Hydroquinone and Quinone Derivatives of the (*Z*)- and (*E*)-β-Thiocrotonates[1]

E. CAMPAIGNE and Yasuo ABE[2]

Chemistry Laboratories, Indiana University, Bloomington, Indiana 47401, U.S.A.

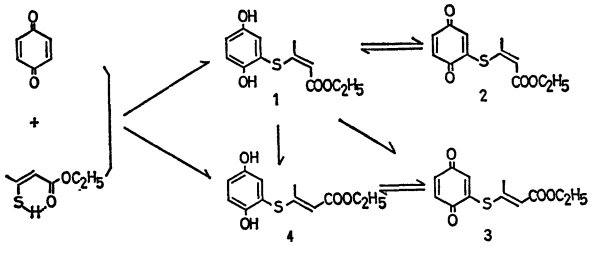
(Received November 4, 1975)

Addition of ethyl thioacetoacetate to *p*-benzoquinone and 1,4-naphthoquinone gave satisfactory yields of the expected ethyl(*Z*)-β-(2,5-dihydroxyphenylthio)crotonate and ethyl(*Z*)-β-(1,4-dihydroxynaphthyl-2-thio)crotonate respectively. In the latter case, at higher temperatures the isomeric ethyl(*E*)-β-(1,4-dihydroxynaphthyl-2-thio)-crotonate was the major product. Oxidation of these compounds with chromic acid gave the corresponding *Z*- and *E*-isomeric quinone derivatives, but oxidation of the *Z*-isomer of the phenyl compound at higher temperatures gave the (*E*)-quinone derivative. All eight isomers in these two series have been isolated, characterized and identified by NMR assignment.

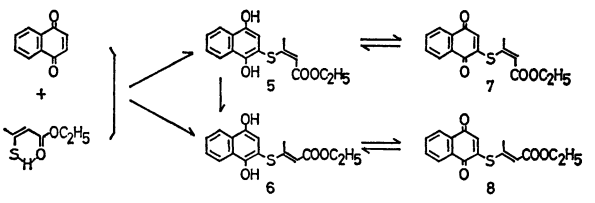
The addition of thiols to *p*-quinones is complicated by the oxidizing power of the quinones, which can oxidize the thiols to disulfides, and oxidize the product hydroquinone to quinone derivatives. This reaction has been discussed in some detail by Snell and Weissberger[3] who found that by deliberately using an excess of quinone, the product could be isolated as the alkyl or arylthioquinone in satisfactory yields from an alcohol solution without added catalyst. Grinev, *et al.*[4] attempted the addition of ethyl thioacetoacetate to *p*-benzoquinone, using zinc chloride as a catalyst, and obtained the desired ethyl β-(2,5-dihydroxyphenylthio)crotonate, in low yield, melting at 176—177 °C. No attempt was made by the authors to assign steric structure to this product. We have reinvestigated the addition of ethyl thioacetoacetate to both *p*-benzoquinone and 1,4-naphthoquinone, and examined the steric structure of products, and also that of the quinones obtained by further oxidation.

Results and Discussion

In Schemes 1 and 2 the reactions and products are outlined. When ethyl thioacetoacetate was mixed with one equivalent of *p*-benzoquinone in ethanol at room temperature a good yield (58%) of ethyl β-(2,5-dihydroxyphenylthio)crotonate of the same melting point as reported by Grinev, *et al.*[4] was obtained. However, concentration of the mother liquors led to the isolation of second isomer, melting at 139—140 °C, in low yield. These two compounds must have the structures shown in Scheme 1 as **1** and **4**. The higher melting compound was assigned the *Z*-configuration **1** on the basis of NMR (see later).



Scheme 1.



Scheme 2.

Oxidation of **1** with chromic acid at 60 °C gave a quinone **2**, whose NMR was consistent with the *Z*-configuration also. The structural relationship of **1** and **2** was confirmed by reduction of **2** with zinc and acetic acid, giving the higher melting isomer **1** again. Surprisingly, oxidation of **1** with chromic acid at 75 °C led to the formation of a mixture which contained a different, higher melting isomeric quinone, the NMR of which indicated the *E*-configuration **3**. This compound was reduced to the lower melting isomeric ethyl β-(2,5-dihydroxyphenylthio)crotonate, assigned the *E*-configuration **4**, consistent with its NMR spectrum. Oxidation of **4** gave a nearly quantitative yield of **3**.

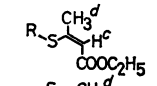
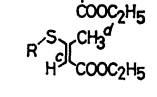
Finally, heating **1** in acetic acid containing a catalytic amount of hydrochloric acid produced a mixture of **1** and **4**. The reverse isomerization did not occur under these conditions, nor was **2** converted to **3** under these conditions. Nevertheless, it seems reasonable to assume that **1** is the kinetically favored product of the addition of the (*Z*)-thioacetoacetic ester (stabilized by hydrogen bonding) to the quinone, but that the *E*-form, **4**, is thermodynamically favored.

Similar observations were made when ethyl thioacetoacetate was allowed to react with 1,4-naphthoquinone in alcohol solution. If care was taken to keep the solution below 40 °C, even during concentration, the crystalline product, melting at 172.5—173 °C, obtained in satisfactory yield, had the *Z*-configuration (**5**) by NMR (Scheme 2). The configuration of pure **5** was maintained at the reflux condition in alcohol. Alternatively, if a similar solution was heated with steam during work-up, and recrystallized from alcohol then a different product melting at 170—171 °C, assigned the *E*-configuration **6** was obtained as a major product. The nearness of melting points of these two isomers complicated the experimental work. However, NMR characteristics are distinctive, and the melting points of the oxidation products are quite different.

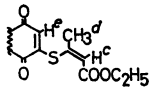
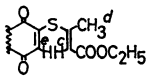
Oxidation of **5** with chromic acid at 60 °C gave the corresponding naphthoquinone **7**, also having the *Z*-configuration, and melting at 97—98 °C, while similar treatment of **6** gave a nearly quantitative yield of

TABLE 1. NMR δ VALUES FOR SELECTED PROTONS OF (*Z*)- AND (*E*)-β-THIOCROTONATES

A. β-Arylthio Derivatives

		R=benzyl[a]	R=2,5-dihydroxyphenyl	R=1,4-dihydroxynaphthyl
	*d*	2.15 (d, 3H, J=1.0)	1.86 (d, 3H, J=1.0)	1.85 (d, 3H, J=1.4)
	c	5.72 (q, 1H, J=1.0)	5.83 (q, 1H, J=1.0)	6.01 (q, 1H, J=1.4)
	*d*	2.39 (d, 3H, J=0.9)	2.34 (d, 3H, J=1.0)	2.43 (d, 3H, J=1.1)
	c	5.61 (broad)	5.17 (q, 1H, J=1.0)	5.23 (q, 1H, J=1.1)

B. p-Quinone Derivatives

		benzoquinone	naphthoquinone
	*d*	2.09 (d, 3H, J=1.0)	2.19 (d, 3H, J=1.3)
	c	6.16 (q, 1H, J=1.0)	6.37 (q, 1H, J=1.3)
	e	6.73 (d, 1H, J=2.5)	7.01 (s, 1H)
	*d*	2.45 (d, 3H, J=0.9)	2.55 (d, 3H, J=1.1)
	c	6.23 (q, 1H, J=0.9)	6.42 (q, 1H, J=1.1)
	e	6.45 (d, 1H, J=2.8)[b]	6.73 (s, 1H)

a) Values from Ref. 5. b) Isopropylthiobenzoquinone shows this proton (*e*) at δ 6.36 (d, 1H, J=2.1 Hz). See Experimental.

ethyl(*E*)-β-(1,4-naphthoquinonyl-2-thio)crotonate, **8**, melting at 119—120 °C. Oxidation of **5** at 75—85 °C gave **7**, but did not give **8** in contrast with the reaction of **1** at the same condition. The reduction of **7** to **5** with zinc dust was quantitative, and **8** did produce **6**, but the reduction was much less facile than with the other quinones. Finally, heating **5** in acetic acid with added hydrochloric acid gave a mixture of isomers, in which **6** predominated, by NMR spectra.

Z- and *E*-isomers of *S*-alkyl derivatives of thioacetoacetic ester, have been examined by Hedegaard, Mortensen, and Lawesson.[5] Alkylation of ethyl thioacetoacetate gave a mixture of the (*Z*)- and (*E*)-β-alkylthiocrotonates, separable by distillation, in a ratio of about 3 to 1. The NMR chemical shifts for the vinyl methyl and vinyl protons of the *Z*- and *E*-isomers of the benzyl derivatives, as assigned by these authors, are shown in Table 1 as reference points. The values are consistent with values assigned to the *cis* and *trans* methyl groups in β,β-dimethylacrylic acid by Anet and Bourn[6] using Nuclear Overhauser effects. These authors assigned the upfield doublet (δ 1.42) to the methyl group *cis* to hydrogen, and the downfield doublet (δ 1.97) to the methyl group *cis* to carboxyl, as predicted by deshielding effects of the carboxyl group.

We have tabulated the significant δ values for our compounds in Table 1. The chemical shifts for the vinylic methyl groups and protons for the arylthio derivatives are shown in part A. Note that the deshielding effect of the *cis*-carboxyl group shows quite well, as the *E*-isomers both show chemical downfield shifts of approximately 0.50 ppm for the vinyl methyl group. On the other hand, a strong shielding effect of the arylthio group on the vinylic protons is observed in the *E*-isomers, which show upfield chemical shifts of about 0.70 ppm over values for this proton in the *Z*-series.

The p-quinone derivatives are compared in part B of Table 1. The chemical shifts for the vinylic methyl groups are consistent with the expected deshielding effect of a *cis* carboxyl group over that of a *trans* carboxyl, equal to about 0.36 ppm in each pair of isomers. However, in this case the vinylic hydrogens in the *E*-isomers show a weak deshielding, (0.06±0.01 ppm) probably the effect of the adjacent p-quinone, held partially coplanar by conjugation through the sulfur atom. The adjacent thiocrotonic ester exerts an interesting effect on the protons at the 3-position of the quinone (labeled *e* on Table 1B). These protons in the *Z*-isomers appear consistently 0.28 ppm downfield from the absorption of their counterparts in the *E*-isomers, due, apparently, to a deshielding of this proton by the carboxylic ester group in the *Z*-structures, not possible in the *E*-configuration. To confirm our identification of this proton, a sample of isopropylthiobenzoquinone, previously reported[3] was synthesized and its NMR spectra determined. The ring proton at the upfield position at δ 6.36 is clearly the 3-proton, shielded by the adjacent alkylthio group. The assignment of the 3-proton in the naphthoquinone series is simpler, since it is the only possible singlet.

Experimental

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. NMR spectra were determined on a Varian Associates EM 360 spectrometer (60 MHz) using TMS as an internal standard, and mass spectra on a Varian Associates MAT CH-7 spectrometer. IR spectra were determined on a Perkin-Elmer Model 137-B Infracord Spectrometer using potassium bromide disks. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Indiana, U.S.A.

*Ethyl (Z)-β-(2,5-Dihydroxyphenylthio)crotonate (**1**).* *a)* To a solution of 15.0 g (0.14 mol) of p-benzoquinone in 200 ml of ethanol was gradually added, with stirring, an ethanol solution of 22.8 g (0.16 mol) of ethyl thioacetoacetate, prepared by the method of Mitra.[7] The reaction mixture turned red and became warm, but after 30 min the color faded to pale brown or tan. Ethanol was removed on a flash evaporator, and the residual oil taken up in warm ethyl acetate. Addition of warm benzene to cloudness and

cooling produced 20.4 g (58%) of **1** as white crystals, mp 174—175 °C (lit,[4] 176—177 °C). NMR (Acetone-d_6): δ 1.23 (t, 3H, J=7 Hz), 1.86 (d, 3H, J=1 Hz), 4.10 (q, 2H, J=7 Hz), 5.83 (q, 1H, J=1 Hz), 6.81—6.89 (m, 3H), 7.84 (s, 2H).

Concentration of the mother liquor gave 5.4 g of crude oily solid which NMR analysis showed was a mixture of **1** and the corresponding *E*-isomer **4**, in a ratio of 1 : 4. This was then taken up in hot benzene and recrystallized, giving 2.1 g (6%) of **4**, mp 138—139 °C (see later).

b) A solution of 1.0 g of ethyl (*Z*)-β-(*p*-benzoquinonylthio)-crotonate (**2**, see later) in 25 ml of glacial acetic acid was stirred while 1.0 g of zinc dust was added in portions. After 45 min the colorless solution was concentrated to a syrup and water added. The white precipitate was collected and recrystallized from benzene–ethyl acetate, giving 1.0 g (98%), of crystals melting at 171—173 °C, shown to be identical to **1**, above, by congruent IR and NMR spectra.

*Ethyl (Z)-β-(p-Benzoquinonylthio)crotonate (**2**).* Chromic acid (1.0 g, 10 mmol) was added all at once to a stirred solution of 2.54 g (10 mmol) of **1** in 50 ml of glacial acetic acid at 60 °C. The temperature was maintained at 60 °C for 10 min, after which the orange solution was poured over 300 g of ice. The precipitate was collected and washed with water, then taken up in benzene and washed again. The benzene extract was dried ($MgSO_4$), evaporated, and the solid recrystallized from ethanol to give 1.1 g (44%) of **2**, mp 71—71.5 °C. IR: 1680, 1653, 1640 (C=O), 1567, 1587 (C=C), 1189 cm^{-1} (C–O). NMR: ($CDCl_3$): δ 1.25 (t, 3H, J=7 Hz), 2.09 (d, 3H, J=1 Hz), 4.14 (q, 2H, J=7 Hz), 6.16 (q, 1H, J=1 Hz), 6.70 (dd, 1H, J=2.5, 10.5 Hz), 6.73 (d, 1H, J=2.5 Hz), 6.82 (d, 1H, J=10.5 Hz). MS (*m/e*): 252 (M^+). Found: C, 57.36; H, 4.92; S, 12.94%. Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.79; S, 12.71%.

*Ethyl(E)-β-(p-Benzoquinonylthio)crotonate (**3**).* *a)* Chromic acid (2.0 g, 20 mmol) was added all at once to a stirred solution of 5.1 g (20 mmol) of **1** in 100 ml of glacial acetic acid maintained at 70—75 °C. After 10 min the hot solution was poured directly over ice and the orange precipitate collected and washed with water. The crude product was chromatographed on acidic alumina (Giulini activity Grade 1) eluted with benzene, forming two orange bands. The first fraction gave **3** (0.8 g, 16%) recrystallized from ethanol, mp 83.5—84 °C. IR: 1709, 1645, 1629 (C=O), 1555 (C=C), 1186 cm^{-1} (C–O). NMR ($CDCl_3$): δ 1.28 (t, 3H, J=6.9 Hz), 2.45 (d, 3H, J=0.9 Hz), 4.16 (q, 2H, J=6.9 Hz), 6.23 (q, 1H, J=0.9 Hz), 6.45 (d, 1H, J=2.8 Hz), 6.67 (dd, 1H, J=9.5, 2.8 Hz), 6.81 (d, 1H, J=9.5 Hz). MS (*m/e*): 252 (M^+). Found: C, 57.37; H, 4.88; S, 12.92%. Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.79; S, 12.71%.

The second fraction from the column worked up in the same way, gave 1.5 g (30% of **2**, identical by melting point and congruent NMR spectra. A mixture melting point of **2** and **3** was depressed.

b) When 0.37 g (1.45 mmol) of ethyl (*E*)-β-(2,5-dihydroxyphenylthio)crotonate (**4**, see later) was oxidized with an equivalent of chromic acid at 60 °C, as described above for the preparation of **2**, the orange precipitate was collected and recrystallized once from ethanol to give 0.31 g (84%) of **3**, mp 80—81 °C, identical with the authentic sample of **3** by IR and NMR spectra without further purification.

*Ethyl (E)-β-(2,5-Dihydroxyphenylthio)crotonate (**4**).* Reduction of 1 g (4 mmol) of **3** with zinc dust in glacial acetic acid, as described for the preparation of **1** (*b*) gave 0.97 g (96%) of white crystals from benzene, mp 139—140 °C. IR: 3356 (OH), 1686 (C=O), 1603 cm^{-1} (C=C). NMR (Acetone-d_6): δ 1.13 (t, 3H, J=7 Hz), 2.34 (d, 3H, J=1 Hz), 3.98 (q, 2H, J=7 Hz), 5.17 (q, 1H, J=1 Hz), 6.83 (m, 3H), 7.80 (s, broad, 1H), 7.99 (s, broad, 1H). MS (*m/e*): 254 (M^+). Found: C, 56.50; H, 5.68; S, 12.88%. Calcd for $C_{12}H_{14}O_4S$: C, 56.32; H, 5.58; S, 12.67%.

*Ethyl (Z)-β-(1,4-Dihydroxynaphthyl-2-thio)crotonate (**5**).* To a solution of 20 g (137 mmol) of ethyl thioacetoacetate in 100 ml of ethanol was added 15.0 g (91 mmol) of finely ground 1,4-naphthoquinone all at once with stirring at room temperature. The deep red solution was let stand three days, then evaporated under reduced pressure, taking care to keep the temperature below 40 °C. Cold benzene was added, and the slurry so obtained was filtered, washed with cold benzene, and dried under reduced pressure, recrystallization of the product from ethanol gave 18 g (63%) of white crystals, mp 172.5—173 °C. IR: 3322 (OH), 1667 (C=O), 1590 (C=C), 1198 cm^{-1} (C–O). NMR (Acetone-d_6): δ 1.26 (t, 3H, J=7.2 Hz), 1.85 (d, 3H, J=1.4 Hz), 4.20 (q, 2H, J=7.2 Hz), 6.01 (q, 1H, J=1.4 Hz), 6.96 (s, 1H), 7.65 (m, 2H), 8.33 (m, 3H), 8.77 (s, broad, 1H). MS (*m/e*): 304 (M^+). Found: C, 63.12; H, 5.33; S, 10.34%. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53%.

*Ethyl (E)-β-(1,4-Dihydroxynaphthyl-2-thio)crotonate (**6**).* The above experiment was repeated, except that after all of the naphthoquinone had dissolved, the red solution was refluxed on a steam bath for an hour, then the ethanol evaporated on a steam bath and the residue crystallized by the addition of benzene. On cooling, the white crystals were collected and recrystallized from ethanol, giving 13.2 g (46%) of **6**, mp 170—171 °C. IR: 3333 (OH), 1686 (C=O), 1603 (C=C), 1200 cm^{-1} (C–O). NMR (Acetone-d_6): δ 1.08 (t, 3H, J=7.3 Hz), 2.43 (d, 3H, J=1.1 Hz), 4.00 (q, 2H, J=7.3 Hz), 5.23 (q, 1H, J=1.1 Hz), 6.90 (s, 1H), 7.57 (m, 2H), 8.22 (m, 3H), 8.28 (s, broad, 1H). MS (*m/e*): 304 (M^+). Found: C, 62.86; H, 5.00; S, 10.79%. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53%.

*Ethyl(Z)-β-(1,4-Naphthoquinonyl-2-thio)crotonate (**7**).* Oxidation of 3.1 g (10 mmol) of **5** with an equivalent of chromic acid below 60 °C, as previously described for the conversion of **1** to **2**, gave 2.8 g (94%) of orange crystals (from ethanol), mp 97—98 °C. IR: 1698, 1656 (C=O), 1592, 1565 (C=C), 1200 cm^{-1} (C–O). NMR ($CDCl_3$): δ 1.28 (t, 3H, J=7.1 Hz), 2.19 (d, 3H, J=1.3 Hz), 4.23 (q, 2H, J=7.1 Hz), 6.37 (q, 1H, J=1.3 Hz), 7.01 (s, 1H), 7.85 (m, 2H), 8.15 (m, 2H). MS (*m/e*): 302 (M^+). Found: C, 63.25; H, 4.76; S, 10.32%. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61%.

Oxidation of **5** at 75—85 °C gave orange crystals **7** in 60% yield. The NMR spectra of mother liquor did not show the presence of *E*-isomer **8**.

*Reduction of **7**.* The zinc dust reduction mixture of 1.0 g of **7** in acetic acid (25 ml) was stirred for 40 min, and worked up in the usual manner to give 0.8 g (80%) of **5**, mp 169—171 °C, identified by congruent NMR spectra.

*Ethyl (E)-β-(1,4-Naphthoquinonyl-2-thio)crotonate (**8**).* Oxidation of 1.0 g (2.9 mmol) of **6** with an equivalent of chromic acid in glacial acetic acid at 60 °C, as previously described, gave 0.92 g (92%) of yellow crystals after one recrystallization from ethanol, mp 119—120 °C. IR: 1710, 1658 (C=O), 1592, 1563 (C=C), 1198 cm^{-1} (C–O). NMR ($CDCl_3$): δ 1.33 (t, 3H, J=7.2 Hz), 2.55 (d, 3H, J=1.1 Hz), 4.27 (q, 2H, J=7.2 Hz), 6.42 (q, 1H, J=1.1 Hz), 6.73 (s, 1H), 7.83 (m, 2H), 8.32 (m, 2H). MS (*m/e*): 302 (M^+). Found: C, 63.77; H, 4.76; S, 10.33%. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61%.

*Reduction of **8**.* The zinc dust reduction mixture of 1.0 g of **8** in acetic acid was stirred for several hours, and worked up in the usual manner to give 0.30 g (30%) of **6**,

mp 169—170 °C, identified by congruent NMR spectra. Concentration of the benzene mother liquors gave 0.63 g (63%) of recovered **8**.

Isomerization of Z-Isomers in Acid Solution. A solution of 1.0 g of **1** in 20 ml of glacial acetic acid, to which 0.5 ml of 1 M HCl had been added, was heated to 75 °C for 10 min, then diluted with water and extracted with ether. After drying and concentrating, the residue was subjected to thin layer chromatography on Silica gel G, using chloroform. The R_f range of 0.18—0.37 was collected and extracted with ether, giving 280 mg of crude **4**, mp 130—133 °C. Recrystallization from benzene gave **4**, mp 138—139 °C, identical to an authentic sample by congruent IR and NMR spectra. Extraction of the R_f 0.37—0.59 range gave approximately 500 mg of crude **1**, having a distinct thiolic odor, indicating some decomposition had occurred.

Similar treatment of **4** resulted only in recovery of 95% of **4** unchanged. Likewise, similar treatment of **2** and **3** led to recovery of starting materials in nearly quantitative yields.

A solution of 1.0 g of **5** was heated to 75 °C in 20 ml of glacial acetic acid containing 0.5 ml of 6 M HCl. After 10 min the mixture was poured over 100 g of ice, the precipitate collected, washed with water and dried, giving 0.60 g of crude solid with a definite thiolic odor. Several recrystallizations from ethanol gave a white solid melting at 167—169 °C which by NMR showed the spectrum of **6**, with traces of **5** still present.

Isopropylthiobenzoquinone. Following the procedure of Snell and Weissberger[3] a mixture of isopropylthiol and two equivalents of *p*-benzoquinone were stirred in ethanol at room temperature for 30 min, and worked up as described to yield 32% of yellow crystals, mp 74—76 °C. NMR ($CDCl_3$): δ 1.39 (d, 6H, J=6.6 Hz), 3.27 (m, 1H, J=6.6 Hz), 6.36 (d, 1H, J=2.1 Hz), 6.63 (dd, 1H, J=10, 2.1 Hz), 6.75 (d, 1H, J=10 Hz).

References

1) Contribution No. 2665, Supported by Public Health Service Research Grant GM-10366-12, to Indiana University.

2) On leave from Radiation Center of Osaka Prefecture, Sakai, Osaka, 593 Japan, 1974—1975.

3) J. M. Snell and A. Weissberger, *J. Amer. Chem. Soc.*, **61**, 450 (1939).

4) A. N. Grinev, G. Y. Uretskaya, E. S. Krichevskii, and T. F. Vlasova, *J. Org. Chem. USSR*, **7**, 862 (1971).

5) B. Hedegaard, J. Z. Mortensen, and S. O. Lawesson, *Tetrahedron*, **27**, 3853 (1971).

6) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

7) S. K. Mitra, *J. Indian Chem. Soc.*, **10**, 71 (1933).