Thyroxine Analogues: Synthesis and Nuclear Magnetic Resonance Spectral Studies of Diphenylamines

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A series of *N*-benzoyl-2,6-di-iododiphenylamines have been prepared by the rearrangement of the benzimidates (Ia—b); the latter are easily obtained by the condensation of the 2,6-di-iodophenols with *N*-*p*-methoxyphenylbenzimidoyl chloride. Preferential hydrolysis of the *N*-benzoyl group by potassium hydroxide helped in the synthesis of the compounds (IIIa—i). The method, however, failed with compounds (IVa—b) although the *O*-methyl group underwent hydrolysis with hydriodic acid.

N.m.r. analysis of the benzimidates and diphenylamines was performed. The phenomenon of the existence of pseudo *cis*- and *trans*-isomers about the C—N amide bond in *N*-benzoyl compounds is also discussed.

In connection with work[1] on thyroxine compounds, efforts have been made to synthesize the iodinated diphenylamine analogues of thyroxine which are expected to show marked physiological activity. Here we describe synthetic and spectral (i.r. and n.m.r.) studies of the diphenylamine derivatives.

p-Cyanophenol on iodination with iodine monochloride in glacial acetic acid gave 4-cyano-2,6-di-iodophenol in high yield. Condensation of this with the imidoyl chloride of *p*-methoxybenzanilide in pyridine gave the benzimidate (Ia) in good yield. Compound (Ia) when heated in *o*-dichlorobenzene (10 min) underwent a smooth Chapman rearrangement to give the *N*-benzoyl-4-cyano-2,6-di-iodo-4′-methoxydiphenylamine (IIa) in almost quantitative yield. This high yield of (IIa) is in con-

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[1] P. Block, jun., *J. Medicin. Chem.*, 1967, **10**, 950.

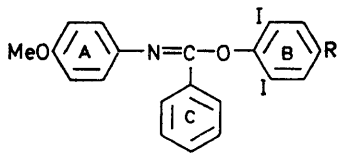
formity with recent predictions: [2] on the basis of entropy and steric factors, enhancement of rate should be observed for electron-withdrawing substituents *ortho* to the migrating aromatic ring in the Chapman rearrangement. Hydrolysis of (IIa) with 40% aqueous ethanolic potassium hydroxide gave the known [3] acid (IIIa) which was esterified to the methyl ester (IIIb) following the method of Cookson.[3] Attempted preparation of 4-cyano-2,6-di-iodo-4′-methoxy-diphenylamine (IIIc) by debenzoylation of (IIa) with a molar equivalent of potassium hydroxide in ethylene glycol [4] gave (IIb) within 10 min. Prolonged boiling under the same conditions produced a yellow reaction medium containing a mixture of (IIb) and (IIIa).

In order to build the alanine side chain at C-4, the *N*-benzoyl compound (IIa) was reduced under Stevens reduction conditions [5] to give the aldehyde (IIc) which could be oxidized with potassium permanganate to (IIb). Condensation of (IIc) with hippuric acid by the standard procedure gave the azlactone (IId) which was hydrolysed to the corresponding cinnamic acid (IIe) by boiling 2N-ethanolic sodium hydroxide. Known methods [3,6] of one-step reduction, demethoxylation, and debenzoylation could be successfully applied to give compound (IVa) with the alanine side-chain at C-4 as the final product. Further iodination of (IVa) gave the tetraiodo-derivative (IVb) in satisfactory yield. Attempts to debenzoylate both (IVa) and (IVb) by known methods [3,7,8] led to the complete destruction of the compounds. This may be due to the formation of the diphenylamine derivative in an intermediate stage, followed by its immediate rearrangement in that highly alkaline medium, facilitated by the electron-donating *para*-substituents of ring A. Failure of the debenzoylation reaction and subsequent loss of the compounds forced us to abandon this route for the synthesis of the diphenylamine analogues of thyroxine.

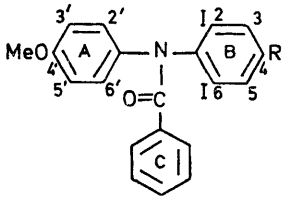
N-Benzoyl-4-formyl-2,6-di-iodo-4′-methoxy-diphenylamine (IIc) easily forms an acetal (IIf) which was debenzoylated by refluxing potassium hydroxide in aqueous methyl cellosolve. The highly crystalline diphenylamine acetal (IIId) thus formed was treated with a catalytic amount of hydrochloric acid in ethanol to regenerate the aldehyde function for subsequent building of the alanine side-chain. 4-Formyl-2,6-di-iodo-4′-methoxydiphenylamine (IIIe) was then condensed with hippuric acid to give the azlactone (IIIf) which upon alkaline hydrolysis furnished the cinnamic acid (IIIg). Attempts to reduce the cinnamic acid to either the saturated compound or the demethoxylated product with a free alanine side-chain were unsuccessful. No pure compound could be isolated from the black tarry reaction products. Failure of these attempted reductions can be rationalized by considering demethoxylation by hydriodic acid and red phosphorous and the extreme susceptibility of the resulting *p*-aminophenyl ether system to oxidation.[3]

Finally, reduction of the aldehyde (IIIe) with aluminium isopropoxide in isopropylalcohol gave the alcohol (IIIh) in very good yield, but attempts to convert it into a suitable derivative for final elaboration of the alanine side-chain at C-4 were unsuccessful, and none of the compound could be isolated.

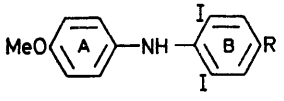
Routine i.r. spectral analysis of the diphenylamine analogues was of great value in their characterization [9] (see Experimental section). Neither of the *N*-benzoyl amino-acids [(IVa) and (IVb)] showed any phenolic or NH stretching, or normal carbonyl peaks, in conformity



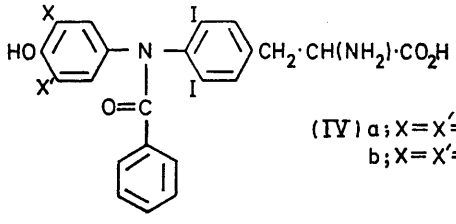
(I) a; R = CN
b; R = Me



(II) R
a; CN
b; CO_2H
c; CHO
d; CO·O·C(Ph):N·C:CH
e; BzNH·C(CO_2H):CH
f; O·CH_2·CH_2·O·CH
g; Me



(III) R
a; CO_2H
b; CO_2Me
c; CN
d; O·CH_2·CH_2·O·CH
e; CHO
f; CO·O·C(Ph):N·C:CH
g; BzNH·C(CO_2H):CH
h; CH_2OH
i; Me



(IV) a; X = X′ = H
b; X = X′ = I

with the behaviour usually exhibited by amino-acids due to Zwitterion formation.[10] From this observation the

[2] H. M. Relles, *J. Org. Chem.*, 1968, **33**, 2245.
[3] R. C. Cookson, *J. Chem. Soc.*, 1953, 643.
[4] A. P. T. Easson, *J. Chem. Soc.*, 1961, 1029.
[5] E. C. Horning, ed., *Org. Synth.*, Coll. Vol. III, 1955, p. 626.
[6] Paul Block, jun., Ph.D. Dissertation, Columbia University, New York, N.Y., 1942.
[7] For a recent review, see J. W. Schulenberg and S. Archer, *Org. Reactions*, 1965, **14**, 1.
[8] A. R. Kidwai and G. M. Devasia, *J. Org. Chem.*, 1962, **27**, 4527.
[9] L. J. Bellamy, ' The Infrared Spectra of Complex Molecules,' John Wiley, New York, 1960.
[10] See ref. 9, ch. 13.

possibility of salt formation by both (IVa) and (IVb) during their preparation and crystallization is excluded.

The n.m.r. spectra (Table) of the diphenylamine derivatives (both *N*-benzoylated and unbenzoylated) were studied along with those of the benzimidates, (Ia) and (Ib).[3] In the benzimidates (Ia) and (Ib), all four aromatic protons of the 1,4-disubstituted ring A appeared as a sharp singlet indicating their chemical equivalence. The C ring protons always gave rise to AX_2B_2 patterns exhibiting multiplets around δ 7·69 ± 0·04 and δ 7·33 ± 0·04 p.p.m. For (Ib), the B ring protons showed the expected up-field shift and merged with the ring C B_2 protons. A singlet for the two equivalent *ortho*-protons of ring B appeared at δ 8·07 p.p.m. for (Ia) and 7·73 p.p.m. for (Ib). The aromatic methoxy and methyl signals were at δ 3·72 ± 0·02 and 2·30 p.p.m.

In the *N*-benzoyl derivatives, (IIa), (IIc), and (IIg) both 4′-methoxy and 3-H, 5-H appeared as two singlets in each case. The C-4 aldehyde (IIc) and methyl (IIg) also exhibited two singlets for each of them. Separation of the two singlets was for 4′-methoxy 0·06 p.p.m.; 4-methyl, 0·09 p.p.m., aldehyde, 0·12 p.p.m. and for the B ring protons 0·11 p.p.m. to 0·14 p.p.m. The A_2B_2 quartet for the A ring protons appeared within 26 to 28 Hz. Hindered rotation about the C–N bond in amides [11] easily explains the observed two signals for each of the functional groups (IIa), (IIc) and (IIg).

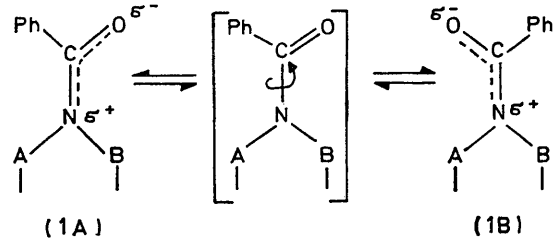
In the *N*-benzoyl compounds the phenomenon of pseudo *cis*- and *trans*-isomerism about C–N amide bond [12] exists and thus, at low temperatures, both isomers (1A) and (1B) are observed in the n.m.r. spectra as is clear from the appearance of two signals for C-OMe, C-Me, C-CHO and 3-H, 5-H. At higher temperatures ($(CD_3)_2SO$, 86°], in all the three *N*-benzoyl derivatives [(IIa), (IIc) and (IIg)] the two signals in each case (Table) coalesce to a single sharp resonance signal showing definite proton count as expected. The energy requirements for surmounting the rotational barrier have been met at *ca.* 86° [Figure 2, n.m.r. spectra of (IIc), both low and high temperatures].* The change in solvent from $CDCl_3$ to $(CD_3)_2SO$ did not cause any shift in the resonance signals.

N.m.r. chemical shifts of protons of the diphenylamine derivatives [a]

	Proton positions															
								C-4 Substitution								
Compounds	Ring A		Ring B		Ring C		NH	CHO or CH(O)O		Acetal	CH_2OH	CO_2CH_3	CH_3		OCH_3	
(Ia)	6·71s		8·07s		7·69m	7·33m									3·72s	
(Ib)	6·73s		7·73s		7·71m	7·37m									3·74s	
(IIa)	6·96d *J* 9·5	6·70d	8·20s	8·06s	7·62m	7·34m									3·80s	3·74s
(IIc)	7·01d *J* 9·5	6·72d	8·43s	8·30s	7·72m	7·38m		9·96s	9·84s						3·84s	3·78s
(IIg)	6·98d *J* 9·5	6·68d	7·75s	7·64s	7·60m	7·29m							2·32s	2·23s	3·81s	3·75s
(IIIb)	6·84s		8·51s				6·02s					3·97s			3·84s	
(IIId)	6·87d *J* 9·5	6·64d	7·99s				5·68s	5·76s		4·13s					3·80s	
(IIIe)	6·86s		8·44s				6·18s	9·80s							3·86s	
(IIIh)	6·81d *J* 9·5	6·56d	7·84s				5·60s				4·62d *J* 3				3·79s	
(IIIi)	6·82d *J* 9·5	6·56	7·70s				5·43s						2·33s		3·79s	

[a] Shifts (p.p.m.) measured in $CDCl_3$ on a Varian A-60 spectrometer with tetramethylsilane as the internal reference. [b] Coupling constants in H_z: s = singlet, d = doublet, m = multiplet.

A comparison of the n.m.r. spectra of the debenzoylated compounds (IIIb), (IIId—e), (IIIh), and (IIIi) having secondary amine group gave clear information about the resonance patterns and chemical shift values of ring A protons, NH and the B-ring protons. In compounds (IIIb) and (IIIe) having a strong electronegative group at C-4, the ring A protons gained chemical equivalence and collapsed from an A_2B_2 quartet to a singlet, but the other three (Table) show the usual A_2B_2 pattern resonating in a small area (*ca.* 26 Hz). Both 3-H, 5-H and NH signals show low-field shifts in (IIIb) and (IIIe) as expected. The position of NH absorption



(1A) (1B)

FIGURE 1 Low temperatures: Both isomers (1A) and (1B) observed. High temperatures: An average isomer observed.

* Spectra for (IIa) and (IIg) are not presented as they showed behaviour at high temperatures exactly like (IIc).

[11] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

[12] S. W. Pelletier and T. N. Oeltmann, *Tetrahedron*, 1968, **24**, 2019.

which always showed a broad peak was definitely established by deuterium exchange. Other functional groups like the acetal, 4-methoxycarbonyl, CH(O)O, CHO, and C-4′ aromatic methoxy showed resonance signals in the usual positions (Table). In case of (IIIh) upon addition

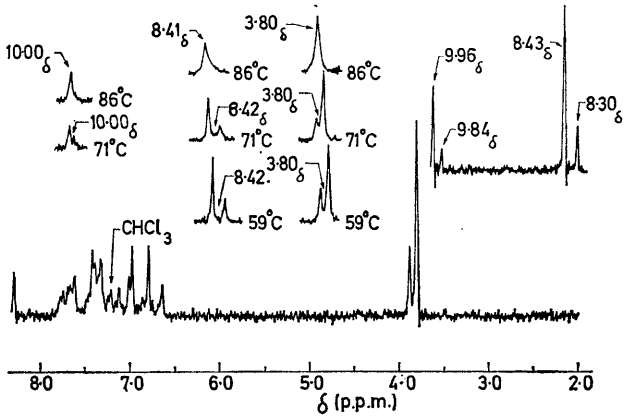


FIGURE 2 N.m.r. spectra of (IIc) at low and high temperatures.

of deuterium oxide, the OH triplet at δ 2·26 p.p.m. (J 6 Hz), formed by coupling of the hydroxy proton with the methylene hydrogens, disappeared, and the methylene doublet at δ 4·62 p.p.m. (J 3 Hz) collapsed to a singlet appearing at δ 4·61.

EXPERIMENTAL *

M.p.s. were taken in capillary tubes in a Hershberg m.p. apparatus and are uncorrected. The n.m.r. spectra were measured with a Varian A-60 spectrometer in deuteriochloroform at ordinary temperature and in perdeuteriodimethyl sulphoxide at high temperatures with a V-6040 variable-temperature system. Tetramethylsilane was used as the internal standard throughout. The i.r. spectra were measured in a Perkin-Elmer 621 spectrophotometer in chloroform solution unless otherwise specified. The n.m.r. data are collected in the Table and discussed in the earlier part of this paper. The analytical data were supplied by Huffman Laboratories, Inc., Wheatridge, Colorado 80033, Crobaugh Laboratories, Cleveland, Ohio, 44114 and University of Singapore, Singapore 10.

4-Cyano-2,6-di-iodophenyl-N-p-methoxyphenylbenzimidate (Ia).—*p*-Methoxybenzanilide (23·8 g, 0·105 mol) and phosphorus pentachloride (21·8 g, 0·105 mol) were heated on a steam-bath until hydrogen chloride ceased to be evolved and a clear green liquid remained. Solid imidoyl chloride was obtained after removal of the phosphoryl chloride with a rotary evaporator (water pump at 50—60°). The 4-cyano-2,6-di-iodophenol (37·1 g, 0·1 mol) in dry pyridine (50 ml) was added to the imidoyl chloride; the mixture was shaken vigorously and then set aside for 1 h after it had attained room temperature. The reaction mixture was poured in water and allowed to crystallize. The product was collected, suspended in dilute NaOH solution, filtered again, washed with water, dried, and crystallized from 3 volumes of carbon tetrachloride to give the benzimidate (Ia) (54 g), as light yellow *needles*, m.p. 156° (from ethyl acetate–hexane), $\nu_{max.}$ 2232 (CN), and 1670 cm^{-1} (C=N) (Found: C, 43·55; H, 2·7; I, 44·0. $C_{21}H_{14}I_2N_2O_2$ requires C, 43·45; H, 2·4; I, 43·8%).

The benzimidate (Ib), prepared by the method of Cookson [3] showed the same yield and m.p. as reported; [3] the n.m.r. proton count was in excellent agreement with the molecular formula $C_{21}H_{17}NO_2I_2$; $\nu_{max.}$ 1670 cm^{-1} (C=N).

Rearrangement of (Ia) *to* (IIa).—The benzimidate (30 g) in *o*-dichlorobenzene (90 ml), was heated under reflux for 10 min; the mixture was then cooled, diluted with pentane (90 ml), and allowed to crystallize. The product was collected and washed with n-pentane and then cold ethanol to give the *N*-benzoyl-4-cyano-2,6-di-iodo-4′-methoxy-diphenylamine (IIa) in almost quantitative yield. Crystallization of (IIa) from benzene–ethanol gave colourless *needles*, m.p. 232—233·5°, $\nu_{max.}$ 2235 (CN) and 1650 cm^{-1} (NCO); M^+ at *m/e* 580 (Found: C, 43·05; H, 2·8; I, 43·8. $C_{21}H_{14}N_2O_2I_2$ requires C, 43·45; H, 2·4; I, 43·8%).

The *N*-benzoyl derivative (IIg) was prepared from (Ib) following essentially the method of Cookson.[3] In the final stage, the crude, grey reaction product was chromatographed on Brockmann alumina with benzene as eluant. Pure (IIg) was obtained as colourless needles in the same yield as reported; [3] it had an m.p. identical with the reported value; [3] the n.m.r. proton count of (IIg) was in good agreement with the molecular formula $C_{21}H_{17}NO_2I_2$; $\nu_{max.}$ 1655 cm^{-1} (NCO).

Hydrolysis of (IIa) *to* (IIIa).—A solution of (IIa) (1 g) and potassium hydroxide (10 g) in 50% ethanol (20 ml) was heated under reflux for 2 h. The cooled solution was acidified and the yellow brown solid which separated was collected, washed with water, dried, and crystallized from ethyl acetate to give yellow needles (0·64 g), m.p. 213° (lit.[3] m.p. 210°), $\nu_{max.}$ 3360 (NH), 3330 (OH) and 1690 cm^{-1} (CO_2H); M^+ at *m/e* 495.

The Methoxycarbonyl Ester (IIIb).—Esterification of (IIIa) by the known method gave the ester (IIIb) which crystallized from ethanol as light yellow needles, m.p. 103° (lit.[3] m.p. 111°), $\nu_{max.}$ 3355 (NH) and 1710 cm^{-1} (CO_2Me). In spite of the discrepancy in m.p., the present compound was found to be pure; the n.m.r. proton count (13H) was in excellent agreement with the molecular formula $C_{11}H_{13}NO_3I_2$.

Hydrolysis of (IIa) *to* (IIb).—Compound (IIa) (1g) was heated under reflux in a 10% solution of sodium hydroxide (1 mol) in 75% ethylene glycol for 10 min; the mixture was cooled, diluted with a few drops of water and acidified to give the acid (IIb) (0·8 g) which crystallized from dilute acetic acid as colourless needles, m.p. 230° (lit.[3] m.p. 230°), $\nu_{max.}$ (KBr) 1690 (CO_2H) and 1650 cm^{-1} (NCO).

Reduction of (IIa).—A mixture of dry ether (120 ml) and anhydrous stannous chloride (21·4 g) [5] was saturated with dry hydrogen chloride (3—4 h). Compound (IIa) was added to the mixture which was again saturated (2 h) with hydrogen chloride whilst being vigorously stirred. It was stirred for a further 1 h and then kept overnight. The ether layer was decanted and the oily yellow aldimine hydrochloride was washed with ether (2 × 25 ml). Hydrolysis with water (*ca.* 200 ml) at the boil for *ca.* 10 min gave upon cooling the mixture the buff-coloured aldehyde (IIc); this was crystallized from acetonitrile to form *needles* (9·3 g), m.p. 143°, $\nu_{max.}$ 1695 (CHO) and 1650 cm^{-1} (NCO) (Found: C, 43·7; H,

* It was not possible to compare compounds (Ib), (IIb), (IIg), (IIIa) and (IIIb) directly with the reported ones due to the nonavailability of the latter.

2·75; I, 43·6. $C_{21}H_{15}I_2NO_3$ requires C, 43·25; H, 2·55; I, 43·55%).

Oxidation of (IIc) *to* (IIb).—To a solution of the aldehyde (IIc) (1 g), in the minimum quantity of aqueous acetone, a solution of potassium permanganate was added at room temperature until the pink colour persisted. After 1 h, addition of water precipitated the acid which was freed from MnO_2 by treatment with dilute HCl. The white product was collected, dissolved in ethanolic alkali, reprecipitated with dilute HCl, and crystallized from dilute acetic acid to give needles (0·75 g) m.p. 229° (lit.[3] m.p. 230°).

The Azlactone (IId).—A mixture of (IIc) (3 g), hippuric acid (0·93 g) freshly fused NaOAc (0·42 g) and acetic anhydride (2 ml) was heated on a steam-bath for 15—20 min. Excess of acetic anhydride and NaOAc was decomposed with cold water and the yellow azlactone (IId) was crystallized from acetone to form *needles* (3 g), m.p. 170—175° (decomp.), $\nu_{max.}$ (Nujol) 1790 (OCO) and 1650 cm^{-1} (NCO) (Found: C, 49·75; H, 3·2; I, 35·35. $C_{30}H_{20}I_2N_2O_4$ requires C, 49·6; H, 2·75; I, 35·0%).

Hydrolysis of (IId) *to the Cinnamic Acid* (IIe).—A solution of the azlactone (2·6 g) in ethanol (60 ml) and 2N-aqueous NaOH (20 ml) was boiled for 10—15 min, diluted with water (80 ml) and again boiled for 10—15 min. The clear solution was cooled and acidified with dilute HCl to give the light yellow cinnamic acid (IIe) (2·5 g). It crystallized from aqueous acetic acid as *needles*, m.p. 190—195° (decomp., $\nu_{max.}$ (KBr) 1710 (CO_2H) and 1650 cm^{-1} (NCO and NHCO) (Found: I, 34·1. $C_{30}H_{22}I_2N_2O_5$ requires I, 34·15%).

Conversion of (IIe) *into* (IVb).—A mixture of (IIe) (2 g), red phosphorus (2 g), HI (0·8 ml), and acetic acid (30 ml) was heated under reflux for 1·5 h. Constant-boiling HBr (5 ml) was added and the mixture was heated under reflux for a further 3·25 h. The solution was filtered and the filtrate was evaporated to dryness in a rotary evaporator. Addition of water to the residue gave (IVa) which crystallized from dilute acetic acid as tan needles, m.p. 210—215° (decomp.), $\nu_{max.}$ (Nujol) 1650 (NCO), 1635 (NH_3^+), and 1610 cm^{-1} (CO_2^-). This phenol (2 g) dissolved in ethylamine (20 ml; 20%) was treated dropwise with iodine in potassium iodide solution (8·2 ml; 1·85N). After 0·5 h the solution was acidified with dilute acetic acid and the excess of iodine was destroyed with a little bisulphite. The precipitated tetraiodo-compound (IVb) (2 g) crystallized from slightly acidic aqueous ethanol as *needles*, m.p. 195—198° (decomp.), $\nu_{max.}$ (Nujol) 1650 (NCO), 1635 (NH_3^+), and 1610 cm^{-1} (CO_2^-) (Found: C, 30·25; H, 2·15; I, 55·5, $C_{22}H_{16}I_4N_2O_4$ requires C, 30·0; H, 1·8; I, 57·7%).

Preparation of the Acetal (IIf).—The acetal was prepared in quantitative yield by heating (IIc) in dry refluxing benzene for 5 h with a molar quantity ethylene glycol and a catalytic amount of toulene-*p*-sulphonic acid. Solvent was removed from the mixture and the residue was washed with hydrogen carbonate solution and water; the product crystallized from boiling acetone as colourless *flakes*, m.p. 228° $\nu_{max.}$ 1650 (NCO) (Found: C, 44·2; H, 3·35; I, 40·6. $C_{23}H_{19}I_2NO_4$ requires C, 44·05; H, 3·05; I, 40·5%).

Debenzoylation of (IIf).—A mixture of methyl cellosolve (15 ml), water (5 ml), KOH pellets (4·1 g), (IIf) (1 g) was heated under reflux. The solution became clear within 55 min but the mixture was heated under reflux for a further 2 h. When the mixture was cooled and diluted with water (4 ml), crystalline solid appeared. The debenzoyl acetal (IIId) (0·75 g) crystallized from ethyl acetate–heptane as colourless *needles*, m.p. 135°, $\nu_{max.}$ 3365 (NH) (Found: C, 37·2; H, 3·15; I, 48·2. $C_{16}H_{15}I_2NO_3$ requires C, 36·75; H, 3·85; I, 48·55%).

Synthesis of (IIIi).—The debenzoylation of compound (IIg) was carried out as described to give (IIIi) in almost quantitative yield. The product crystallized from ethyl acetate–heptane as colourless *needles*, m.p. 125°, $\nu_{max.}$ 3370 (NH (Found: C, 36·45; H, 2·9; I, 55·0. $C_{14}H_{13}I_2NO$ requires C, 36·15; H, 2·8; I, 54·6%).

Deacetalization of (IIId).—Deacetalization was achieved by boiling (IIId) (0·85 g) in ethanol (10 ml) and water (2 ml) with 3—5 drops of 5N-HCl for 2—3 min. Yellow crystals of (IIIe) (0·72 g) appeared from the cooled mixture and crystallized from ethanol as *needles*, m.p. 113°, $\nu_{max.}$ 3360 (NH) and 1680 cm^{-1} (CHO). The aldehyde became red on exposure to air even for one night (Found: C, 34·65; H, 2·45; I, 52·75; N, 3·1. $C_{14}H_{11}I_2NO_2$ requires C, 35·1; H, 2·3; I, 53·0; N, 2·9%).

The Cinammic Acid (IIIg).—The orange azlactone (IIIf) [m.p. 197°, $\nu_{max.}$ 3360 (NH), 1780 (OCO), and 1660 cm^{-1} (C=N) (Found: C, 44·6; H, 2·8; I, 40·9. $C_{23}H_{16}I_2N_2O$ requires C, 44·35; H, 2·6; I, 40·85%)], was prepared from (IIIe) as described above and crystallized as *needles* from acetone–methanol; hydrolysis gave (IIIg) as yellow *needles* m.p. 244—245° (decomp.) (from EtOAc) $\nu_{max.}$ (KBr) 3360 (NH), 3240 (NHCO), 1690 (CO_2H), and 1650 cm^{-1} (NHCO) (Found: C, 43·4; H, 3·35; N, 4·2. $C_{23}H_8I_2N_2O_4$ requires C, 43·15; H, 2·8; N, 4·35%).

Reduction of (IIIe) *to* (IIIh).—The aldehyde (IIIe) (2 g), dry isopropyl alcohol (5 ml) and freshly prepared aluminium isopropoxide (1 g) were heated under reflux for 3—4 h until the distillate showed a negative DNP test for acetone. The reaction product was cooled, decomposed with dilute HCl, and taken into chloroform. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and evaporated to leave solid (IIIh) (1·88 g). This alcohol crystallized from benzene–heptane as faint yellow *flakes*, m.p. 115°, $\nu_{max.}$ 3600 (CH_2OH) and 3363 cm^{-1} (NH) (Found: C, 34·9; H, 2·75; I, 52·9. $C_{14}H_{13}I_2NO_2$ requires C, 34·95; H, 2·7; I, 52·85%).

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