-2-nitroethylene (VI). Apparently dehydration to I precedes nitration at the α-position. When the nitration is carried out without use of a solvent, I and V give a good yield of a tetranitro derivative of the probable structure VII. One nitro group must replace the α-hydrogen, because the α-nitro derivative VI, too, can be converted into the tetranitro compound (VII).



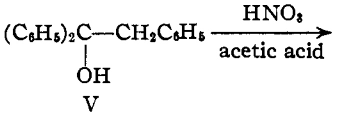
I, R = OH
II, R = OCH_3



III

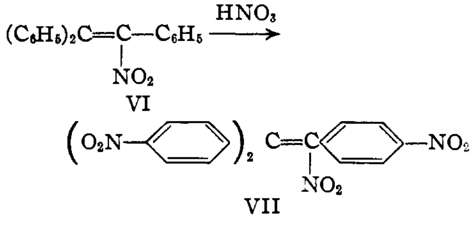


IV



$$(C_6H_5)_2\underset{\displaystyle OH}{C}-CH_2C_6H_5 \xrightarrow[\text{acetic acid}]{HNO_3}$$

V



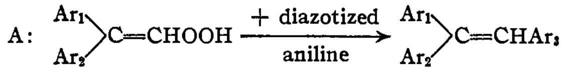
$$(C_6H_5)_2C{=}\underset{\displaystyle NO_2}{C}-C_6H_5 \xrightarrow{HNO_3}$$

VI

VII

We have been unable to isolate intermediates between the mono- and tetra-nitro derivatives.

A new method of wide applicability was found in the coupling of β,β-diarylacrylic acids VIII with diazotized anilines, in analogy to the Meerwein synthesis of stilbenes from cinnamic acids[8] (scheme A). The data represented in Table I show that meta- and para-substituted anilines give comparable results. The method failed, however, when ortho-substituents were present.



It is noteworthy that under the experimental conditions used, the diarylacrylic acids concerned undergo partial decarboxylation prior to the coupling reaction. Thus, the dianisylacrylic acid (Expt. 2 in Table-I) gave besides the expected 1,1-di-(*p*-anisyl)-2(*p*-nitrophenyl)-ethylene about 50% of dianisylethylene, although we reported previously that the acid loses carbon dioxide in aqueous suspension only upon prolonged boiling.[9]

The Meerwein synthesis of stilbenes yields exclusively the *trans* forms. However, no conclusion about the sterical specificity of the reaction can be drawn from this fact, because only *trans*-cinnamic acids have been used.[10] It was therefore of interest to investigate the coupling of isomeric β,β-diarylacrylic acids (VIII, $Ar_1 \neq Ar_2$). The two forms of β-phenyl-β(*p*-bromophenyl)-acrylic acid (X),[9] upon reaction with diazotized *p*-nitroaniline, yielded the same product (XI). It is evident that in one case isomerization has taken place. In this connection it may be mentioned that α-phenylcinnamic acid, which upon decarboxylation yields *cis*-stilbene,[11] does not undergo a Meerwein coupling, but under the conditions of the experiment yields exclusively *trans*-stilbene.

The most interesting of the new compounds are the nitro derivatives in view of the versatility of the aromatic nitro group, and of the inaccessibility of these derivatives by any other method. It was shown previously,[12] that it is impossible to reduce

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(1) Robson, *Proc. Soc. Exptl. Biol. Med.*, **38**, 153 (1938); Robson, Schönberg and Fahim, *Nature*, **142**, 292 (1938).

(2) Schönberg, Robson, Tadros and Fahim, *J. Chem. Soc.*, 1327 (1940).

(3) Hell and Wiegandt, *Ber.*, **37**, 1429 (1904); Ley and Kirchner, *Z. anorg. Chem.*, **173**, 408 (1927); Buisignies, *Compt. rend.*, **151**, 516 (1910); Koelsch, THIS JOURNAL, **54**, 2487 (1932).

(4) F. Bergmann, *ibid.*, **64**, 69 (1942); Koelsch and Prill, *ibid.*, **67**, 1296 (1945).

(5) Hellermann, Cohn and Hoen, *ibid.*, **50**, 1716 (1928); Hellermann and Garner, *ibid.*, **57**, 139 (1935).

(6) Staudinger and Kon, *Ann.*, **384**, 89 (1911).

(7) Shilov, *J. Russ. Phys.-Chem. Soc.*, **62**, 95 (1930); *C. A.*, **24**, 4289 (1930).

(8) Meerwein, Buchner and van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

(9) F. Bergmann and co-workers, THIS JOURNAL, **70**, 1612 (1948).

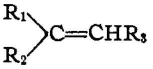
(10) F. Bergmann and Weinberg, *J. Org. Chem.*, **6**, 134 (1941).

(11) Stoermer and Voht, *Ann.*, **409**, 39 (1915).

(12) F. Bergmann and Schapiro, *J. Org. Chem.*, **12**, 57 (1947).

TABLE I

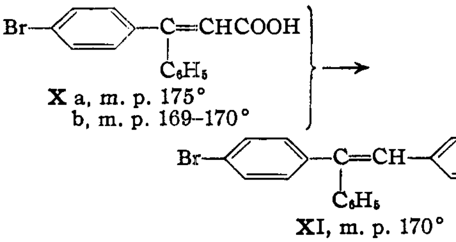
TRIARYLETHYLENES,


$R_1R_2C{=}CHR_3$

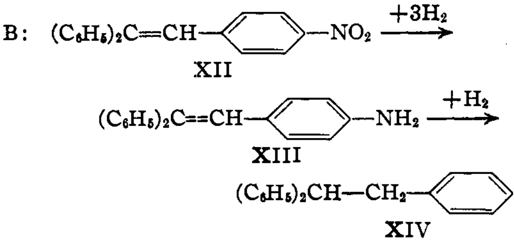
R_1	R_2	R_3	B. p. °C.	B. p. Mm.	M. p., °C.	Yield, %	Crystal form	Solvent	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Phenyl[a]		*p*- Ni-	193–194	1.5	148	48	Brown cols.	Butyl acetate	$C_{20}H_{15}O_2N$	79.7	5.0	4.7	79.7	5.3	4.7
p-Anisyl[a]		*p*- tro-	225–230	1.25	131	28	Prism rods	Benz.–petr. eth.	$C_{22}H_{19}O_4N$	73.1	5.3	3.9	73.3	5.6	3.9
p-Fluorophenyl[a]		*p*- phen-	200–230	0.25	145	50	Rhombohedr. plates	Benz.–petr. eth.	$C_{20}H_{13}O_2F_2N$	71.2	3.9	4.2	71.3	3.9	4.2
p-Tolyl[b]		*m*- yl	200–220	0.05	102	30[f]	Twinned prisms	*n*-Propanol	$C_{22}H_{19}O_2N$	80.2	5.8	4.3	80.0	6.0	4.2
Phenyl[c]		*p*-Tolyl	140–145	0.05	74	11	Elong. prisms	Ethanol	$C_{21}H_{18}$	93.3	6.7		93.0	7.0	
p-Anisyl[d]		*p*-Tolyl	210–215	1.5	97	Small	Prism rods	Petr. ether	$C_{23}H_{22}O_2$	83.6	6.7		83.8	7.0	
p-Fluoroph.[a]	Phenyl	*p*- Nitro-	210–230	0.15	149.5	35	Coarse prisms	Tol.–petr. ether	$C_{20}H_{14}O_2NF$	75.2	4.4	4.4	75.2	4.6	4.7
p-Bromoph.[e]	Phenyl	*p*- phenyl	240–260	0.8	170	30	Yellow prisms	Toluene	$C_{20}H_{14}O_2NBr$	63.2	3.6		63.1	3.8	

[a] Coupling temp., 25–35°. [b] Coupling temp., 32–45°. [c] Coupling temp., 27–28°. [d] Coupling temp., 27–35°. [e] Coupling temp., 25–50°. [f] Yield calculated on acid consumed. About 50% of the acid was recovered from the alkaline washings by acidification.

catalytically the nitro group of various nitrostilbenes without attack on the double bond. In the nitro-triphenylethylenes, however, the reactivity of the ethylenic bond is lowered so much that the hydrogenation can be interrupted exactly after absorption of three moles of hydrogen to yield about 70% of the unsaturated amine (see scheme B).


X a, m. p. 175°
b, m. p. 169–170°

XI, m. p. 170°


B:

XII

XIII

XIV

Experimental[13]

Meerwein Coupling—General Procedure.—The method used for the coupling reactions may be exemplified for the first case, reaction of diphenylacrylic acid with *p*-nitroaniline. The general results are summarized in Table I.

To a solution of diphenylacrylic acid (9.5 g.) in acetone (200 cc.), cooled to +5°, was added a clear solution of diazotized *p*-nitroaniline (5.8 g.). Solid sodium acetate (11 g.) and a solution of cupric chloride (2 g.) in a little water were added immediately. The temperature was allowed to rise slowly, until at 25° reaction set in. After the strong evolution of gas was over (about fifteen minutes), the mixture was heated to 35° for one hour. Acetone and a small amount of *p*-chloronitrobenzene were removed by steam distillation. The remaining sirup was dissolved in benzene, washed with alkali, dried and distilled *in vacuo*, b. p. 193–194° (1.5 mm.). The yellow-red distillate crystallized upon trituration with ethanol. Recrystallization from butanol or butyl acetate gave brown, polyhedric columns of 1,1-diphenyl-2-(*p*-nitrophenyl)-ethylene (XII), m. p. 148°. The substance is dimorphic and appears sometimes in small yellow prisms of m. p. 158–160°, especially from dilute solutions.

When di-(*p*-anisyl)-acrylic acid was used in the reaction, distillation of the neutral portion gave first a large amount (about 50% of theoretical) of dianisylethylene, b. p. 185–195° (1.2 mm.), followed by the expected coupling product.

In experiment 8, the higher-melting form of β-phenyl-β-(*p*-bromophenyl)-acrylic acid (Xa), m. p. 175°, gave a 30% yield of 1-phenyl-1-(*p*-bromophenyl)-2-(*p*-nitrophenyl)-ethylene (XI), m. p. 170°. The isomeric acid (Xb), m. p. 169–170°, reacted under exactly the same conditions, but only 11% of the expected ethylene was obtained. This compound showed no depression of m. p. with the foregoing reaction product.

Reactions of 1,1-Diphenyl-2-(*p*-nitrophenyl)-ethylene (XII). (a) Bromination.—The ethylene (XII) in chloroform solution showed no visible reaction with bromine at room temperature. Upon heating on a water-bath, strong evolution of hydrogen bromide set in. After five minutes the mixture was cooled and petroleum ether added to precipitate the reaction product. 1,1-Diphenyl-2-(*p*-nitrophenyl)-2-bromoethylene crystallized from butyl acetate in prisms, m. p. 178°.

Anal. Calcd. for $C_{20}H_{14}O_2NBr$: N, 3.7. Found: N, 3.9.

(b) **Catalytic Reduction.**—The ethylene XII (1 g.) was suspended in ethyl acetate (35 cc.) and reduced in the presence of Raney nickel. After absorption of 240 cc. of hydrogen (calcd. for 3 moles, 242 cc.; $T = 239°$; $p = 754$ mm.), the reaction was interrupted. A yellowish oil was isolated, which showed no tendency to crystallize and was therefore acetylated directly. The acetyl derivative of XIII crystallized from butanol in lancets or from toluene–petroleum ether (1:1) in long flat tetragonal prisms, m. p. 169–170°; yield 0.7 g. (70%).

Anal. Calcd. for $C_{22}H_{19}ON$: N, 4.5. Found: N, 4.6.

When the hydrogenation was continued to completion, the speed of the reaction slowed appreciably after the absorption of the first three moles of hydrogen. The oily reduction product (XIV) was transformed again into its acetyl derivative. It crystallized from benzene–petroleum ether in big flat prisms, m. p. 128–129°.

Anal. Calcd. for $C_{22}H_{21}ON$: C, 83.8; H, 6.7; N, 4.4. Found: C, 83.6; H, 6.8; N, 4.7.

Nitration of Triphenylethylene (I) and 1,1,2-Triphenylethanol (V).—(a) In acetic acid: The carbinol V (2 g.) was dissolved in acetic acid (20 cc.) and fuming nitric acid (d. 1.51) (0.55 g., 1.2 equiv.) added dropwise at room temperature. An exothermic reaction took place and the temperature rose to 50°. The mixture was then heated to 65° for twenty minutes and poured onto ice. The granular precipitate was dried and recrystallized from butyl acetate as yellow prisms, m. p. 172° (VI); yield 0.7 g.

Anal. Calcd. for $C_{20}H_{15}O_2N$: C, 79.7; H, 5.0. Found: C, 79.9; H, 5.3.

The same product, but in higher yields, was obtained by the use of 2.2 or 3.2 equivalents of nitric acid. The

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[13] All melting points are uncorrected.

product is identical with the substance resulting from nitration of triphenylethylene itself.

(b) Without solvent: The carbinol V (15 g.) was added in small portions to fuming nitric acid (75 cc.) with stirring. A violent reaction took place, which raised the temperature to 70°. The reaction was completed by heating the mixture to 80° for one and one-half hours. Upon standing for several days, the reaction product crystallized out. It was filtered off, washed with nitric acid, then with water and dried; crude yield, 20 g., 83%. The tetranitro derivative (VII?) crystallized from benzene or butyl acetate in yellow prisms, m. p. 205°.

Anal. Calcd. for $C_{20}H_{12}O_8N_4$: C, 55.0; H, 2.8; N, 12.8. Found: C, 55.4; H, 2.6; N, 12.5.

The same product was obtained, but in a less satisfactory form, by nitration of triphenylethylene or α-nitrotriphenylethylene (VI) with fuming nitric acid.

Summary

The coupling of β,β-diarylacrylic acids with diazotized anilines opens a new route to substituted triarylethylenes. Geometrical isomers of the acids yielded identical coupling products.

Under the experimental conditions of this reaction, α-phenylcinnamic acid is decarboxylated to *trans*-stilbene. Decarboxylation is also a side-reaction for β,β-diarylacrylic acids.

1,1-Diphenyl-2-(*p*-nitrophenyl)-ethylene can be reduced catalytically stepwise first to the unsaturated, then to the saturated, amine. Nitration of triphenylethylene, the corresponding carbinol or its α-nitro derivative with fuming nitric acid in the absence of a solvent produces a tetranitro derivative.

Rechovot, Palestine Received August 25, 1947

[Contribution from the Department of Biochemistry, Cornell University Medical College]

Reactions of Mustard-type Vesicants with α-Amino Acids[1]

By Vincent du Vigneaud, Carl M. Stevens,[2] Harold F. McDuffie, Jr.,[3] John L. Wood[4] and Herbert McKennis, Jr.[5]

Early in World War II it was considered that reactions between mustard gas (H) and certain enzymes possibly played a role in the mechanism of vesication by H-type compounds. As part of a collaborative effort to uncover the mechanism of vesication by chemical warfare agents, reactions between H-type compounds and proteins were studied in a number of laboratories. Prior to our investigations, published work[6] and available unpublished British reports[7] indicated that the properties of several proteins were altered by treatment with mustard gas. To gain insight into the protein-H reactions, this Laboratory and others investigated the preparation and nature of compounds formed by the reaction of H-type vesicants with amino acids. This report covers part of this one aspect of the larger problem.

From the chemical standpoint, studies on mustard gas are complicated by the fact that H contains two reactive halogens. Since it was already known[8] that several compounds of the type $RSCH_2CH_2Cl$ possess vesicant action, we sought to simplify the problem by employing these "one-handed" vesicants in our chemical studies. Although these compounds containing only one β-chloroethyl group are potent vesicants, they are quantitatively much less vesicant than H itself. Qualitatively their physiological action parallels that of H. The "one-handed" agents, therefore, must be capable of entering into the chemical reactions essential to vesication. The fact that the structures and properties of the molecules closely resemble those of H itself makes it highly probable that the mechanism of vesication is essentially the same in each case. These considerations caused us to focus our attention largely on the one-handed vesicants, which for convenience are designated as follows:

$C_6H_5CH_2SCH_2CH_2Cl$	Benzyl-H
$CH_3SCH_2CH_2Cl$	Methyl-H
$CH_3CH_2SCH_2CH_2Cl$	Ethyl-H
$CH_3CH_2CH_2CH_2SCH_2CH_2Cl$	Butyl-H

A survey of the general literature[9] indicated that H-type vesicants reacted readily with sulfhydryl, amino and phenolic hydroxyl groups in alkaline solution. Furthermore, a derivative of an α-amino acid had been reported. It was the product formed by the reaction[10] of H and glycine ethyl ester, having the structure I.[11]

$$S(CH_2CH_2NHCH_2COOC_2H_5)_2 \qquad \text{I}$$

In our experiments we studied the reactions of most of the naturally occurring amino acids with vesciants of the type $RSCH_2CH_2Cl$, where R has the structures indicated above.

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[6] Berenblum and Wormall, *Biochem. J.*, **33**, 75 (1939).

[7] Berenblum (1940); Pirie (1941); Peters (1941).

[8] See, for instance, Kirner, This Journal, **55**, 3501 (1933); Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

[9] See Jackson, *Chem. Rev.*, **15**, 425 (1934).

[10] For recently published observations on this reaction as well as other studies on the reaction of amino acids with H and related compounds, see Boursnell, Francis and Wormall, *Biochem. J.*, **40**, 737 (1946).

[11] Cashmore and McCombie, *J. Chem. Soc.*, 2884 (1923).