SPECTROCHEMICAL STUDY OF AMINO-ACID ANHYDRIDES.(3)

III. LIGHT ABSORPTION OF SOME N-SUBSTITUTED DIKETOPIPERAZINES AND SOME OTHER AMINO-ACID ANHYDRIDES.(4)

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In the preceeding paper,(3) Y. Shibata and the author have reported on the ultra-violet absorption of some C-substituted derivatives of diketopiperazines. The light absorption of these substances was almost coincident with that of the amino-acids from which the anhydrides are derived. An

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(3) The 1st and 2nd reports, see this Bulletin, **1** (1926), 71; and **2** (1927), 324.

(4) Read before the Chemical Society of Japan, May 11th, 1929.

exceptional case was, however, found in C,C'-dibenzylderivatives, which showed no selective absorption, although the substance contains effective chromophore groups in its molecule. Further studies of the ultra-violet absorption and the behaviour of some N-substituted diketopiperazines were now attempted. Sarcosine anhydride, which is an N,N'-dimethyldiketopiperazine shows too no selective absorption and moreover its spectrogram is quite identical with that of diketopiperazine⁽¹⁾ (Fig. 3). If the substituents in the N,N' position of diketopiperazines are phenyl or benzyl group, no selective absorptions are either observed in the compound produced, though phenylamino and benzylamino-acetic acids which are regarded to be the mother substances of the former show more or less distinct absorption bands in the ultra-violet region (Fig. 1 and Fig. 2). The relation between the optical behaviours of N,N'-diphenyldiketopiperazine and N-phenylglycine is exactly comparable to that between acetanilide and aniline. Thus it may probably be concluded that the ring formation of diketopiperazine is

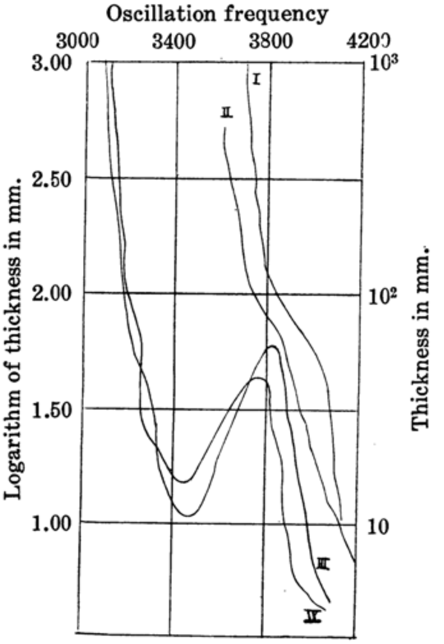

Fig. 1.

I Acetanilide 0.001 mol
II N, N'-diphenyldiketopiperazine
III Aniline
IV N-phenylglycine and its ethyl ester

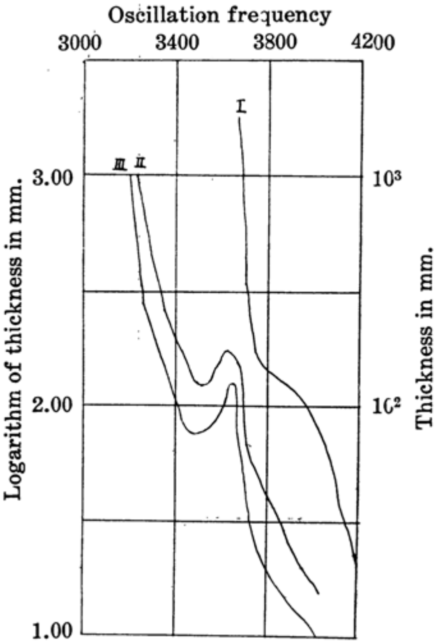

Fig. 2.

I N, N'-dibenzyldiketopiperazine
II Benzylamine 0.001 mol
III Benzylaminoacetic acid ethyl ester 0.001 mol

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(1) Ibid., **1** (1926), 71.

due to the acylation of amino groups of amino-acids. It seems further that the introduction of acyl groups in N-atoms of diketopiperazine causes the displacement of its end absorption in the ultra-violet regularly towards the region of longer wave-lengths according to the augmentation of molecular weight of substituted products, only with the exception of N,N'-dichloracetyl-diketopiperazine which absorbs light less than N,N'-diacetyl-diketopiperazine (Fig. 3). Hydantoin, which may be regarded as another kind of amino-acid anhydride, and its corresponding acid or acid ester show nearly the identical absorption to each other. Neither γ-phenylhydantoin nor phenyl-urea, both of which are acylated products of aromatic groups, was found to give any selective absorption, while aniline possesses a remarkable absorption band in the ultra violet (Fig. 4).

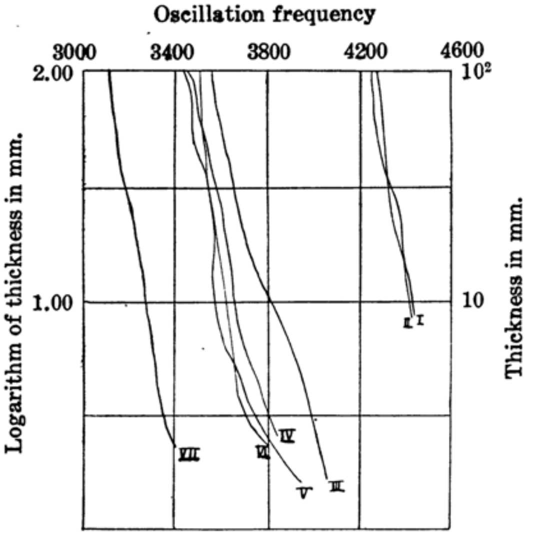

Fig. 3.

I	Sarcosine anhydride	0.01 mol	
II	Glycine anhydride	,,	
III	N, N'dichloracetyl-diketopiperazine	,,	(in CH_3COOH)
IV	N, N'diacetyl-diketopiperazine	,,	(in alcohol)
V	Hippuric acid	,,	(,,)
VI	N, N'dipropionyl-diketopiperazine	,,	(,,)
VII	N, N'dibenzoyl-diketopiperazine	,,	(in CH_3COOH)

Azlactones are also amino-acid anhydrides derived from hippuric acid and they have generally distinct yellow colour. The azlactones of benzaldehyde and furfural were also studied; they showed analogous absorption with each other, but by the closer comparison of these absorption curves it was

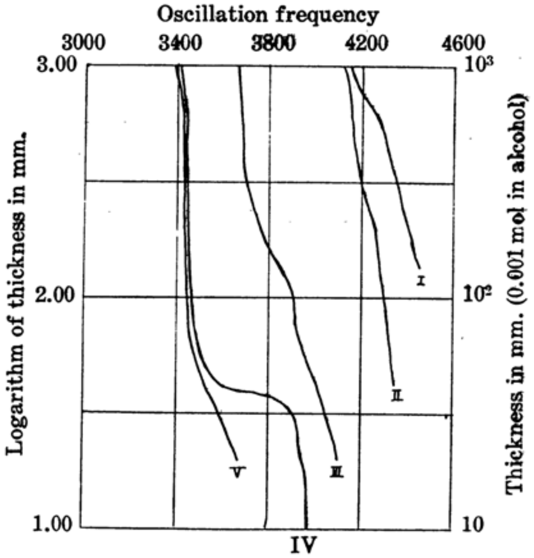

Fig. 4.

I Hydantoic acid ethyl ester
II Hydantoin
III γ-Phenylhydantoin
IV Phenylurea
V γ-Phenylhydantoic acid

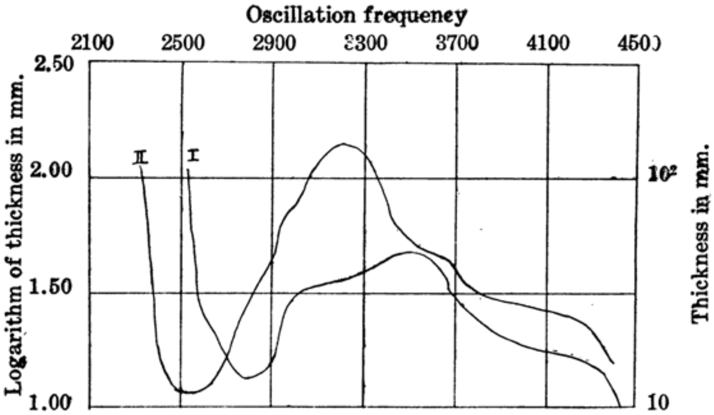

Fig. 5.

I Benzazlactone 0.0001 mol (in alcohol)
II Furfuralazlactone ,, (,,)

known that azlactone of furfural absorbs more bathochromic and hyperchromic than the other (Fig. 5), the fact being quite coincident with that observed by Dr. I. Kasiwagi in his study of furyl ketones.(1)

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(1) Ibid., 1 (1926), 150.

Experimentals.

N-phenylglycocoll. Commercial product was repeatedly recrystallised from water and alcohol alternately (m.p. 123.5–124.5°) and its alcoholic solution (0.001 mol) was spectroscopically examined (see Fig. 1.)

N-phenylglycocoll ethylester. The preparation method given by Bischoff and Hausdörfer⁽¹⁾ was followed, starting from monochloracetic ester and aniline; the product was recrystallised thrice from petroleum ether (m.p. 55.5–56.5°). The absorption curve of its 0.001 mol alcoholic solution was identical with that of the free acid, the maxima of the absorption being observed at $\lambda=3450\text{Å}$. The spectrograms are also nearly identical with that of aniline in the alcoholic solution, the absorption maximum of which is shown at $\lambda=3460$ Å (Fig. 1).

N,N'-diphenyl-diketopiperazine. N-phenylglycocoll was heated in an oil-bath at the temperature of 140°. On cooling, the dark solid mass was obtained, which was washed with small quantity of luke-warm alcohol and recrystallised from glacial acetic acid (m.p. 265°).⁽²⁾ The 0.01 mol glacial acetic acid solution gave only an end absorption which is identical with that of acetanilide, while its corresponding amino-acid shows a distinct absorption band (Fig. 1). From this remarkable fact it will most probably be concluded that the diketopiperazine takes the acid-amide constitution.

Benzylamino-acetic Acid. Instead of the free acid, its ethyl ester was synthesized from benzylamine and monochloracetic ester (b.p. 137±1° under 8 mm. pressure).⁽³⁾

Benzylamine. Commercial product was purified by fractional distillation and the portion boiling at 182–183° was dissolved in alcohol which was previously boiled (to expel the dissolved carbon dioxide). The absorption maximum of the amino-acid (ester) in alcoholic solution was observed at $\lambda=3490$ Å and that of the benzylamine at $\lambda=3500$ Å (Fig. 2).

N,N'-dibenzyl-diketopiperazine. The sample was afforded by Dr. T. Sasaki.⁽⁴⁾ In 0.01 mol glacial acetic acid solution, no absorption band was observed except an inflection in the absorption curve (Fig. 2).

Diacetyl-diketopiperazine. Glycine anhydride was boiled with 10 times acetic anhydride for about 6 hours, then the latter was expelled in vacuo,

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(1) *Ber.*, **25** (1892), 2270.

(2) P. Meyer, *Ber.*, **10** (1877), 1967.

(3) Mannich and Kuphal, *Ber.*, **45** (1912), 313.

(4) T. Sasaki and T. Hashimoto, *Ber.*, **54** (1921), 2692.

and the product was three times recrystallized from alcohol (m.p. 102.5°).⑴ The curve showing its end absorption is situated in the spectrum region of longer wave-length than that of glycine anhydride (Fig. 3)

Dipropionyl-diketopiperazine. Well powdered glycine anhydride (1.1 gr.) was heated with 10 gr. propionic anhydride at 130–140° for about five hours, the liquid part was then distilled off in vacuo on a water bath and the dark coloured crystalline residue was then drained on a porous plate; yield 2 gr. (98% of the theor. amount). Twice recrystallizations from alcohol suffice to render the raw product quite pure as crystals with silverly lustre of m.p. 114.5°. Sasaki's reaction and sodium nitroprusside reaction are both positive.

Anal. Subst. = 4.925 mg.; N_2 = 0.541 c.c. (27°, 761.8 mm.) Subst. = 0.0988 gr.; CO_2 = 0.1907 gr.; H_2O = 0.0536 gr. Found: N = 12.5; C = 52.6; H = 6.1%. Calc. for $C_{10}H_{14}N_2O_4$; C = 53.1; H = 6.2; N = 12.39%.

The substance has a peculiar form of crystal: when the alcoholic solution is left for free evaporation, we obtain very thin square plates which are often as large as 1 cm^2. just like a cover-glass of microscopy. Like the acetyl product it has a tendency to decompose, on standing for a long time in the air and with sodium alcoholate it gives the odour of ethyl propionate. The end absorption was coincident with that of the acetyl derivative (Fig. 3).

Dichloracetyl-diketopiperazine. This substance was first obtained by E. Abderhalden and E. Klarmann⑵ by heating the glycine anhydride and chloracetyl chloride in nitrobenzene at 140°. The present author synthesized it by the interaction of glycine anhydride and chloracetic anhydride.⑶ Glycine andride 1.1 gr. was well mixed with 15 gr. of chloracetic anhydride and warmed on a water-bath for an hour (when an oil bath of 140–145° is used instead of a water-bath, a quarter of an hour is sufficient to complete the reaction, prolonged heating giving rather worse result). The cooled reaction mass was washed with small quantities of warm ether to remove chloracetic acid and anhydride completely; the brown crystalline residue which weighed 2.3 gr. (yield: 84% of the theor. amount) was three times recrystallised from boiling glacial acetic acid (m.p. 169°). The substance is very difficultly soluble in cold water, ether, alcohol, ethyl acetate,

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(1) A.P.N. Franchimont and H. Friedmann, *Rec. trav. chim. Pays-bas*, **27** (1908), 192; E. Abderhalden and E. Komm, *Z. physiol. Chem.* **139** (1924), 181.

(2) *Z. physiol. Chem.*, **129** (1923), 320.

(3) Chloracetic anhydride can easily be prepared by heating the mixture of chloracetic acid (freshly distilled) and phosphorus pentoxide for a short time and the successive vacuum distillation (Bischoff and Walden, *Ber.*, **27** (1894), 2949). A considerable part of the chloracetic acid remains unaltered and goes over in the distillate. This fraction is again treated with the pentoxide just as in the preparation of chloracetyl chloride.

benzene and a little soluble in xylene, amyl alcohol, amyl acetate, nitrobenzene and glacial acetic acid; the latter three solvents can be used for recrystallization of this substance. The Abderhalden and Klarmann's process was also followed by the author and the reaction product was found identical with that described just above.

Anal. Subst.=4.388 mg.; N_2=0,395 c.c. (12.6°, 755.9 mm.) Found: N=10.64%. Calc. for $C_8H_8O_4N_2Cl_2$: N=10.49%.

Subst.=4.72 mg., 0.0870 gr.; AgCl=5.02 mg., 0.0950 gr. Found: Cl=26.3, 27.0%. Calc.: Cl=26.6%.

Abderhalden and Klarmann have not succeeded in obtaining diglycyl-diketopiperazine by treating the product with alcoholic ammonia.(1) This process was tried again by the present author, but in vain; and the further trial of obtaining diphthalylglycyl-diketopiperazine by the interaction between potassium phthalimide and the chloracetyl derivative has been also without success, only potassium chloride, phthalimide and somewhat complicated decomposition products being given in the reaction.

Dibenzoyl-diketopiperaine. This substance was prepared according to Sasaki's description(2) and the product was recrystallized from glacial acetic acid (m.p. 137°). The end absorption of the substance was found at the spectrum region of comparatively longer wave-length. Moreover the absorption was not coincident with that of the corresponding amino-acid—hippuric acid (Fig. 3).

Diacetyl-leucine-anhydride. Leucine anhydride (0.5 gr.) was heated with 5 c.c. acetic anhydride at 150° for 6 hours, the liquid part was then distilled off in vacuo and the residue was washed with ether and recrystallised from alcohol; yield 0.3 gr., m.p. 138.5°.

Anal. Subst.=4.318 mg.; N_2=0.337 c.c. (14.2°, 767.6 mm.). Found: N=9.06%. Calc. for $C_{16}H_{26}N_2O_4$: N=8.91%.

Hydantoin and Hydantoic Acid Ethyl Ester.(3) The ester was prepared from glycine ester hydrochloride and potassium cyanate (m.p. 137.5–138.5°), and by evaporating this substance with hydrochloric acid, hydantoin was prepared (m.p. 215°).

γ-Phenylhydantoin and γ-Phenylhydantoic Acid. This acid was prepared from glycocoll and phenyl isocyanate (m.p. 192°)(4) and then trans-

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(1) *Z. physiol. Chem.*, **135** (1924), 200.

(2) *Ber.*, **54** (1921), 2691.

(3) C. Harries and Weiss, *Ber.*, **33** (1901), 3418.

(4) Paal, *Ber.*, **27** (1894), 974.

formed into hydantoin by boiling with hydrochloric acid (m.p. 155°).⁽¹⁾ From the absorption curves, we can possibly conclude that the ring formation in this case scarcely influences on the light absorption (Fig. 4).

Phenyl-urea. Aniline (hydrochloride) and potassium cyanate were coupled to monophenyl-urea (m.p. 146–7°).⁽²⁾ Phenyl-urea shows no selective absorption but in its absorption curve only a slight inflection is observed (Fig. 4). From the results of optical studies obtained with acetanilide, diphenyl-diketopiperazine, γ-phenyl-hydantoin and phenyl-urea, it may be concluded that the absorption band of aniline (also perhaps of other aromatic amido derivatives) vanishes by the introduction of acyl groups to the amido group.

Azlactone of Benzaldehyde. The substance was prepared by the condensation of benzaldehyde with hippuric acid, in the presence of acetic anhydride and fused sodium acetate (m.p. 164.5°).⁽³⁾

Azlactone of Furfural. By replacing benzaldehyde with furfural in the preceding condensation, the azlactone was obtained (m.p. 170.5°).⁽⁴⁾

Both azlactones are yellowish substances and they show wide absorption bands, absorption maximum of the former substance being observed at 2760 Å, while that of the latter at 2550 Å. (Fig. 5).

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(1) Mouneyrat, *Ber.*, **33** (1900), 2393.
(2) Weith, *Ber.*, **9** (1876), 820.
(3) Erlenmeyer, jun., *Ann.*, **275** (1893), 1.
(4) Erlenmeyer, jun., *Ann.*, **337** (1904), 283.