

Potential Fibrinolytic Agents: Versatile Synthetic Route to Novel 4-(Branched alkyl)benzoic Acids *via* β -Monosubstituted or β,β -Disubstituted Styrene-4-carboxylic Acids

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Abstract □ A versatile and unambiguous synthetic route to some novel 4-(branched alkyl)benzoic acids *via* their β -monosubstituted or β,β -disubstituted styrene-4-carboxylic acid precursors is described. The procedure starts with readily available aldehydes or ketones and the common intermediate *p*-bromobenzyltriphenylphosphonium bromide in a Wittig reaction and proceeds in good yield through *p*-bromostyrene and *p*-cyanostyrene intermediates. Several benzoic acid derivatives were of potential biological interest as fibrinolytic agents.

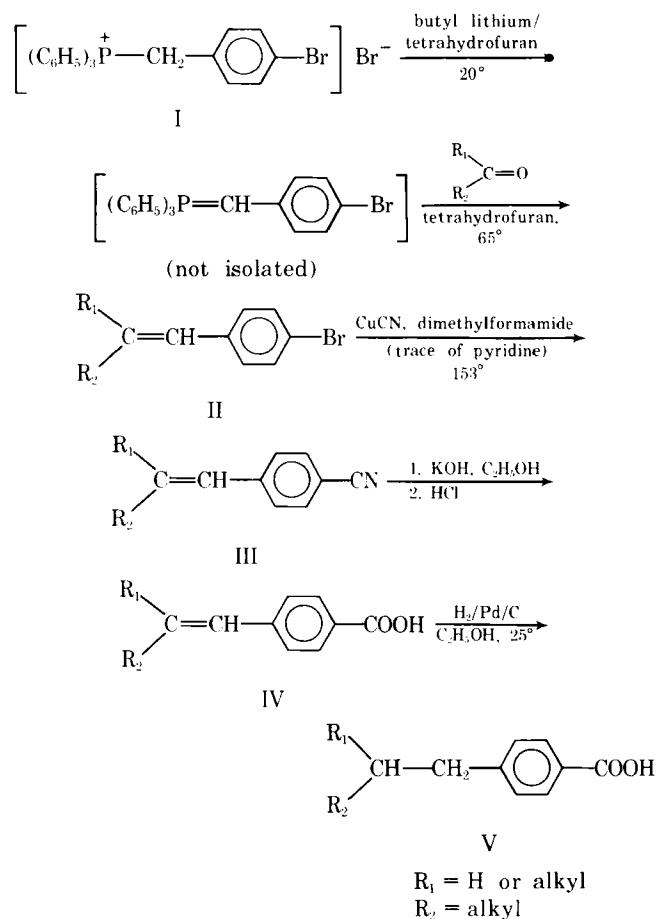
Keyphrases □ 4-Alkylbenzoic acids, branched—synthesis *via* β -mono- or β,β -disubstituted styrene-4-carboxylic acids, potential fibrinolytic agents □ Styrene-4-carboxylic acids, β -mono- and β,β -disubstituted—precursors in synthesis of 4-(branched alkyl)benzoic acids, potential fibrinolytic agents □ Fibrinolytic agents, potential—synthesis of 4-(branched alkyl)benzoic acids *via* β -mono- or β,β -disubstituted styrene-4-carboxylic acids

This report describes an unambiguous synthetic route to some novel 4-(branched alkyl)benzoic acids and their β -monosubstituted or β,β -disubstituted styrene-4-carboxylic acid precursors, starting from readily available symmetrical or unsymmetrical dialkyl ketones or carboxaldehydes and *p*-bromobenzyltriphenylphosphonium bromide in a Wittig reaction (Scheme I). Such compounds were of interest because of anticipated activity in the activation of the fibrinolytic system for the dissolution of fibrin blood clots. This interest was generated by observations that many compounds with similar features (*i.e.*, aromatic acids with bulky substituent groups such as *o*-thymotic acid) exhibited fibrinolytic activity in an *in vitro* test system involving plasminogen activation (1). Test results, however, subsequently indicated activity for derivatives IV and V only at levels judged too high for potential therapeutic utility (see *Experimental*).

DISCUSSION

An interest in benzoic acids substituted in the *para*-position with a branched hydrocarbon moiety quickly led to the finding that very few such compounds had been reported. In fact, nearly all *p*-alkylbenzoic acids previously reported are *n*-alkyl compounds (2-5), simple three- to five-carbon branched alkyl derivatives (3, 6), or, in a few cases, highly symmetrical larger branched chain compounds (such as that with a 2,2,4,4-tetramethylpentyl substituent) (3, 6, 7).

The only generally applicable synthetic procedures for preparing saturated compounds appear to be those involving Friedel-Crafts *para*-acetylation of alkylbenzenes, followed by oxidative degradation of the acetyl group to a carboxyl group or *para*-acylation (or alkylation) of toluene, followed by oxidation of the methyl group to a carboxyl group. As expected, these procedures may be complicated in the Friedel-Crafts step by benzene ring position isomerization, dialkylation or dealkylation, or isomerization in the



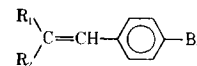
Scheme I

side chain (8-11). Also less than desirable are low yield oxidation procedures and often high temperature catalytic oxidations (3, 4, 6, 7).

The synthesis of unsaturated styrene carboxylic acids usually involves dehydration of an alcohol, which, with β -substituted compounds, might proceed in more than one manner to give contaminating double bond isomers.

The synthetic route (Scheme I) starts with the phosphonium salt *p*-bromobenzyltriphenylphosphonium bromide (I). Treatment of I in tetrahydrofuran with butyl lithium at 25° affords the orange phosphorane solution to which either a straight chain or branched aldehyde or unhindered straight chain or branched ketone is added, giving the *p*-bromostyrene (II), normally after refluxing several hours in tetrahydrofuran. Compounds and yields prepared by this method are shown in Table I.

Conversion of the bromo compounds (II) to the corresponding nitriles (III) with cuprous cyanide in refluxing dimethylformamide (trace of pyridine) proceeds smoothly, affording products and yields listed in Table II. Hydrolysis of the nitriles (III) to the unsaturated acids (IV) is readily accomplished with potassium hydroxide in refluxing ethanol (Table III). Where the unsaturated acids (IV) are *cis-trans*-isomer mixtures (*i.e.*, R₁ = R₂) (not shown

Table I—Properties of β -Substituted 4-Bromostyrenes

Compound	R ₁	R ₂	Empirical Formula	Boiling Point (mm)	Yield, % from I	Purity by Vapor Phase Chromatography
IIa	Ethyl	Ethyl	C ₁₂ H ₁₅ Br	88.5–89° (0.7)	65.3	98
IIb	<i>n</i> -Propyl	<i>n</i> -Propyl	C ₁₄ H ₁₉ Br	101° (0.6)	52.0	97
IIc	<i>n</i> -Butyl	<i>n</i> -Butyl	C ₁₆ H ₂₃ Br	136–139° (1.2)	42.0	99
IIc	Pentamethylene	Pentamethylene	C ₁₃ H ₁₅ Br	103–104° (0.4)	61.5	96
IIe	<i>n</i> -Propyl	<i>n</i> -Pentyl	C ₁₆ H ₂₃ Br	135–136° (1.0)	39.7	99 ^a
IIf	Hydrogen	3-(<i>n</i> -Heptyl)	C ₁₅ H ₂₁ Br	125–128° (1.3)	75	87, 99 ^a
IIg	Hydrogen	3-(<i>n</i> -Pentyl)	C ₁₃ H ₁₇ Br	114–116° (2.5)	60	99 ^a
					(estimated accidental loss)	
IIh	Hydrogen	Cyclohexyl	C ₁₄ H ₁₇ Br	120–145° (1.0)	61.3	92, 100 ^a
IIi	Hydrogen	α -Naphthyl	C ₁₈ H ₁₃ Br	mp 103–107°	~20	Homogeneous ^a TLC
IIj	Hydrogen	β -Naphthyl	C ₁₈ H ₁₃ Br	mp 70–74°	~32	Homogeneous ^a TLC
				ethanol		
				ethanol		

^a *cis-trans*-Isomer mixtures.

in Table III), these materials are hydrogenated directly to the saturated acids (V) (Table IV), as are the purified unsaturated acids (IV). Nearly quantitative yields are observed in the hydrogenation step.

Several points concerning this synthetic scheme and the compounds prepared thereby deserve special mention. Of primary significance is the fact that the route outlined is simple and completely unambiguous with regard to the position of the double bond in the unsaturated acids produced; moreover, it allows for no isomerization of alkyl groupings. Therefore, it appears to have distinct advantages over routes utilizing Friedel-Crafts reactions or possible ones involving alcohol formation through a Grignard-type reaction, followed by formation of a double bond through elimination of water or a halogen acid. Success of the latter approach seems unlikely. Great difficulty was experienced in preparing Grignard reagents from secondary alkyl halides (particularly with large alkyl groups) to add to *p*-bromobenzaldehyde. Likewise, the successful use of alkyl ketones or aldehydes to add to a 4-substituted benzyl magnesium halide appears doubtful because of a complicating *para*-substituent (*i.e.*, halogen, cyano, or ester).

With bromo intermediates (II), nitriles (III), and unsaturated acids (IV), where R₁ = R₂, varying mixtures of *cis-trans*-isomers

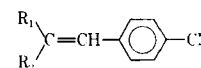
were observed, and relative proportions could be quantitatively estimated by vapor phase chromatography in the cases of II and III. No attempt was made to separate isomers on a preparative scale; however, monitoring of distillation fractions indicated that this would probably be feasible in most cases.

Attempted use of the phosphonium salt 4-cyanobenzyltriphenylphosphonium bromide as the Wittig reactant in place of the 4-bromo compound failed completely, presumably because of the deleterious effect of the electron-withdrawing cyano group on the nucleophilic reactivity of the ylid carbon atom. The use of ketones branched on the α -carbon atoms (*i.e.*, 3,5-dimethyl-4-heptanone or phenyl *n*-heptyl ketone) retarded the reaction under conditions employed (refluxing tetrahydrofuran) to such an extent that synthetic utility was eliminated.

Preparation of the unsaturated acid (IVa) by reaction of *p*-bromostyrene (IIa) with magnesium and subsequent carbonation afforded small amounts of product; however, dissolution of magnesium was very sluggish and this route was abandoned.

Attempted hydrolysis of *p*-cyanostyrenes (III) with hydrochloric acid rather than base led rapidly to extensive decomposition of the starting material and none of the desired products.

It appears from the examples discussed that this synthetic route

Table II—Properties of β -Substituted *p*-Cyanostyrenes

Compound	R ₁	R ₂	Boiling Point (mm)	Yield, % from II	Purity by Vapor Phase Chromatography	Empirical Formula	Analysis, % ^a	
							Calc.	Found
IIIa	Ethyl	Ethyl	85–86° (0.1)	84.1	99+	C ₁₃ H ₁₅ N	C 84.28 H 8.16 N 7.56	84.07 7.93 7.70
IIIb	<i>n</i> -Propyl	<i>n</i> -Propyl	115–117° (0.3)	70.5	100	C ₁₅ H ₁₉ N	—	—
IIIc	<i>n</i> -Butyl	<i>n</i> -Butyl	135–136° (0.4)	58.5	96–98	C ₁₇ H ₂₃ N	—	—
IIId	Pentamethylene	Pentamethylene	128–129° (0.8) mp 37–38°	55.9	99+	C ₁₄ H ₁₅ N	C 85.23 H 7.66 N 7.10	84.97 7.47 7.21
IIIe	<i>n</i> -Propyl	<i>n</i> -Pentyl	128–130° (0.1)	84.2	— ^b	C ₁₇ H ₂₃ N	—	—
IIIf	Hydrogen	3-(<i>n</i> -Heptyl)	105–112° (0.2)	79	87 ^b	C ₁₆ H ₂₁ N	—	—
IIIg	Hydrogen	3-(<i>n</i> -Pentyl)	108–114° (0.7)	70.3	100 ^b	C ₁₄ H ₁₇ N	C 84.37 H 8.60 N 7.03	84.46 8.25 7.18
IIIh	Hydrogen	Cyclohexyl	110–115° (0.1)	51	100 ^b	C ₁₅ H ₁₇ N	C 85.26 H 8.11 N 6.63	85.19 7.92 6.78
IIIi	Hydrogen	α -Naphthyl	Crude solid not purified	80	— ^b	C ₁₉ H ₁₃ N	—	—
IIIj	Hydrogen	β -Naphthyl	Crude solid not purified	79	— ^b	C ₁₉ H ₁₃ N	—	—

^a Satisfactory analytical data ($\pm 0.4\%$ for C, H, and N) were reported for IIIa, IIId, IIIg, and IIIh. Other compounds were converted to the acids (IV). ^b *cis-trans*-Isomer mixtures.

Table III—Styrene-4-carboxylic Acids (IV)^a

Compound	R ₁	R ₂	Melting Point	Yield, % from III	Empirical Formula	Analysis, % ^b	
						Calc.	Found
IVa	Ethyl	Ethyl	129–133°	73.5	C ₁₃ H ₁₆ O ₂	C 76.44 H 7.90	76.42 7.72
IVb	<i>n</i> -Propyl	<i>n</i> -Propyl	107.5–109°	73.7	C ₁₅ H ₂₀ O ₂	C 77.55 H 8.68	77.47 8.32
IVc	<i>n</i> -Butyl	<i>n</i> -Butyl	97.5–99°	85.7	C ₁₇ H ₂₄ O	C 78.42 H 9.29	78.16 8.95
IVd	Pentamethylene		180–182°	76.5	C ₁₄ H ₁₆ O ₂	C 77.75 H 7.46	77.99 7.40

^a Contains only purified "symmetrical" acids (i.e., R₁ = R₂). ^b Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds in the table.

Table IV—Saturated 4-Alkylbenzoic Acids (V)

Compound	R ₁	R ₂	Melting Point	Yield, % from III or IV	Empirical Formula	Analysis, % ^a	
						Calc.	Found
Va	Ethyl	Ethyl	134.5–136°	91.5 ^b	C ₁₃ H ₁₈ O ₂	C 75.69 H 8.79	76.00 8.69
Vb	<i>n</i> -Propyl	<i>n</i> -Propyl	142.5–144°	83.5 ^b	C ₁₅ H ₂₂ O ₂	C 76.88 H 9.46	77.27 9.09
Vc	<i>n</i> -Butyl	<i>n</i> -Butyl	121–122°	88.8 ^b	C ₁₇ H ₂₆ O ₂	C 77.81 H 9.99	77.42 9.71
Vd	Pentamethylene		180.5–182°	90 ^{+b}	C ₁₄ H ₁₈ O ₂	C 77.03 H 8.31	77.54 8.06
Ve	<i>n</i> -Propyl	<i>n</i> -Pentyl	106.5–107.5°	75.1 ^c	C ₁₇ H ₂₆ O ₂	C 77.81 H 9.99	78.17 9.46
Vf	Hydrogen	3-(<i>n</i> -Heptyl)	81–82°	57.7 ^c	C ₁₆ H ₂₄ O ₂	C 77.37 H 9.74	77.51 9.48
Vg	Hydrogen	3-(<i>n</i> -Pentyl)	125.5–126.5°	76.3 ^c	C ₁₄ H ₂₀ O ₂	C 76.32 H 9.15	76.45 8.93
Vh	Hydrogen	Cyclohexyl	178.5–180°	71.0 ^c	C ₁₅ H ₂₀ O ₂	C 77.55 H 8.68	77.83 8.57
Vi	Hydrogen	α -Naphthyl	175–176°	50.5 ^c	C ₁₉ H ₁₆ O ₂	C 82.58 H 5.84	82.44 5.83
Vj	Hydrogen	β -Naphthyl	206.5–208°	66.4 ^c	C ₁₉ H ₁₆ O ₂	C 82.58 H 5.84	82.51 5.93

^a See Footnote *b*, Table III. ^b From IV. ^c From III.

will be general for aldehydes, including those branched in the α -position, and for ketones, except those with α -branching, at least under the reaction conditions employed in these experiments. It seems reasonable that *meta*-substituted acids also could be readily produced by this method, starting with *m*-bromotoluene.

It may be possible to employ this method for the synthesis of 4-alkylbenzoic acids or styrene carboxylic acids with branching on the α -position of the *para*-substituent, starting with an α -branched *p*-bromobenzyl bromide. However, α -substituents, particularly if large, may hinder successful completion of the Wittig reaction.

EXPERIMENTAL¹

Chemical Synthesis—*p*-Bromobenzyl bromide, mp 60–61.5°, was prepared from *p*-bromotoluene² according to the method of Weizmann and Patai (12). The reaction of this material with triphenylphosphine² in toluene, according to the procedure of Hoffmann (13), gave the phosphonium salt (I), mp 278°, which was

¹ All melting points were determined using a Thomas-Hoover Uni-Melt capillary melting-point apparatus and are uncorrected. NMR spectra were obtained using a Varian A60-A NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from an internal tetramethylsilane standard. Vapor phase chromatography was done on an F&M model 810 instrument, employing a 0.6-cm \times 1.8-m (0.25-in. \times 6-ft) glass column of 5% QF-1 on acid-washed dimethylchlorosilane on Chromosorb BG (100–120 mesh).

² Aldrich Chemical Co.

dried *in vacuo* and stored over phosphorus pentoxide. All ketones and aldehydes were freshly distilled, their purity was determined by vapor phase chromatography, and they were stored under nitrogen over 4A molecular sieves. The solvents used (tetrahydrofuran and dimethylformamide) were distilled and stored over 4A molecular sieves.

Wittig Reaction: 4-(2-Ethyl-1-buten-1-yl)bromobenzene (IIa)—To a stirred suspension of 32.8 g (64 mmoles) of *p*-bromobenzyltriphenylphosphonium bromide (I) in 80 ml of dry distilled tetrahydrofuran (under nitrogen) was added, over 30 min, 40 ml of 1.60 *N* *n*-butyl lithium in hexane (64 mmoles); the temperature was kept between 20 and 25°. The highly colored (orange-yellow) suspension was stirred for an additional 1 hr, 100 mg of benzoic acid was added, and 6.55 g (76 mmoles, 20% excess) of freshly distilled diethyl ketone was added dropwise over 30 min. Little if any temperature increase was observed.

The mixture was then heated to reflux for 24 hr under nitrogen, during which time the color gradually faded. The mixture was neutralized with a small amount of dilute hydrochloric acid, the solvent was removed *in vacuo*, and the residue was steam distilled until the distillate was clear. The combined distillates were extracted with ether; the extracts were dried over magnesium sulfate, filtered, and evaporated to a yellow oil. Vacuum distillation afforded a small amount of starting diethyl ketone in early fractions and then 10.0 g (65.3%) of a colorless oil, bp 88.5–89° (0.7 mm). The material was estimated to have a purity of 98% by vapor phase chromatography; IR (near): 1630 (weak, double bond) cm⁻¹ and no evidence of carbonyl absorption.

Although all Wittig reaction mixtures were refluxed for about 24 hr, reactions with aldehydes appeared to proceed quite rapidly, even at room temperature, as judged by the fading of the phosphorane color. With ketones, the addition of a trace of benzoic acid appeared to catalyze the reaction significantly. All *p*-bromostyrenes were separated from the by-product triphenylphosphine oxide by steam distillation except III and IIj, which were not volatile. In these cases, materials were purified by fractional crystallization from ethanol or chloroform-hexane mixtures. The purity of the *p*-bromostyrenes (IIa-IIIh) was estimated by vapor phase chromatography. Good resolution of *cis*-*trans*-isomers was achieved with IIe-IIIh, and relative quantities of each in various distillation fractions could be estimated readily from peak areas.

Nitrile Preparation: 4-(2-Ethyl-1-buten-1-yl)benzonitrile (IIIa)—A mixture of 4.78 g (20 mmoles) of IIa (98% pure by vapor phase chromatography), 2.0 g (22 mmoles) of cupric cyanide, 20 ml of dry dimethylformamide, and 12 drops of pyridine was heated to reflux in an oil bath (180°) for 20 hr under nitrogen. The dark mixture (suspension) was cooled and poured into a mixture of 40 ml of concentrated ammonium hydroxide and 40 g of ice. The mixture was extracted thoroughly with ether, and more cold aqueous ammonium hydroxide was added until the solids were completely dissolved. The combined ether extracts were washed thoroughly with dilute ammonium hydroxide, water, 3 N HCl, saturated sodium bicarbonate, and water and then were finally dried over magnesium sulfate.

Evaporation of the filtered ether extracts left a brown liquid, which was distilled *in vacuo*, giving a main fraction of 3.12 g (84.1%) of nearly colorless liquid, bp 102–103° (0.6 mm). Vapor phase chromatography indicated greater than 99% purity. The material was redistilled for analysis, bp 85–86° (0.1 mm); IR (KBr): 1635 (C=C, s) and 2220 (C≡N, vs) cm^{-1} .

Anal.—Calc. for $\text{C}_{13}\text{H}_{15}\text{N}$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.07; H, 7.93; N, 7.70.

The nitriles prepared were examined for homogeneity by vapor phase chromatography (Table II). In IIIf–IIIh, it was readily possible also to resolve *cis*- and *trans*-isomers and to estimate relative percentages of each in crude materials and various distillation fractions. NMR spectra of nitriles supported fully the assigned structures.

Nitrile Hydrolysis to Unsaturated Acids: 4-(2-Ethyl-1-buten-1-yl)benzoic Acid (IVa)—To a solution of 3.0 g of potassium hydroxide in 15 ml of ethanol were added 1.50 g (8.1 mmoles) of IIIa and 10 mg of hydroquinone, and the mixture was heated to reflux in a stainless steel flask overnight. After the addition of 20 ml of water, ethanol was removed *in vacuo* and the aqueous solution was chilled and acidified with 6 ml of concentrated hydrochloric acid. The copious white precipitate was extracted into several portions of ether, and the combined extracts were dried over magnesium sulfate.

Filtration and evaporation of the filtrates left 1.57 g of white solid, mp 121–128°. Recrystallization from acetonitrile and finally sublimation at 90–100° (0.1 mm) gave the analytically pure material, mp 129–133° (1.21 g, 73.5%); TLC [fluorescent silica, benzene-dioxane-acetic acid (90:25:4)]: R_f 0.52; NMR (deuteriochloroform): δ 0.93 (t, 3H, $J = 7$ Hz, CH_3), 0.97 (t, 3H, $J = 7$ Hz, CH_3), 2.09 (q, 2H, $J = 7$ Hz, CH_2), 2.15 (q, 2H, $J = 7$ Hz, CH_2)³, 6.15 (s, 1H, vinyl proton), 7.18 (d, 2H, $J = 8$ Hz, protons *ortho* to alkyl group), 7.97 (d, 2H, $J = 8$ Hz, protons *ortho* to carboxyl group), and 12.43 (s, 1H, carboxyl) ppm; IR (KBr): 1670 (COOH) and 1645 (sh) (double bond) cm^{-1} .

Anal.—Calc. for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C, 76.44; H, 7.90. Found: C, 76.42; H, 7.72.

All "symmetrical" unsaturated acids (IVa–IVd) were highly crystalline and were purified easily by sublimation or recrystallization from acetonitrile or ethanol. Nonsymmetrical unsaturated acids all appeared to be mixtures of *cis*-*trans*-isomers and were noncrystalline or broadly melting solids. Their purity, however, was judged as good by TLC and all were hydrogenated readily to crystalline saturated acids (Ve–Vj). Attempted hydrolysis of unsaturated nitriles with strong mineral acid rather than base led to extensive decomposition and was completely unsuccessful.

Hydrogenation of Unsaturated to Saturated Acids: 4-(2-Ethyl-1-butyl)benzoic Acid (Va)—To a solution of 760 mg (3.7 mmoles) of IVa in 50 ml of 95% ethanol was added 100 mg of 5% Pd/C⁴. The mixture was shaken at room temperature on a Paar apparatus under an atmosphere of hydrogen at about 2.1 kg/cm² (30 lb/in.²). After 2 hr, the catalyst was removed by filtration through sintered glass, and the filtrate was evaporated *in vacuo*, leaving a white solid, mp 132.5–135°. Sublimation at 120° (0.5 mm) gave 700 mg (91.5%) of material, which was further purified by recrystallization from acetonitrile and sublimation, mp 134.5–135°; TLC [fluorescent silica, benzene-dioxane-acetic acid (90:25:4)]: R_f 0.62; NMR (deuteriochloroform): δ 0.7–1.8 (m, complex, 11H, $\text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3$), 2.62 (d, 2H, $J = 6$ Hz, CH_2), 7.23 (d, 2H, $J = 8$ Hz, aromatic protons *ortho* to alkyl substituent), 8.03 (d, 2H, $J = 8$ Hz, aromatic protons *ortho* to carboxyl group), and 12.28 (s, 1H, COOH) ppm; IR (KBr): 1670 (COOH) cm^{-1} .

Anal.—Calc. for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 76.69; H, 8.79. Found: C, 76.00, H, 8.69.

All saturated acids reported in Table IV were readily purified by sublimation and/or recrystallization from acetonitrile or ethanol. NMR spectra of all saturated acids supported completely the assigned structures.

Fibrinolytic Testing—Saturated and unsaturated compounds (IV and V) were tested utilizing the hanging clot method described by Baumgarten *et al.* (14). Measurable lytic activity was observed at levels of 1 mg/ml but not at lower levels normally required for activity in *in vivo* systems and for clinical utility (1).

REFERENCES

- (1) K. N. von Kualla, *Arzneim.-Forsch.*, **18**, 407(1968).
- (2) A. Zaki and H. Fahim, *J. Chem. Soc.*, **1942**, 308.
- (3) R. S. Barker and A. Saffer, U.S. pat. 2,966,515 (1961); through *Chem. Abstr.*, **55**, P17482h(1961).
- (4) J. B. Braunworth, U.S. pat. 3,046,305 (1963); through *Chem. Abstr.*, **57**, 16500c(1963).
- (5) S. Matsuda, M. Ogawa, and M. Nishishita, *Kogyo Kagaku Zasshi*, **60**, 600(1957).
- (6) G. W. Hearne, T. W. Evans, and V. W. Buls, U.S. pat. 2,478,654 (1952); through *Chem. Abstr.*, **46**, P6153(1952).
- (7) E. B. Sokolova, M. P. Shebanova, and V. I. Ishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **4**, 657(1961); through *Chem. Abstr.*, **56**, 7182(1962).
- (8) D. V. Nightingale and H. B. Hucker, *J. Org. Chem.*, **18**, 1529(1953).
- (9) D. V. Nightingale, H. B. Hucker, and O. L. Wright, *ibid.*, **18**, 244(1953).
- (10) H. Pines and A. W. Shaw, *ibid.*, **20**, 373(1955).
- (11) J. C. Butler, L. L. Ferstandig, and R. P. Clark, *J. Amer. Chem. Soc.*, **76**, 1906(1954).
- (12) M. Weizmann and S. Patai, *ibid.*, **68**, 150(1946).
- (13) H. Hoffmann, *Justus Liebigs Ann. Chem.*, **634**, 1(1959).
- (14) W. Baumgarten, J. L. Ciminera, and R. B. Cole, *Vox Sang.*, **5**, 416(1960).

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³ These two pairs of triplets and quartets overlap each other, being displaced from each other by only about 4–5 Hz. This presumably arises because one ethyl group is *trans* to the phenyl ring while the other is *cis* to it.

⁴ Engelhard.