SPECTROCHEMICAL STUDY OF AMINO-ACID ANHYDRIDES.(1)

IV. LIGHT ABSORPTION OF DERIVATIVES OF AZLACTONE, DIKETOPIPERAZINE, HYDANTOIN AND THIOHYDANTOIN.

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In the foregoing reports,(2) the ultra-violet absorptions of derivatives of diketopiperazines, azlactones and hydantoins were described, and those experiments were discussed from the standpoint of chemical constitution. In this paper, the light absorption of some derivatives of benzal azlactone,

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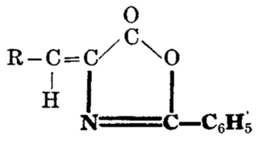
(1) Read before the Chemical Society of Japan, April 3rd, 1930.

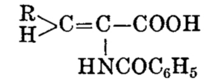
(2) For the 1st, 2nd and 3rd reports, see this Bulletin, **1** (1926), 71; **2** (1927), 324; and **4** (1929), 202.

diketopiperazine and hydantoin, and, further, those of thiohydantoin and the hydrolysis products of azlactones is described. The substances examined are as follows:

Azlactone of *o*-acetoxybenzal hippuric acid
Azlactone of *m*-acetoxybenzal hippuric acid
Azlactone of *p*-acetoxybenzal hippuric acid
Azlactone of *o*-methoxybenzal hippuric acid
Azlactone of *m*-methoxybenzal hippuric acid
Azlactone of *p*-methoxybenzal hippuric acid

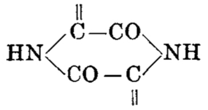


α-Benzoylamino-cinnamic acid
α-Benzoylamino-β-furyl-acrylic acid
α-Benzoylamino-*o*-oxycinnamic acid
α-Benzoylamino-*m*-oxycinnamic acid
α-Benzoylamino-*p*-oxycinnamic acid
α-Benzoylamino-*o*-methoxycinnamic acid
α-Benzoylamino-*m*-methoxycinnamic acid
α-Benzoylamino-*p*-methoxycinnamic acid

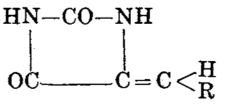


$\begin{matrix}R\\H\end{matrix}\!>C=\underset{\textstyle HNCOC_6H_5}{\underset{|}{C}}-COOH$

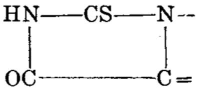
Dibenzal diketopiperazine
Difurfural diketopiperazine



4-Benzal hydantoin
4-Furfural hydantoin



2-Thio-hydantoin
2-Thio-3-acetyl-hydantoin
2-Thio-3-benzoyl-hydantoin
2-Thio-3-acetyl-4-benzyl-hydantoin
2-Thio-4-benzyl-hydantoin
2-Thio-4-(*p*-oxybenzyl)-hydantoin
2-Thio 4-benzal-hydantoin
2-Thio-4-furfural-hydantion



It was remarked in the preceeding report that the azlactone of furfural hippuric acid was more bathochromic and, at the same time, more hyperchromic than the benzal azlactone. Such relation had also been observed by Dr. I. Kasiwagi(1) in his study of furyl ketones. In the present studies, the furfural derivatives of diketopiperazine, hydantoin and thiohydantoin are found to be more bathochromic and hyperchromic than the correspond-

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(1) This Bulletin, **1** (1926), 150.

ing benzal derivatives (Figs. 1, 2 and 3). In the condensation products of hippuric acid and the three monoxybenzaldehydes, the absorption maxima

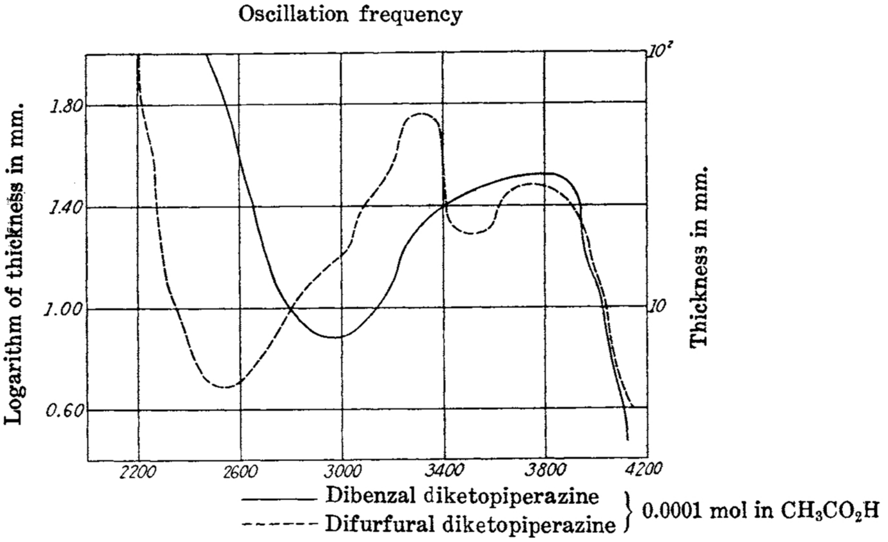


Fig. 1.

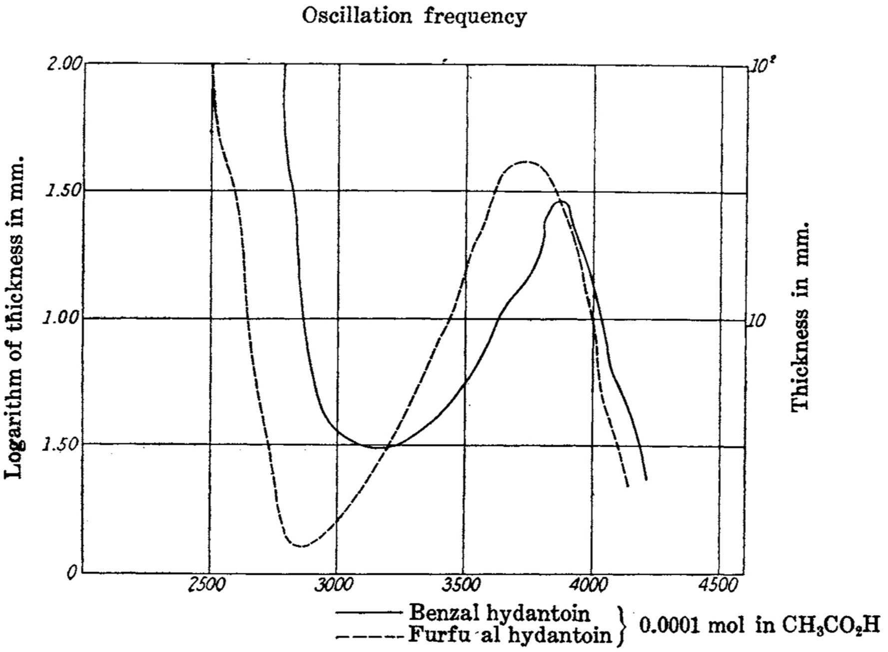


Fig. 2.

of azlactones of benzal, *o*-, *m*-, and *p*- acetoxybenzal hippuric acids are found nearly at the same wave-length of 3580 Å (Fig. 4).

Of the azlactones of three methoxybenzal hippuric acids, the *o*- and *p*- methoxy compounds show the identity in the absorption maxima, and the meta compound is less bathochromic than others (Fig. 5).

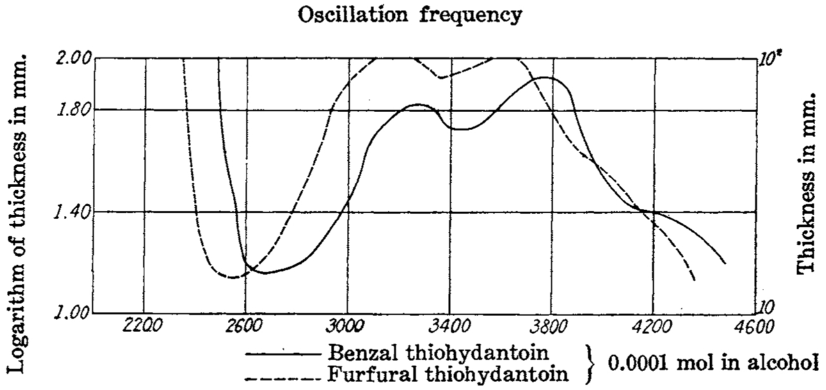


Fig. 3.

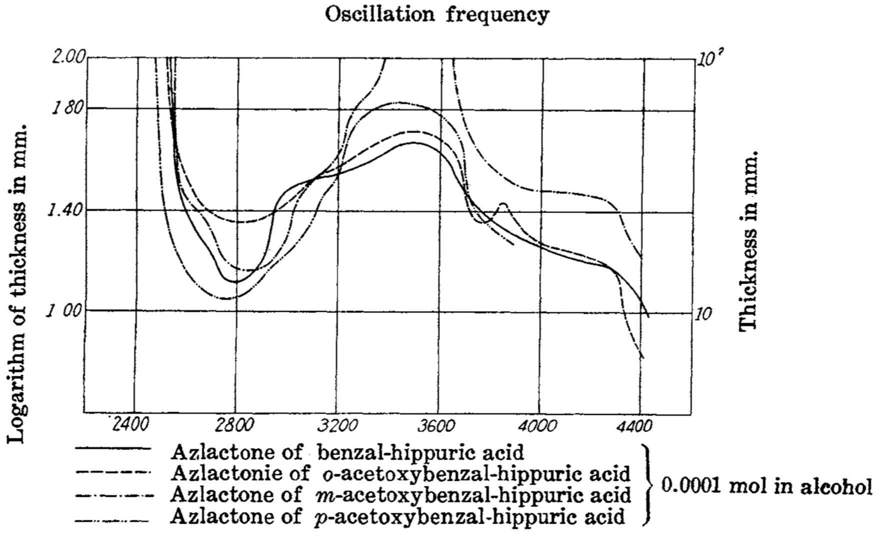
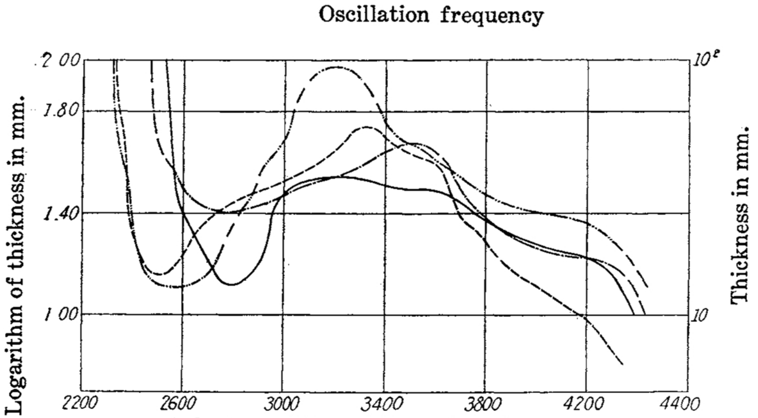


Fig. 4.

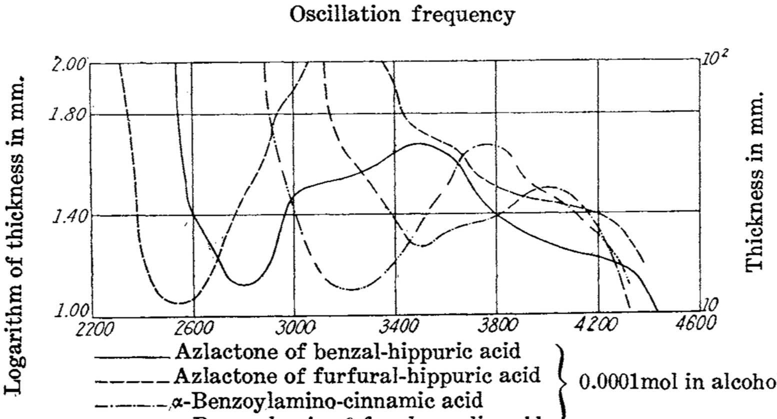
Azlactones are easily hydrolysed by dilute caustic soda to open the ring and form *α*-benzoylamino-*β*-aryl-acrylic acid, and the products are colourless and far less bathochromic than the corresponding azlactones (Figs. 6, 7, 8 and 9). It may be due to the rearrangement of the chromophore (substituted azomethine) group $-N=C=$ in the azlactones, to the non-absorbing benzoylamino group in the course of hydrolysis.

Of these α-benzoylamino-β-aryl-acrylic acids, the β-furyl acid is more bathochromic than the β-phenyl acid. Thus another example is added to the rule described above. For three hydroxy- and three methoxy-α-benzoylamino-cinnamic acids, the substitution of methyl group in the hydroxy group is not found essential to the light absorption (Figs. 7, 8 and 9).



——— Azlactone of benzal-hippuric acid
– – – – Azlactone of *o*-methoxybenzal-hippuric acid
— · — · Azlactone of *m*-methoxybenzal-hippuric acid
— ·· — ·· Azlactone of *p*-methoxybenzal-hippuric acid
} 0.0001 mol in alcohol

Fig. 5.



——— Azlactone of benzal-hippuric acid
– – – – Azlactone of furfural-hippuric acid
— · — · α-Benzoylamino-cinnamic acid
— ·· — ·· α-Benzoylamino-β-furyl-acrylic acid
} 0.0001mol in alcohol

Fig. 6.

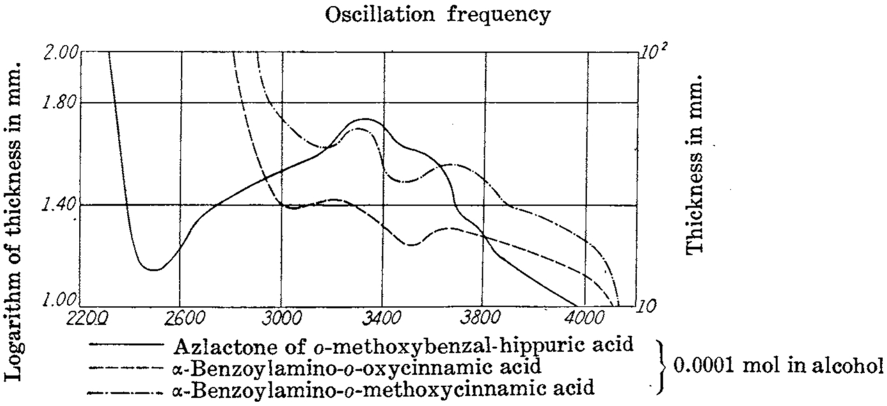


Fig. 7.

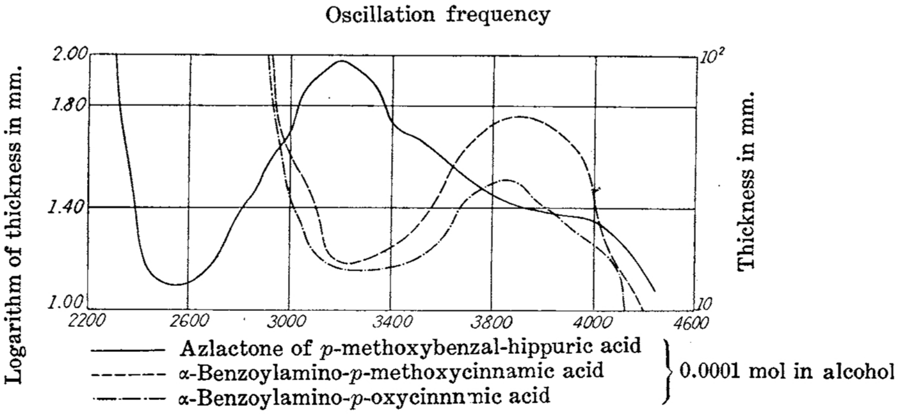


Fig. 8.

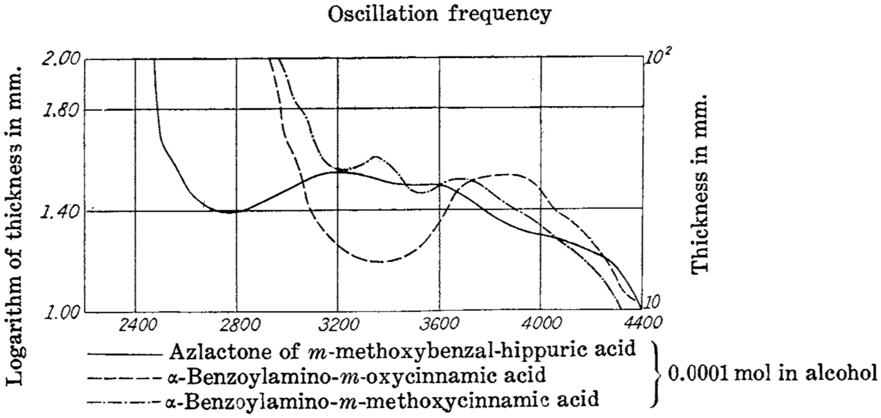


Fig. 9.

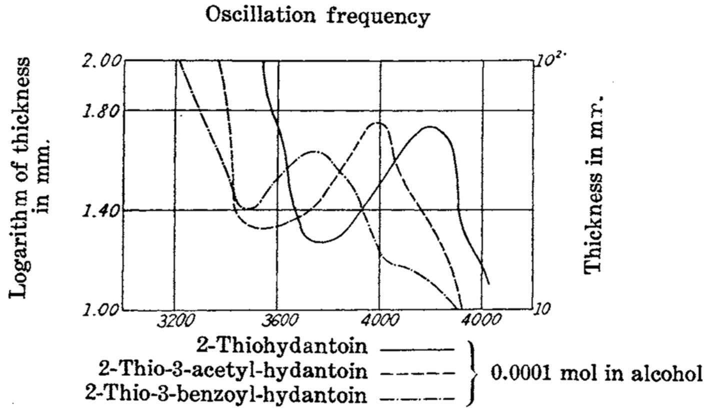


Fig. 10.

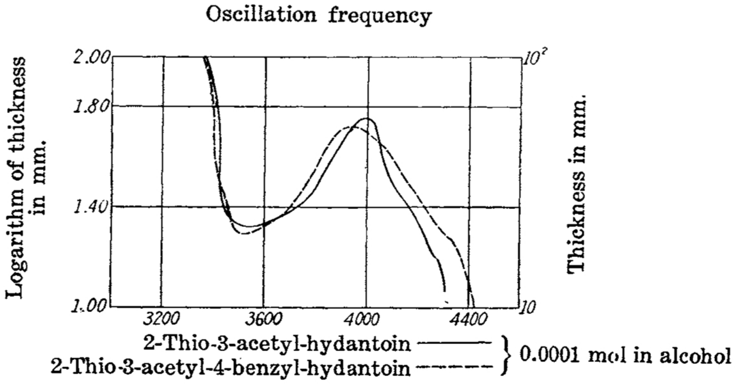


Fig. 11.

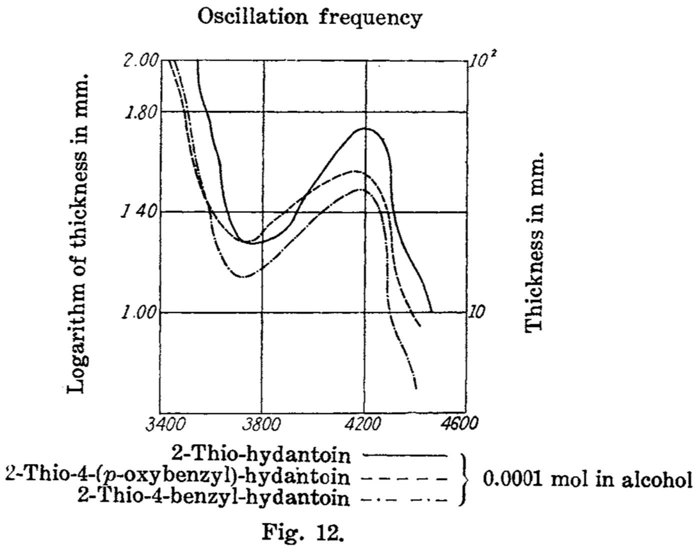


Fig. 12.

Thiohydantoins were first synthesized from amino acids by Prof. S. Komatsu.(1) In the present studies, the method is modified a little, and better results in the yield and the purity of the product is thereby obtained. The introduction of benzoyl or acetyl group in the position 3 gives a little bathochromic effect, and the interchange of these groups has only a slight influence on the absorption maxima (Fig. 10). 2-Thiohydantoin and its derivatives are more bathochromic owing to the existence of thiocarbonyl group =CS which is a more effective chromophore group than the carbonyl. The introduction of benzyl or oxybenzyl group in the position 4 of the hydantoin nucleus exerts almost no influence on the behaviour of light absorption (Figs. 11 and 12).

Experimentals.

The spectrograms were taken with the aid of Adam Hilger's quartz spectrograph; iron arc was used as the light source and the solutions were illuminated in the Baly tube provided with quartz plates. Alcohol was generally used as the solvent, but, in the case of the material insoluble in alcohol, glacial acetic acid was used instead. The concentrations are noted in the feet of the diagrams.

α-Benzoylamino-cinnamic acid. Benzal azlactone (2 gr.) was boiled in 200 c.c. of 0.5% caustic soda for 2 hours, filtered when cold and slightly acidified with hydrochloric acid.(2) The product was recrystallized from ten fold quantity of alcohol; m.p. 225–227° under decomposition (Erlenmeyer; 210–228° under decomposition).

α-Benzoylamino-β-furyl-acrylic acid.(3) Furfural azlactone was treated in the same manner as the preceeding; m.p. 211–212.5° under decomposition.

Azlactone of o-acetoxybenzal hippuric acid and α-Benzoylamino-o-oxycinnamic acid. The azlactone was prepared by the condensation of hippuric acid and salicyl aldehyde in the presence of sodium acetate and acetic anhydride(4). By this method, beside the azlactone, benzoylamidocoumaranone was produced. According to Erlenmeyer and Stadlin, these products were to be easily separated by the mere recrystallisation from ethyl alcohol. The procedure was literally followed, but on microscopical observation of the azlactone, this was found to contain not a small quantity of white needles of the coumaranone and on further recrystallisation from alcohol, the purification was accompanied by the loss of material and was

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(1) *J. Chem. Soc. Japan*, **31** (1910), 688.

(2) E. Erlenmeyer, jun., *Ann.*, **275** (1893), 10.

(3) E. Erlenmeyer, jun. and W. Stadlin, *Ann.*, **337** (1904), 284.

(4) E. Erlenmeyer, jun. and W. Stadlin, *Ann.*, **337** (1904), 290.

found rather difficult. Thus the method of separation was modified. The crude mixture was dissolved in benzene and to the solution, petroleum ether was added. The coumaranone first crystallized out and was separated by filtration; on addition of further quantity of petroleum ether to the filtrate, the azlactone was separated. This contained still a small quantity of coumaranone but the latter was easily removed by agitating the liquid and then decanting the supernatant suspension. The azlactone thus purified, on recrystallisation from alcohol, melted at 158.5° and showed no change of the melting point on further recrystallisation. (According to Erlenmeyer and Stadlin the melting point was 137–138°).

Anal. Found: C=70.1; H=4.40; N=4.58, 4.60%. Calc. for $C_{18}H_{13}O_4N$: C=70.4; H=4.27; N=4.56%.

On hydrolysis of the azlactone with dilute caustic soda, benzoylamino-coumaric acid was produced and after recrystallisation from alcohol, the melting point was 199.5° under decomposition (Erlenmeyer: 185.5)(1).

Anal. Found: N=5.13%. Calc. for $C_{16}H_{13}O_4N$: N=4.95%.

Azlactone of *o*-methoxybenzal hippuric acid and *α*-Benzoylamino-*o*-methoxycinnamic acid. One mol of *o*-methoxy-benzaldehyde (b.p. 236–240°, prepared from dimethyl sulphate and salicyl aldehyde(2)), 1 mol of hippuric acid and 1 mol of fused sodium acetate was intimately mixed with 3 mol of acetic anhydride; the mixture was heated for 30 minutes on a water bath. On cooling, the product was treated with large quantity of water, filtered and washed with dilute alcohol. The azlactone was recrystallized from alcohol. Light yellow needles of a little less intense colour than anisal azlactone, melted at 161°.

Anal. Found: N=5.17, 5.16%. Calc. for $C_{17}H_{13}O_3N$: N=5.02%.

The azlactone was hydrolysed with 100 times 1.5% caustic soda by heating for 5 hours on a water bath. The white crystals of benzoylamino-*o*-methoxycinnamic acid which separated on acidifying the hydrolysate, was recrystallized from alcohol; m.p. 208°.

Anal. Found: N=4.95%. Calc. for $C_{17}H_{15}O_4N$: N=4.71%.

Azlactone of *m*-acetoxybenzal hippuric acid and *α*-Benzoylamino-*m*-oxy-cinnamic acid. The azlactone was prepared by the condensation of *m*-oxy-benzaldehyde and hippuric acid; m.p. 148°(3) (Erlenmeyer and

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(1) Plöchl and Wolfrum, *Ber.*, **18** (1885), 1183.

(2) Katschalowsky and St. v. Kostanecki, *Ber.*, **37** (1904), 2347, foot-note.

(3) Erlenmeyer, jun. and F. Wittenberg, *Ann.*, **337** (1904), 294.

Wittenberg: 145°); and the acid was obtained by the hydrolysis of the former; m.p. 213–214° (Erlenmeyer and Wittenberg: 204°).

Azlactone of *m*-methoxybenzal hippuric acid and α-Benzoylamino-*m*-methoxy-cinnamic acid. The azlactone was prepared according to the procedure of R. Pschorr;⁽¹⁾ the acid was obtained in the usual manner and was recrystallized from dilute alcohol; m.p. 164.5°.

Azlactone of *p*-acetoxybenzal hippuric acid and α-Benzoylamino-*p*-oxy-cinnamic acid. The materials were prepared according to the description of Erlenmeyer and Halsey;⁽²⁾ m.p. 177.5° and 231–232° (E. and H.; 172–173° and 228–229°).

Azlactone of *p*-methoxybenzal hippuric acid and α-Benzoylamino-*p*-methoxy-cinnamic acid. The materials were prepared according to the procedure of Erlenmeyer and Wittenberg; the melting points were coincident with their description.⁽³⁾

Dibenzal diketopiperazine and Difurfural diketopiperazine. The former was obtained from Dr. T. Sasaki⁽⁴⁾ and the latter was prepared after his method.⁽⁵⁾

4-Benzal hydantoin and 4-Furfural hydantoin. The both substances were prepared, according to the method of Wheeler and Hoffman, benzaldehyde, hydantoin, anhydrous sodium acetate, acetic acid and acetic anhydride being used for the former, and replacing the benzaldehyde with furfural and omitting acetic anhydride for the latter.⁽⁶⁾

2-Thio-3-acetyl-hydantoin and 2-Thio-hydantoin. The former substance was first obtained by Prof. S. Komatsu by the condensation of glycocoll and potassium rhodanate in the presence of acetic acid and acetic anhydride, and the latter also by him by the hydrolysis of the former.⁽⁷⁾ Here, instead of potassium rhodanate, ammonium salt was used and the procedure was a little revised. Ten gr. of glycocoll and 13 gr. of ammonium rhodanate were well pulverised and intimately mixed, to which 50 c.c. acetic anhydride and 5 c.c. acetic acid were added. The mixture was heated on a water bath

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(1) *Ann.*, **391** (1912), 44.

(2) Erlenmeyer, jun. and J. T. Halsey, *Ann.*, **307** (1899), 139.

(3) Erlenmeyer, jun. and Wittenberg, ibid. Dakin reports a little higher melting points, i.e. 158° and 230–232 (not sharp) instead of 156.5° and 225° (*J. Biol. Chem.*, **8** (1910), 11).

(4) T. Sasaki, *Ber.*, **54** (1921), 163.

(5) T. Sasaki, *Ber.*, **54** (1921), 2057.

(6) H.L. Wheeler and C. Hoffman, *Am. Chem. Journ.*, **45** (1911), 371 and 380.

(7) S. Komatsu, *J. Chem. Soc. Japan.*, **31** (1910), 688. T. B. Johnson and H.B. Nicolet, *J. Am. Chem. Soc.*, **33** (1911), 1937.

when content of the flask became clear light yellow liquid. The colour did not change further as when potassium rhodanate was used. In the course of five minutes, the liquid effervesced vigorously and the temperature rose spontaneously as high as 120°. The flask was taken off from the water bath, and when the violent reaction ceased, it was again heated for further ten minutes. The further treatment was the same as Komatsu's. The yield was 16 gr. (ca. 80% of the calculation); m.p. 174–175°. Komatsu, and also Johnson and Nicolet obtained thiohydantoin by evaporating the acetyl- (or benzoyl-) thiohydantoin with concentrated hydrochloric acid on the water bath. The procedure was followed, but always an intensely coloured product was obtained which was difficultly decolourised by recrystallisation from alcohol even with the aid of charcoal. If the acetyl- or benzoyl-thiohydantoin was boiled for 30 minutes with 15 times quantity of concentrated hydrochloric acid, colourless white needles of thiohydantoin was abundantly separated, on cooling; m.p. ca. 130° under decomposition.

2-Thio-3-benzoyl-hydantoin. The substance was prepared from hippuric acid and glycocoll and was recrystallized several times from alcohol; m.p. 163–164°.

2-Thio-3-acetyl-4-benzyl-hydantoin and 2-Thio-4-benzyl-hydantoin. The former substance was prepared by the condensation of phenylalanine and ammonium rhodanate and the latter by evaporating the former with hydrochloric acid; m.p. 167° and 183°.(1) (2)

2-Thio-4-(*p*-oxybenzyl)-hydantoin. The substance was prepared by the condensation of tyrosine with ammonium rhodanate, m.p. 211–212°; as the 3-acetyl derivative could not be easily isolated, it was not spectroscopically examined.

2-Thio-4-benzal hydantoin. The material was prepared by the condensation of benzaldehyde with 3-benzoyl- or 3-acetyl-hydantoin in the presence of anhydrous sodium acetate and glacial acetic acid.(3) The yellow substance, after purification, darkened on heating towards 258° and melted at 260° under decomposition.

2-Thio-4-furfural hydantoin. Two gr. of benzoyl-thio-hydantoin (or 1.5 gr. of acetyl-thio-hydantoin), 2.5 gr. of furfural, 4 gr. of anhydrous sodium

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(1) Johnson and W.B. O'brien, J. *Biol. Chem.*, **12** (1912), 205.

(2) Johnson and Nicolet, *Am. Chem. Journ.*, **49** (1915), 197.

(3) Ibid.

(4) Johnson and Nicolet, *J. Am. Chem. Soc.*, **33** (1911), 1973. Johnson and O'brien, *J. Biol. Chem.*, **12** (1912), 210.

acetate and 8 c.c. of glacial acetic acid were intimately mixed in a flask, and heated in an oil bath for 3 hours at 130°. On dilution the content of the flask with large volume of water, dark crystals were obtained; yield nearly theoretical. Recrystallisation from alcohol gave orange yellow crystals of m.p. 255° under decomposition.

Anal. Found: N=14.9%. Calc. for $C_{10}H_8ON_2S$: N=14.4%.

In conclusion, the author wishes to express his best gratefulness to Prof. K. Shibata and Prof. Y. Shibata for their kind guidances in this research and to Dr. T. Sasaki for supplying him with samples. He is also indebted to the Imperial Academy, a part of the research expenses being defrayed from its grant.

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