Reactions of Some α- and β-Substituted Styrenes in the Presence of Ethylaluminum Dichloride[1]

REUVEN WOLOVSKY* AND NETTA MAOZ

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Received March 23, 1973

The reaction of 0.1 equiv of EADC under mild conditions on some styrene derivatives gives rise mainly to the formation of indan-type cyclic dimers and in some cases also cyclic trimers. The initially formed carbonium ion can simultaneously also lead by different pathways to products derived from alkylation of the aromatic solvent or to a reduced hydrocarbon. The latter is not a catalytic process as it consumes 1 equiv of the reagent to liberate ethylene.

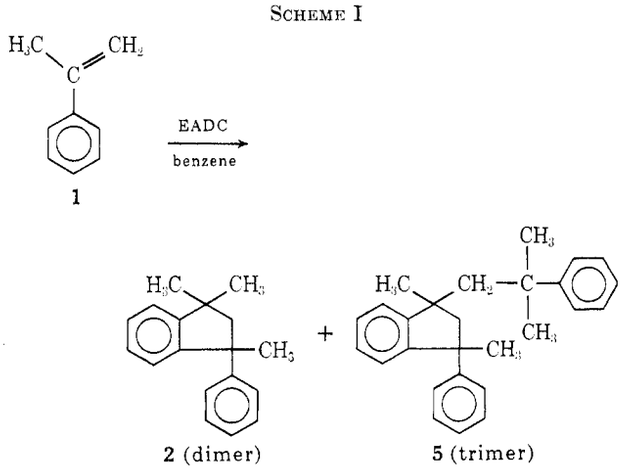
It has been found in our laboratory[2] that EADC acts as a very potent catalyst in the cycloalkylation of benzene, giving rise to cycloalkylbenzenes in almost quantitative conversion in a few minutes at room temperature. In this reaction, the EADC functions in catalytic amounts as a Lewis acid in a typical Friedel–Crafts alkylation.

It has also been known that some styrene derivatives undergo a cyclodimerization reaction to form saturated indan-type derivatives when treated with acids or Lewis acids. Thus Bergmann, *et al.*,[3] showed that by the action of an acid and a Lewis acid on α-methylstyrene (**1**) the saturated dimer 1,1,3-trimethyl-3-phenylindan (**2**) is obtained. Similarly, 1,1-diphenylethylene (**3**) gave 1,3,3-triphenyl-1-methylindan (**4**) as saturated dimer.[4]

In a recent communication,[5] Alberola has shown that styrene and some styrene derivatives like α-methylstyrene, β-methylstyrene, 1,1-diphenylethylene, or 1,1-diphenylpropene-1 undergo a hydroalumination reaction in 70–90% yield when carried out in benzene solution at 80° in the presence of an equivalent amount of diethylaluminum chloride (DEAC). Hydrolysis of the organometallic intermediate gave rise to the corresponding alkane.[6] An intramolecular hydride ion shift from the ethyl group of the reagent accompanied by a release of ethylene was shown to have taken place. Similar results were obtained by the action of ethylaluminum dichloride (EADC).

The above results prompted us to repeat Alberola's experiment on α-methylstyrene. In fact we carried out the reaction on a benzene solution of **1** in the presence of EADC under both "drastic" and "mild" conditions. Under the drastic conditions we tried to follow as closely as possible the conditions used by Alberola, *i.e.*, 1 equiv of EADC under reflux in benzene for 5 hr. Under the mild conditions we allowed only 0.1 equiv of EADC to react for 5 min at room temperature. In both cases the main products obtained by us were the substituted indan-type dimer **2** and trimer 1,3-dimethyl-1-(2′-methyl-2′-phenylpropyl)-3-phenylindan (**5**) as given in Scheme I.

SCHEME I



The reaction of α-methylstyrene with EADC yielded dimers and trimers in different proportions depending on temperature, as shown in Table I.

TABLE I

REACTION OF α-METHYLSTYRENE IN BENZENE IN THE PRESENCE OF EADC AT VARIOUS TEMPERATURES

Temp, °C	4[a]	25[a]	80[b]
Cyclic dimer[c] **2**, %	37	52	73
Cyclic trimer[c] **5**, %	55	28	13

[a] EADC, 0.1 equiv. [b] EADC, 1 equiv. [c] The yields are calculated from glc curves.

β-Methylstyrene (**6**) similarly gave under mild conditions 46% of the cyclic dimer 1-ethyl-2-methyl-3-phenylindan (**7**) and 17% of the cyclic trimer 1-(3′-phenyl-2′-pentyl)-2-methyl-3-phenylindan (**8**).

Reaction of 1,1-diphenylethylene (**3**) with EADC in benzene yielded under mild conditions 70% of the known cyclic dimer **4** through path A (*vide infra*, Scheme II), 11% of the saturated product 1,1-diphenylethane (**9**) obtained *via* path C, and some higher boiling products. However, under the drastic conditions, the cyclic dimer **4** initially formed underwent a further decomposition reaction to produce a new cyclic product, 1-methyl-3,3-diphenylindan (**10**).

(1) Presented first in Tel-Aviv at the annual meeting of the Israel Chemical Society; *cf.* R. Wolovsky and N. Maoz, Proceedings of the 41st Annual Meeting of the Israel Chemical Society, 1971, p 222.

(2) (a) R. Wolovsky and N. Maoz, *Israel J. Chem.*, **8**, 6p (1970); (b) R. Wolovsky, N. Maoz, and Z. Nir, *Synthesis*, 656 (1970); (c) R. Wolovsky and N. Maoz, Proceedings of the 41st Annual Meeting of the Israel Chemical Society, 1971, p 221.

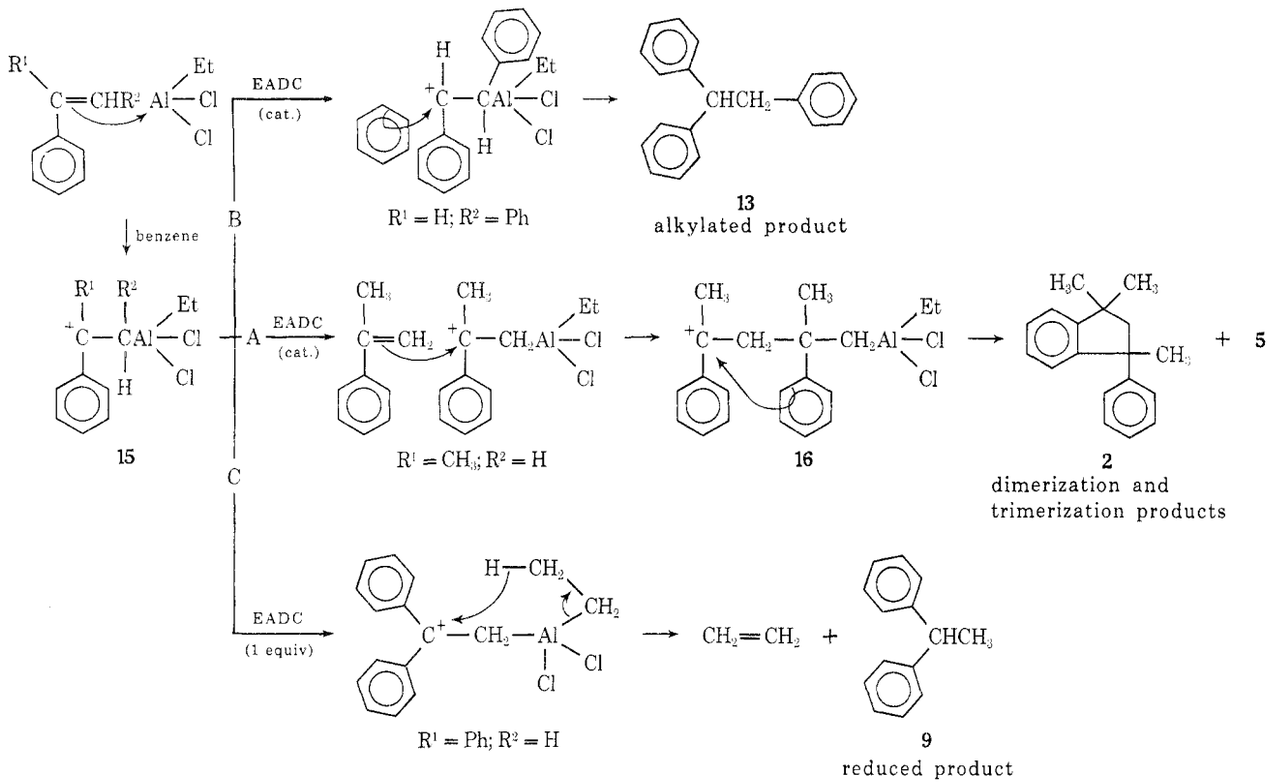
(3) (a) E. Bergmann, H. Taubadel, and H. Weiss, *Chem. Ber.*, **64B**, 1493 (1931); (b) J. C. Petropoulos and J. J. Fischer, *J. Amer. Chem. Soc.*, **80**, 1938 (1958); (c) R. L. McLaughlin, U. S. Patent 3,161,692 (1964); *Chem. Abstr.*, **62**, 9082*d* (1965).

(4) (a) E. Bergmann and H. Weiss, *Justus Liebigs Ann. Chem.*, **480**, 49 (1930); (b) A. G. Evans and D. Price, *J. Chem. Soc.*, 2982 (1959); (c) A. G. Evans and D. Oven, *ibid.*, 4123 (1959); (d) A. G. Evans, E. A. James, and E. D. Oven, *ibid.*, 3532 (1959); (e) A. Uchida, Y. Hamano, Y. Mukai, and S. Matsuda, *Ind. Eng. Chem. Prod. Res. Develop.*, **10**, 372 (1971).

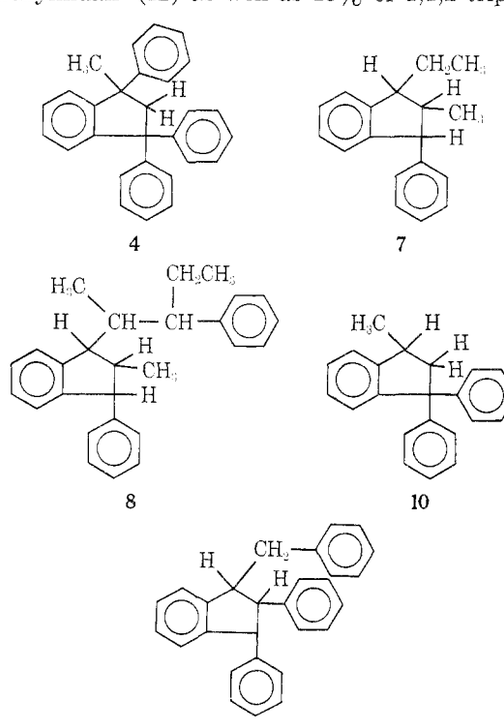
(5) A. Alberola, *Tetrahedron Lett.*, 3471 (1970).

(6) The hydroalumination reaction of butadiene by triisobutylaluminum followed by hydrolysis with methanol to yield 29% of butane in addition to other products was observed in the polymerization reaction under conditions where no solvent was used; *cf.* E. Marcus, D. L. MacPeak, and S. T. Tinsley, *J. Org. Chem.*, **34**, 1931 (1969).

SCHEME II



trans-Stilbene (**11**) reacted under mild conditions *via* path A to yield 73% of the cyclic dimer 1-benzyl-2,3-diphenylindan[7] (**12**) as well as 10% of 1,1,2-triphenyl-



ethane (**13**) by path B (alkylation of the solvent). *cis*-Stilbene (**14**) reacted similarly to yield 34% of **12** through path A and 47% of **13** *via* path B.

(7) (a) E. Bergmann, D. Winter, and W. Schreiber, *Justus Liebigs Ann. Chem.*, **500**, 122 (1933); (b) G. Montaudo and G. Purrelo, *Ann. Chim. (Rome)*, **51**, 865 (1961); *Chem. Abstr.*, **56**, 10021*d* (1962); (c) M. Salzwedel, V. Werner, and D. Schulte-Frohlinde, *Angew. Chem.*, **76**, 989 (1964).

Experimental Section

Materials.—α-Methylstyrene, β-methylstyrene, and *trans*-stilbene were purchased from Fluka, *cis*-stilbene from Koch-Light, and 1,1-diphenylethylene from Eastman. α-Methylstyrene was distilled before use; all other starting materials were used as purchased. EADC was obtained from Texas Alkyls as a 20% solution in benzene (1 ml of solution ≅1.6 mmole of EADC). Benzene was distilled over sodium before use. All reactions were carried out under a nitrogen atmosphere and the EADC reagent solutions were added with a syringe to the magnetically stirred solutions. The products were checked for their purity by glc.

Instruments.—Nmr spectra were taken on a Varian A-60 instrument in CCl_4 solution using TMS as an internal standard. The decoupling experiment was carried out on a Bruker HFX-10 instrument operating at 90 MHz. Mass spectra were run on an Atlas CH4 mass spectrometer. A slightly modified Packard Model 7400 series research gas chromatograph, to which an additional heater was added, was used for the glc analyses. A flame ionization detector was used throughout in conjunction with a 1:10 gas splitter for sample collection. Aluminum columns 6 ft × 0.25 in. o.d. filled with 0.5% OV 17 on Chromosorb W were used; the nitrogen flow rate was 300 ml/min.

Reaction of α-Methylstyrene (1). A. Mild Conditions.—To a solution of 1.18 g (0.01 mol) of **1** in 30 ml of benzene, 0.64 ml (0.001 mol) of a benzene solution of EADC was added. A red color developed immediately. The reaction mixture was stirred for 5 min at room temperature and terminated by adding a few drops of methanol. The solution was then washed with water and dried over anhydrous sodium sulfate, and the benzene was removed. The remaining oily residue was distilled in a Büchi ball-tube fractionator. The cyclic dimer **2** distilled at 80° (0.1 mm), yielding 0.67 g (57%) of an oil[8] (lit.[9] mp 52°), *m/e* 236, glc retention time 2.3 min (programmed between 60 and 300° at a rate of 30°/min), and the cyclic trimer **5** distilled at 135° (0.1 mm), yielding 0.33 g (28%) of a mixture of isomers, *m/e* 354, retention time 4.5 min.

B. Drastic Conditions.—The reaction was carried out as above, but now equimolar quantities of EADC reagent were

(8) R. A. Benkeser, J. Hooz, T. V. Liston, and E. A. Tresillyan, *J. Amer. Chem. Soc.*, **85**, 3984 (1963).

(9) L. M. Adams, R. J. Lee, and F. T. Wadsworth, *J. Org. Chem.*, **24**, 1186 (1959).

used and the mixture was refluxed for 5 hr. The same products as above were obtained but the proportions were different (*cf.* Table I).

trans-β-**Methylstyrene** (**6**).—To a solution of 1.18 g (0.01 mol) of **6** in 30 ml of benzene, 2 ml (0.0032 mol) of a 20% benzene solution of EADC was added, causing development of a yellowish color. The reaction mixture was stirred for 15 min at room temperature and terminated with methanol as above. The benzene solution was washed, dried, and evaporated. The remaining oil was chromatographed on 150 g of basic Woelm alumina using as eluent increasing proportions of benzene in hexane. There was obtained 0.55 g (47%) of the cyclic dimer[10] **7** as a mixture of isomers, *m/e* 236, retention time 2.4 min (under conditions as above). Then the cyclic trimer **8** (mixture of isomers) was eluted, 0.20 g (17%), *m/e* 354, retention time 4.7 min. Further elution gave mixtures of higher molecular weight products which were not analyzed.

1,1-Diphenylethylene (**3**). **A.**—A 1.8-g (0.01 mol) portion of **3** was dissolved in 30 ml of benzene to which 0.8 ml (0.0013 mol) of a 20% benzene solution of EADC was added. A green color developed immediately. After stirring at room temperature for 5 min, the reaction was terminated with methanol and worked up as above, leaving a residue of 1.71 g. Chromatography as above gave fractions which were analyzed by glc and combined accordingly. There was obtained first 0.2 g (11%) of 1,1-diphenylethane[11] (**9**), *m/e* 182, retention time 1.5 min (when programmed between 100 and 400° at a rate of 40°/min). Second to elute was the cyclic dimer 1,3,3-triphenyl-1-methylindan (**4**), 1.25 g (70%), *m/e* 360, mp 143° (lit.[4b] mp 143°; also *cf.* ref 13), retention time 2.9 min. Then followed by elution higher molecular weight unidentified products.

B.—To a solution of 1.8 g (0.01 mol) of **3** in 30% ml of benzene was added 7 ml (0.011 mol) of the 20% EADC reagent. The reaction mixture was stirred at room temperature for 5 hr, decomposed with dilute HCl, and worked up as above to give 1.66 g of an oil. The oil was dissolved in chloroform, and, upon addition of hexane, 0.59 g (33%) of the crude dimer **4** was precipitated, mp 137–140°. The remaining 1.07 g was chromatographed as above to render first 0.15 g (8%) of **9**, *m/e* 182, retention time 1.5 min, followed by 0.31 g (17%) of the degradation product 1-methyl-3,3-diphenylindan (**10**), *m/e* 284, retention time 2.2 min, mp 89–90° from ethyl acetate.

Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 93.06; H, 7.20.

The third compound to be eluted was the cyclic dimer **4**, 0.31 g (17%), mp 143–144°. The last to elute were again higher molecular weight unidentified product mixtures.

C.—The reaction was carried out with 1 equiv of EADC as above but now under reflux for 5 hr. Work-up and chromatography yielded 0.20 g (11%) of **9**, 0.27 g (15%) of **10**, and 0.34 g (19%) of **4**.

1,3,3-Triphenyl-1-methylindan (**4**).—To a solution of 0.36 g (0.001 mol) of **4** in 6 ml of benzene was added 0.7 ml (0.0011 mol) of the 20% EADC reagent and the mixture was refluxed for 5 hr. Decomposition with dilute HCl and work-up yielded 0.33 g of an oil. Trituration with ethanol recovered 0.2 g (55%) of crystalline starting material **4**. Chromatography of the residue yielded 0.11 g (31%) of crystalline **10**, mp 88–89°, *m/e* 284, retention time 2.2 min. A mixture melting point with **10** obtained from the reaction of **3** gave no depression. Following from the chromatography there were recovered 3% of **4** and other unidentified products.

trans-**Stilbene** (**11**).—A solution of 1.8 g (0.01 mol) of **11** in 30 ml of benzene was treated with 0.64 ml (0.001 mol) of a 20% EADC–benzene solution. A red color developed immediately upon the addition of the reagent. Stirring for 5 min at room temperature followed by decomposition with methanol and work-up yielded an oil that was distilled at 0.1 mm in a Büchi ball-tube fractionator to give three fractions. Fraction A, distilling at 80°, gave 0.01 g of starting material **11**. Fraction B, distilling at 140°, gave 0.55 g of a mixture of **12**, *m/e* 360, retention time 3.0 min, and **13**, *m/e* 258, retention time 2.2 min. Fraction C, distilling at 170°, gave 0.95 g of **12** only as a mixture of isomers (lit.[7a] mp 184°), *m/e* 360, retention time 3.0 min. Chromatographic separation of fraction B gave 0.18 g of pure **13** and 0.34 g of pure **12**. The overall yields of **13** and **12** were 10 and 72%, respectively.

cis-**Stilbene** (**14**).—The reaction of **14** was carried out in the same way as that with **11**. The yields were 0.93 g (52%) of the alkylation product **13**, mp 54–55° from ethanol (lit.[12] mp 54.5°), and 0.68 g (38%) of the cyclic dimer **12** (isomer mixture[13]).

Discussion

When a certain styrene derivative is allowed to react with EADC in benzene solution, the EADC reagent[14] attacks the double bond to produce first a carbonium ion (**15**), which may in turn react further in one or more of the pathways A, B, and C outlined in Scheme II, depending on the derivative and conditions used. Path A leads to the formation of cyclic dimers and trimers, path B leads to alkylation products of the solvent (benzene), while path C, consuming the reagent in a noncatalytic reaction, leads after hydrolysis to the reduced product. As illustrated in Scheme II, path A, the monomeric carbonium ion **15** reacts with a second molecule of **1** to produce the dimeric carbonium ion **16**. The latter may now react in two ways: (a) it may undergo an intramolecular ring closure to render the indan system **17**, which with the aid of a proton released in the cyclization step regenerates the catalyst and forms the dimer **2**, or, alternatively, (b) it may first undergo an oligomerization step by the attack of another molecule of α-methylstyrene to form a trimeric carbonium ion[15] **18**, followed by cyclization in an irreversible intramolecular attack. The proton liberated in the cyclization reaction regenerates the catalyst, giving rise to the cyclic trimer **5** (Scheme III). The action of catalyst regeneration can take place whether the molecule is in the monomeric or oligomeric stage as well as whether in the carbonium ion, cyclized, or unsaturated form (*vide infra*). Path A thus requires only catalytic amounts of EADC. For similar reasons catalytic amounts are sufficient also for path B.

An additional pool from which protons can temporarily be "borrowed" to regenerate the catalyst (and thus make it more efficient) is the reversible,[16] very fast reaction of the linear dimer or trimer carbonium ions **16** and **18** to form the corresponding unsaturated linear compounds, thereby acting as an auxiliary pool for temporarily available protons.

The irreversible intramolecular formation of the indan type dimer and trimer is very considerably enhanced through the "locking" effect[17] of the substituents on the side chain. The α-substituted side chain in the carbonium ion of the linear dimer or trimer forces a preferred conformation to prevail with the carbonium ion in close proximity to the ortho position of the neighboring aromatic ring. The intramolecular cyclization is thus a more preferred reaction over the competing intermolecular attack of

(10) (a) J. M. Van der Zaden and Th. R. Rix, *Recl. Trav. Chim. Pays-Bas*, **75**, 1166 (1956); (b) *ibid.*, **75**, 1343 (1956).

(11) "Dictionary of Carbon Compounds," Vol. V, Oxford University Press, London, 1965, p 1279.

(12) Reference 11, p 3199.

(13) See ref 7.

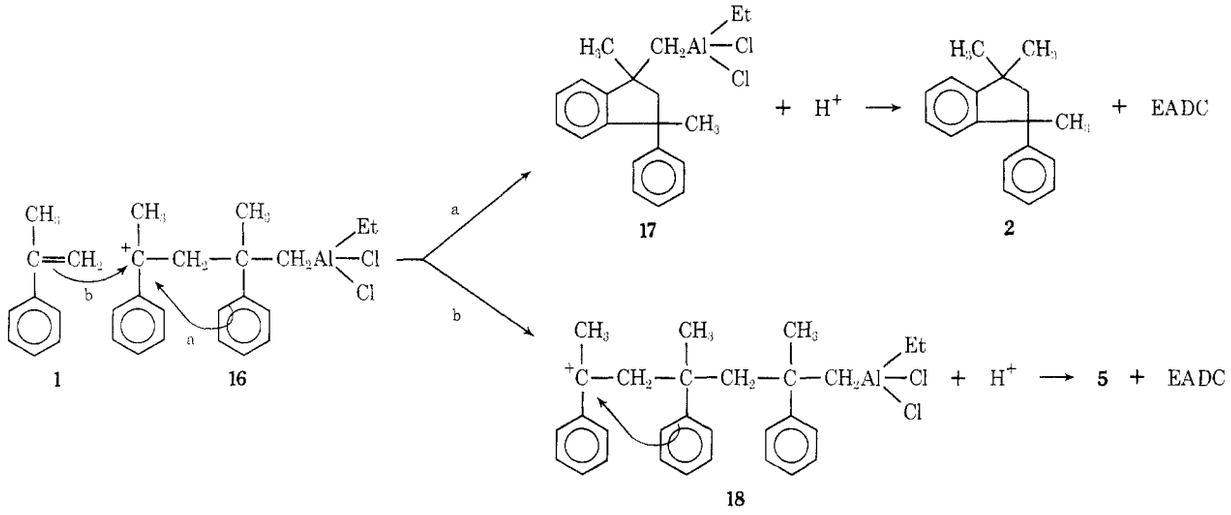
(14) C. G. Overberger, E. M. Pearce, and D. Tanner, *J. Amer. Chem. Soc.*, **80**, 1761 (1958).

(15) The possibility that very small amounts of promoting substances or cocatalysts (*e.g.*, traces of water, protonic acids, or alkyl halides) combine with the EADC to form an ionic complex which provides the cations necessary for the initiation of the reaction cannot be excluded.

(16) L. R. C. Barclay, "Friedel-Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 944.

(17) (a) S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970); (b) *J. Amer. Chem. Soc.*, **92**, 4377 (1970); (c) *ibid.*, **94**, 9158 (1972).

SCHEME III



another monomer to give oligomerization. Cyclization rate enhancement due to the *gem*-dimethyl effect in somewhat related systems has been shown[17] to increase cyclization rates by a factor as high as 10^6.

At a somewhat lower temperature (4°) α-methylstyrene yielded more trimer than dimer (trimer:dimer 1.48), while at higher temperature this relation changes considerably (at 25° trimer:dimer 0.54 and at 80° trimer:dimer 0.18). This result may be a reflection of the difference in the dependence of reaction rates on temperature of the two competing reactions. Cationic polymerizations[18] of α-methylstyrene are known to take place at low temperature (~−80°); however, at room temperature only dimers and trimers were observed.

Reaction of β-methylstyrene through path A yielded similar results to those of α-methylstyrene but in lower yield. This may be attributed to the fact that the chain is less substituted in the α position to the aromatic ring.

Path B represents alkylation of the aromatic solvent by the olefin. The carbonium ion **15** of *trans*- or *cis*-stilbene, in addition to the dimerization reaction to some extent through path A, reacts to a larger extent with the benzene used as solvent to produce the alkylation product 1,1,2-triphenylethane (**13**) in substantial yield. This reaction requires also only catalytic amount of the reagent (*vide supra*). Path C involves an intramolecular hydride ion shift from the ethyl group of the reagent, leading after hydrolysis to the reduction of the double bond[5] along with the consumption of an equimolar quantity of EADC. This pathway has taken place to some extent in the reaction of 1,1-diphenylethylene along with its main reaction through path A, leading to the corresponding cyclic dimer **4**.

Nmr Spectra.[19]—The cyclic dimer of α-methylstyrene possesses an asymmetric carbon atom next to the methylene[20] of the indan ring. The nonequivalence of the geminal protons in the nonplanar five-membered ring is exhibited in their nmr spectrum giving rise to an AB pattern quartet centered at 2.3 ppm with a splitting constant J = 13 Hz. Similarly, and for the very same reason, the cyclic dimer of 1,1-diphenylethylene shows in the nmr for the geminal protons a quartet centered at 3.7 ppm with a splitting constant of J = 14 Hz. The nonequivalent methylene protons in **10**, in addition to their geminal splitting, are also split by the presence of a vicinal proton next to the methylene, giving rise to a somewhat more complex pattern in the region 3.3–2.2 ppm for all three protons. The methyl protons of this compound, however, are split by their geminal proton into a doublet centered at 1.4 ppm with J = 6 Hz. A similar splitting constant of J = 6 Hz was obtained for the methyl doublet also when taken on a 90-MHz instrument. A decoupling experiment was conducted where the methyl doublet collapsed into a singlet upon irradiation at a frequency of 3 ppm.

Compounds **5**, **7**, **8**, and **12** are most probably mixtures of geometrical isomers, a fact that is well reflected in the complexity of their nmr spectra. Of particular mention may be the cyclic dimer of stilbene **12**, where the isomer mixture derived from *trans*-stilbene was different from the mixture derived from *cis*-stilbene. This is also well reflected in the difference in the relative abundance of various peaks in the mass spectrometric fragmentation.

The cyclic nature of the dimers, trimers, and the degradation product **10** obtained in these reactions was based mainly on the proper ratio obtained in their nmr spectra between the aromatic and aliphatic protons.

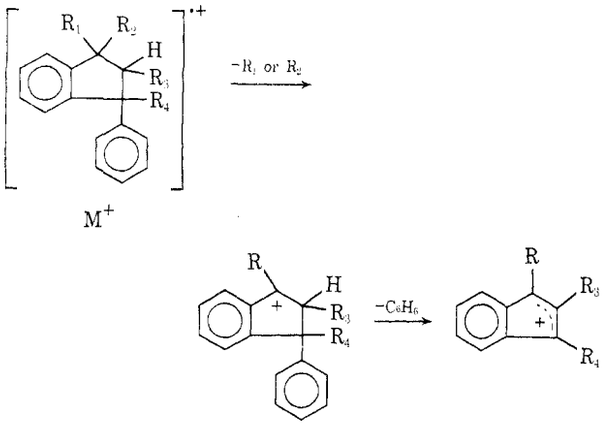
Mass Spectra.[19]—The mass spectra of all the 3-phenylindan derivatives taken exhibit a common general fragmentation pattern. The common step in the fragmentation of the molecular ion is rupture of a substituent in position 1, leaving a positive charge stabilized at the benzylic position 1, while a phenyl substituent at position 3 is still attached to the indan nucleus. This is followed by a loss of a neutral molecule C_6H_6 (phenyl from position 3 and hydrogen from position 2) to give an indan carbonium ion which is now stabilized by two benzylic positions, 1 and 3.

Degradation of 4 to 10.—In the reaction of 1,1-diphenylethylene with 1 equiv of EADC on prolonged

(18) (a) F. S. Dainton and R. H. Tomlinson, *J. Chem. Soc.*, 151 (1953); (b) D. C. Pepper, *Quart. Rev., Chem. Soc.*, **8**, 88 (1954); (c) "Friedel–Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 1293.

(19) See paragraph at end of paper regarding supplementary material.

(20) R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 129.



reaction time, in addition to the dimerization and reduction products **4** and **9** obtained through paths A and C, there was formed also compound **10**. This compound is a product of a secondary reaction of the cyclic dimer **4** obtained through path A. To prove this point, pure **4** was submitted to the reaction under the drastic conditions to yield **10** as the major product[21]

(21) Adams[9] reported a somewhat similar degradation of **2** to 1,1,3-triphenylindan when **2** was heated with $AlCl_3$ at 110° for 6 hr.

(*ca.* 73% of the fraction that underwent reaction). Based on the nmr data (splitting of the methyl) we conclude that, in the degradation process of **4** to **10**, the substitution of phenyl by hydrogen occurred on the phenyl in position 1 next to the methyl rather than one of the two geminal phenyls in position 3 (see above).

Acknowledgment.—This project has been supported in part by a grant from the National Council for Research and Development (Israel).

Registry No.—**1**, 98-83-9; **2**, 3910-35-8; **3**, 530-48-3; **4**, 19303-32-3; **5**, 41906-71-2; **6**, 637-50-3; **7**, 30170-60-6; **8**, 41906-72-3; **9**, 612-00-0; **10**, 30098-24-9; **11**, 103-30-0; **12**, 41906-73-4; **13**, 1520-42-9; **14**, 645-49-8; EADC, 563-43-9.

Supplementary Material Available.—A figure with the nmr spectra of compounds **2**, **4**, and **10** as well as two tables summarizing the nmr and mass spectral data for all the products discussed will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4040.

A General Synthesis of 3-(Substituted benzoyl)-3-Substituted Alkanoic Acids

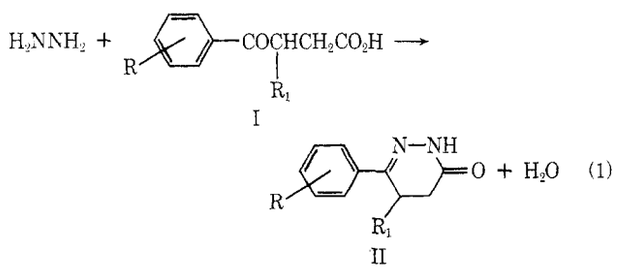
Francis J. McEvoy and George R. Allen, Jr.*

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received June 28, 1973

A general method for the preparation of 3-(substituted benzoyl)-3-substituted alkanoic acids is described. The key feature of the method is the conversion of a quaternary salt (V) derived from the Mannich base of a phenone into the corresponding γ-keto nitrile (VI), hydrolysis of which furnishes the acid. The transformation of V into VI by cyanide proceeds in two stages: (1) β elimination, and (2) conjugate hydrocyanation of the resulting enone. The efficiency of the method is compared to (1) the preparation of γ-keto esters by alkylation of enamines with ethyl bromoacetate and (2) the reduction of β-benzoylcrotonic acids obtained by condensation of phenones with glyoxalic acid.

We required a general synthesis of 3-(substituted benzoyl)-3-substituted propionic acids (I) in order to evaluate a series of pharmacologically interesting 6-(substituted phenyl)-5-substituted 4,5-dihydro-3-(2*H*)-pyridazinones (II),[1] which are readily prepared by reaction of I with hydrazine (eq 1).[1,2] Many of the procedures



described in the literature for the preparation of I rely on anionic condensations between ketones and esters,[3] and do not appear applicable to those reactants having substituents containing active hydrogens (see below). Those acid catalyzed procedures, *e.g.*, Friedel–Crafts condensations, compatible with substituents possessing active hydrogens usually give mixtures containing the isomeric 3-(substituted benzoyl)-2-substituted propionic acid.[1,4] In this paper we describe a method of apparent generality for the preparation of I; moreover, its effectiveness is compared with that of two other procedures.

The general method is based on an improved synthesis of γ-keto nitriles (VI), the hydrolysis of which readily furnish I (see Scheme I).[5,6] The preparation of certain γ-keto nitriles by treatment of Mannich bases with aqueous alkali cyanide has been reported by Knott,[6] and we have used a modification of this procedure to prepare the requisite intermediates. Thus, ketones III were converted into Mannich bases IV using the procedure of Back,[7] and reaction of the crude IV with methyl iodide furnished the quaternary salts

(1) W. V. Curran and A. Ross, *J. Med Chem.*, submitted for publication.

(2) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **75**, 1117 (1953), and references cited therein.

(3) (a) W. H. Puterbaugh and R. L. Readshaw, *J. Amer. Chem. Soc.*, **82**, 3635 (1960); (b) W. Cocker, L. O. Hopkins, L. Mabrouk, J. McCormick, and T. B. H. McMurray, *J. Chem. Soc.*, 2230 (1960); (c) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958); (d) J. A. Marshall and S. F. Brady, *ibid*, **35**, 4068 (1970); (e) W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.*, **71**, 3463 (1949).

(4) A. G. Peto in "Friedel-Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, pp 573, 583.

(5) C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).

(6) E. B. Knott, *J. Chem. Soc.* 1190 (1947).

(7) W. Back, *Arch. Pharm. (Weinheim)*, **303**, 491 (1970).