similar shift due to C—O—C vibration was observed in the 8.3 μ region.[9]

EXPERIMENTAL

The esters were prepared by the procedure of Kramer *et al.*[1] Procedure A was used to obtain the red isomer while procedure B, using pyridine yielded the orange product. The analyses, melting points, and spectral characteristics of the esters have been previously reported.[1]

Spontaneous hydrolysis. A 2 × $10^{-3}M$ solution of the ester in dioxane was aliquoted and diluted with tris buffer *p*H 8.5 so as to obtain a 2 × $10^{-5}M$ solution. This solution was placed in a DU spectrophotometer cell at room temperature and its absorbance obtained at the λ_{max} of the hydrolysis product at 10 minute intervals for 1 hr. *vs.* a blank containing no ester. This was repeated at 5° intervals, from 25° to 45°. The buffer was thermostated at the working temperature and adjusted to *p*H 8.5 against standard buffer which was maintained at room temperature. This thermostated buffer was then used in the hydrolysis study. The Beckman DU spectrophotometer's cell compartment was maintained at the investigative temperature by the use of thermospacers and a circulating bath. The extinction coefficient and the absorbance values were used to calculate the concentration of hydrolysis product.

Spectral studies. Ultraviolet, visible and infrared spectra were obtained using a Perkin-Elmer Model 13U Spectrophotometer. The ultraviolet and visible spectra were determined in peroxide-free dioxane[11] at concentrations of 2 × $10^{-5}M$ and 2 × $10^{-4}M$ respectively. The infrared spectra were determined in potassium bromide pellets (1 mg. of ester per 200 mg. of bromide) using a sodium chloride prism.

Gas chromatography. The samples were chromatographed on a one foot column with a packing of 30% silicone grease on 40–100 mesh Celite 545. The block temperature was 240° and the column temperature was 200°. A helium flow of 45 ml. per min. was used with 400 ma. on the bridge circuit and a chart speed of 10″/hr. The orange form emerged in 2.5 minutes and the red form in 3.75 minutes. No other peaks appeared. A mixture of the red and yellow samples gave two peaks.

Acknowledgment. The authors are greatly indebted to Dr. P. A. S. Smith and Dr. Paul Goldberg for their many helpful comments in preparing the paper. Also, we wish to thank Mr. L. D. Metcalfe for obtaining the gas chromatograph, and Messrs. H. L. Stroterhoff and N. M. Ingber for their technical assistance.

ARMY CHEMICAL CENTER, MD.

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(11) W. Dasler and C. D. Bauer, *Ind. and Eng. Chem. Anal. Ed.*, **18**, 52 (1946).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Applications of the Nenitzescu Reaction

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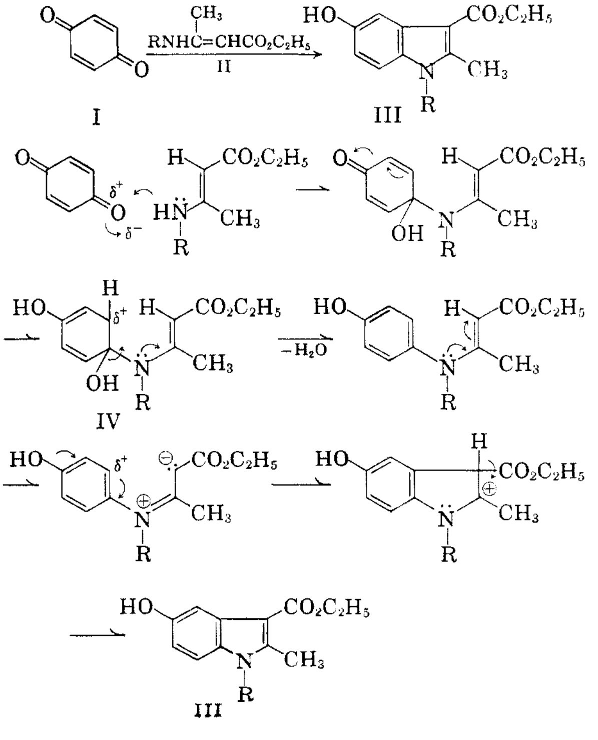
A group of 1-substituted 3-carbethoxy-5-hydroxy-2-methylindoles was prepared from ethyl *N*-substituted β-aminocrotonates and a mechanism proposed for the Nenitzescu reaction.

Several recent publications,[2–7] especially those of Grinev and co-workers,[2–5] have rendered it desirable that we record certain findings in our applications of the Nenitzescu[8,9] reaction for the synthesis of 5-hydroxyindole types. Our interest lay in the use of the indole derivatives as intermediates for other syntheses, and attempts were



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[1] Present address: McNeil Laboratories, Phila. 32, Pa.

[2] A. N. Grinev, N. K. Kul'bovskaya, and A. P. Terent'ev, *Zhur. Obshacei Khim.*, **25**, 1355 (1955); *Chem. Abstr.*, **50**, 4903g (1956).

[3] A. N. Grinev, N. E. Rozdevich, and A. P. Terent'ev, *Zhur. Obschei Khim.*, **27**, 1690 (1957); *Chem. Abstr.*, **52**, 3762b (1958).

[4] A. N. Grinev, I. A. Zaĭtsev, N. K. Venevtseva, and A. P. Terent'ev, *Zhur. Obschei Khim.*, **28**, 1853 (1958); *Chem. Abstr.*, **53**, 1299b (1959).

[5] A. N. Grinev, V. N. Ermakova, and A. P. Terent'ev, *Doklady, Akad. Nauk S.S.R.*, **121**, 862 (1958); *Chem. Abstr.*, **53**, 1167e (1959).

[6] H. J. Teuber and G. Thaler, *Chem. Ber.*, **91**, 2264 (1958).

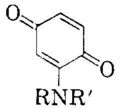
[7] J. H. Koehneke and M. E. Speeter, U. S. Patent **2,707,187**; *Chem. Abstr.*, **50**, 5035e (1956).

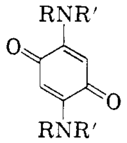
[8] C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110^8 (1930).

[9] R. Beer, K. Clarke, H. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

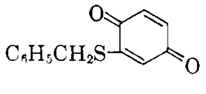
made to improve the yields. The method involved reaction of a 1,4-benzoquinone (I) with a β-aminocrotonic ester (II) in ethanol or acetone to produce a 3-carbethoxy-5-hydroxy-2-methylindole-(III). An ionic mechanism for this transformation is proposed below.

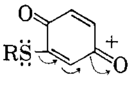
In the present work, which was terminated as a result of several intervening circumstances, a small group of the indole derivatives of structure III was made. The ethyl β-aminocrotonates required for this were made by the method of Michaelis[10] or that of Cope,[11] and included the parent compound, and the *N*-methyl, *N*-hexyl-, *N*-(3-dimethylaminopropyl)-, and *N*-benzyl derivatives. Excellent yields of these were obtained. These esters were subjected to the Nenitzescu reaction, to form the desired compounds, albeit in poor to very poor yields, ranging from 10–35%. Attempts were made to isolate coproducts from the garnet mother-liquors in several instances. It was considered (*cf.* ref. 12) that compounds of structure V or VI might have been formed, however no discrete substances were obtained.


V


VI

This is an aspect of an over-all program designed for the sythesis of compounds having effects on the central nervous system. For several reasons it was desirable to prepare at least one indole type from 2-benzylmercapto-1,4-benzoquinone, VII. Previous workers[4,6,9] have shown preference for the 6-sustituted indole types (IX) as products derived from 2-substituted 1,4-benzoquinones, but without indicating reason for this choice over the alternative types X and XI. Grinev[2] viewed the structure of the product in a noncommital way. From a consideration of structural features in the 2-substituted 1,4-benzoquinones having an *o*-, *p*- directing substituent, we concur with the previous view that 6-substituted indole derivatives do result. In our particular instance, examination of the features present in VII (indicated in detail as VIII) leads us to find the 6-benzylmercapto structure XII to be much preferred, expecially in light of the inductive effects in the intermediates (*e.g.*, IV). It was intended that this feature of the Nenitzescu reaction be demonstrated conclusively through use of the benzylmercapto group, which could be removed readily by hydrogenolysis. Unfortunately for this aspect, conditions now preclude continuation of this work, and the structure XII must be based on mechanistic features. It may be noted that the presence of the 2-substituent (or of 2, 3-disubstitution) on the benzoquinone leads to better yields of product than when 1,4-benzoquinone itself was used. This would be consistent with the intermediate forms in the proposed mechanism and also with probable steric effects, including those in V and VI. The very low yield of the 1-(3-dimethylaminopropyl) type may be ascribable to the presence of the basic group.


VII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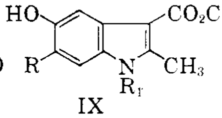
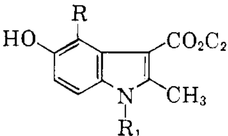
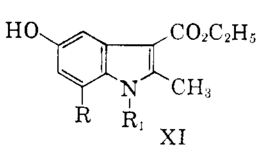
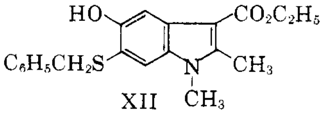

IX


X


XI


XII

EXPERIMENTAL[13]

A. *Ethyl β-aminocrotonates.* The conversion of ethyl acetoacetate to β-aminocrotonate followed the scheme of Michaelis,[10] and the closely related one of Glickman and Cope[11] was used for the β-methylamino compound. In the preparation of the β-aminocrotonic ester derivatives here required, very slight modification of the earlier methods was employed. A 10% excess of amine was added to ethyl acetoacetate, with stirring during 2 to 3 hr., meanwhile maintaining the temperature at 45–50° by adjusting the rate of addition or by cooling in a water bath. After standing at 25° for one day, the mixture was heated at 90–95° for 2 hr., the layers separated, and the crude ester was dried over sodium sulfate. Excellent yields of the ethyl β-aminocrotonates were obtained by fractionation of the crude materials; all were colorless oils.

Ethyl β-hexylaminocrotonate: 92.3% yield; b.p. 108–109° (0.3 mm.); n_D^{25} 1.4852.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.48; H, 10.70; N, 6.60.

Ethyl β-(3-dimethylaminopropylamino) crotonate: 97% yield; b.p. 93–93.5° (0.2 mm.); n_D^{25} 1.4954.

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: N, 13.08; O, 14.93. Found: N,[14] 12.72; O, 14.50.

Ethyl β-benzylaminocrotonate: 88.5% yield; b.p. 129–130° (0.4 mm.); n_D^{25} 1.5554.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.05; H, 7.70; N, 6.41.

B. *2-Benzylthio-1,4-benzoquinone* was prepared by application of the method[15,16] used for 2-phenylthiobenzoquinone rather than that which Alcalay[17] had used. A solution of 64.8 g. (0.6 mole) of benzoquinone in 2.2 l. of ethanol was

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(10) A. Michaelis, *Ann.*, **366**, 337 (1909).

(11) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1019 (1945).

(12) C. J. Cavallito, A. E. Soria, and J. O. Hoppe, *J. Am. Chem. Soc.*, **72**, 2661 (1950).

(13) Melting points are corrected values; boiling points are not. Analyses were carried out under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer in the Analytical Section of this Institute.

(14) Determined by acetous-perchloric acid titration, after the method of G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).

(15) J. M. Snell and A. Weissberger, *J. Am. Chem. Soc.*, **61**, 452 (1939).

(16) O. Dimroth, L. Kraft, and K. Achinger, *Ann.*, **545**, 130 (1940).

stirred at 20° and 37.3 g. (0.3 mole) of benzyl mercaptan in 300 ml. of ethanol was added during 10 min. The mixture became maroon, and then changed to garnet as the temperature rose to 31°. Solid began to separate after about 20 min. After stirring for 1.5 hr., the temperature had fallen to 25°. The red-orange solid was then collected and washed with about 75 ml. of cold ethanol (to remove hydroquinone) and dried, giving 34.0 g. of crude 2-benzylthiobenzoquinone, m.p. 119–121.5°. Evaporation of the filtrates under reduced pressures left a nearly black residue, which was boiled in about 300 ml. of ethanol and the solution chilled. The reddish crystals were collected, washed with about 50 ml. of cold ethanol and dried; 22.2 g. of product melting at 122–123° resulted. Crystallization of the two fractions (81.5% yield) from hexane gave 43.1 g. (62.4% yield, based on benzyl mercaptan) of pure compound as fan-shaped aggregates of orange-red needles, m.p. 124–124.5° (lit.,[17] m.p. 119°).

Anal. Calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; O, 13.90; S, 13.92. Found: C, 68.20; H, 4.36; O, 13.80; S, 14.18.

A ten-fold run gave a 60% yield of 2-benzylthiobenzoquinone (m.p. 123–124°, from carbon tetrachloride) and an alcohol-insoluble fraction (50 g.) which melted over 200°. The latter was crystallized twice from diethylene glycol methyl ether (Methylcarbitol) to give 37.0 grams of lustrous scarlet plates which melted at 230.5–231.5°. This proved to be the 3,6-*bis*(benzylthio) compound, for which Posner and Lipski[18] recorded the m.p. 223–224°.

Anal. Calcd. for $C_{20}H_{16}O_2S_2$: C, 68.15; H, 4.58; S, 18.19. Found: C, 67.90; H, 4.70; S, 18.37.

C. *Nenitzescu reactions.* The limited accessibility of the original work of Nenitzescu[8] renders desirable a recounting of the procedure. It is to be noted that, while the yields were generally very low, the ease of manipulation was considerable. All of the new 1-substituted 3-carbethoxy-5-hydroxy-2-methylindoles were made as described for the parent type.

Ethyl 5-hydroxy-2-methylindole-3-carboxylate. Ethyl β-aminocrotonate (1104 g., 8.55 moles) was dissolved in acetone (6 l.) and an atmosphere of nitrogen was maintained over the stirred solution and the addition of *p*-benzoquinone (970 g., 8.95 moles) made in 20 min. There was little exothermic effect until the red solution was warmed to about 40°, whereupon ensuing reaction caused sufficient liberation of heat to start vigorous boiling. Gentle cooling was applied for some 20 min., after which time, there was refluxing for 0.5 hr. without need for warming. It was further refluxed for 1 hr., and then nearly 5 l. of solvent were removed, with the still under nitrogen. After chilling, the sticky garnet magma was filtered, washed at the pump with 2 l. of cold 1:10 mixture of acetone and pentane, then it was slurried in a minimal amount of acetone and stored in the cold for a day. The crude ester was collected, washed with some cold acetone, and dried. Six hundred forty-three grams (34.3% yield) of light tan solid resulted, m.p. 200–202°. The crude product could be crystallized well from methanol containing traces of sodium dithionite, or from aqueous acetone, however the large batch was more readily purified by a somewhat different method. It was dissolved in hot acetic acid to produce a solution of some 3 liters volume, then hot ethyl acetate was added, after charcoaling, to a total volume of 4 l. The purified ester was collected after chilling, then it was washed with cold ethyl acetate and dried. Ethyl 5-hydroxy-2-methylindole-3-carboxylate was obtained as fine white needles, m.p. 211–212° (lit.[2,3] reports m.p. 205°); the yield was 483 g., or 25.8%. Other preparations of the "Nenitzescu product" gave purified yields of 22–28%, and only intractable gums were obtained from the liquors.

Ethyl 1,2-dimethyl-5-hydroxyindole-3-carboxylate was obtained in 32% yield in the form of cryptocrystals from Methylcellosolve; m.p. 211–212° (lit.[2] m.p. 207–208°).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.91; H, 6.44; N, 6.19.

Ethyl 1-hexyl-5-hydroxy-2-methylindole-3-carboxylate: 22% yield of chalky, cryptocrystalline solid, m.p. 134.5–135° (from cyclohexane).

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.28; H, 8.30; N, 15.83. Found: C, 71.66; H, 8.19; N, 15.70.

Ethyl 1-(3-dimethylaminopropyl)-5-hydroxy-1-methylindole-3-carboxylate hydrochloride was a light tan cryptocrystalline solid, m.p. 267.5–269.5°. It was prepared directly from the crude Nenitzescu product and crystallized repeatedly from aqueous ethanol; the yield of pure product was only 10%.

Anal. Calcd. for $C_{16}H_{22}N_2O_3 \cdot HCl$: N, 8.22; Cl, 10.40. Found: N, 8.25; Cl, 10.43.

Ethyl 1-benzyl-5-hydroxy-1-methylindole-3-carboxylate was a pinkish cryptocrystalline solid as obtained from ethyl acetate, m.p. 196.5–197.5°. The yield was 22%.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; O, 15.52. Found: C, 73.92; H, 6.17; O, 15.85.

Ethyl 6-benzylthio-1,2-dimethyl-5-hydroxyindole-3-carboxylate. 2-Benzylmercapto-1,4-benzoquinone (228 g., 0.99 mole) was caused to react with ethyl β-methylaminocrotonate (144 g., 1 mole) in acetone (1 l.) in the usual manner. The yield of crude product (162 g., m.p. 176–180°) was 46%. It was crystallized from glacial acetic acid to obtain a 38% yield of pure compound in the form of off-white needles, m.p. 182.5–184°.

Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; S, 9.02. Found: C, 67.53; H, 5.68; S, 8.93.

Acknowledgments. The friendly interest of Dr. C. M. Suter has been appreciated as have been the discussions with Drs. J. R. Mayer and J. T. Suh.

RENSSELAER, N. Y.

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[17] W. Alcalay, *Helv. Chim. Acta*, 30, 578 (1947).

[18] T. Posner and J. Lipski, *Ann.*, 336, 150 (1904).

[CONTRIBUTION FROM THE PHYSICAL RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Vinylation Rates of Primary, Secondary, and Tertiary Alcohols

EARL D. HOLLY

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Because of the low acidity of tertiary alcohols and since alkoxide ion is the catalyst, it is necessary to use an alkali metal alkoxide rather than a hydroxide in the vinylation of tertiary alcohols. Relative vinylation rates of *n*-, *sec*- and *tert*-butyl alcohols are reported. It is suggested that F-strain in the transition state accounts for the order of vinylation rates.

The base-catalyzed vinylation of alcohols was reported in 1931 by W. Reppe.[1] At the time of the present work no description of the vinylation of a tertiary alcohol had appeared despite considerable interest in the vinylation reaction.[2–8] Since the

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[1] W. Reppe, U. S. Patent 1,959,927 (1934); Ger. Patent 584,840 (1932); Brit. Patent 369,297 (1932); French Patent 724,955 (1931).

[2] P. B. Reports 40,816; 1112; 13,366; 11,394; 67,694, and 18,842-s.