

NAPHTHOQUINONE SERIES

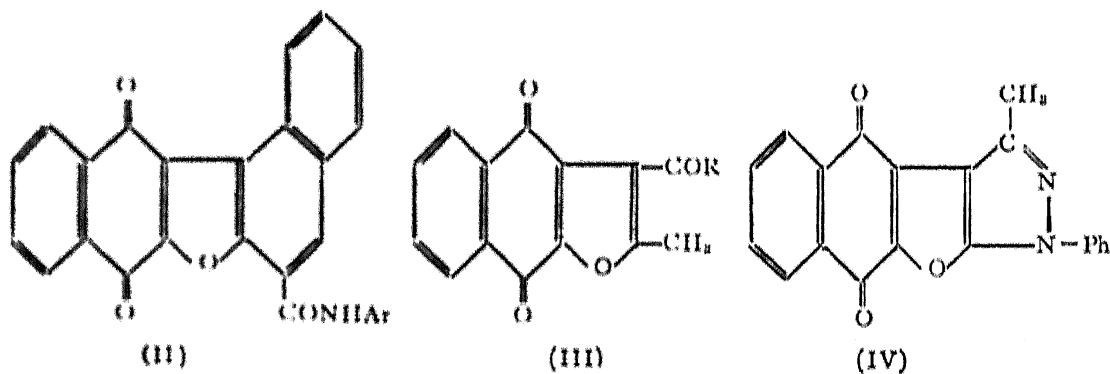
Part V. Reaction of 2:3-Dichloro-1:4-naphthoquinone with β -Ketoesters, Diethyl Malonate, Acetyl Acetone and Acetoacetanilide in Pyridine

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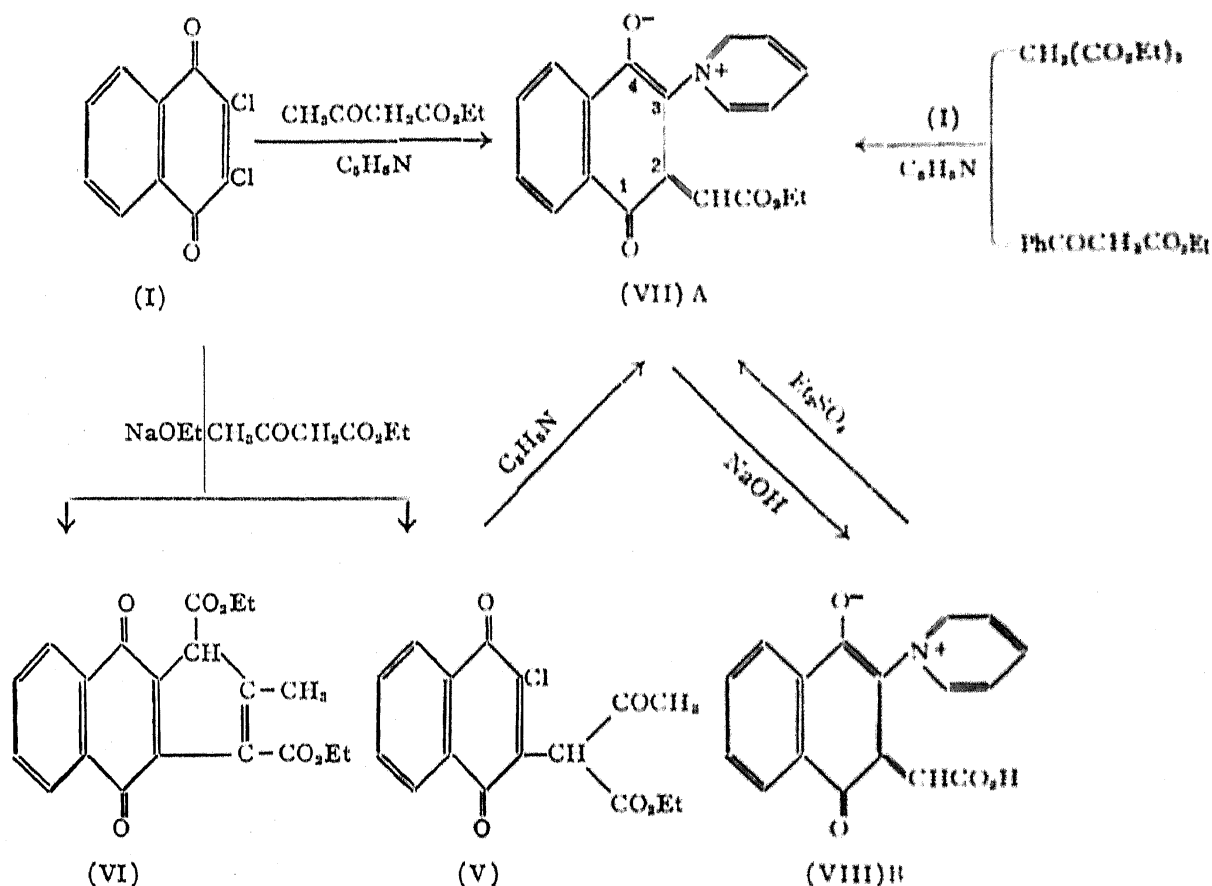
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SYNTHESIS of brazanquinone vat dyes of the type (II) by the condensation of 2:3-dichloro-1:4-naphthoquinone (I) with *o*-hydroxycarboxyarylides in pyridine was described in the previous communications.¹ The present work was initially undertaken with the view to prepare furanonaphthoquinone vat dyes, such as (III), starting from (I) and azoic coupling components containing a reactive methylene group. Condensation of (I) with the latter type of compounds in presence of sodium ethoxide leading to 3-chloro-2-substituted and 2:3-disubstituted 1:4-naphthoquinones has been described in the previous paper.² Ring closure of the latter gives deep coloured naphthindene³ derivatives. Eistert⁴ has likewise observed that



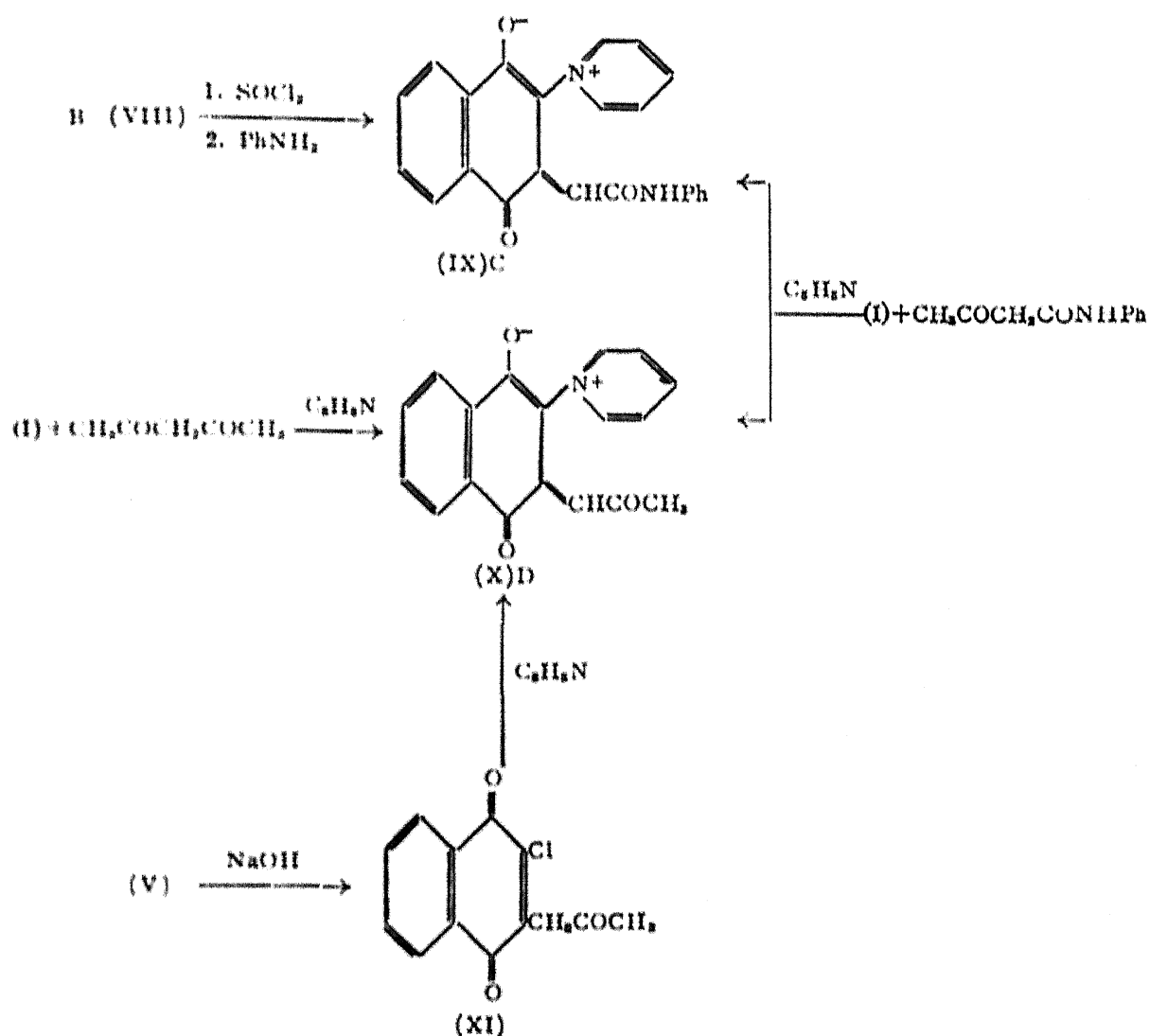
R = Aryl, Alkyl, OEt or NHAr

reaction of (I) with 1-phenyl-3-methyl-5-pyrazolone in the presence of sodium ethoxide leads to an open chain 2:3-bis-pyrazolyl derivative. However, when the above condensation was carried out in pyridine, Eistert obtained the furanonaphthoquinone derivative (IV). It appeared likely therefore that the condensation of (I) with compounds containing a reactive methylene group in pyridine might lead to the desired furanonaphthoquinone derivatives. A brief account of the present work has already been reported by us recently² and the present paper gives further details.



Whereas reaction of (I) with ethylacetoacetate in the presence of sodium ethoxide gave (V) and (VI),³ condensation in pyridine yielded a nitrogen-containing orange quinonoid compound (A). The latter is considered to be 1-keto-2-carboethoxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (VII) on the basis of its properties, elementary composition and the following considerations:

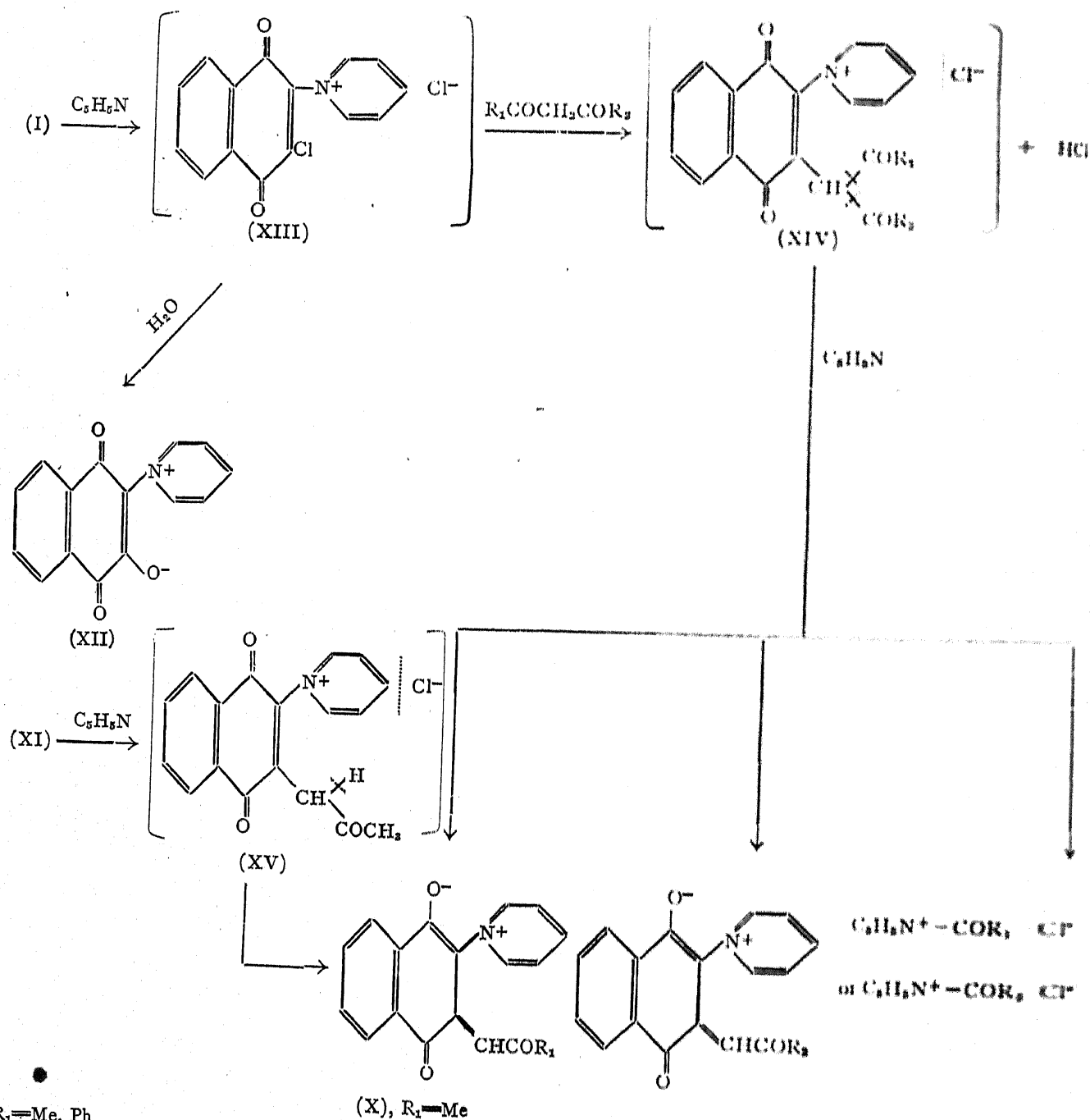
- (1) (A) was also obtained by boiling (V) with pyridine.
- (2) Hydrolysis of (A) with alcoholic sodium hydroxide gives an acid (B) showing the presence of an ester group in (A).
- (3) Esterification of (B) gave back (A), confirming the presence of the carboethoxy group in (A).
- (4) Acid (B) gave the anilide (C) through the acid chloride (using thionyl chloride).
- (5) Condensation of diethyl malonate and ethyl benzoylacetate with (I) in pyridine gave (A).



In view of the above facts, compounds (B) and (C) should be constituted as 1-keto-2-carboxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (VIII) and 1-keto-2-carboxyanilidomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (IX) respectively. The reaction of acetoacetanilide with (I) in pyridine gave two products: (a) violet needles, m.p. 255° , and (b) a red crystalline product (D), m.p. $204-5^\circ$. The former proved to be identical with (C) obtained from (A) through the acid chloride. The product (D) was considered to be 1-keto-2-acetomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (X) on the basis of its elementary analysis and the following considerations:

- (1) Condensation of (I) with acetyl acetone in pyridine gave (D).
- (2) Mild alkaline hydrolysis of (V) gave 2-acetyl-3-chloro-1:4-naphthoquinone (XI), which on treatment with boiling pyridine gave (D).

CHART I

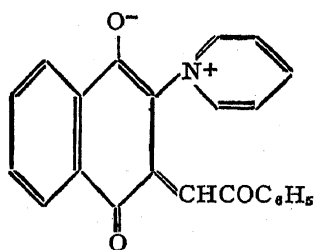


$R_1=Me, Ph$

$R_2=OEt, NPh$

The synthesis of the above compounds is explicable on the basis of the reaction mechanism shown in Chart I. The synthesis of a "pyridinium anhydride" by the reaction of (I) with pyridine was first described by Ullmann and Ettisch,⁵ who suggested that it was formed through an unstable

intermediate such as (XIII). Eistert⁴ later suggested the pyridinium betaine structure (XII) to the above compound. In the reaction of (I) with ethyl acetoacetate also, (XIII) is probably formed and it then reacts with ethyl acetoacetate to give the intermediate compound, such as (XIV). The latter then undergoes fission in two directions leading to (X) and (VII). Simultaneous elimination of a chloride ion and COCH_3 or COR fragments probably takes place with the formation of the corresponding N-substituted pyridinium chlorides. The synthesis of (VII) from (V) is explicable on similar grounds. When (XI) is treated with pyridine, (XV) is probably formed and the latter then leads to (X) with the loss of hydrogen chloride which is taken up by pyridine present.

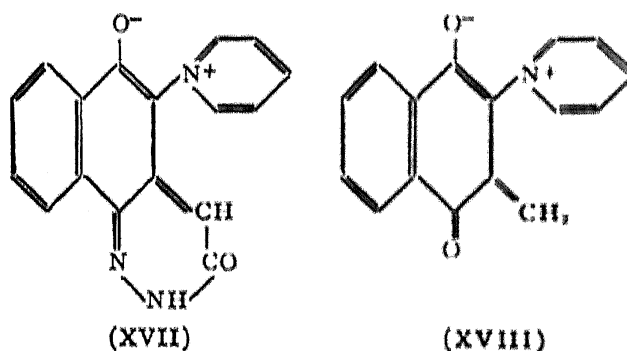


(XVI)

Further evidence in support of the above reaction mechanism was provided by the study of the reaction of (I) with diethyl malonate, ethyl benzoylacetate and acetyl acetone in pyridine. Reaction of diethyl malonate and ethyl benzoylacetate and (I) in pyridine gave (VII). Attempts to isolate (XVI), which may be expected to be formed in the condensation of ethyl benzoylacetate were unsuccessful. In the case of acetoacetanilide, however, both the products of fission, *viz.*, (IX) and (X), were isolated. The reaction of (I) with acetyl acetone gave (X) in good yield. Attempts to isolate N-acylpyridinium chlorides in the above condensations, were unsuccessful. This failure may, however, be due to the known instability of N-acylpyridinium chlorides.⁶

The possibility of the prior formation of (V), in the reaction of (I) with ethyl acetoacetate in pyridine and its subsequent condensation with pyridine to give the intermediate (XIV), was also considered. In order to test this possibility, attempts to synthesize (V) by condensation of (I) with ethyl acetoacetate in the presence of acid binding agents which do not react with (I), such as diethylaniline, were undertaken. These and other attempts to isolate (V) from the reaction of acetoacetic ester with (I) in pyridine, however, proved unsuccessful. These experiments give further support to the reaction mechanism suggested earlier,

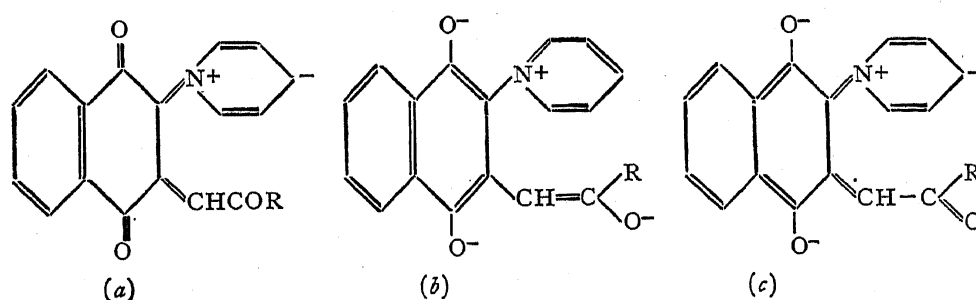
Compounds (VII) to (X) are similar to the enol betaines of the indan-pyridinium series described by Stafford⁷ and probably exist as resonance hybrids of several polar forms. The positive charge is probably fixed on the nitrogen atom whereas the negative charge may be located on several other atoms. The compounds described above have sharp and high melting points, with the exception of the acid (VIII) which melts with decomposition at 307–8°. Their stable nature is illustrated by (VII) which is unaffected by cold concentrated sulphuric acid, hot concentrated hydrochloric acid, a brief treatment with boiling 10% aqueous sodium hydroxide and reduction by alkaline hydrosulphite (brownish red vat) and subsequent reoxidation. The ester group in (VII) does not react with aniline in boiling toluene or with 50% aqueous hydrazine. Although the stability of the carboethoxy group indicates its participation in the polarization of (VII), it nevertheless reacts under vigorous conditions. Thus it is hydrolysed by boiling alcoholic alkali and reacts with boiling alcoholic 85% hydrazine hydrate. The reaction with the latter reagent led to a hydrazide which cyclized *in situ* to give the dihydropyridazone derivative (XVII). Compounds (IX) and (X) are also stable to reduction with hot alkaline hydrosulphite solution, but these and (VII) have no substantivity to cotton.



In view of the decomposition of the acid (VIII) at its melting point, it was decarboxylated when 1-keto-2-methylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (XVIII) was obtained in almost quantitative yield. The latter represents the basic structure from which the above pyridinium oxides are derived.

Colour and vattability of the naphthoquinone pyridinium betaines

The deep colour of the above compounds can be explained on the basis of the combination of the extended conjugated system and the polar nature of the molecule and, in addition, contributing structures such as (a) which involve charge separation in the nitrogen-containing part of the molecule,



Although the above compounds do not contain a *p*-quinone grouping, they are nevertheless vattable probably due to the presence of a pair of carbonyl groups (one of which is in the naphthalene ring) connected by a conjugated chain which forms, in effect, a quinonoid system. A close parallel is the case of pyrimidanthrones⁸ which contain one cyclic carbonyl group and are still vattable, on account of the resonance stabilization of the anion of the leuco compounds. The above pyridinium betaines, on reduction with alkaline hydrosulphite, probably give rise to an anion which is stabilised by resonance between structures such as (b) and (c).

In view of the known antimetabolic activity⁹ of certain naphthoquinones and their general physiological activity, the biological activity of the above and related compounds will be examined.

EXPERIMENTAL

1-Keto-2-carboethoxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (VII)

2:3-Dichloro-1:4-naphthoquinone (I) (9.08 g.) was gradually added to a boiling solution of ethyl acetoacetate (5.2 g.) in pyridine (75 c.c.). The solution quickly changed its colour as follows: olive green → bluish black → brown → reddish brown. The mixture was then boiled under reflux for 3 hours and the clear solution was cooled to 0°. The dark brown sticky product which separated was collected, washed with a little ether and finally triturated with more ether (100 c.c.) before filtration. The brown crystalline residue (6.2 g.), m.p. 148–51°, was recrystallized (norit) from 95% alcohol (300 c.c.), when it gave lustrous orange brown elongated plates (4 g.), m.p. 154°, unaltered by further crystallization and purification by chromatography (Found: C, 70.6; H, 4.4; N, 4.7. $C_{19}H_{15}NO_4$ requires C, 71.0; H, 4.7; N, 4.4%). The ether washings on concentration gave another crop (0.3 g.) of the above product. A further quantity (1.5 g.) was obtained from the pyridine on keeping at 0° for 2 days (total yield 62.5%). Its solutions in benzene and ether are brownish red when concentrated and

yellow when dilute and show strong green fluorescence, whereas its solution in alcohol does not show fluorescence.

Preparation of (VII) from (V)

A mixture of (V) (2.0 g.) and pyridine (20 c.c.) was refluxed for 1½ hours. After gradually cooling to 0°, the mixture was filtered when a brick-red residue (0.7 g.) was obtained. After washing with alcohol and drying, the product, m.p. 145–55°, was extracted with hot benzene (30 c.c.). The orange coloured extract, after treating with norit and concentration, gave orange crystals, m.p. 154–55°; undepressed when mixed with (VII).

1-Keto-2-carboxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (VIII)

An aqueous alcoholic solution (30 c.c. of 75% alcohol) of sodium hydroxide (1.0 g.) was added gradually to a boiling suspension of the ester (VII) (2.5 g.) in alcohol (130 c.c.). Hydrolysis took place almost immediately with the separation (in about 10 minutes) of a pink coloured gelatinous precipitate of the sodium salt of the acid (VIII). Alcohol was then distilled under reduced pressure and the sodium salt was dissolved in boiling water and treated with concentrated hydrochloric acid. The carboxylic acid (VIII), which precipitated on cooling, was collected, washed acid-free (Congo Red) and dried. The crude acid, m.p. 275–80° (decomp.), was crystallized from acetic acid when it gave violet needles (2.0 g.), m.p. 307–8° (decomp.) (Found: C, 69.3; H, 3.5; N, 5.2. $C_{17}H_{11}NO_4$ requires C, 69.6; H, 3.8; N, 4.8%).

Esterification of the acid (VIII)

A mixture of the acid (VIII) (0.1 g.), diethyl sulphate (0.4 c.c.), anhydrous potassium carbonate (1.0 g.) and dry acetone (20 c.c.) was refluxed for 20 hours. The orange-coloured acetone solution was filtered and poured into water. The precipitate (50 mg.), m.p. 140–50°, was crystallized (norit) from alcohol when it gave orange-brown plates, m.p. 154–55°, undepressed when mixed with (VII).

1-Keto-2-carboxyanilidomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (IX) and 1-keto-2-acetomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (X)

A mixture of (I) (1.5 g.), acetoacetanilide (0.85 g.) and pyridine (10 c.c.) was refluxed for 2 hours. After cooling, the mixture was filtered and the crystalline residue was washed with alcohol and ether and dried. The product (0.75 g.), m.p. 239–42°, on recrystallization from pyridine, gave (IX)

as violet-needles, m.p. 255° (Found: C, 74.7; H, 4.1; N, 7.7. $C_{23}H_{16}N_2O_3$ requires C, 75.0; H, 4.4; N, 7.6%).

Dilution of the pyridine mother-liquor with alcohol gave a red coloured precipitate (0.15 g.), m.p. 194–95°, which after crystallization from aqueous pyridine gave (X) as red needles, m.p. 204° (Found: C, 74.6; H, 4.0; N, 5.2. $C_{18}H_{13}NO_3$ requires C, 74.2; H, 4.4; N, 4.8%).

Conversion of (VIII) to (IX)

The acid (VIII) (0.6 g.) was refluxed with thionyl chloride (6.0 c.c.) for 40 minutes when a red coloured product separated. The excess thionyl chloride was removed by distillation under reduced pressure. Dry benzene (15 c.c.) was added and the solvent was removed under reduced pressure. This operation was repeated four times in order to ensure complete removal of thionyl chloride. The residue (acid chloride) was then boiled in dry benzene (50 c.c.) and a solution of aniline (0.6 g.) in benzene (10 c.c.) was added. The colour of the solution quickly changed from orange to deep violet and a crystalline residue separated out gradually. The mixture was refluxed for 5 hours and filtered hot. The product was washed with benzene, dried (0.32 g.) and crystallized from pyridine when it gave violet needles, m.p. 255°. The m.p. of the product was undepressed when mixed with (IX) described above. The filtrate on cooling gave a second crop of red violet needles (0.27 g.), m.p. 252–55°.

3-Chloro-2-acetyl-1:4-naphthoquinone (XI)

A fine powder of (V) (1.0 g.) was gradually added to ice-cold (5°) aqueous sodium hydroxide (20 c.c. of 5%) under stirring. After leaving for 15 minutes the initial blue colour of the solution gradually changed to brown. Dilute hydrochloric acid (15 c.c. 1:2) was added dropwise to the clear solution during 15 minutes keeping the solution vigorously stirred and cooled at 5°. The mixture finally became yellow and a granular precipitate separated. The latter was separated, washed free from acid and crystallized (norit) from 95% alcohol (15 c.c.) when it gave yellow needles, m.p. 147–48° (yield, 0.3 g.), raised to 150–51°, by recrystallization from the same solvent (Found: C, 63.1; H, 3.9. $C_{13}H_9ClO_3$ requires C, 62.8; H, 3.6%).

Compound (XI) was treated with boiling pyridine for 1 hour. Chromatographing a benzene solution of the reaction product on alumina led to the isolation of a red crystalline substance, m.p. 200–5°, which was found to be identical with (X).

Reaction of (I) with diethyl malonate in pyridine

A mixture of (I) (2.27 g.) and dry pyridine (10 c.c.) was gently heated for 15 minutes on a water-bath when a brown resinous solid separated out. Diethyl malonate (2.0 g.) was then added, followed by more pyridine (2 c.c.). The mixture was refluxed for 1½ hours and cooled in ice when a brownish residue (0.9 g.) was obtained, which was identified as the betaine (XII). The mother-liquor was extracted with ether (250 c.c.), the extract washed with dilute hydrochloric acid, water, dried and solvent removed by distillation. The brown coloured residue (0.2 g.) was found to be identical with (VII).

Reaction of (I) with ethyl benzoylacetate in pyridine

A mixture of (I) (4.5 g.) and dry pyridine (20 c.c.) was heated on water-bath as above. Ethyl benzoylacetate (7.6 g.) was then added and the mixture was refluxed for 2 hours. The brown coloured crystalline product (1.0 g.), m.p. 147–49° which separated on cooling, was collected and re-crystallized from alcohol when it gave a crystalline substance which was found to be identical with (VII). The mother-liquor on prolonged standing gave a second crop of the reaction product (1.0 g.).

Reaction of (I) with acetyl acetone in pyridine

A mixture of (I) (2.27 g.) and dry pyridine (10 c.c.) was heated on a water-bath as in the above experiment. Acetyl acetone (1.5 g.) was added and the mixture was refluxed for 2 hours. After cooling to room temperature, the mixture was filtered and the residue (1.25 g.), m.p. 195–200°, was crystallized from benzene when it gave red needles, m.p. 204–5°; un-depressed when mixed with (X) described above.

Synthesis of (XVII) from (VII)

A mixture of (VII) (1.0 g.), 85% aqueous hydrazine hydrate solution (2.0 c.c.) and absolute alcohol (25 c.c.) was refluxed for 6 hours. The solution turned red gradually and a yellow product separated out, which was collected and washed with alcohol. The product (0.95 g.) after three crystallizations from nitrobenzene gave silky yellow needles of (XVII), which did not melt up to 300° (Found: C, 70.7; H, 3.7; N, 14.4. $C_{17}H_{11}N_3O_2$ requires C, 70.6; H, 3.8; N, 14.5%).

1-Keto-2-methylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (XVIII)

The acid (VIII) (0.24 g.) and copper bronze (5 mg.) were refluxed in quinoline (3.0 c.c.) for 1½ hours. The mixture was filtered and the residue was washed with quinoline (2 c.c.). The quinoline extract on cooling to 0° deposited short orange needles which were collected and washed with benzene

(20 c.c.). Yield 50 mg., m.p. 236°. Recrystallization from benzene gave minute orange needles, m.p. 240° (Found: C, 76.8; H, 4.0; N, 6.0. $C_{16}H_{11}NO_2$ requires C, 77.1; H, 4.4; N, 5.6%). Removal of benzene from the washings gave a further quantity (50 mg.) of the product, m.p. 235°. The quinoline mother-liquor on steam distillation gave another crop of the product (0.1 g.) (total yield 98%). The benzene solutions are yellow when dilute and orange red when concentrated and show strong green fluorescence.

SUMMARY

The condensation of 2:3-dichloro-1:4-naphthoquinone (I) with compounds containing a reactive methylene group in pyridine was studied. The reaction of (I) with ethyl acetoacetate in pyridine gave 1-keto-2-carboethoxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (VII). The constitution assigned to (VII) is supported by its alternative synthesis from (I) and diethyl malonate or ethyl benzoylacetate in pyridine. Hydrolysis of (VII) gave 1-keto-2-carboxymethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide which was converted to 1-keto-2-carboxyanilidomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide (IX) and 1-keto-2-methylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide.

The reaction of acetoacetanilide with (I) in pyridine gave (IX) and 1-keto-2-acetomethylenyl-1:2-dihydronaphthalene-3-pyridinium-4-oxide. The latter was also synthesized from 2-chloro-3-acetyl-1:4-naphthoquinone and acetyl acetone by reaction of these substances with (I) in pyridine.

A reaction mechanism to account for the formation of the above compounds is suggested.

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