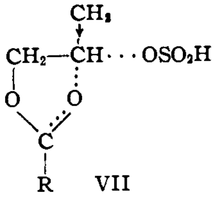

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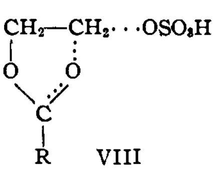
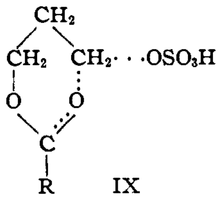
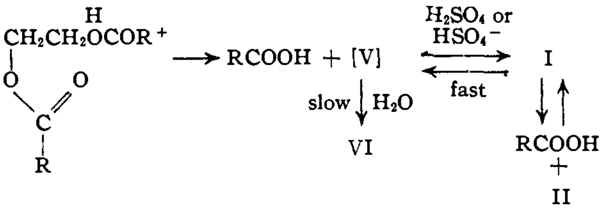


VIII



IX

It is also possible to formulate a mechanism in terms of alkyl–oxygen fission. This seems desirable in view of the apparently large difference in the rate of cleavage of lauric acid from the ethylene and propylene glycol esters as compared with that of pentamethylene glycol dilaurate and methyl laurate. The driving force again would be neighboring group participation to give at once the cyclic carbonium ion V. If, now, this ion is only an unstable intermediate which reacts rapidly with either sulfuric acid or bisulfate ion, the formation of monoester monosulfate can be accounted for. Further cleavage of lauric acid from this compound might be assisted by participation of the sulfate group. The formation of monoester precursor would then consist in a slow but thermodynamically preferred hydration of the ion V to VI. This mechanism is summarized below.



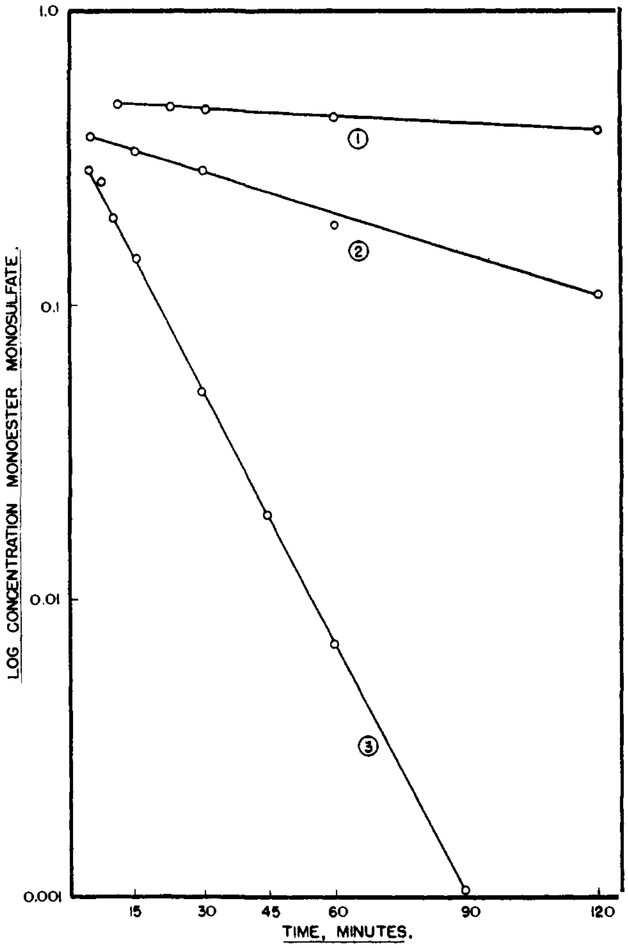


Fig. 9.—Comparative rates of disappearance of monoester monosulfate in the reaction of glycol dilaurates with six moles of sulfuric acid at 40°: dilaurate of trimethylene glycol, 1; ethylene glycol, 2; propylene glycol, 3.

Acknowledgment.—We wish to thank Drs. R. B. Wearn, A. I. Gebhart, W. G. Alsop, J. F. Gerecht, S. Schmukler and Mr. J. V. Schurman for advice and encouragement. We also thank Mr. F. F. Cesark for his assistance in the experimental work.

JERSEY CITY 2, N. J.

[CONTRIBUTION NO. 1034 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Phenylation of Esters by Reaction with Bromobenzene and Sodium Amide

BY WILLIAM W. LEAKE[1] AND ROBERT LEVINE

RECEIVED OCTOBER 1, 1958

Five monobasic esters and three malonic esters have been phenylated in fair to good yields by reaction with bromobenzene and excess sodium amide in liquid ammonia solution. The reaction of diethyl malonate with sodium amide, bromobenzene and ethyl bromide gave a mixture of diethyl phenylmalonate, diethyl ethylphenylmalonate and N-ethylaniline.

Recently[2] we reported that ketone anions can be phenylated by reaction with benzyne, the dehydrohalogenated halobenzene. The present paper is concerned with the phenylation of several monobasic and dibasic esters by their reaction with bromobenzene and excess sodium amide in liquid ammonia solution.

The results of the phenylation of the monobasic esters are found in Table I. It can be seen that in each reaction some or all of the following types of products were obtained: (1) monophenylated ester, (2) diphenylated ester, (3) aniline and (4) N-acylaniline. Thus, the phenylation of ethyl acetate gave a mixture of ethyl phenylacetate (I) (42%); ethyl diphenylacetate (II) (14%); aniline (III) (21%) and acetanilide (IV) (15%).

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[1] Monsanto Chemical Co. Research Fellow.

[2] W. W. Leake and R. Levine, THIS JOURNAL, **81**, 1169 (1959).

TABLE I

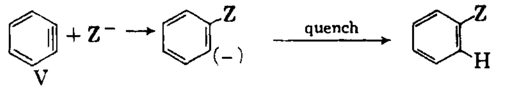
REACTIONS OF MONOBASIC ESTERS WITH BROMOBENZENE AND SODIUM AMIDE

		Products		
			B.p.	
Ester	Yield,[a] %	Formula	°C.	Mm.
$CH_3CO_2C_2H_5$	42	$C_6H_5CH_2CO_2C_2H_5$	123–128[b,c]	27.5
	14	$(C_6H_5)_2CHCO_2C_2H_5$	57–58[d,e] (m.p.)	
	15	$CH_3CONHC_6H_5$	113.4–114.2 (m.p.)	
	21	$C_6H_5NH_2$	100–103[f]	58.5
$CH_3CO_2C_4H_9$-*t*	40	$C_6H_5CH_2CO_2C_4H_9$-*t*	107–112[g,h]	12
	16	$(C_6H_5)_2CHCO_2C_4H_9$-*t*	80–81[d,i] (m.p.)	
	27	$CH_3CONHC_6H_5$	113.5–114.2 (m.p.)	
$C_2H_5CO_2C_2H_5$	>30	$(C_6H_5)(CH_3)CHCO_2C_2H_5$	107–131[j]	35.1
	28	$C_2H_5CONHC_6H_5$	104–104.8 (m.p.)	
$C_2H_5CO_2C_4H_9$-*t*	38	$(C_6H_5)(CH_3)CHCO_2C_4H_9$-*t*	104–109[k]	10.6
	39	$C_2H_5CONHC_6H_5$	104.2–105.2 (m.p.)	
$C_6H_5CH_2CO_2C_2H_5$	63	$(C_6H_5)_2CHCO_2C_2H_5$	57–58[d,e] (m.p.)	
	11	$C_6H_5NH_2$	87–89[f]	30

[a] In all of these reactions, the ester (two equivalents) was added to sodium amide (four equivalents) followed by the addition of bromobenzene (one equivalent). Stirring was continued for 10 minutes and then the reaction was quenched. [b] See ref. 12. [c] Hydrolysis with 20% aqueous sodium hydroxide gave phenylacetic acid, m.p. 76.4–77.6° alone and when mixed with an authentic sample. [d] See ref. 7. [e] Hydrolysis with 20% aqueous sodium hydroxide gave diphenylacetic acid, m.p. 144.5–145.5° alone and when mixed with an authentic sample. [f] N-Benzoyl derivative, m.p. 160–161° alone and when mixed with an authentic sample. [g] D. L. Yabroff and C. W. Porter, THIS JOURNAL, **54**, 2453 (1932). [h] Cleavage by *p*-toluenesulfonic acid (D. S. Breslow, E. Baumgarten and C. R. Hauser, *ibid.*, **66**, 1286 (1944)) gave phenylacetic acid, m.p. 76.5–77.4°. [i] Cleavage by *p*-toluenesulfonic acid gave diphenylacetic acid, m.p. 144.5–145.5°. [j] This crude ester fraction was hydrolyzed with 20% aqueous sodium hydroxide to give a 30% yield of α-phenylpropionic acid, b.p. 131–136° at 5.3 mm. (lit. value, 153–155° at 20 mm., A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946)). The acid was further identified by conversion, *via* its acid chloride, to α-phenylpropionamide, m.p. 94.5–95.5° alone and when mixed with an authentic sample. Therefore, the yield of ethyl α-phenylpropionate is at least 30% of theory. [k] *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.91; H, 8.88. A sample was cleaved to α-phenylpropionic acid, which was identified as described in footnote *j*.

$$CH_3CO_2C_2H_5 + C_6H_5Br \xrightarrow{NaNH_2/NH_3} \underset{I}{C_6H_5CH_2CO_2C_2H_5} + \underset{II}{(C_6H_5)_2CHCO_2C_2H_5} + \underset{III}{C_6H_5NH_2} + \underset{IV}{CH_3CONHC_6H_5}$$

Compounds I, II and III no doubt arise from the addition of the anion of the nonphenylated ester, the monophenylated ester and amide ion to benzyne (V).



V

Z^- = ester anions and amide ion

The acetanilide appears to be formed by the nucleophilic attack of sodioaniline at the carbonyl carbon atom of some of the ester which has not been converted to its anion.

$$CH_3CO_2C_2H_5 \xrightarrow[2,\ \text{quench}]{1,\ Na^+(NHC_6H_5)^-} C_2H_5OH + CH_3CONHC_6H_5$$

It can be seen that ethyl and *t*-butyl acetate gave essentially the same yields of mono- and diphenylated products. Similarly, ethyl and *t*-butyl propionate have been monophenylated in comparable yields. That higher yields of anilides were obtained in the reactions of *t*-butyl esters than with ethyl esters appears surprising since in the ammonolysis[3] and alkaline hydrolysis[4] of esters, both of which also involve the nucleophilic attack by a basic reagent at the carbonyl carbon atom of the ester, *t*-butyl esters are less reactive than ethyl esters. However, these results may be rationalized in the following way. In the presence of sodium amide, carboxylic esters having α-hydrogen atoms generally exhibit two types of reactions, *viz.*, (1) the base may remove an α-hydrogen atom from the ester VI to give the anion VII and (2) the base may react with the carbonyl carbon atom of the ester to give the corresponding amide VIII.[5]

$$\underset{VI}{RCH_2CO_2R'} + Na^+NH_2^- \longrightarrow \underset{VII}{Na^+(RCHCO_2R')^-} + NH_3$$

$$\longrightarrow \underset{VIII}{RCH_2CONH_2} + Na^+OR^-$$

R = H and CH_3; R′ = C_2H_5 and *t*-C_4H_9

Since it would be expected[3,5] that the carbonyl carbon atom of ethyl acetate (VI, R = H and R′ = C_2H_5) would be attacked by sodium amide more extensively than the carbonyl carbon atom of *t*-butyl acetate (VI, R = H and R′ = *t*-butyl), it is probable that more acetamide[6] (VIII, R = H) would be formed in the ethyl acetate than in the *t*-butyl acetate reaction. Hence, less ethyl acetate than *t*-butyl acetate will be available for reaction with sodioaniline and therefore it would be expected that less acetanilide and more aniline would be produced in the former than in the latter reaction. A similar argument can be given to account for the fact that more propionanilide is formed in the phenylation of *t*-butyl propionate than in the phenylation of ethyl propionate.

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(3) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 211.

(5) In this connection see C. R. Hauser, R. Levine and R. F. Kibler, THIS JOURNAL, **68**, 26 (1946).

(6) However, no acetamide was isolated from these reactions probably because it is so very soluble in water.

Since ethyl acetate gave a mixture of mono- and diphenylated products, it was of interest to phenylate ethyl phenylacetate. The yield (63%) of ethyl diphenylacetate compares very favorably with that (52%) obtained earlier[7] by the reaction of diethyl carbonate with potassium diphenylmethide.

The results of the phenylation of three malonic esters are found in Table II. The reacion of diethyl malonate, bromobenzene and excess sodium amide in liquid ammonia gave diethyl phenylmalonate (51%) and aniline (18%). That it has been possible to directly phenylate malonic ester is especially interesting because of statements[8,9] such as the following which have appeared in the literature: "It is not possible to substitute aryl groups into diethyl malonate and the synthesis of the important drug, phenobarbital, has to take this factor into account."[8]

TABLE II

REACTIONS OF MALONIC ESTERS WITH BROMOBENZENE AND SODIUM AMIDE[a]

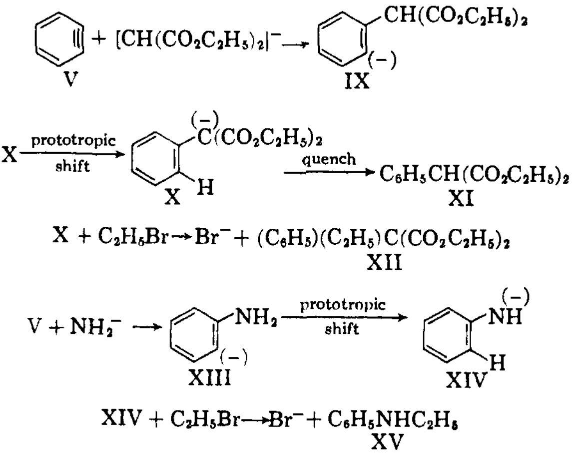
Ester	Yield of Product, %		
	Phenylated ester	Aniline[b]	Diphenylamine[c]
$CH_2(CO_2C_2H_5)_2$	$C_6H_5CH(CO_2C_2H_5)_2$, 51 B.p. 124–127° at 1.5 mm.[d]	18	0
$C_2H_5CH(CO_2C_2H_5)_2$	$(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2$, 22 B.p. 120–125° at 1.2 mm.[e,f]	9	6
$CH_2(CO_2CH_3)_2$	$C_6H_5CH(CO_2CH_3)_2$, 37[g] B.p. 131–133° at 4.6 mm. M.p. 51.2–52.2°[h]	17	3

[a] See footnote *a* of Table I. [b] B.p. 104–105° at 60 mm., N-benzoyl derivative, m.p. 160–161° alone and when mixed with an authentic sample. [c] Isolated as its hydrochloride and then converted to the free base, m.p. 55–56° alone and when mixed with an authentic sample. [d] See ref. 13. [e] Lit. value 169–171° at 19 mm., see ref. 13. [f] Hydrolysis with 5 *N* sodium hydroxide gave ethylphenylmalonic acid, m.p. 154.5–155.5° [A. L. Bernoulli and H. Jakubowicz, *Helv. Chim. Acta*, 4, 1018 (1921)]. [g] Phenylmalonamide [1%, m.p. 230–233° alone and when mixed with an authentic sample (see ref. 19)] was also obtained. [h] See ref. 18.

It has also been found that from the interaction of equivalents of diethyl malonate, bromobenzene and sodium amide (conditions under which benzyne is not formed) none of the phenylated malonic ester and only recovered starting materials were obtained.[10]

Diethyl ethylmalonate has also been phenylated to give aniline (9%), diphenylamine (6%) and a low yield (22%) of diethyl ethylphenylmalonate, which was condensed with urea to give phenobarbital. Dimethyl malonate was phenylated in a lower yield (37%) than diethyl malonate and in addition phenylmalonamide (1%), aniline (17%) and diphenylamine (3%) were obtained.

It was also of interest to attempt to prepare diethyl ethylphenylmalonate by phenylating malonic ester and then ethylating the product without isolating any intermediates. Therefore, diethyl malonate (two equivalents) was added to sodium amide (four equivalents) followed by bromobenzene (one equivalent). Finally, ethyl bromide (two equivalents) was added and the reaction mixture was processed to give a mixture of diethyl phenylmalonate (XI, 11%), diethyl ethylphenylmalonate (XII, 39%) and N-ethylaniline (XV, 21%). The probable course of this reaction is represented in the scheme



Finally, when dimethyl malonate was subjected to the phenylation-ethylation reaction, none of the desired dimethyl ethylphenylmalonate was isolated. Instead, a mixture of dimethyl phenylmalonate (22%), phenylmalonamide (25%) and N-ethylaniline (21%) was obtained.

Experimental

Phenylation of Ethyl Acetate.—Sodium amide (1.0 mole in 750–800 ml. of anhydrous liquid ammonia) was prepared by the previously described method.[11] Ethyl acetate (0.5 mole, 44.1 g.) was added over a 15-minute period and then the mixture was stirred for an additional 15 minutes. Bromobenzene (0.25 mole, 39.3 g.) was added over a 10–15 minute period and the mixture was stirred for an additional 10 minutes. The reaction was quenched by the addition of solid ammonium chloride (1.25 moles, 70.0 g.) and the liquid ammonia was replaced by adding ether and warming the mixture on a water-bath until the ether started to reflux. The mixture was poured onto crushed ice, was made strongly acidic with concentrated hydrochloric acid, was extracted with several portions of ether and the combined extracts (extract 1) were dried over anhydrous sodium sulfate. The residual aqueous phase was made basic with solid sodium carbonate, was extracted with several portions of ether and the combined extracts (extract 2) were dried over anhydrous sodium sulfate. The solvent from extract 1 was removed and the residue was filtered to give 3.7 g. (11.1%) of acetanilide, m.p. 113.4–114.2°. Distillation of the filtrate gave 17.1 g. (41.7%) of ethyl phenylacetate, b.p. 123–128° at 27.5 mm.[12]; 10.0 g. of a solid material, b.p. 119–135° at 0.9 mm.; and 2.8 g. of a non-distillable, tarry residue. The solid material was washed with cold 30–60° petroleum ether to give an additional 1.4 g. (4.2%) of acetanilide, m.p. 113.4–114.2°, which was insoluble in the solvent. Evaporation of the petroleum ether washings gave 8.6 g. (14.3%) of ethyl diphenylacetate,[7] m.p. 57–58° (from 95% ethanol) alone and when mixed with an authentic sample. Hydrolysis of the ethyl phenylacetate with 20% aqueous sodium hydroxide gave phenylacetic acid, m.p. 76.4–77.6° alone and when mixed with an authentic sample. Similarly, ethyl diphenylacetate was converted to diphenylacetic acid, m.p. 144.5–145.5° alone and when mixed with an authentic sample. The acetanilide was hydrolyzed with 50% sulfuric acid to give aniline, which was identified as its

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(7) R. S. Yost and C. R. Hauser, THIS JOURNAL, 69, 2325 (1947).

(8) A. Berger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 120.

(9) For a similar statement see F. C. Whitmore, "Organic Chemistry," 2nd edition, D. Van Nostrand Co., Inc., New York, N. Y., 1951, p. 379.

(10) Similar results were obtained (see ref. 2) in the phenylation of ketones.

(11) R. Levine and C. R. Hauser, THIS JOURNAL, 66, 1768 (1944).

(12) R. Adams and A. F. Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 270.

N-benzoyl derivative, m.p. 160–161° alone and when mixed with an authentic sample. Distillation of extract 2 gave 5.0 g. (21.4%) of aniline, b.p. 100–103° at 58.5 mm.

Phenylation of Diethyl Malonate.—Sodium amide (2.0 moles), diethyl malonate (1.0 mole, 160.2 g.) and bromobenzene (0.5 mole, 78.6 g.) were allowed to react using the procedure described above for the phenylation of ethyl acetate. Distillation of the combined acidic extracts gave 94.7 g. of recovered diethyl malonate, b.p. 93–95° at 16 mm., and 60.4 g. (51.2%) of diethyl phenylmalonate, A, b.p. 124–127° at 1.5 mm.[13] Distillation of the basic ether extracts gave 8.2 g. (17.6%) of aniline, b.p. 104–105° at 60 mm. That compound A is diethyl phenylmalonate was shown in the following ways: (1) molecular weight determinations by the saponification equivalent method[14] gave values of 235.16, 239.96 and 240.36; calcd. mol. wt. of A is 236.26; (2) A mixture of A, urea and sodium ethoxide in anhydrous ethanol was heated in a sealed tube at 115° for three hours according to the procedure described[13] for similar reactions to give 5-phenylbarbituric acid, m.p. 260.5–261.5°, from hot water[15]; (3) A mixture of potassium hydroxide (0.36 mole, 20.0 g.) in 20 ml. of water and A (0.1 mole, 23.6 g.) was refluxed for two hours. Then, 20 ml. of water was added and 20 ml. of liquid was distilled to remove the ethanol which was formed. Then, concentrated sulfuric acid (0.33 mole, 32 g.) was added slowly. The mixture was refluxed for an additional three hours and then was cooled to room temperature. It was made strongly basic with aqueous potassium hydroxide, extracted with several portions of ether and the extracts were discarded. The residue was acidified with dilute sulfuric acid and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed to give 8.2 g. (60.3%) of phenylacetic acid, m.p. 77.0–77.8° alone and when mixed with an authentic sample. This procedure is a modification of that described[16] for the conversion of diethyl *sec*-butylmalonate to 3-methylpentanoic acid.

Phenylation Followed by Ethylation of Malonic Esters. (a) Diethyl Malonate.—The last reaction was repeated except that ethyl bromide (1.0 mole, 109.0 g.) was added after the addition of the bromobenzene was completed. The reaction mixture was stirred for an additional 15 minutes and was then processed as described above. Distillation of the combined acidic extracts gave 108.5 g. of a mixture of bromobenzene and diethyl malonate, b.p. 100–127° at 59.3 mm., and 64.4 g. of a mixture of diethyl phenylmalonate and diethyl ethylphenylmalonate, b.p. 130–140° at 2.6 mm. (mixture A). From the basic extract there was obtained 12.7 g. of N-ethylaniline, b.p. 126–131° at 63.5 mm. (lit.[17] 123.6° at 60.0 mm.); N-benzoyl derivative, m.p. 59.0–60.0 alone and when mixed with an authentic sample. The average molecular weight of mixture A was 258.03 (based on three determinations). Therefore, mixture A consists of 20.5% of diethyl phenylmalonate (calcd. mol. wt. 236.26) and 79.5% of diethyl ethylphenylmalonate (calcd. mol. wt. 264.31) and thus the actual yield of the former ester is 11.2% and that of the latter ester is 38.8%.

(b) Dimethyl Malonate.—The last reaction was repeated except that the diethyl malonate was replaced by dimethyl malonate (1.0 mole, 132.0 g.). Processing the reaction mixture gave 22.4 g. (21.5%) of dimethyl phenylmalonate, b.p. 131.0–133.5° at 5.0 mm., m.p. 51.2–52.2°[18]; 22.4 g. (25.3%) of phenylmalonamide, m.p. 230–233° alone and when mixed with an authentic sample[19]; and 13.0 g. (21.4%) of N-ethylaniline, b.p. 122–127° at 59.0 mm.[17]

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[13] W. L. Nelson and L. H. Cretcher, This Journal, **50**, 2758 (1928).

[14] S. Siggia, "Quantitative Organic Analysis Via Functional Groups," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 46.

[15] H. J. Morsman, *Helv. Chim. Acta*, **18**, 1254 (1935).

[16] E. B. Vliet, C. S. Marvel and C. M. Hsueh, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 416.

[17] D. R. Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

[18] A. H. Wallingford, A. H. Homeyer and D. M. Jones, This Journal, **63**, 2056 (1941).

[19] A. W. Dox and L. Yoder, *ibid.*, **44**, 1564 (1922).

PITTSBURGH 13, PENNA.

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Dissociation Constants of Nitronaphthoic Acids[1]

BY ERNST BERLINER AND EDITH H. WINICOV[2]

RECEIVED SEPTEMBER 13, 1958

The dissociation constants of 13 nitronaphthoic acids have been determined potentiometrically at 25° in 50% aqueous butyl Cellosolve. The results are discussed in terms of conjugation in the naphthalene system. A set of σ-values has been derived from the dissociation constants.

Although far more attention has been paid to substituent effects in the benzene than in the naphthalene series, there has been some activity in recent years in the study of substituted naphthalenes. As a contribution to this latter field, we wish to report the dissociation constants of nitronaphthoic acids. The main purpose of this study was to learn something about the extent of conjugation among the various positions in napthalene and the transmission of substituent effects; but substituent constants for the differently situated nitro groups, comparable to those in the benzene series, have also been established. Some σ-constants for nitro groups on naphthalene have previously been reported and will be referred to below.

It was particularly important to determine the dissociation constants of as many of the acids as possible, and under the same set of conditions, because only then can a coherent picture be obtained. Of the 14 possible nitronaphthoic acids, only 3-nitro-2-naphthoic acid could not be prepared, and hence the study included 13 nitronaphthoic acids, as well as the two unsubstituted ones.[3] The solvent was 50% by volume aqueous butyl Cellosolve, which was chosen because of the low solubility of some of the acids, and because values for the dissociation constants of substituted benzoic acids are available in the same solvent.[4]

Results and Discussion.—The dissociation constants were determined at 25° by potentiometric titration, using a Beckman model G *p*H meter. They were determined in triplicate, except for 7-

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[1] Taken from a dissertation submitted by Mrs. E. H. Winicov to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree, June, 1958.

[2] Eastman Kodak Fellow 1956–1957.

[3] We are very much indebted to Dr. J. Vaughan of the University of Canterbury, Christchurch, New Zealand, for the sample of 2-nitro-1-naphthoic acid; see R. D. Topsom and J. Vaughan, *J. Chem. Soc.*, 2842 (1957).

[4] E. Berliner and E. A. Blommers, This Journal, **73**, 2479 (1951).