

**Preparation of Peptide-like 2,5-Disubstituted
p-Benzoquinone Derivatives,
Peptide-like Polyoxo Compounds*. II****

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A description is given of the reaction products of p-benzoquinone with glycine benzyl ester [Ic], with β -alanine ethyl ester [Id] and with glycyglycine ethyl ester [Ie].

The bacteriostatic activity of quinones is very well known¹. There are several theories of the mechanism of this activity, based on the fact that quinones show an inhibitive action on certain enzymes. It has been shown later that p-benzoquinone, as well as other substituted benzoquinones and naphthoquinones, inhibit the action of some enzymes^{2, 3}, and that this inhibitive action is not in correlation with their redox potential, or with their antibacterial activity. The antibacterial action of certain quinones has been interpreted as being due to their interaction with vital thiol groups^{4, 5} and amino groups⁶ of p-aminobenzoic acid. Following Cooper and coworkers⁷, the germicidal action of quinones is due more to the reaction of quinones with individual amino acids than with proteins. The first qualitative investigation of the reaction of quinones with amino acids and proteins was carried out by Raciborski⁸. Later Suida⁹ showed that in the dyeing of animal tissues with quinones, the amino groups are also involved. The quinones which have dyeing properties must have the unchanged and unsubstituted $-\text{CO} \cdot \text{CH} : \text{CH} \cdot \text{CO}$ -group.

In these circumstances it seemed to be of some interest to investigate the action of quinones on amino acids and peptides. Fischer has shown¹⁰ that glycine ethyl ester and DL-alanine ethyl ester react with benzoquinone to give 2,5-disubstituted p-benzoquinones [Ia-b]. We have, therefore, as the first step in the investigation of these reactions, prepared condensation products of p-benzoquinone with glycine benzyl ester [Ic], with β -alanine ethyl ester [Id], and with glycyglycine ethyl ester [Ie]. In every instance intensively red

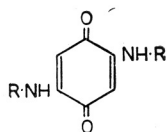
* This series of papers deals with colored compounds, cyclic or acyclic, containing at least one $-\text{CO} \cdot \text{NH}-$ group and a chromophore system with two or more $>\text{C}=\text{O}$ groups. To a certain extent this series of compounds corresponds, by definition, to Brockmann's definition of »chromopeptides« [*Angew. Chem.* 66 (1954) 1].

** Paper I, N. Allegretti, K. Balenović, V. Fišter and R. Munk, *Experientia* 9 (1953) 416.

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colored compounds of quinonoid character were obtained. If vital amino groups inactivate quinones as antibacterial agents, we can expect that compounds of the formula [I] will probably be of low antibacterial activity, as compared with other quinones.

Further investigation of this series of compounds is in progress, *inter alia* of their antibacterial activity.



- Ia, R = CH₂COOC₂H₅
 Ib, R = CH(CH₃)COOC₂H₅
 Ic, R = CH₂COOCH₂C₆H₅
 Id, R = CH₂CH₂COOC₂H₅
 Ie, R = CH₂CONHCH₂COOC₂H₅

EXPERIMENTAL*

2,5-Diglycinoquinone dibenzyl ester [Ic]

Glycine benzyl ester hydrochloride prepared according to Erlanger and Brand¹¹ (14.6 g., 0.072 mole) was suspended in chloroform (100 ml.) and saturated with dry ammonia. The ammonium chloride was filtered off and washed with chloroform. The combined filtrates were evaporated *in vacuo*. The residual glycine benzyl ester was dissolved in absolute ethanol (20 ml.) in a flask fitted with a dropping funnel with a mercury sealed stirrer and calcium chloride tube. At -5°C a solution of p-benzoquinone (13.9 g., 0.128 mole) in absolute ethanol (200 ml.) was gradually added during half an hour with stirring. After stirring the mixture for two hours, the red crystalline precipitate of 2,5-diglycinoquinone dibenzyl ester was filtered off and washed with 10–15 ml. of cold ethanol. Yield 16.3 g. (51.6%) of red needles, m. p. 201–204°. After several recrystallizations from ethyl acetate, m. p. 214° (corr.). From the mother liquor, quinhydrone (4.1 g.) was isolated.

Anal. 9.97 mg subst.: 24.30 mg. CO₂, 4.62 mg H₂O
 C₂₄H₂₂N₂O₆ (434.43) calc'd: C 66.35; H 5.10%
 found: C 66.51; H 5.19%

2,5-Di-β-alaninoquinone diethyl ester [Id].

β-Alanine ethyl ester hydrochloride prepared according to Hoogewerff and Van Dorp¹² was converted to the free base as described in the preparation of glycine benzyl ester. To a solution of β-alanine ethyl ester (10 g., 0.085 mole) in ethanol (10 ml.), a solution of quinone (14 g., 0.129 mole) in ether (175 ml.) was added, and the mixture left at room temperature overnight. After cooling to -12°, the crystals were collected and extracted with hot chloroform. The chloroform extracts were evaporated to dryness under reduced pressure, and the residue dissolved in the minimum quantity of methanol. After cooling the crude 2,5-di-β-alaninoquinone diethyl ester separated, yield 7.5 g. (52.1%), m. p. 138°. Repeated recrystallization from methanol gave red needles, m. p. 144–145°.

Anal. 9.10 mg. subst.: 19.05 mg. CO₂, 5.35 mg. H₂O
 C₁₆H₂₂N₂O₆ (388.35) calc'd: C 56.79; H 6.55%
 found: C 57.13; H 6.58%

From the ethereal mother liquor quinhydrone could be isolated in the usual manner.

Di[glycyl-glycino]quinone diethyl ester [Ie].

Glycylglycine hydrochloride monohydrate was prepared according to Sheehan and Frank.¹³ From this compound glycylglycine ethyl ester was prepared according to

* The melting points are uncorrected, unless otherwise stated.

Fischer and Fournéau¹⁴ and Dunn and coworkers¹⁵. A suspension of glycyglycine ethyl ester (1.64 g., 0.010 mole) in absolute ethanol (10 ml.) was cooled to 0°, and a solution of p-benzoquinone (1.62 g., 0.015 mole) in absolute ethanol (25 ml.) gradually added during 20 minutes. The mixture was left overnight at -10°, and then the crystals collected. Yield of crude di[glycyglycino]quinone diethyl ester 1.58 g., (36.3%), m. p. 210.5–211.5°. After repeated recrystallization from 70% ethanol, red needles with the m. p. 230.2° were obtained.

Anal. 9.70 mg subst.: 18.20 mg. CO₂, 4.95 mg. H₂O
 C₁₈H₂₄N₄O₈ (424.40) calc'd: C 50.94; H 5.70%
 found: C 51.20; H 5.71%

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IZVOD

**Preparacija 2,5-disupstituiranih derivata p-benzokinona peptidnog karaktera.
 Poliakso spojevi peptidnog karaktera. II**

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Opisani su reakcioni produkti p-benzokinona s glicinbenzil esterom [Ic], s β-alanin etil esterom [Id] i s glicilglicin etil esterom [Ie].

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