also 5 or 10% fluorination; potassium fluoride produced complete fluorination.

At 300° the rates of both reactions were so greatly reduced that much sulfuryl chlorofluoride came through undecomposed and little fluorination resulted.

Fluorination of Sulfuryl Chloride.—In all experiments identical results were obtained in the reaction of sulfuryl chloride with metal fluorides and in the reaction of an equimolal mixture of sulfur dioxide and chlorine with metal fluorides. At 400° sulfuryl chloride decomposes rapidly into sulfur dioxide and chlorine. The reacting systems in the two cases were accordingly substantially the same consisting of sulfur dioxide, chlorine and a small equilibrium concentration of sulfuryl chloride. The overall reaction may be written

$$SO_2 + Cl_2 + 2MF \longrightarrow SO_2F_2 + 2MCl$$

The fluorination reactions here observed were in accord with those involving sulfuryl chlorofluoride. With potassium fluoride complete fluorination resulted; sodium fluoride produced partial fluorination; other fluorides were without effect. Some of the results are given in Table II.

Discussion and Conclusions

The results of the fluorination experiments may be correlated with the data of Table I. Since in the reaction

$$SO_2 + Cl_2 + 2MF \longrightarrow SO_2F_2 + 2MCl$$

complete fluorination is obtained with potassium fluoride, it follows that all fluorinating agents which have a free energy difference of less than 29,000 cal. for their chloride fluoride couplet will produce similar results at equilibrium. Agents which have free energy differences for their couplets between the approximate limits of 34,000 and 40,000 cal. will produce observable equilibrium. Calcium fluoride and others which have values in excess of 48,000 cal. will be without appreciable effect. Some of the equilibrium systems are being investigated in order to obtain the free energies of formation of the metal fluorides.

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Summary

1. Sulfuryl fluoride has been prepared by direct fluorination of sulfuryl chloride, or an equimolar mixture of sulfur dioxide and chlorine, with potassium or sodium fluorides at 400°.

2. Thermal decomposition of sulfuryl chlorofluoride into sulfur dioxide, chlorine and sulfuryl fluoride at 300 to 400° was observed.

3. The thermochemistry of halogen exchange reactions is briefly summarized.

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The Formation of Diketopiperazines from Dipeptide Amides[1a]

BY H. T. HUANG AND CARL NIEMANN[1b]

It has been observed that the acetates of glycyl-DL- and L-phenylalaninamide[2] and glycylglycinamide[2] are readily transformed into DL- and L-3(6)-benzyl-2,5-diketopiperazine and 2,5-diketopiperazine, respectively, when aqueous or methanolic solutions of the acetates are either warmed or allowed to stand at room temperature for several days. However, when the acetates of glycyl-DL-phenylalaninmethylamide, glycyl-DL-phenylalaninbenzylamide, diglycylglycine and triglycylglycine, or the hydrochloride of glycyl-DL-phenylalaninamide are similarly treated no diketopiperazine formation is observed.

From the data available for dipeptide esters and amides it appears that facile diketopiperazine formation is in part dependent upon the availability of a primary or secondary amino group and for dipeptide amides is restricted to primary amides. With either dipeptide esters or amides it is possible that the amino group may be activated, in the sense used by Gordon, Miller and Day,[3] by intramolecular hydrogen bonding.

Glycyl-L-phenylalaninamide has been recommended as a substrate for the quantitative estimation of chymotrypsin activity.[2] In view of the ease of formation of L-3(6)-benzyl-2,5-diketopiperazine from this dipeptide amide, even in weakly acidic solutions, it is clear that caution should be exercised in using this peptide as a substrate in enzymatic studies, particularly at low substrate concentrations and temperatures above 25°.

Experimental[4]

Carbobenzoxyglycyl-DL-phenylalaninamide (I).—Acylation of an ethyl acetate solution of DL-phenylalanine methyl ester prepared from 12 g. of the hydrochloride, with 12 g. of carbobenzoxyglycyl chloride[2,5] gave 12.9 g. of sirupy carbobenzoxyglycyl-DL-phenylalanine methyl ester (II). A portion of II was crystallized from methanol and then recrystallized from a mixture of benzene and ether to give II, clusters of soft fibrous needles, m. p. 80–81°.

(1) (a) This work was supported in part by a grant from Eli Lilly and Co. (b) Responsible co-author.

(2) J. S. Fruton and M. Bergmann, *J. Biol. Chem.*, **145**, 253 (1942).

(3) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948); **71**, 1245 (1949).

(4) All melting points are corrected.

(5) M. Bergmann and L. Zervas, *Ber.*, **65** II, 1192 (1932).

Anal. Calcd. for $C_{20}H_{22}O_5N_2$ (370): C, 64.8; H, 6.0; N, 7.6. Found: C, 65.2; H, 6.3; N, 7.6.

A solution of 11 g. of sirupy II in 100 ml. of methanol previously saturated with ammonia was allowed to stand at 25° for two days, the solvent removed to give 8.4 g. of crude amide and the product recrystallized first from aqueous methanol and then from a mixture of methanol and ether to give I, clumps of fine stunted needles, m. p. 160°.

Anal. Calcd. for $C_{19}H_{21}O_4N_3$ (355): C, 64.3; H, 6.0; N, 11.8. Found: C, 64.4; H, 6.0; N, 11.9.

Glycyl-DL-phenylalaninamide Acetate (III).—A suspension of 2 g. of I in 50 ml. of methanol containing 0.3 ml. of glacial acetic acid was hydrogenated at 25° and atmospheric pressure over 1 g. of 4.3% palladized charcoal, the catalyst removed, the clear solution evaporated *in vacuo*, at 25° or less, to a thick sirup, the latter triturated with ethyl acetate, and the crystalline product recrystallized from a mixture of methanol and ethyl acetate, avoiding temperatures in excess of 25°, to give 1.1 g. of III; silky needles, m. p. 115–117° with immediate resolidification to give a product of m. p. greater than 260°.

Anal. Calcd. for $C_{11}H_{15}O_2N_3 \cdot C_2H_4O_2$ (281): C, 55.5; H, 6.8; N, 14.9. Found: C, 55.3; H, 6.9; N, 14.8.

A methanolic solution of III evaporated at elevated temperatures gave upon cooling DL-3(6)-benzyl-2,5-diketopiperazine (IV), prisms sparingly soluble in cold methanol, acetone, benzene and chloroform, m. p. 270° after recrystallization from methanol or after sublimation *in vacuo* and further recrystallization from methanol. The m. p. of IV has been reported to be 280°.[6]

Anal. Calcd. for $C_{11}H_{12}O_2N_2$ (204): C, 64.7; H, 5.9; N, 13.7. Found: C, 64.9; H, 5.9; N, 13.7.

IV was also obtained from a methanolic solution of III heated at 40° for two hours, from an aqueous solution of III similarly treated, or from a methanolic solution of III maintained at 25° for several days.

Glycyl-DL-phenylalaninamide Hydrochloride (V).—A suspension of 1.9 g. of I in 50 ml. of methanol containing 1 ml. of concentrated hydrochloric acid was hydrogenated as before, the solution freed of catalyst, evaporated to dryness at 25°, taken up in methanol, and the solution evaporated to give 1.16 g. of crude V which was recrystallized from methanol to give V, dense elongated rhombs, m. p. 155–157° with preliminary softening. V was recovered unchanged from hot methanol solutions.

Anal. Calcd. for $C_{11}H_{15}O_2N_3 \cdot HCl \cdot {}^1/_2H_2O$ (227): C, 49.7; H, 6.4; N, 15.8; Cl, 13.4. Found: C, 49.8; H, 6.4; N, 15.6; Cl, 13.6.

L-3(6)-Benzyl-2,5-diketopiperazine (VI).—The crude product obtained from the hydrogenation of carbobenzoxyglycyl-L-phenylalaninamide[2] was taken up in warm methanol, the solution cooled, and the product recrystallized from water to give VI; long silky needles, m. p. 260°. Sublimation *in vacuo* failed to raise the m. p. which is reported to be 265.5°.[7]

Anal. Calcd. for $C_{11}H_{12}O_2N_2$ (204): C, 64.7; H, 5.9; N, 13.7. Found: C, 64.7; H, 6.1; N, 13.6.

Carbobenzoxyglycyl-DL-phenylalaninmethylamide (VII).—A solution of 3 g. of sirupy II in 50 ml. of 30% aqueous methylamine and 50 ml. of methanol was allowed to stand at 25° for three days and the solvents evaporated to give 3 g. of crude VII, m. p. 130–135°. Three recrystallizations from a mixture of methanol and ether gave VII; transparent needles, m. p. 148°.

Anal. Calcd. for $C_{20}H_{23}O_4N_3$ (369): C, 65.1; H, 6.3; N, 11.4. Found: C, 65.1; H, 6.3; N, 11.3.

Glycyl-DL-phenylalaninmethylamide Acetate (VIII).—One gram of VII in 50 ml. of methanol containing 0.4 ml. of glacial acetic acid was hydrogenated over 0.5 g. of 4.3% palladized charcoal, the catalyst removed, the solution concentrated and the residue triturated with ethyl acetate to give 0.6 g. of crude VIII which was recrystallized from a mixture of methanol and ethyl acetate to give VIII, soft fine needles, m. p. 171–172° with preliminary sintering at 160°.

Anal. Calcd. for $C_{12}H_{17}O_2N_3 \cdot C_2H_4O_2$ (295): C, 56.9; H, 7.2; N, 14.2. Found: C, 56.9; H, 7.1; N, 14.1.

VIII melted to give a clear solution with no evidence of resolidification and was recovered unchanged from methanol solutions which had been heated at 40° for two hours or allowed to stand at 25° for one week.

Carbobenzoxyglycyl-DL-phenylalaninbenzylamide (IX).—A solution of 4 g. of sirupy II and 4 g. of benzylamine in 30 ml. of methanol was kept at 25° for two days, the solvent removed, the residue taken up in ethanol, refluxed for twelve hours, the solution concentrated and triturated with water to give 3.1 g. of crude IX, m. p. 122–125°, which was recrystallized thrice from methanol and once from a benzene–ether mixture to give IX; long silky needles, m. p. 162–163°.

Anal. Calcd. for $C_{26}H_{27}O_4N_3$ (446): C, 70.2; H, 6.1; N, 9.4. Found: C, 70.1; H, 6.2; N, 9.4.

Glycyl-DL-phenylalaninbenzylamide Acetate (X).—Hydrogenolysis of 0.8 g. of IX gave a solution which was evaporated to dryness, the crystalline residue taken up in boiling methanol, the solution concentrated *in vacuo* to a small volume, and 10 ml. of ethyl acetate added to give 0.6 g. of X; long silky needles, m. p. 116–118°.

Anal. Calcd. for $C_{18}H_{21}O_2N_3 \cdot C_2H_4O_2$ (371): C, 64.6; H, 6.7; N, 11.3. Found: C, 64.4; H, 7.0; N, 11.2.

Glycylglycinamide Acetate (XI).—Carbobenzoxyglycylglycinamide (1.1 g.), needles, m. p. 170–172°, in contrast to the value of 179–181° previously reported,[2] was hydrogenated in the usual manner, the catalyst removed, the solution evaporated *in vacuo* at 25° or below, the residue taken up in methanol, the solution concentrated until crystals began to separate whereupon ethyl acetate was added, and the mixture stored at 5° for twelve hours to give 0.55 g. of XI; prisms, m. p. 130–134° with immediate resolidification.

Anal. Calcd. for $C_{12}H_{15}O_4N_3$ (265): C, 54.3; H, 5.7; N, 15.8. Found: C, 54.4; H, 5.8; N, 15.9.

Anal. Calcd. for $C_4H_9O_2N_3 \cdot C_2H_4O_2$ (191): C, 37.7; H, 6.9; N, 22.0. Found: C, 37.4; H, 6.9; N, 21.6.

A methanolic solution of XI upon heating at 40° for two hours, on standing at room temperature for several days, gave 2,5-diketopiperazine (XII); prisms, m. p. 307–309°, no depression with an authentic sample of XII.

Anal. Calcd. for $C_4H_6O_2N_2$ (114): C, 42.1; H, 5.3. Found: C, 41.8; H, 5.6.

Summary

The facile formation of diketopiperazines from dipeptide amides has been observed and has been shown to be limited to primary amides.

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(6) E. Fischer and P. Blank, *Ann.*, **354**, 4 (1907).

(7) E. Fischer and W. Schoeller, *ibid.*, **357**, 22 (1907).