(B) Dicyanoethylated product (25 g.) boiled mainly at 245–246° (6 mm.), $n^{20}D$ 1.4900, $d^{20}_{20}$ 1.113. This water-insoluble product gave no reaction with acetyl chloride. It was miscible with acetone and benzene, soluble in ethanol, but much less so in ether.

*Anal.* Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.63; H, 7.02; N, 12.28. Found: C, 52.75; H, 6.61; N, 12.23.

**Behavior of 2-Hydroxyethyl Sulfide toward Methyl Acrylate.**—Over 85% of this sulfide was recovered when the reaction of 23.0 g. of it with 38 g. methyl acrylate in the presence of 0.13 g. Triton B solution was attempted. As in the above case, the mixture was heated for four hours on the steam-bath prior to distillation.

**Crystallographic Examination of β-Benzenesulfonylpropionic Acid and its Amide.**—β-Benzenesulfonylpropionic acid is uniaxial and positive. It has a high birefringence: $N_\omega$ (or $n_\alpha$) 1.569, $N_\epsilon$ (or $n_\gamma$) 1.620. It seems to be tetragonal but may be hexagonal.

The amide is triclinic with these indices: $n_\alpha$ 1.530, $n_\gamma$ 1.640, indicating a high birefringence (0.110). Because of the elongation of the crystal fragments, orientation to obtain $n_\beta$ was not possible.

**Acknowledgments.**—Most of the micro combustion analyses (carbon, hydrogen, nitrogen) reported in this paper were performed by Mrs. M. M. Ledyard. A few were carried out by Miss W. A. Brandt, Miss Rita Pivan and Dr. T. S. Ma. We are indebted to M. D. Quigley of the Geology Department, Northwestern University for the crystallographic data.

## Summary

The chemistry of the addition of alkanethiols and thiophenols to acrylic and methacrylic derivatives (nitrile, ester, salt, aldehyde) is presented. The role of catalysts is considered in some detail.

EVANSTON, ILLINOIS RECEIVED JANUARY 11, 1947

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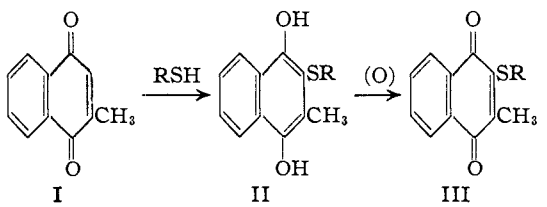
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# The Addition of Sulfhydryl Derivatives to 2-Methyl-1,4-naphthoquinone[1]

BY LOUIS F. FIESER AND RICHARD B. TURNER

Although the alkyl substituent of 2-methyl-1,4-naphthoquinone prevents or greatly inhibits the addition of most reagents of the HA-type that add readily to unsubstituted quinones, it does not interfere markedly with the addition of sulfhydryl compounds.[2] This addition reaction has been utilized in the present investigation as a route to the synthesis of 2,3-disubstituted 1,4-naphthoquinones of types that seemed to offer some prospect of having antihemorrhagic or bacteriostatic activity[3] or of having application in chemotherapy.

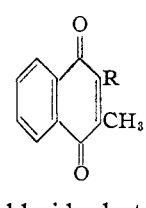
The initial addition, usually conducted in alcoholic solution at room temperature, affords a thio-substituted methylnaphthohydroquinone (II) that subsequently may become partially oxidized by interaction with the starting quinone. Usually it was found expedient to submit the total reaction mixture to oxidation with silver oxide in ether solution and to isolate the product in the oxidized form (III). Substituted derivatives of the type




I II III

III were obtained in reactions with thioglycolic acid, benzyl mercaptan, α-mercaptostearic acid, and homocysteine.

S-(2-Methyl-1,4-naphthoquinonyl-3)-thioglycolic acid (IV) is a crystalline solid soluble in aqueous bicarbonate solution. Assays for vitamin K activity in the chick (eighteen hour method) were kindly carried out on this and other new compounds by Dr. W. L. Sampson of the Merck Institute for Therapeutic Research. The quinone IV was found to possess half the antihemorrhagic activity (ED = 2γ) of vitamin $K_1$. Since this quinone, like $K_1$, is fully substituted and hence not subject to interfering side reactions with body constituents to be expected of administered 2-methyl-1,4-naphthoquinone,[2] and since it is more readily accessible than $K_1$ and has the added feature of forming water-soluble salts, the substance may warrant consideration for application to vitamin K therapy. The quinone acid IV was conjugated with glycine through its acid




IV, R = $-SCH_2CO_2H$
V, R = $-SCH_2CH_2CHCO_2H$ (NH2)
VI, R = $-SCHC_{16}H_{33}$-*n* ($CO_2H$)

chloride, but the conjugate has an ED value between 5 and 50γ. The amino acid derivative V, prepared from methylnaphthoquinone and homocysteine, is practically insoluble in both water and organic solvents and it is likewise only weakly active in the chick assay (ED = 50γ). The quinone resulting from the addition of *s*-butyl mercaptan is an oil but was obtained in a pure con-

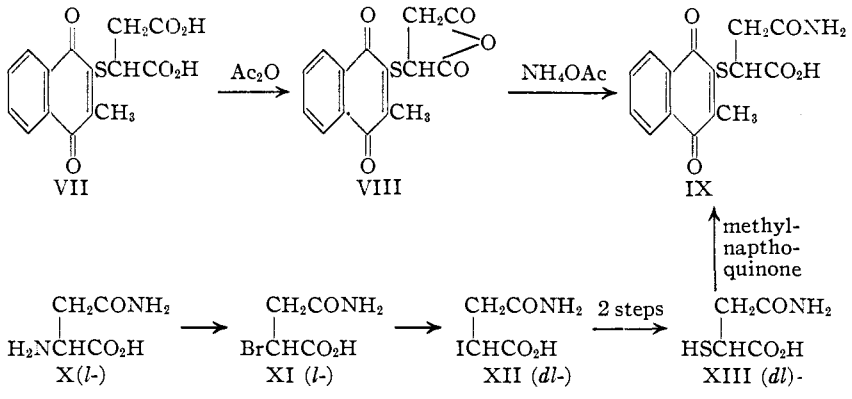
(1) From the doctoral dissertation of Richard B. Turner, May 1, 1942. The research was assisted by a fellowship from the Allied Chemical and Dyestuff Corporation in 1941–1942.

(2) Preliminary qualitative observations: Fieser, *Ann. Internal Med.*, **15**, 648 (1941); the analogous addition of thioglycolic acid to trimethylbenzoquinone is described by Snell and Weissberger, THIS JOURNAL, **61**, 450 (1939).

(3) See discussion of quinone acids by Fieser, Gates and Kilmer, *ibid.*, **62**, 2966 (1940).

dition through the solid hydroquinone by the procedure developed for the isolation of vitamin $K_1$.[4] The addition of α-mercaptostearic acid, followed by oxidation, gave the quinone VI as a crystalline solid; the substance seems of interest because it is a higher fatty acid having a prosthetic group that supplies the function of an oxido-reduction catalyst.

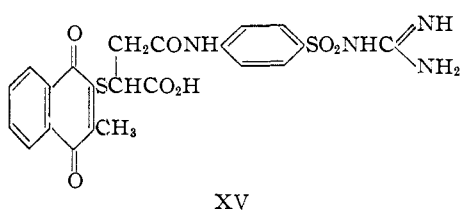
The reaction of methylnaphthoquinone with thiomalic acid proceeded best when an alcoholic solution of the components was shaken with silver oxide. The resulting substituted quinone VII forms an anhydride (VIII) and this reacts readily with arylamines to form amides. The more basic alkylamines and ammonia seem to have a destructive action but react satisfactorily with the anhydride in the form of their acetic acid salts. Although the anhydride ring can open in two ways, the reactions all gave single, homogeneous products, and these all probably conform to the structural type IX predicted from such analogy as is available[5] and established for the unsubstituted amide by synthesis from *l*-asparagine (X), which is known to have the β-structure.[6] Known methods were applied for the conversion to the *l*-bromide (XI), the *dl*-iodide (XII), the xanthogen derivative, and the inactive thiomalamic acid XIII, and the addition of this substance to methylnaphthoquinone gave a product (IX) identical with the amide obtained by opening the anhydride ring of XIII.




VII VIII IX

X(*l*-) XI (*l*-) XII (*dl*-) XIII (*dl*)-

Several amides were prepared by the reaction of the same anhydride (VIII) with sulfonamide drugs. Sulfaguanidine might condense through either the arylamino or the highly basic guanidino group, but since the reaction product, like guanidine[7] and unlike sulfaguanidine, gave no evidence of undergoing diazotization on treatment with nitrous acid, the structure must be that shown in formula XIV.



XV

## Experimental[8]

**Preparation of Mercaptans.**—*s*-**Butyl mercaptan,** b. p. 83–84°, was prepared from the bromide, b. p. 89–91°, by reaction with thiourea and hydrolysis.[9] α-**Mercaptostearic acid,** m. p. 74–76°, was obtained through the crude α-bromo acid,[10] m. p. 55–57°, and the recrystallized pseudothiohydantoin,[11] m. p. 173–175°. **Thiomalic acid,** m. p. 148–149°, was prepared from bromosuccinic acid and potassium ethyl xanthogenate and hydrolysis with ammonia.[12] *dl*-β-Thiomalamic acid, m. p. 101–103°, was obtained from *l*-asparagine monohydrate (14 g.) through *l*-β-bromosuccinamic acid,[13] m. p. 145–147°, *dl*-β-iodosuccinamic acid,[14] m. p. 115–117°, and the xanthogen derivative,[14] m. p. 123–125°.

**Thiol Additions.**—Table I summarizes the yields, properties, and analyses of products isolated from the addition of various thiols to 2-methyl-1,4-naphthoquinone. Further details concerning the reactions are recorded in the following notes.

The best result with **thioglycolic acid** was obtained by adding a solution of 9 g. of this reagent in 25 cc. of ethanol to a solution (25°) of 17.6 g. of methylnaphthoquinone in 400 cc. of ethanol. The solution was allowed to stand at 25° overnight, when it had become dark red, and the bulk of the solvent was removed in vacuum. The residue was shaken with aqueous sodium hydrosulfite solution (since the quinone seemed to be subject to destruction by alkali), and the product was taken up in ether and extracted with five portions of sodium carbonate solution containing a little hydrosulfite. The combined extract was washed once with ether, acidified with acetic acid, and the hydroquinone was extracted with ether and the dried ethereal solution shaken for one-half hour with 3 g. of silver oxide and 3 g. of anhydrous magnesium sulfate. The solid recovered from the resulting bright yellow solution was crystallized from benzene–ligroin and afforded 6.92 g. of satisfactory substituted quinone in two crops, m. p. 158–160° (6.2 g.) and 156–158°. The yield dropped from 27 to 18% when only 0.5 mole of thiol was employed.

The reaction mixture from the addition of **benzylmercaptan** was reduced and an ethereal solution extracted with 2% potassium hydroxide containing hydrosulfite to remove methylnaphthohydroquinone; the residual ether solution was dried and shaken with silver oxide; removal of the solvent gave an oil that soon solidified.

The reaction product obtained in the same way from *s*-**butyl mercaptan** (1.87 g.) was an oil that failed to crystallize. The oil was therefore reduced by shaking an ethereal solution with aqueous hydrosulfite and the ether was replaced by ligroin and the solution chilled. The hydroquinone separated as a white crystalline solid that on two recrystallizations gave rosets of white needles,

(4) Fieser, THIS JOURNAL, **61**, 2559 (1939).

(5) Reaction of bromosuccinic acid with ammonia to give β-hydroxysuccinamic acid, Lutz, *Ber.*, **35**, 2462 (1902).

(6) Piutti, *Gazz. chim. ital.*, **18**, 457 (1888).

(7) Bancroft and Ridgway, *J. Phys. Chem.*, **35**, 2950 (1931).

(8) All melting points are corrected.

(9) Backer and Dykstra, *Rec. trav. chim.*, **51**, 289 (1932).

(10) Hell and Sadomsky, *Ber.*, **24**, 2388 (1891).

(11) Nicolet and Bate, THIS JOURNAL, **49**, 2064 (1927).

(12) Billmann, *Ann.*, **339**, 351 (1905).

(13) Kallenberg, *Ber.*, **50**, 90 (1917).

(14) Holmberg and Lenander, *Arkiv. Kemi, Mineral Geol.*, **6**, No. 17 (1917).

TABLE I

3-SUBSTITUTED 2-METHYL-1,4-NAPHTHOQUINONES OBTAINED FROM THIOLS

| No. | 3-Substituent | Thiol addition in ethanol Moles thiol | Yield, % | Cryst. solvent | M. p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | —$SCH_2CO_2H$ | 1.0 | 27 | $C_6H_6$–lig. | 159.6–161.2 | $C_{13}H_{10}O_4S$ | 59.33 | 3.84 | 59.49 | 4.06 |
| 2 | —$SCH_2C_6H_5$ | 1.0 | 28 | MeOH | 71.5–72.5 | $C_{18}H_{14}O_2S$ | 73.44 | 4.79 | 73.40 | 4.68 |
| 3 | —$SCH(CH_3)C_2H_5$ | 1.0 | 18 | | Oil | $C_{15}H_{16}O_2S$ | 69.20 | 6.19 | 68.95 | 6.02 |
| 4 | —$SCH(CO_2H)C_{16}H_{33}$-*n* | 0.5 | 59 | EtOH | 103.8–104.5 | $C_{29}H_{42}O_4S$ | 71.57 | 8.70 | 71.50 | 8.76 |
| 5 | —$SCH_2CH_2CH(NH_2)CO_2H$ | .5 | 70 | | 200.2–201.4 dec. | $C_{15}H_{15}O_4NS$ | 59.00 | 4.95 | 58.79 | 5.05 |
| 6 | —$SCH(CO_2H)CH_2CO_2H$ | 1.0 | 50 | EtOH–$H_2O$ | 183.4–184.4 | $C_{15}H_{12}O_6S$ | 56.24 | 3.78 | 56.38 | 3.94 |
| 7 | Anhydride | | | $C_6H_6$–lig. | 149–150 | $C_{15}H_{10}O_5S$ | 59.59 | 3.33 | 59.80 | 3.41 |
| 8 | —$S(CO_2H)CH_2CONH_2$ | 0.5 | 14 | EtOH–$H_2O$ | 169–170 | | | | | |

TABLE II

3-SUBSTITUTED 2-METHYL-1,4-NAPHTHOQUINONES BY CONJUGATION

| No. | | Yield, % | M. p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| 9 | —$SCH_2CONHCH_2CO_2H$ | 29 | 193.5–194.0 dec. | $C_{15}H_{13}O_5NS$ | 56.42 | 4.10 | 56.21 | 4.38 |
| 10 | —$SCH(CO_2H)CH_2CONHC_6H_5$ | 96 | 167.2–167.8 | $C_{21}H_{17}O_5NS$ | 63.79 | 4.33 | 63.62 | 4.26 |
| 11 | —$SCH(CO_2H)CH_2CONHC_4H_9$-*n* | 72 | 132.6–133.2 | $C_{19}H_{21}O_5NS$ | 60.78 | 5.64 | 60.72 | 5.87 |
| 8a | —$SCH(CO_2H)CH_2CONH_2$ | 49 | 169.2–170.3 dec. | $C_{15}H_{13}O_5NS$ | 56.41 | 4.10 | 56.56 | 4.19 |
| 12 | —$SCH(CO_2H)CH_2CO$—$N^4$—sulfanilamide | 78 | 187.6–188.2 dec. | $C_{21}H_{18}O_7N_2S_2$ | 53.14 | 3.82 | 52.96 | 4.05 |
| 13 | —$SCH(CO_2H)CH_2CO$—$N^4$—sulfaguanidine | 83 | 198.2–199.6 dec. | $C_{22}H_{20}O_7N_4S_2$ | 51.15 | 3.90 | 51.03 | 4.13 |
| 14 | —$SCH(CO_2H)CH_2CO$—$N^4$—sulfadiazine | 45 | 204.8–206.0 dec. | $C_{25}H_{20}O_7N_4S_2$ | 54.24 | 3.65 | 54.24 | 3.83 |
| 15 | —$SCH(CO_2H)CH_2CO$—$N^4$—sulfapyridine | 24 | 205.5–206.4 dec. | $C_{26}H_{21}O_7N_3S_2$ | 56.49 | 3.84 | 56.49 | 4.06 |
| 16 | —$SCH(CO_2H)CH_2CO$—$N^4$—sulfathiazole | 55 | 204.1–205.0 dec. | $C_{24}H_{19}O_8N_3S_3$ | 51.69 | 3.43 | 51.56 | 3.59 |

m. p. 75–76°. Oxidation of an ethereal solution of this material with silver oxide and magnesium sulfate gave a bright orange oil that resisted attempts to effect crystallization.

A mixture prepared from cold solutions of 2.3 g. of α-mercaptostearic acid in 30 cc. of alcohol and 2.5 g. of methylnaphthoquinone in 70 cc. of alcohol rapidly deepened in color and deposited a bright yellow solid. After eight hours the mixture was chilled in ice and the product collected (2.1 g., m. p. 97.2–100.5°). The recrystallized product formed long, thin microplates; it is soluble in alcohol, ether or ligroin and produces characteristic foaming in aqueous alkaline solutions.

The **homocysteine** derivative (No. 5) could not be recrystallized and hence was prepared by mixing filtered solutions of 1.72 g. of methylnaphthoquinone and 0.68 g. of homocysteine in 200 cc. of alcohol and 20 cc. of water, respectively. The solution rapidly turned dark red, and after twenty minutes golden orange plates began to separate on the walls and bottom of the flask. The product was collected after fifteen hours and washed with water, alcohol and ether. The substance is soluble in dilute hydrochloric or acetic acid, and in soda solution, but is insoluble in the usual organic solvents.

A solution of 4 g. of **thiomalic acid** and 4.8 g. of methylnaphthoquinone in 200 cc. of absolute ethanol was allowed to stand overnight and then shaken with silver oxide and magnesium sulfate for fifteen minutes. The resulting red-brown solution was concentrated and reduced with aqueous hydrosulfite solution, and a small amount of methylnaphthoquinone that separated was removed by filtration. The filtrate was extracted with ether and the extract shaken with silver oxide–magnesium sulfate and the yellow ethereal solution clarified with Norit and evaporated. The residual product was crystallized first from benzene containing a little alcohol by the addition of ligroin, and recrystallized from alcohol–water. The **anhydride** (No. 7) was prepared by heating the dibasic acid (3 g.) with acetic anhydride (5 cc.) on the steam-bath for two hours; the solution was concentrated to dryness at reduced pressure and the residue crystallized from benzene–ligroin (2.6 g., m. p. 148–149°, 92%). A thrice recrystallized sample formed rosets of bright yellow needles.

The reaction product No. 8 from ***dl*-β-thiomalamic acid** was obtained by evaporating the solvent (after four hours) and triturating the residue with ether. The yellow solid was recrystallized twice from dilute alcohol.

**Amide Conjugates.**—The properties and analyses of the conjugates are recorded in Table II; notes concerning the preparations are given in the following paragraphs.

**S-(2-Methyl-1,4-naphthoquinonyl-3)-thioglycolylglycine** (No. 9) was prepared best from the acid chloride obtained by heating 350 mg. of the acid (no. 1) with 2 cc. of pure thionyl chloride in a bath at 60° for one hour. The residue remaining after removal of excess reagent in vacuum was treated in 5 cc. of dioxane with 200 mg. of glycine in hot acetic acid solution. The solution was heated for one-half hour on the steam-bath and then diluted with water, extracted with ethyl acetate, and the extract washed three times with water. The dried extract after concentration deposited 122 mg. (29%) of product, m. p. 193–194°, dec. The substance crystallizes from alcohol in minute yellow needles. The yield was only 5% when phosphorus trichloride was used in the first step and the reaction with glycine conducted in the presence of sodium carbonate.

**Reactions of S-(2-Methyl-1,4-naphthoquinonyl-3)-thiomalic Anhydride (No. 7).**—When a boiling benzene solution of 200 mg. of No. 7 was treated with 0.06 cc. of **aniline** the product (No. 10) separated immediately; m. p. 165–167°. Crystallization from dilute alcohol gave clusters of fine, bright yellow needles. A similar reaction with ***n*-butylamine** gave a red oil that could not be purified. A satisfactory procedure consisted in adding 25 mg. of *n*-butylamine plus one equivalent of acetic acid to 100 mg. of no. 7 in 5 cc. of dioxane at room temperature. After standing overnight the solution, which was still clear yellow, was concentrated to a volume of about 1 cc. and diluted with water. The oil that separated soon solidified and afforded 90 mg. of product, m. p. 133–137°. The substance (No. 11) crystallized from benzene–ligroin in clusters of light yellow microprisms.

The reaction with **ammonia** was conducted by adding

55 mg. of ammonium acetate to a solution of 155 mg. of the anhydride in 5 cc. of ethyl acetate and 1 cc. of acetic acid. After standing overnight the solution was diluted with ligroin and chilled, when 80 mg. of the amide No. 8a separated, m. p. 160.6–162.4°. Crystallization from dilute alcohol gave a yellow powder that gave no depression when mixed with material prepared as described above (No. 8).

For conjugation with **sulfanilamide,** a solution of 302 mg. of the anhydride and 172 mg. of the amine in acetone was allowed to stand for one hour, concentrated, and the yellow solid that separated crystallized from alcohol–water; 370 mg., m. p. 185.6–188.2°. The substance (No. 12) forms small yellow crystals; it is soluble in alcohol, acetone, and dilute sodium bicarbonate solution. The reaction with **sulfaguanidine** was conducted similarly in acetone and the product precipitated by saturating the solution with ether (m. p. 197–198.5°); recrystallization from methyl cellosolve–water gave a yellow microcrystalline powder. The conjugate is soluble also in ethylene glycol and in dilute sodium carbonate solution and somewhat soluble in alcohol and in acetone. Treatment with sodium nitrite and acetic acid at 0°, followed by the addition of alkaline β-naphthol solution, resulted in no coloration, whereas sulfaguanidine on similar treatment gave a brilliant purple solution. The amide from **sulfadiazine** was obtained in the same way and purified by dissolving it in a mixture of hot ethylene glycol (readily soluble) and methyl cellosolve (to moderate the temperature) and adding water; the substance is practically insoluble in most solvents. The amide from **sulfapyridine**, prepared in acetone at 25°, is moderately soluble in dioxane or methyl cellosolve and was crystallized from the latter solvent diluted with water. The reaction of the anhydride (400 mg.) with **sulfathiazole** (340 mg.) was conducted in boiling acetone and the product that separated was recrystallized from ethyleneglycol–methyl cellosolve–water; like the related amides, the substance was obtained as an orange microcrystalline powder.

## Summary

Several 2,3-disubstituted naphthoquinones of types thought to possess potentialities for biological activity were prepared by the addition of mercaptans to 2-methyl-1,4-naphthoquinone. The quinone obtained from thiomalic acid was conjugated through the anhydride with several amines.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE 38, MASSACHUSETTS RECEIVED APRIL 23, 1947

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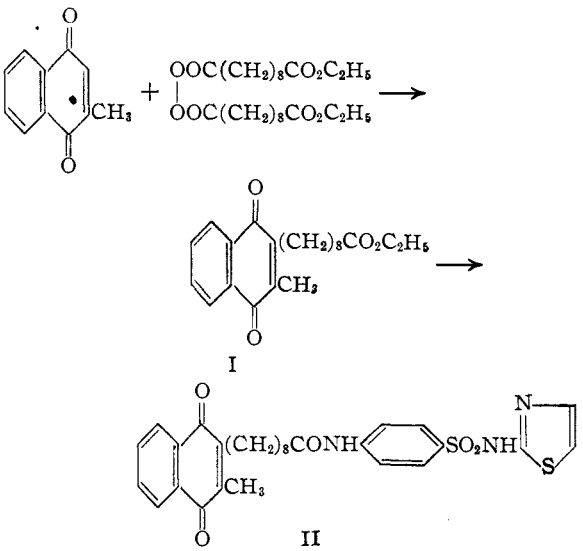
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# Naphthoquinone Acids and Ketols[1]

BY LOUIS F. FIESER AND RICHARD B. TURNER

For an extension of the project outlined in the preceding paper[2] a satisfactory route was sought to 1,4-naphthoquinones with an acidic side chain in the 2-position and a protective methyl group at position 3. Fieser, Gates and Kilmer[3] obtained γ-(1,4-naphthoquinonyl-3)-butyric acid by a rather lengthy synthesis but found that the reaction with lead tetraacetate[4] afforded the methyl-substituted derivative in only 3.8% yield. C-Methylation of the same acid with diazomethane[5] was tried in the present work and found to give no better results. The introduction of the acid side chain by the reaction of the half ester of a dibasic acid with methylnaphthoquinone and red lead according to one of the procedures of Fieser and Chang[4] also proved unsatisfactory (5.6% yield). When, however, the procedure for effecting alkylation with a diacyl peroxide was discovered,[6] this method was tried and found to be well adapted to the problem at hand. Disuccinoyl and diglutaroyl peroxide, obtainable from the anhydrides and alkaline hydrogen peroxide, react with methylnaphthoquinone in hot acetic acid to give methylnaphthoquinonylpropionic and butyric acids in yields up to 40%. The peroxide obtained from ethyl hydrogen sebacate through the acid chloride affords the pelargonic ester I in 41% yield. The one-step synthesis thus provides an easy route to naphthoquinone acids of the type sought.




The acid derived from I was conjugated through the acid chloride with each of four sulfonamide drugs to products exemplified by II. In another series of reactions the acid chloride III was converted through the diazoketone to the ketol IV and its acetate. 2-Hydroxy-1,4-naphthoquinone was similarly alkylated with disebacoyl peroxide

(1) From the doctoral dissertation of Richard B. Turner, May 1, 1942. The research was assisted by a fellowship from the Allied Chemical and Dyestuff Corporation in 1941–1942.

(2) Fieser and Turner, THIS JOURNAL, 69, 2335 (1947).

(3) Fieser, Gates and Kilmer, *ibid.*, 62, 2966 (1940).

(4) Fieser and Chang, *ibid.*, 64, 2043 (1942).

(5) Fieser and Peters, *ibid.*, 53, 4080 (1931); Fieser and Hartwell, *ibid.*, 57, 1479 (1935); Bergmann and Bergmann, *J. Org. Chem.*, 3, 128 (1938).

(6) Fieser and Oxford, THIS JOURNAL, 64, 2060 (1942).