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A REINVESTIGATION OF THE REACTION OF p-BENZOQUINONE WITH CYSTEINE ETHYL ESTER: REVISION OF A STRUCTURAL ASSIGNMENT

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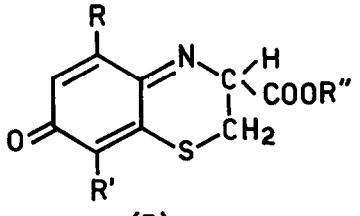
It has been reported[1,2] that cysteine and its ethyl ester react with 1,4-benzoquinones to give mainly cyclic iminoquinones of the type (I). In the light of more recent work[3,4] on similar reactions in the o-quinone series, the isolation of such unstable products appeared improbable, particularly when the previous structure assignment was indefinite. Accordingly, we have repeated the reaction of p-benzoquinone with L-cysteine exactly as originally described by Kuhn[1], and have obtained as reported a dark-brown



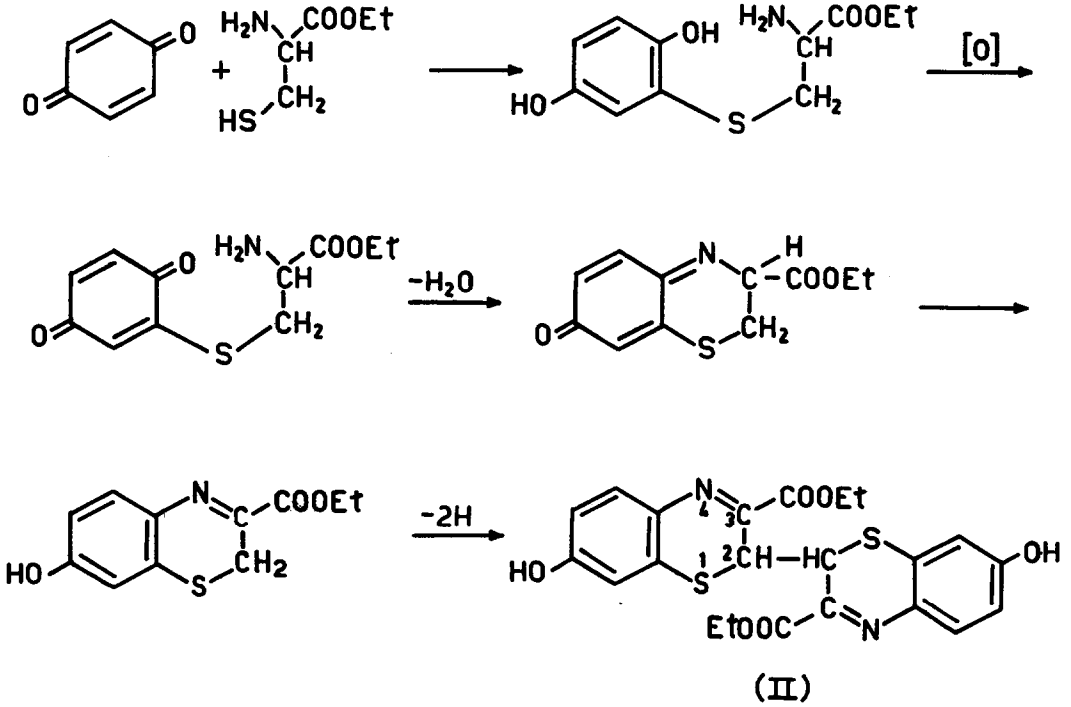
(I)

amorphous powder, rather insoluble in common organic solvents, but soluble in dilute alkalies. However, by t.l.c. on Kiesegel F_{254} (eluent: $CHCl_3$-MeOH 88:12,v/v) it was found that the product was in fact a complex mixture of substances and it was not further investigated.

Reaction of p-benzoquinone with L-cysteine ethyl ester was reported[1] to give a yellow crystalline substance, m.p. 300° (dec.) in 33% yield. The proposed structure (I) (R,R'=H; R''=C_2H_5) cannot account for a broad absorption band at 3250 cm^{-1} in the IR spectrum (Nujol) of the reaction product;

in addition there is no absorption frequency attributable to the quinonoid system proposed in (I). Moreover, t.l.c. on silica ($CHCl_3$-MeOH, 95:5, v/v) showed that the product was a mixture of two yellow substances A (R_f=0.30) and B (R_f=0) which could be isolated making use of their different solubilities in methanol. The UV spectrum of compound A, λ_{max}(MeOH) 368, 274 and 245 nm (log ϵ 3.09, 3.36 and 3.43) was almost identical with that of compound B, λ_{max}(MeOH) 366, 272 and 246 nm (log ϵ 3.07, 3.34 and 3.39), being the chromophore closely reminiscent with that characteristic of 2H--1,4-benzothiazines[5]. Elemental analyses and mass spectrometry[6] showed that the two products were indeed isomers with the molecular formula $C_{22}H_{20}N_2O_6S_2$.

On this basis we assumed that A and B were the two possible diastereoisomers corresponding to the gross[7] structure (II), arising most probably by initial condensation of p-benzoquinone with cysteine ethyl ester, followed by oxidative coupling of the resulting 2H-1,4-benzothiazine intermediate (Scheme I).



(II)

SCHEME I

Because of the unfavourable solubility properties, an NMR spectrum of compound B could not be obtained, but the NMR spectrum[6] of the isomer A, measured in $(CD_3)_2SO$, was in complete agreement with the symmetrical structure (II). Apart from the signals arising from the two carbethoxyl groups, the spectrum exhibits a sharp singlet at 4.09 δ (2H), which is assigned to the C-2 protons of the thiazine rings[5], a singlet at 6.74 δ for the two aromatic protons at C-8, a doublet of doublets at 6.82 δ (J 8.0 and 2.2 Hz) for the protons at C-6, and a doublet at 7.45 δ (J 8.0 Hz) which accounts for the remaining protons at C-5.

Thus, the results of this investigation provides evidence that the reaction of 1,4-benzoquinones with L-cysteine ethyl ester follows a pathway which is essentially similar to that observed in the o-quinone series.

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REFERENCES

1. R. Kuhn and H. Beinert, Ber. 77, 606 (1944).

2. R. Kuhn and I. Hammer, Ber., 84, 91 (1951).

3. W.S. Powel and R.A. Heacock, Can. J. Chem., 47, 2102 (1969).

4. G. Prota, O. Petrillo, C. Santacroce and D. Sica, J. Heterocyclic Chem., 7, 555 (1970).

5. D. Sica, C. Santacroce and G. Prota, J. Heterocyclic Chem., 7, 1143 (1970).

6. Elemental analyses gave for compound A : C, 55.52; H, 4.65; N, 5.93; S, 13.32%; M^+ 472, and for compound B : C, 55.72; H, 4.68; N, 5.89; S, 13.29%; M^+ 472, $C_{22}H_{20}N_2O_6S_2$ requires : C, 55.91; H, 4.27; N, 5.93; S, 13.57%; M 472.
The mass spectra were obtained with an AEI MS-902 spectrometer using

the direct inlet system at an ionization potential of 70 eV (probe temperature 230° ca.).

7. The relative stereochemistry of the bi-benzothiazine isomers (TT) has not yet been investigated.

8. The NMR spectrum was recorded with a Perkin-Elmer R-12A spectrometer with internal TMS reference.