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p-Vinylbenzoic and *p*-Vinylphenylacetic Acids

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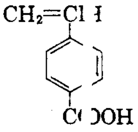
Preparative methods for *p*-vinylbenzoic and *p*-vinylphenylacetic acids have been worked out. (*p*-Vinylbenzoyl)acetone (VII) and ethyl α-(*p*-vinylphenylacetyl)acetoacetate (IX) have been synthesized. In orienting experiments, it has been found that the two compounds polymerize very quickly and that the polymers obtained have no chelating properties. Further experiments in this direction have, therefore, been abandoned.

The purpose of this study was to prepare polystyrenes substituted in the benzene rings by 1,3-diketone groupings which would be capable of forming chelates with heavy metal ions and thus represent exchange resins endowed with a specific affinity. The starting materials were *p*-vinylbenzoic and *p*-vinylphenylacetic acid. *p*-Vinylbenzoic acid (I) has been prepared before by Marvel and Overberger,[1] but in over-all yields of only 1.8 to 4.1%, and by Emerson[2] in better yield, but by a method not easily applied to the preparation of larger quantities. *p*-Vinylphenylacetic acid (II) has not been synthesized before.

When methyl *p*-ethylbenzoate (III, R = H) was brominated with *N*-bromosuccinimide, the expected bromo-compound (III, R = Br) was obtained in 82% yield, but the bromine atom was unexpectedly refractory towards pyridine or collidine. Alcoholic alkali gave *p*-(α-ethoxyethyl)-benzoic acid, and silver hydroxide methyl *p*-(α-hydroxyethyl)benzoate (III, R = OH), in 43 and 20% yield, respectively. The latter could be smoothly (85%) dehydrated to the methyl ester of (I) by the usual method employing potassium hydrogen sulfate; however, the over-all yield, calculated on (III, R = H), was only 14%. An over-all yield of 37% was obtained from the easily available *p*-methylacetophenone. It was oxidized with permanganate to *p*-acetylbenzoic acid (IV), the methyl ester of which was reduced to (III, R = OH) smoothly by means of sodium borohydride.

The reaction of methyl phenylacetate with acetyl chloride in the presence of aluminum chloride gave 66% of a monoacetyl derivative; its structure (V) was proven by oxidation to terephthalic acid. Whilst with aluminum isopropoxide instead of the expected carbinol VI its isopropyl ether was obtained,[3] sodium borohydride effected the reduction smoothly, and VI could be dehydrated by means of potassium hydrogen sulfate to the methyl ester of II.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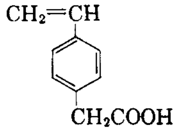
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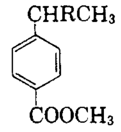
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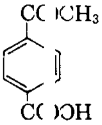
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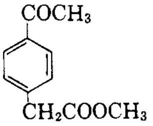
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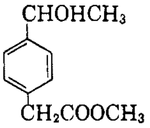
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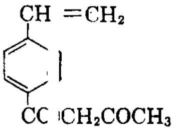
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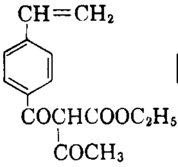
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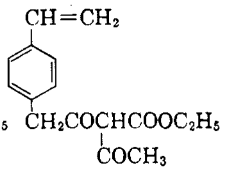
IX

Methyl *p*-vinylbenzoate condensed with acetone in the presence of sodium hydride to give *p*-vinylbenzoylacetone (VII) in 16% yield. The condensation, on the other hand, of *p*-vinylbenzoyl chloride—which was prepared from the sodium salt of I and oxalyl chloride—with the magnesium enolate of ethyl acetoacetate gave directly the polymer of the expected ketoester VIII in 81% yield. This may well be due to the presence of a *p*-divinylbenzene system in the enol form of VIII. The methyl ester of II, on the other hand, gave in this reaction in 30% yield the desired keto ester IX, together with some polymeric material, whilst the condensation with acetone led practically only to polymeric material.[3a]

Preliminary experiments have shown that the tendency to polymerization of the two vinylmonomers VII and IX is so great that their transformation into the copper and uranium chelates is accompanied by polymerization. On the other hand, judging from the intensity of the color reaction, the complex formed from the two monomers with ferric chloride in methanol appears to be quite stable in solution. Further attempts to

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(1) C. S. Marvel and C. G. Overberger, *J. Am. Chem. Soc.*, **67**, 2250 (1945).

(2) W. S. Emerson, J. W. Heyd, H. E. Lucas, E. C. Chapin, G. R. Owen, and R. W. Shortridge, *J. Am. Chem. Soc.*, **68**, 674 (1946). *Cf.* the recent papers by J. Cazes, *Compt. Rend. Acad. Sciences*, **247**, 1874 (1958) and G. S. Kolesnikov and T. A. Soboleva, *Izvest. Akad. Nauk S.S.S.R., otdel Khim. Nauk*, 762 (1958); *Chem. Abstr.*, **52**, 20025 (1958).

(3) Such cases have been observed before. See A. L. Wilds, *Org. Reactions*, II, 190 (1944).

(3a) The polymer of methacroylacetone has been described recently by R. Teyssié and G. Smets, *Makromol. Chem.*, **26**, 245 (1958).

prepare polymers that exhibit specific chelating properties have been abandoned.

In the course of this study, we have tried in vain to replace—by means of metallic lithium or butyl lithium—the bromine atom in methyl *p*-bromophenylacetate and *p*-bromobenzoate and in *p*-bromophenylmethylcarbinol.[4]

EXPERIMENTAL

p-Ethylbenzoic acid. From 400 g. of sodium hydroxide in 3.4 l. of water and 290 g. of bromine a solution of sodium hypobromite was prepared at a temperature not exceeding 5°, and 195 g. of *p*-ethylacetophenone[5] was added within 1 hr. and at a temperature of 0 to 5°. The stirring was continued for 1 hr. at 35° and the solution gently heated to 90°, so that the bromoform formed could evaporate (2 hr.). The solution was cooled, treated with a solution of 30 g. of sodium bisulfite in 200 ml. of water, freed from colored impurities by extraction with ligroin (60–90°), and acidified. After recrystallization from alcohol or cyclohexane, the compound melted at 112°; its yield was 153 g. (79%). The *methyl ester*[6] boiled at 121–123° (20 mm.) [lit.[2] 127–130° (24 mm.)]; it was obtained in 91% yield.

Methyl p-(α-bromoethyl)benzoate (III, R = Br). A mixture of 148 g. of the foregoing ester, 160 g. of *N*-bromosuccinimide, 0.1 g. of benzoyl peroxide, and 600 ml. of carbon tetrachloride was refluxed for 45 min., filtered, and distilled. The compound boiled at 135–138° (1 mm.) with slight decomposition; yield, 180 g. (82%).

p-(α-Ethoxyethyl)benzoic acid. To a cold solution of 24 g. of potassium hydroxide in 40 ml. of ethanol, 24 g. of the foregoing ester was added. The mixture was refluxed for 2 hr., filtered, and acidified with an excess of 10% hydrochloric acid. The acid (14 g.; 43%) crystallized nicely from aqueous alcohol and melted at 105°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 67.8; H, 6.8.

p-Acetylbenzoic acid (IV). A mixture of 288 g. of *p*-methylacetophenone, prepared in analogy to the *p*-ethyl compound[5] in 95% yield, 60 g. of magnesium sulfate, and 3 l. of water was heated at 60° and 158 g. of potassium permanganate (less than the theoretical quantity!) added in portions of about 30 g. with stirring, so that a new portion was only added when the preceding one had been completely reduced. (The reaction is strongly exothermic and has to be checked with cold water from time to time.) The reaction mixture was acidified with dilute sulfuric acid, the manganese dioxide reduced with a saturated solution of sodium bisulfite, the solution cooled to 5°, and the solid filtered and washed with petroleum ether (100–120°). Recrystallization from water gave 72 g. of IV, m.p. 200–201°.

From the filtrate (two phases), 180 g. of *p*-methylacetophenone was recovered by extraction with petroleum ether. It is not advisable to increase the conversion by using an excess of the oxidant or more stringent conditions; this only leads to the formation of terephthalic acid. The *methyl ester* was prepared by the method of Clinton and Laskowski[6] in 89% yield. It formed, after recrystallization from carbon tetrachloride or hexane, colorless plates of m.p. 93–94°.[2]

Methyl p-(α-hydroxyethyl)benzoate (III, R = OH). To a suspension of 87 g. of the methyl ester of (IV) in 300 ml. of ether, a solution of 5 g. of sodium borohydride in 28 ml. of anhydrous methanol was added slowly (20 min.) with agitation and cooling with ice water. The reaction was continued for 4 hr. and the mixture acidified with 10% hydrochloric acid. The layers were separated and the aqueous phase extracted with ether. The product (yield, 64 g., 73%) boiled at 134° (3 mm.) [lit.[2]: 134° (4 mm.)].

Methyl p-vinylbenzoate. The following conditions, if strictly adhered to, give optimum yields. A Claisen flask of 25-ml. capacity (for the distillation of solids) was half filled with anhydrous potassium hydrogen sulfate and in a vacuum of 1–2 mm. heated at 200–215° for 15 min. Through a dropping funnel (tip inside the salt layer!) 18.5 g. of (III, R = OH) was added within about 2 hr., so that the temperature of the distilling vapors did not exceed 90° (at 1 mm.) and the potassium salt remained dry all the time. The distillate was redistilled; it boiled at 87° (1 mm.) and showed a m.p. of 36° (lit.[2]: m.p. 35–36.5°). The yield was 14 g. (84%).

p-Vinyl-benzoylacetone (VII). Following the method of Swamer and Hauser,[7] a solution of 16 g. of methyl *p*-vinylbenzoate and 9 g. of acetone in 50 ml. of ether was added to a suspension of 2.4 g. of sodium hydride in 250 ml. of ether at 0° and in an atmosphere of nitrogen. When the reaction had subsided, the stirring was continued for 4 hr. at 0° and 15 hr. at room temperature. The product was decomposed with 5 ml. of methanol at −10° and acidified with 7 ml. of glacial acetic acid at 0°. The ethereal solution was filtered, washed with sodium bicarbonate solution and water, dried, and distilled. The product (yield, 3 g., 16%) boiled at 123–125° (1.5 mm.). 35% of the starting material was recovered.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.0; H, 6.4.

Polymeric ethyl α-(p-vinylbenzoyl)-acetoacetate (VIII). (*a*) The hydrolysis of 16 g. of methyl *p*-vinylbenzoate was carried out at room temperature with a solution of 8 g. of sodium hydroxide in 80 ml. of anhydrous ethanol and in the presence of 0.1 g. of copper powder. After 24 hr., the sodium salt was filtered, dried, dissolved in 20 ml. of water, and acidified. *p*-Vinylbenzoic acid (I), recrystallized from aqueous alcohol, melted at 142°[1]; its yield was 12 g. (81%).

(*b*) *p-Vinylbenzoyl chloride* was prepared in benzene solution from 17 g. of sodium *p*-vinylbenzoate and 15 g. of oxalyl chloride in 100 ml. of benzene in the presence of 0.1 g. of copper powder. After 3 hr., the benzene was evaporated *in vacuo*, replaced twice by fresh benzene, and the operation repeated. The benzene solution was used eventually for the next step.

(*c*) Following the method of Viscontini and Merckling,[8] the magnesium enolate was prepared from 13 g. of ethyl acetoacetate, and at 0–10° the chloride prepared from 17 g. of sodium *p*-vinylbenzoate added. After 12 hr., the product was decomposed with 10% sulfuric acid and the ethereal solution washed with water, sodium bicarbonate solution, and again water, and dried, and the solvent distilled. A viscous polymer was obtained which initially gave the color reaction with ferric chloride and a green copper complex; after a short time it became hard, and the color reactions were negative. Analysis showed that the product had the expected composition. Yield was 81%.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.8; H, 6.8.

Methyl p-acetylphenylacetate (V). At 0° and with agitation, 150 g. of methyl phenylacetate, prepared by the method of Clinton and Laskowski[6] (b.p. 119°/25 mm.; 94%) was added slowly to a suspension of 293 g. of aluminum chloride in 600 ml. of carbon disulfide. To the product, which consisted of 2 liquid layers, 94 g. of acetyl chloride was added within about 90 min. and the mixture refluxed for 10 hr. and decomposed with 2 kg. of ice and 1 l. of concentrated hydrochloric acid. The organic layer was washed with 10% hydro-

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[4] Successful experiments of this kind, though not in very good yield, have been reported by R. G. Jones and H. Gilman, *Org. Reactions*, **VI**, 339 (1951).

[5] D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).

[6] Prepared by the method of R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

[7] F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).

[8] M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).

chloric acid, water, 10% sodium carbonate solution, and again water, dried, and distilled. The product, which was obtained in 66% yield (128 g.), boiled at 136° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 69.0; H, 6.4.

Oxidation to terephthalic acid. A mixture of 2 g. of (V), 1 g. of sodium carbonate, 8 g. of potassium permanganate, and 100 ml. of water was refluxed for 30 min. The solution was filtered and acidified; yield of terephthalic acid, 1.2 g. (76%). The product was identified by the mixed m.p. of its dimethyl ester with an authentic specimen.

Methyl p-(α-isopropoxyethyl)-phenylacetate. A mixture of 192 g. of V, 224 g. of aluminum isopropoxide, and 1500 ml. of isopropyl alcohol was heated in a column in the usual manner, until no more acetone appeared in the distillate. Then the excess isopropyl alcohol was distilled off and the residue treated with 700 ml. of water, 400 ml. of concentrated hydrochloric acid, and 50 ml. of benzene. The product was extracted with ether; it boiled at 140–160° (0.05 mm.) and, on redistillation, at 148° (0.05 mm.). Its yield was 135 g. (57%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5. Found: C, 71.4; H, 8.3.

Methyl p-(α-hydroxyethyl)-phenylacetate (VI). In the manner described for the preparation of III (R = OH), 192 g. of V in 600 ml. of ether was reduced with 10 g. of sodium borohydride in 50 ml. of methanol. The product (153 g., 79%) boiled at 144° (2 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 68.2; H, 7.6.

Methyl p-vinylphenylacetate (*as* II). In the manner described above, 19.5 g. of VI was dehydrated over potassium hydrogen sulfate. The unsaturated ester, of which 16 g. (91%) was obtained, boiled at 107° (2 mm.).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 75.1; H, 6.5.

p-Vinylphenylacetic acid (V). A mixture of 39 g. of the foregoing ester, 17 g. of potassium hydroxide in 100 ml. of anhydrous ethanol, and 0.2 g. of copper powder was kept at room temperature for 24 hr. The alcohol was distilled *in vacuo* and the residue acidified with cold dilute sulfuric acid. Successive recrystallization from aqueous ethanol and petroleum ether gave 30 g. (92%) of the desired acid, which melted at 101°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C 74.1; H, 6.1.

Ethyl α-(p-vinylphenylacetyl)acetoacetate (IX). In the manner described for the synthesis of VIII, the chloride of (II) was prepared from 20 g. of potassium *p*-vinylphenylacetate and 15 g. of oxalyl chloride in 100 ml. of benzene and the solution added to the magnesium enolate of 13 g. of ethyl acetoacetate. After 12 hr. at room temperature, the product was worked up. Two distillations gave the pure ester IX, b.p. 144° (0.4 mm.) in a yield of 9 g. (30%); the residue was polymeric.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.8.

An attempt to prepare the copper chelate from the crude product gave a dark green solution which, however, polymerized almost instantaneously. Also in the condensation of methyl *p*-vinylphenylacetate and acetone, in the presence of sodium hydride, most of the ester that reacted was converted into a polymer, and only a very small fraction boiling at 143–149° (1.5 mm.) was obtained, which gave the ferric chloride reaction expected of (*p*-vinylphenylacetyl)-acetone.

p-Bromophenylacetic acid, purified by sublimation and then melting at 114°, was prepared from *p*-bromoacetophenone[9] by the method of Schwenk and Bloch[10]; the yield was 20%, when the time of the hydrolysis of the thiomorpholide was extended to 25 hr.

Ethyl p-Bromophenylacetate was prepared as usual and boiled at 152° (22 mm.).

Methyl p-Bromobenzoate was obtained from the acid by the method of Clinton and Laskowski[6] in 92% yield (after recrystallization from ligroin it melted at 79–80°), and *p-bromophenyl-methyl-carbinol* according to Ziegler and Tiemann.[11] None of these substances exchanged the bromine atom for lithium, when treated with lithium metal or butyl lithium in ethereal solution.

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(9) R. Adams and C. R. Noller, *Org. Syntheses*, **Coll. Vol. I,** 109 (1941).

(10) E. Schwenk and E. Bloch, *J. Am. Chem. Soc.*, **64,** 3051 (1942).

(11) K. Ziegler and P. Tiemann, *Ber.*, **55,** 3406 (1922).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Friedel-Crafts Acylations of 1-Phenyl-2,5-dimethylpyrrole and 1,2-Diphenyl-5-methylpyrrole

RICHARD RIPS AND N. P. BUU-HOÏ

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Friedel-Crafts acylations of 1-phenyl-2,5-dimethylpyrrole yield diketones when acetyl and propionyl chloride are used, and both mono- and di-ketones with benzoyl and anisoyl chloride. On the other hand, 1,2-diphenyl-5-methylpyrrole gives predominantly monoketones with both types of acid chlorides, substitution occurring at the 4-position. Condensation of 3,4-diacylpyrroles with hydrazine hydrate leads to derivatives of 5,6-diazaisoindole, a new heterocyclic nucleus analogous to purine.

Although the pharmacological potentialities of the pyrrole nucleus have not yet been thoroughly investigated, several compounds in this series have already shown promising activity as possible antispasmodics and sedatives.[1] For further work in this field, pyrrole ketones represent convenient intermediates, and Friedel-Crafts acylations of some 1,2,5-trisubstituted pyrroles have therefore been investigated. 1-Phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II), readily prepared by Knorr-Paal condensation of aniline with

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(1) *Cf.* N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press; E. Cionga, *Compt. rend.*, **200,** 780 (1935).