white, amorphous appearing solid tinged with yellow, m. p. 123-125°; neut. equiv. 181, 183;  $[\alpha]^{25}D - 7.2$  (c, 3.7; H<sub>2</sub>O). A sample of the glucamine (2.6 g.) was dissolved in the least possible amount of hot absolute methanol, filtered hot, cooled in an ice-salt mixture and the curdy precipitate quickly filtered, pressed as dry as possible and dried *in vacuo* over phosphorus pentoxide. The white solid (2.02 g.) softened at 123° and melted indistinctly at 127-128°;  $[\alpha]^{25}D - 7.5$  (c, 2.7; H<sub>2</sub>O). The neut. equiv. was found to be 179 to 180° as compared with a value of 181 calculated for *d*-glucamine. The methanol filtrate was concentrated to yield an additional 0.33 g. of a slightly yellow solid, m. p. 127-128°. Roux gives for *d*glucamine m. p. 128°,  $[\alpha]^{15}D - 7.9$  (c, 10; H<sub>2</sub>O).

It seems unnecessary to detail the long series of experiments which were made in attempting to obtain pure glucamine. No definite information has been gained through them with respect to products of the hydrogenation other than glucamine. The hydrogenation goes smoothly and the neutral equivalent of the crude product indicates that 80% or more of the glucose has been converted to basic compounds. The use of the methods recommended by Roux and by Flint and Salzberg did not give us products which were pure, although it is rather simple to obtain a product in good yield which has a neutral equivalent in the vicinity of 200. Such products are unquestionably mixtures.

## Summary

d-Glucose in a methanol-ammonia solution reacts smoothly with hydrogen over Raney nickel at  $100-115^{\circ}$  at 150 atm. within less than an hour, to give a mixture of products, from which d-glucamine may be separated in 26% yield as the benzal derivative. Pure d-glucamine may be obtained quantitatively by the hydrolysis of the benzal derivative.

MADISON, WISCONSIN

**RECEIVED AUGUST 26, 1940** 

[Contribution from the College of Pharmacy, University of Michigan]

# Local Anesthetics in the Naphthalene Series<sup>1</sup>

BY F. F. BLICKE, H. C. PARKE AND E. L. JENNER

A short time  $ago^2$  we described the preparation of twenty-one dialkylaminoalkyl esters of 3-, 4-, 5and 6-amino-1-naphthoic acids. A number of these have been shown<sup>3</sup> to be strong local anesthetics.

In view of the very favorable properties of many esters in this series and in particular of  $\beta$ -diethylaminoethyl 4-amino-1-naphthoate, the naphthalene analog of procaine, our study has been extended to include certain dialkylaminoalkyl and dialkylaminoalkoxyalkyl<sup>4</sup> esters of 4-amino-1naphthoic, 5-amino-1-naphthoic and 5-amino-2naphthoic acids. Furthermore, a number of dialkylaminoalkylamides<sup>5</sup> of 4-amino-1-naphthoic acid have been prepared.<sup>6</sup>

In addition we have synthesized the di-4-aminobenzoyl derivative of ethyldi- $\beta$ -hydroxyethyl-

(1) We wish to express our indebtedness to Parke, Davis and Company, whose support made this investigation possible.

(2) Blicke and Parke, THIS JOURNAL, 61, 1200 (1939).

(4) Ruberg and Shriner (THIS JOURNAL, 57, 1581 (1935)) have shown that dialkylaminoalkoxyalkyl esters of 4-aminobenzoic acid are strong local anesthetics.

(5) A few alkyl- and dialkylamides of 4-aminobenzoic acid have been found by Wenker (*ibid.*, **60**, 1081 (1938)) to exhibit local anesthetic activity. The  $\beta$ -diethylaminoethylamide of 2-butoxyquinoline-4-carboxylic acid (nupercaine) has been on the market for some years.

(6) We wish to call attention to the recent publications of Cook and Hill (*ibid.*, **62**, 1995, 1998 (1940)) who have discovered the local anesthetic activities of esters of 2-dialkylamino-3-hydroxy- and 1-dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes. amine. Its relationship to procaine is apparent from the following formulas

$$\begin{array}{c} H_2N-C_6H_4-COO-CH_2CH_2\\H_2N-C_6H_4-COO-CH_2CH_2\\H_2N-C_6H_4-COO-CH_2CH_2\\H_2N-C_6H_4-COO-CH_2CH_2\\CH_3CH_2\\N-CH_2CH_3\\CH_3CH_2\\Procaine\end{array}$$

The esters and amides were obtained by interaction of the required dialkylamino alcohol or dialkylaminoamine and the nitro acid chloride with subsequent reduction of the nitro group in the nitro ester or nitro amide.

The hydrochlorides of the esters and amides have been tested pharmacologically by L. W. Rowe in the Parke, Davis and Company Laboratories and a detailed report will be published by him in another journal. All of the compounds exhibited activity to some degree but the amides were found to be much less satisfactory as local anesthetics than the esters.

The di-4-aminobenzoyl derivative of ethyldi- $\beta$ -hydroxyethyl-amine<sup>7</sup> is a weak anesthetic.

<sup>(3)</sup> Rowe, J. Am. Pharm. Assoc., 29, 241 (1940).

<sup>(7)</sup> Pyman (J. Chem. Soc., **93**, 1796 (1908)) stated that the corresponding dibenzoyl compound has very little local anesthetic action; the dibenzoyl derivative of methyldi- $(\gamma$ -hydroxypropyl)-amine, likewise, seems to be only slightly active (Wichura, Z. exptl. Path. Therap., **20**, 11 (1919)).

Dec., 1940

#### **Experimental Part**

 $\beta,\beta$ -Dimethyl- $\gamma$ -diethylaminopropyl alcohol was obtained by use of the method of Mannich, Lesser and Silten.<sup>8</sup>

α-Methyl-β-dibutylaminoethyl Alcohol.—A mixture of 29 g. of propylene oxide and 35 g. of anhydrous methyl alcohol was added, slowly, to 65 g. of dibutylamine which had been poured into a magnesium citrate bottle and cooled. The material was heated to  $45-50^{\circ}$  for four hours, the alcohol removed by distillation and the residue fractionated through a long column; b. p. 111–112° at 17 mm.; yield 80–85%.

 $\beta$ -( $\beta$ '-Diethylaminoethoxy)- and  $\beta$ -( $\beta$ '-Di-*n*-butylaminoethoxy)-ethyl Alcohol.—A mixture of 50 g. (0.4 mole) of diglycol chlorohydrin and 58.5 g. (0.8 mole) of diethylamine (or di-*n*-butylamine) was heated on a steam-bath for forty-eight hours, the mixture cooled and the precipitated diethylamine hydrochloride removed by filtration. The filtrate was diluted with ether, the solution treated with strong sodium hydroxide solution, the ether layer separated, dried over stick sodium hydroxide and the solvent removed.  $\beta$ -( $\beta$ '-Diethylaminoethoxy)-ethyl alcohol boiled at 101– 105° at 9 mm.<sup>10</sup> and  $\beta$ -( $\beta$ '-di-*n*-butylaminoethoxy)-ethyl alcohol at 142–144° at 11 mm.

 $\beta$ -Diethylaminoethylamine boiled at 143–144° and  $\gamma$ -diethylaminopropylamine at 164–166°.<sup>11</sup>

 $\gamma$  - (N - Piperidyl) - propylamine.<sup>12</sup>  $\gamma$  - Bromopropylphthalimide (1.92 moles) was prepared from trimethylene bromide according to the directions published for  $\beta$ bromoethylphthalimide.<sup>13</sup> To the phthalimide there was added 10 moles of piperidine, dissolved in 1400 cc. of xylene, the mixture refluxed for eight hours, the precipitated piperidine hydrobromide filtered and the filtrate distilled until the xylene and excess piperidine had been removed. The residue was mixed with 1.92 moles of sodium hydroxide, dissolved in 200 cc. of water, heated on a steam-bath for thirty-six hours and then treated with a mixture of 500 cc. of concd. hydrochloric acid and an equal volume of water. An additional two liters of concd. hydrochloric acid was added, the mixture refluxed for six hours, the precipitated phthalic acid filtered and the filtrate evaporated to dryness. The residue was dissolved in 600 cc. of water, 900 g. of solid sodium hydroxide added, the mixture extracted three times with 300 cc. portions of ether, the ether solution dried with stick sodium hydroxide, the solvent removed and the amine distilled; b. p. 201-203° at 740 mm.;<sup>14</sup> yield 210 g. (77%).

5-Nitro-2-naphthonitrile.—A solution of 47 g. of 5nitro-2-naphthylamine<sup>15</sup> in 200 cc. of acetic acid was treated with hydrogen chloride, the pasty mixture of the amine hydrochloride cooled to 15° and 45 cc. of freshly

- (9) Wenker (THIS JOURNAL,  $60,\ 158$  (1938)) found the boiling point to be  $130^\circ$  at 15 mm.
- (10) Horne and Shriner (*ibid*, **54**, 2925 (1932)), who obtained the alcohol from diethylamine and ethylene oxide, reported  $92-95^{\circ}$  at 7 mm.
- (11) Magidson and Grigorsky (*Ber.*, **69**, 401, 402 (1932)) found  $145-149^{\circ}$  for the former and  $162-165^{\circ}$  for the latter substance.

(12) Our preparative procedure is based on one used by Magidson, Grigorovskił and Gal'perin (J. Gen. Chem., U. S. S. R., **8**, 56 (1938); C. A., **32**, 5406 (1938), for another product.

(14) Lehmann (Ber., 27, 2177 (1894)) reported 204° at 751 mm.

prepared isoamyl nitrite added in one portion. The clear solution was poured, slowly, into 750 cc. of absolute ether which was stirred and maintained at  $0^{\circ}$ ; the precipitated, oily diazonium chloride solidified rapidly. The ether was decanted, the precipitate washed with ether and dissolved, immediately, in 1 liter of ice water.

To a solution of 188 g, of copper sulfate and 45 g, of sodium chloride in 750 cc. of hot water there was added slowly, with agitation, a solution of 38 g. of sodium hydrogen sulfite and 27 g. of sodium hydroxide in 375 cc. of water. The mixture was cooled, the supernatant liquid decanted and the precipitated cuprous chloride washed twice with 300-cc. portions of water. The chloride was suspended in 1 liter of water and 94 g. of sodium cyanide added.16 The clear solution was stirred and to it the diazonium solution was added, slowly, from a dropping funnel which extended below the surface of the liquid. After complete addition, the temperature was raised to 90° and maintained there for two hours. The mixture was cooled, the precipitated material boiled with 1 liter of 50% acetic acid and filtered from tarry products. The brownish yellow nitrile, obtained from the cooled solution, melted at 164-167°.17

5-Nitro-2-naphthoic Acid.—A mixture of 3 g. of the nitrile, 20 cc. of 50% acetic acid and 10 cc. of concd. sulfuric acid was refluxed for two hours, cooled, the precipitate treated with hot sodium carbonate solution, filtered and the filtrate acidified; yield 3 g.; m. p. 291–293°18 after recrystallization from acetic acid.

5-Nitro-2-naphthoyl Chloride.—The acid was heated with three times the calcd. amount of thionyl chloride (practical) in an oil-bath at  $150^{\circ}$  for five hours and the excess thionyl chloride removed under diminished pressure. The naphthoyl chloride boiled at  $223-224^{\circ}$  (13 mm.) and melted at  $126-128^{\circ}$  after recrystallization from petroleum ether (90-100°).

Anal. Calcd. for  $C_{11}H_6O_8NC1$ : Cl, 15.07. Found: Cl, 14.88.

Esters and Amides of Various Nitro and Amino Naphthoic Acid.—In order to obtain the nitro amides, a benzene solution of the dialkylaminoalkylamine was added, dropwise, to a warm, stirred benzene solution of the nitronaphthoyl chloride. After twenty-four hours the amide hydrochloride, which precipitated gradually in good yield, was filtered.

All nitro esters and nitro amides, with the exception of those mentioned below, were reduced to the corresponding amino esters by stannous chloride and hydrogen chloride in acetic acid solution.<sup>19</sup>

In order to reduce compounds 8, 10, 12, 14, 17, 19, 21, 23 and 25, the base was liberated with sodium carbonate from an aqueous solution of 1.3 g. of the hydrochloride, extracted with ether, the solvent removed, the base dissolved in 100 cc. of absolute alcohol, 0.5 g. of Raney nickel catalyst added and the compound hydrogenated under three and one-half atmospheres pressure. The mixture

(16) Directions for the preparation of cuprous cyanide were taken from Anderson and Bachmann, "Laboratory Manual of Organic Chemistry," Edwards Brothers, Ann Arbor, Michigan, 1939, p. 436.

- (17) Friedländer, Heilpern and Spielfogel (Mitt. Tech. Wien., [2]
   8, 316 (1899); Chem. Zentr., 70, I, 288 (1899)) found 168°.
- (18) Ekstrand (J. prakt. Chem., [2] 42, 273 (1890)) reported 293°.
  (19) Ref. 2, p. 1201.

<sup>(8)</sup> Mannich, Lesser and Silten, Ber., 65, 378 (1932).

<sup>(13) &</sup>quot;Organic Syntheses," Coll. Vol. I, p. 114

<sup>(15)</sup> Cohen, Cook, Hewett and Girard, J. Chem. Soc., 656 (1934).

Esters and $Amides^a$							
	Naphthoate esters (hydrochlorides)	Solvent, alcohol	Color	M. p., °C.	Formula	Calcd.	Found
1	$\alpha$ -Methyl- $\beta$ -dibutylaminoethyl 4-amino-1-	Isopropyl	Light yellow	178-179	$C_{42}H_{33}O_2N_2Cl$	9.02	9.03
$^{2}$	β-Diethylaminoethyl 5-nitro-2-	Abs. EtOH	<b>U</b> .	204 - 205	$C_{17}H_{21}O_4N_2Cl$	10.06	10.04
3	β-Diethylaminoethyl 5-amino-2-	Abs. Et	Yellow	207-208	$C_{17}H_{23}O_2N_2C1$	10.99	10.89
4	$\gamma$ -Diethylaminopropyl 5-nitro-2-	Butyl	Colorless	194-196	$C_{18}H_{28}O_4N_2Cl$	9.67	9.79
5	$\gamma$ -Diethylaminopropyl 5-amino-2-	Isopropyl	Brown	156 - 158	$C_{15}H_{25}O_2N_2Cl$	10.53	10.47
6	$\beta,\beta$ -Dimethyl- $\gamma$ -diethylaminopropyl 5-						
	nitro-2-	Isopropyl	Tan	107-109	$C_{20}H_{27}O_4N_2Cl$	8.98	8.78
7	$\beta,\beta$ -Dimethyl- $\gamma$ -diethylaminopropyl 5-						
	amino-2-	Abs. Et	Brown	190 - 192	$C_{20}H_{29}O_2N_2Cl$	9.72	9.79
8	$\beta$ -( $\beta$ '-Diethylaminoethoxy)-ethyl 4-nitro-1-	Benzene	Light yellow	112-113	$C_{19}H_{25}O_5N_2Cl$	8.94	9.00
9	$\beta$ -( $\beta'$ -Diethylaminoethoxy)-ethyl 4-amino-1-	Isopropyl	Light yellow	113-115	$C_{19}H_{27}O_3N_2Cl$	9.66	9.83
10	$\beta$ -( $\beta'$ -Di- <i>n</i> -butylaminoethoxy)-ethyl 4-						
	nitro-1-	Benzene	Light yellow	97-98	$C_{23}H_{33}O_5N_2Cl$	7.83	7.93
11	$\beta$ -( $\beta$ -Di- <i>n</i> -butylaminoethoxy)-ethyl 4-						
	amino-1-	Isopropyl	Light yellow	135 - 136	$C_{23}H_{35}O_{3}N_{2}Cl$	8.38	8.36
12	$\beta$ -( $\beta'$ -Diethylaminoethoxy)-ethyl 5-nitro-1-	Butyl	Colorless	173 - 175	$C_{19}H_{25}O_5N_2Cl$	8.94	8.99
13	$\beta$ -( $\beta'$ -Diethylaminoethoxy)-ethyl 5-amino-1-	Isopropyl	Yellow	118 - 120	$C_{19}H_{27}O_{3}N_{2}Cl$	9.66	9.69
14	$\beta$ -( $\beta'$ -Di- <i>n</i> -butylaminoethoxy)-ethyl 5-						
	nitro-1-	Benzene	Colorless	113 - 115	$C_{23}H_{33}O_5N_2Cl$	7.83	7.95
15	$\beta$ -( $\beta$ '-Di- <i>n</i> -butylaminoethoxy)-ethyl 5-						
	amino-1-	Isopropyl	Yellow	114 - 116	$C_{23}H_{85}O_3N_2Cl$	8.38	8.43
	Naphthoic acid amides (hydrochlorides)						
16	$\beta$ -Diethylaminoethylamide of 3-nitro-1-	Isopropyl	Light yellow	167 - 169	$C_{17}H_{22}O_{3}N_{3}Cl$	10.11	9.96
17	β-Diethylaminoethylamide of 4-nitro-1-	Isopropyl	Light yellow	152 - 154	$C_{17}H_{22}O_3N_3Cl$	10.11	10.12
18	$\beta$ -Diethylaminoethylamide of 4-amino-1-	Abs, Et	Tan	175 - 177	$C_{17}H_{24}ON_3Cl$	11.05	10.95
19	$\gamma$ -Diethylaminopropylamide of 4-nitro-1-	Isopropyl	Light yellow	152 - 154	$C_{18}H_{24}O_{3}N_{3}Cl$	9.72	9.70
20	$\gamma$ -Diethylaminopropylamide of 4-amino-1-	Isopropyl	Tan	198 - 200	$C_{18}H_{26}ON_3Cl$	10.59	10.63
21	$\gamma$ -(N-Piperidyl)-propylamide of 4-nitro-1-	Isopropyl	Light yellow	178 - 180	$C_{19}H_{24}O_3N_3Cl$	9.39	9.42
22	$\gamma$ -(N-Piperidyl)-propylamide of 4-amino-1-	Abs. Et	Tan	205 - 207	C <sub>19</sub> H <sub>26</sub> ON <sub>3</sub> Cl	10.19	10.14
23	$\beta$ -(4-Morpholyl)- 4-nitrobenzoic acid	Abs. Et	Colorless	223 - 224	$C_{13}H_{18}O_4N_3Cl$	11.19	11.19
24	Ethylamide of 4-aminobenzoic acid	Abs. Et	Light yellow	209 - 210	$C_{13}H_{20}O_2N_3Cl$	12.41	12.27
25	$\beta$ -(4-Morpholyl)-ethylamide of 4-nitro-1-	Abs. Et	Tan	223 - 224	$C_{17}H_{20}O_4N_3Cl$	9.69	9.70
26	$\beta$ -(4-Morpholyl)-ethylamide of 4-amino-1-	EtOAc +	Tan	239 - 242	$C_{17}H_{22}O_2N_3Cl$	10.56	10.50
		HOAc					

TABLE I

# <sup>a</sup> The bases of some of the amides were obtained in crystalline form. The base of compound 23 (m. p. $120-121^{\circ}$ ) was recrystallized from petroleum ether (90-100°); the base of 24 (m. p. $155-158^{\circ}$ ) and the base of 26 from isopropyl alcohol; the base of 25 (m. p. $129-131^{\circ}$ ) from benzene. Since the melting points of compounds 3, 9 and 15 were found to be very close to those of the corresponding nitro esters the former were analyzed for nitrogen by Mr. Chamberlain of Parke, Davis and Company. Compound 3, Calcd. 8.69; found 8.66. Compound 9, Calcd. 7.64; found 7.49. Compound 15, Calcd. 6.62; found 6.45. A mixture of compounds 2 and 3 melted at 189-194°; a mixture of 14 and 15 at 103-100°.

was shaken for two hours although reduction appeared to be complete in about twenty minutes. The oily, yellow product obtained was treated with the amount of concd. hydrochloric acid necessary for the formation of a monohydrochloride and cooled for twenty-four hours, whereupon it became crystalline. The properties of the new derivatives are summarized in Table I.

Di-4-aminobenzoyl Derivative of Ethyldi- $\beta$ -hydroxyethyl-amine.—A mixture of 37.1 g. of 4-nitrobenzoyl chloride, 13.3 g. of ethyldi- $\beta$ -hydroxyethyl-amine<sup>20</sup> and 100 cc. of benzene was refluxed for three hours, the solvent decanted, the oily precipitate washed with petroleum ether and then with 10% sodium carbonate solution whereupon it became solid. The base, which melted at 120–121° after recrystallization from methyl alcohol, was dissolved in benzene and treated with hydrogen chloride. The pre-

(20) Knorr and Schmidt, Ber., 31, 1073 (1898).

cipitated hydrochloride of the di-4-nitrobenzoyl derivative, which solidified after some time, was recrystallized from a mixture of ethyl acetate and acetic acid; m. p.  $178-179^{\circ}$ .

Anal. Calcd. for  $C_{20}H_{22}O_{\delta}N_{3}C1$ : Cl, 7.58. Found: Cl, 7.58.

To obtain the amino compound, 4.3 g. of the nitro base, dissolved in 10 cc. of acetic acid, was reduced with 13.6 g. of stannous chloride dihydrate and excess hydrogen chloride. The base was recrystallized from 50% alcohol; m. p. 99-101°.

To 0.5 g. of the base, dissolved in 5 cc. of absolute alcohol, there was added 0.12 cc. of concd. hydrochloric acid. After several hours the precipitated monohydrochloride was recrystallized from alcohol; m. p. 199–201°.

Anal. Calcd. for  $C_{20}H_{20}O_4N_3Cl$ : Cl, 8.69. Found: Cl, 8.86.

Dec., 1940

### Summary

A number of dialkvlaminoalkvl and dialkvlaminoalkoxyalkyl esters of amino-1- and amino-2naphthoic acid as well as dialkylaminoalkylamides of amino-1-naphthoic acid have been described.

The amides seem to be much less satisfactory as local anesthetics than the esters.

ANN ARBOR, MICHIGAN **Received September 16, 1940** 

## [CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

# The Introduction of Substituted Vinyl Groups. VI. The Regeneration of Substituted Vinyl Malonic Esters from their Sodium Enolates<sup>1</sup>

BY ARTHUR C. COPE AND ELIZABETH M. HARDY

The alkylation of sodium enolates prepared from alkylidene malonic and cyanoacetic esters affords a rather general method for preparing substituted vinyl alkyl malonic and cyanoacetic esters.<sup>2</sup> While the alkyl group introduced on



the  $\alpha$  carbon atom locks the double bond in the  $\beta, \gamma$ -position, a similar introduction of hydrogen would give an ester capable of isomerizing to the original  $\alpha,\beta$ -unsaturated ester by a simple prototropic shift.

Kon and his associates<sup>3</sup> have developed a technique for regenerating esters containing a mobile three-carbon system from their sodium or potassium enolates, in which petroleum ether suspensions of the enolates are treated with a weak organic acid. Under these non-polar conditions enol-keto change occurs, but in many cases threecarbon tautomerism is arrested or retarded, so that the labile esters corresponding in structure to the metal enolates can be isolated. This procedure was applied<sup>4</sup> to one alkylidene malonic ester, ethyl cyclopentylidenemalonate, I. The ester regenerated from the sodium or potassium enolate prepared from I had but a small exaltation in molecular refraction, and a high additive capacity for iodine chloride, indicating that it was largely

ethyl 1-cyclopentenyl malonate, II. Accurate

$$\begin{array}{c|c} CH_2--CH_2 & \\ & \searrow C=-C(COOC_2H_{\delta})_2 \\ CH_2--CH_2 & \\ I & & \searrow C--CH(COOC_2H_{\delta})_2 \\ & & & \bigcirc CH_2--CH_2 \\ & & & & \bigcirc CH_2--CH_1 \\ & & & & & II \end{array}$$

analysis of the regenerated ester by the iodine chloride addition method was not possible, but the molecular refraction data indicated that it contained at least 82% of II.

The reaction of secondary alkylidene malonic esters with sodamide in liquid ammonia<sup>5</sup> now affords a more satisfactory method for preparing sodium enolates from such esters than was available at the time of Kon's work. We have regenerated the labile esters from the sodium enolates prepared from the three readily available esters of this type: i. e., ethyl isopropylidenemalonate, ethyl cyclopentylidenemalonate and ethyl 1-methylpropylidenemalonate. It has been found possible to determine the purity of the regenerated esters fairly accurately by the method of polarographic analysis.

Treatment of an ether suspension of the sodium enolate prepared from ethyl isopropylidenemalonate with benzoic acid, acetic acid, dilute hydrochloric acid or water gave samples of ethyl isopropenylmalonate of approximately equal purity. The three carbon system of the ester is sufficiently immobile to resist isomerization by cold dilute acids and bases. Decomposition of ether suspensions of the sodium endates prepared from the three alkylidene malonic esters with dilute hydrochloric acid was consequently employed in preparing the  $\beta$ ,  $\gamma$ -unsaturated esters whose properties are listed in Table I. The prop-

(5) Cope and Hancock, THIS JOURNAL, 60, 2644, 2901 (1938).

<sup>(1)</sup> Supported by a grant from the Penrose Fund of the American Philosophical Society. (2) THIS JOURNAL, 62, 314 (1940), and preceding papers in this

series. (3) Kon and Nanji, J. Chem. Soc., 560 (1931); Gidvani, Kon and

Wright, ibid., 1027 (1932).

<sup>(4)</sup> Kon and Ling, ibid., 596 (1934); Hugh and Kon, ibid., 778 (1930).