carded. The second filtrate was evaporated to a small volume (20–40 ml.) and allowed to stand overnight at room temperature. The 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione[2] (VIIIa), which crystallized, was removed. On further standing with slow evaporation of solvent, the crude 5-ethyl-5-phenyl-2-alkoxyhexahydropyrimidine-4,6-dione (VII, Table I) separated and was purified by repeated fractional crystallization from acetone, ethyl acetate or alcohol. In some instances where older and less active Raney nickel was used at the outset, appreciable quantities of the alkoxy compounds were obtained by concentration of the initial filtrate and repeated fractional crystallization of the crude product.

Further treatment of the 5-ethyl-5-phenyl-2-alkoxyhexahydropyrimidine-4,6-diones with fresh Raney nickel furnished nearly a quantitative yield of 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione.

PHILADELPHIA, PA.
LIVERPOOL, ENGLAND

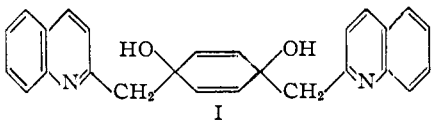
NOTES

Structure of the "Adduct" of Benzoquinone and Quinaldine

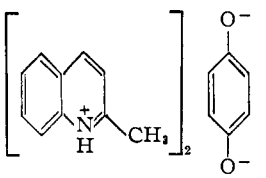
BY AKSEL A. BOTHNER-BY

RECEIVED AUGUST 13, 1954

Bell[1] has reported the preparation of a crystalline material, m.p. 154°, by the reaction of benzoquinone and quinaldine in refluxing xylene. The compound gave hydroquinone diacetate on treatment with acetic anhydride, and analytical figures agreeing roughly with its formulation as an adduct of one mole of benzoquinone with two moles of quinaldine. On the basis of this evidence, he suggested the structure I for the product.



I



II

Since the aldol condensation leading to such a formulation did not seem very likely, nor did the manner of formation of hydroquinone diacetate seem clear, a further investigation into the structure was undertaken. The preparation of the material by the method given by Bell succeeded perfectly, but purification by crystallization was rendered difficult by tar formed during the reaction. It was found that pure white crystals could be obtained by sublimation at 160° at atmospheric pressure, and by recrystallization from ethyl acetate. An elementary analysis of the material gave figures agreeing better with an empirical formula $C_{26}H_{24}O_2N_2$ than with the empirical formula of an adduct ($C_{26}H_{22}O_2N_2$). The preparation of hydroquinone diacetate was repeated as described by Bell, and from the mother liquors it was possible to isolate in good yield quinaldine, identified as its picrate. Treatment of the "adduct" with cold dilute alkali also liberated quinaldine. All these facts point directly to the conclusion that the compound is actually an adduct of hydroquinone and quinaldine, rather than of benzoquinone and quinaldine. Such was easily demonstrated to be the case by the synthesis of the compound from these reactants. Solution of the two components in ethyl acetate resulted in quantitative formation of the compound m.p. 153–155°, identical in every respect with that obtained by Bell's procedure.

The compound in the solid state displays a diffuse infrared absorption band in the region 3.5–4.0 μ, and consequently is formulated as a salt, although it is probably completely dissociated in solution. Its formation from quinone and quinaldine is explained readily on the assumption that a part of the quinaldine is oxidized by the quinone, which is thereby reduced to hydroquinone. The salt then precipitates from the very non-polar solvent. The formation of a salt from a weak base and a weak acid, not ordinarily observed, may be promoted in this case by complexing in the crystal. That other factors than simple stoichiometry are involved is apparent from other examples of salt formation of this kind: hydroquinone and quinoline react to give a compound of the empirical formulas (quinoline)$_2$(hydroquinone),[2,3] while hydroquinone and pyridine react in a 1:1 relationship.[2]

Structure II is suggested for the compound.

Experimental

Preparation from Quinone and Quinaldine.—Quinone was freshly sublimed, and quinaldine and xylene were freshly distilled. The directions of Bell were followed. An analytical sample was prepared by sublimation, recrystallization from ethyl acetate, and resublimation, m.p. 154–155°.

Anal.[4] Calcd. for $C_{26}H_{22}O_2N_2$: C, 79.16; H, 5.62; N, 7.10. For $C_{26}H_{24}O_2N_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.64; H, 6.35; N, 7.00.

Reaction with Acetic Anhydride.—Purified "adduct" (0.666 g.) was heated on the steam-bath for two minutes with acetic anhydride (2.00 ml.), then allowed to stand overnight. Water (8.0 ml.) was added, and the suspension was then shaken for 15 minutes, and filtered. Colorless platelets of hydroquinone diacetate, m.p.[5] and mixed m.p. 122–123° were obtained in 71% yield. The filtrate was

(1) F. Bell, *J. Chem. Soc.*, 348 (1953).

(2) A. Baeyer and V. Villiger, *Ber.*, **35**, 1208 (1902).

(3) A. Bolland, *Monatsh.*, **31**, 419 (1910).

(4) Microanalysis by S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

(5) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948,

concentrated *in vacuo* and taken up in 20 ml. of ether. The ether solution was washed with aqueous potassium carbonate, with water, dried with anhydrous sodium sulfate, and evaporated to give 0.209 g. of a yellow oil with a smoky odor. About 10 mg. of the oil was dissolved in 0.1 ml. of ethanol, and a saturated ethanolic solution of picric acid added dropwise until precipitation was complete. The precipitate was centrifuged off and recrystallized from 4.0 ml. of ethanol to give quinaldine picrate, m.p.[5] and mixed m.p. 191–192°. Assuming the oil to have been pure quinaldine, the yield was 80%.

Preparation from Hydroquinone and Quinaldine.—Hydroquinone (0.200 g.) and quinaldine (0.70 ml.) were refluxed together in 10 ml. of ethyl acetate until solution was complete. A colorless crystalline precipitate was obtained on cooling and scratching. Recrystallization from ethyl acetate yielded material melting at 153–155°, mixed melting point with the material prepared from quinone and quinaldine 153–155°, yield 0.882 g. The ultraviolet and infrared absorption spectra of the substances prepared by the two methods were identical.

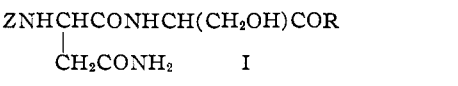
DEPARTMENT OF CHEMISTRY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS

Peptide Derivatives Containing Two Trifunctional Amino Acids. II

BY R. F. FISCHER AND R. R. WHETSTONE

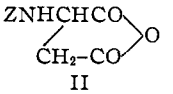
RECEIVED MAY 27, 1954

Our previous communication[1] was concerned largely with the preparation of peptides of L-histidine, L-serine and L-tyrosine. This paper deals with the synthesis of a number of new L-asparaginyl and L-aspartyl peptide derivatives of L-serine. Although very few L-asparaginyl peptides have been described in the literature,[2] du Vigneaud and associates[3] recently have prepared an L-asparaginyl peptide *via* the pyrophosphite route. Since the reagents for the closely related mixed carbonic anhydride coupling[4] are more readily available, this method was chosen, and carbobenzoxy-L-asparaginyl-L-serine methyl ester (I, R = OCH_3) and carbobenzoxy-L-asparaginyl-L-serylglycine ethyl ester (I, R = $NHCH_2CO_2C_2H_5$) have been obtained from carbobenzoxy-L-asparagine and the corresponding amino esters using ethyl chloroformate and triethylamine. Though the purified products were obtained in only 10–20% yield, the ease of the reaction makes it attractive. It is probable also that the yields can be improved considerably by minor changes in technique.



I

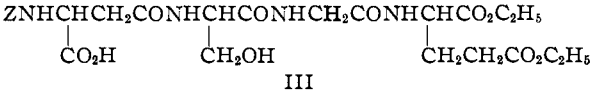
The preparation of pure L-aspartyl peptides presents more difficulty. Because of the nearly equal reactivity of groups attached to the two carboxyls of L-aspartic acid, it was considered undesirable to employ the mixed anhydride procedure.[5] Le Quesne and Young[6] have shown recently that the mixtures obtained by reaction of carbobenzoxy-L-aspartic anhydride(II) with amino acid esters can



II

be separated by fractional extraction, and therefore and also because of the mild conditions employed in the reaction, this route was chosen for coupling with L-serine derivatives.

Since the carboxyl group alpha to an amine is somewhat more acidic than one in the β-position, extractions with small amounts of weak base tend to remove the β-peptide derivatives in preference to the α-isomer. In our hands, reaction of II with L-serylglycyl-L-glutamic acid diethyl ester gave a mixture which was extracted in seven portions with sodium carbonate. On acidification, the first two extracts crystallized spontaneously, the third crystallized partly on seeding, and the remainder stayed oily even when seeded with the crystalline compound. In this case, then, it is probable that the crystalline isomer is the β-derivative III.



III

Attempts to form crystalline derivatives of the oily α-isomer (amide, anilide, hydrazide, free acid) led only to gels or oils.

When the anhydride coupling was carried out with L-serine methyl ester or with L-serylglycine methyl ester, crystalline products separated from the reaction mixture, leaving about equal amounts of oily materials in solution. Therefore no direct comparison of the acid strengths of these compounds could be made. The crystalline isomers were shown to be homogeneous by fractional extraction, but again no crystalline derivatives of the oily materials could be obtained. Shortly after the preparation of the above compounds, our work in this field was terminated, and it was not possible for us to determine the configurations of the crystalline products, although, by analogy to III, they may be the β-isomers.

Several methods are available for determining these configurations. Sachs and Brand[7] have shown that both the amino and the peptide nitrogens of γ-glutamyl peptides react in the Van Slyke nitrogen determination, while only the amino nitrogen of the α-peptide is detected. This should also be applicable to the free aspartyl peptides. Another method would involve comparison of the diamides prepared from both the aspartyl and asparaginyl derivatives which were prepared earlier. To this end, the crystalline carbobenzoxy-L-aspartyl-L-serylglycine methyl ester was converted to the dimethyl ester, but termination of the work precluded carrying out the preparation of the amides.

Experimental[8]

Carbobenzoxy-L-asparaginyl Compounds.—These were prepared by minor modification of the mixed anhydride

(1) R. F. Fischer and R. R. Whetstone, THIS JOURNAL, **76**, 5076 (1954).

(2) E. Fischer and E. Koenigs, *Ber.*, **40**, 2048 (1907).

(3) V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts and P. G. Katsoyannis, THIS JOURNAL **76**, 3115 (1954).

(4) R. A. Boissonas and J. Schumann, *Helv. Chim. Acta*, **35**, 2237 (1952).

(5) After the completion of this work, Y. Liwschitz and A. Zilkha, THIS JOURNAL, **76**, 3698 (1954), reported the preferential synthesis of DL-α-aspartyl peptides using essentially this technique.

(6) W. J. Le Quesne and G. T. Young, *J. Chem. Soc.*, 24 (1952).

(7) H. Sachs and E. Brand, THIS JOURNAL, **75**, 4608 (1953).

(8) Melting points are corrected.