Tetrahedron, 1959, Vol. 6, pp. 304 to 311. Pergamon Press Ltd. Printed in Northern Ireland.

ANHYDROBIISATIC ACID

6:12-OXA-5:6:11:12-TETRAHYDROPHENHOMAZINE-6:12-DICARBOXYLIC ACID

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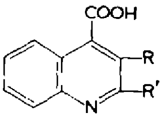
(*Received* 4 *November* 1958)

Abstract—Anhydrobiisatic acid (IVa), a new type of compound containing the phenhomazine ring system, has been obtained by self-condensation of isatic acid—(*o*-aminophenyl)glyoxylic acid—. The structure of this acid has been established and derivatives have been prepared. N:N'-Dimethylanhydrobiisatic acid (IVc) has been resolved into optically active components.

It has long been known that isatin will dissolve in aqueous alkalies to give salts of isatic acid.[1,2,3] These salts, in aqueous or aqueous-alcoholic solution, can condense with ketones (Pfitzinger reaction)[4] to furnish substituted cinchoninic acids (I).



I

Condensation of isatin with various diketones, were found to give the best yields of substituted cinchoninic acids by heating the dry potassium salt of isatic acid with the diketone in the absence of solvent.[5] The yields were usually reproducible, but in some cases, when repeating the experiments, the reaction either failed or gave only traces of the expected product. As the conditions were identical, the only reason for such failure could lie in the composition of the derivative prepared from isatin and potassium hydroxide.

The reaction between isatin and aqueous potassium hydroxide has therefore been investigated. According to experimental conditions, two different potassium salts can be obtained; a *yellow* one, which is the major product when isatin is treated with one equivalent of 20% aqueous potassium hydroxide at temperatures below 40°, and a *colourless* salt, resulting from the reaction of isatin with excess of concentrated (40%) aqueous potassium hydroxide under reflux. By heating the yellow salt in aqueous alkali, it is converted to the colourless compound, whereas the latter is not changed under similar conditions. Two series of salts can be derived from these compounds; the yellow salt gives an orange lead and yellow barium and silver salts; the colourless potassium salt, on the other hand, affords colourless salts with these metals. The iron, copper and nickel salts, in both series, are coloured, with slight differences between the corresponding members of each series.

It is the yellow potassium salt which condenses with diketones to give substituted cinchoninic acids; the colourless salt does not react. By acidifying an aqueous

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* Taken, in part, from the Ph.D. dissertation of Lj. Lorenc.

[1] O. L. Erdmann, *J. Prakt. Chem.* **24**, 1 (1841); *Ann. Chim. Phys.* **3**, 355 (1841).

[2] A. Laurent, *Ann. Chim. Phys.* **3**, 371 (1841).

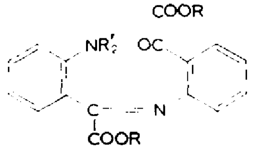
[3] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).

[4] For references, see W. C. Sumpter, *Chem. Rev.* **34**, 393–434 (1944).

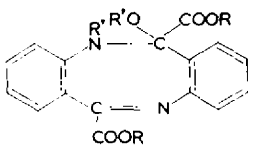
[5] Gj. Stefanović, M. Pavičić-Woss, Lj. Lorenc and M. Lj. Mihailović, *Tetrahedron*, **6**, 97 (1959).

solution containing the yellow salt, isatin is immediately formed, whereas from the colourless salt, a colourless acid, m.p. 176°, is obtained, which can be isolated and purified. In aqueous solution this acid is slowly converted to isatin, the conversion being accelerated by heating or addition of acid. However, it is stable in the solid state when perfectly pure. The same acid is obtained by decomposing the colourless lead salt with hydrogen sulphide. On the other hand, the orange lead salt, when treated in the same way, gives isatin as the sole product.

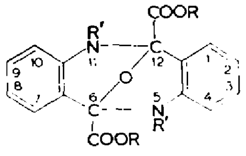
From analytical data and from the chemical behaviour just mentioned, it can be concluded that the yellow potassium salt and related salts are salts of isatic acid, whereas the colourless salts and the corresponding acid, m.p. 176°, are condensation products of isatic acid, formed from two molecules of the acid with elimination of water. Three structures* can be envisaged for the new *anhydrobiisatic acid* (II, III or IV), in agreement with the molecular formula $C_{16}H_{12}O_5N_2$.



II



III



IV

(a) $R = R' = H$ (b) $R = CH_3, R' = H$ (c) $R = H, R' = CH_3$
(d) $R = R' = CH_3$

It appears from the literature that the compounds described as salts of isatic acid are either mixtures of both salts or salts of one or the other series. Erdmann[1] reported a colourless potassium salt and colourless barium and lead salts, whereas the silver salt is described either as colourless or yellow. In contrast, Laurent[2] obtained a pale yellow potassium salt and yellow silver and lead salts. The sodium, silver and lead salts prepared by Heller[3] were all yellow. Attempts to obtain isatic acid from these salts failed; isatin was always the final product.[1,2,3,6] Only in one case, namely by treating the colourless lead salt with hydrogen sulphide, was Erdmann[1] able to isolate a colourless solid which, in aqueous solution, underwent facile conversion to isatin. This product was regarded by Erdmann as isatic acid. However, from the present work, it appears that this compound is in fact anhydrobiisatic acid rather than isatic acid. Moreover, it is now well known that isatic acid and its N-alkyl or N-aryl derivatives cannot be isolated, in contrast to N-acylated isatic acids, which have been prepared in several instances.[7]

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* Structures corresponding to II[8] and III[9] have been ascribed (without any proof) to anhydro*bis*(*o*-aminobenzaldehyde), a self-condensation product of *o*-aminobenzaldehyde. Similar constitutions have been also proposed for higher condensation products of *o*-aminobenzaldehyde.[10]

[6] L. Claisen and J. Shadwell, *Ber. Dtsch. Chem. Ges.* **12**, 350 (1879); G. Heller, *Ibid.* **37**, 938 (footnote 2) (1904); E. Deussen, G. Heller and O. Nötzel, *Ibid.* **40**, 1300 (1907).

[7] W. Suida, *Ber. Dtsch. Chem. Ges.* **11**, 584 (1878); C. Schotten, *Ibid.* **24**, 772 (1891); M. T. Bogert and F. P. Nabenhauer, *J. Amer. Chem. Soc.* **46**, 1702 (1924); J. A. Aeschlimann, *J. Chem. Soc.* 2902 (1926); R. K. Callow and E. Hope, *Ibid.* 1191 (1929); W. Steinkopf and H. Wilhelm, *Liebigs Ann.* **546**, 211 (1942); R. Johnstone and J. R. Price, *Aust. J. Chem.* **7**, 209 (1954); T. Sato and M. Ohto, *Bull. Chem. Soc. Japan* **28**, 480 (1955).

[8] P. Friedländer and R. Henriques, *Ber. Dtsch. Chem. Ges.* **15**, 2105 (1882); P. Friedländer and C. F. Göhring, *Ibid.* **17**, 456 (1884).

[9] P. Friedländer, *C. R. Acad. Sci., Paris* **136**, 370 (1902).

[10] E. Bamberger and E. Demuth, *Ber. Dtsch. Chem. Ges.* **36**, 835 (1903); E. Bamberger, *Ibid.* **36**, 2046 (1903); *Ibid.* **60B**, 314 (1927); F. Seidel, *Ibid.* **59**, 1894 (1926).

Anhydrobiisatic acid is quite a strong acid, pK_1 (water) 2·88. It does not undergo reactions characteristic for the carbonyl, hydroxyl and primary amino groups. Hydrogenation in the presence of platinum, platinic oxide, palladium or Raney nickel was unsuccessful. Its colourless potassium salt is not attacked by sodium borohydride in aqueous solution, even after prolonged heating. By treating anhydrobiisatic acid with diazomethane in anhydrous ether, a compound having the molecular formula $C_{18}H_{16}O_5N_2$ (analysis and molecular weight determination) was isolated. It, therefore contains two additional CH_2 groups.* This compound, stable in contrast to the free acid, is insoluble in sodium bicarbonate solution but can easily be saponified to the starting acid. These properties (and the saponification value) correspond to the dimethyl ester of anhydrobiisatic acid (although it is insoluble in ether and melts higher than the acid from which it is derived). It is also resistant to catalytic hydro-genation and does not give derivatives with specific reagents for the carbonyl, primary amino hydroxyl groups. The behaviour of anhydrobiisatic acid and of its dimethyl ester, and the fact that all compounds of this series (with the exception of the iron, copper and nickel salts) are colourless, make structures II and III improbable.†

Conclusive evidence for structure IV is obtained from methylation experiments of anhydrobiisatic acid. When the silver salt of anhydrobiisatic acid is treated with methyl iodide in anhydrous ether, a new acid is formed, m.p. 154°, isomeric with the dimethyl ester of anhydrobiisatic acid. The same acid, but crystallizing with two molecules of water (m.p. 118°), is obtained from the potassium salt of anhydrobiisatic acid and dimethyl sulphate, in aqueous solution.‡ Examples reported in the literature,[13] indicate that methylation of salts of amino acids with dimethyl sulphate and methyl iodide, in aqueous or anhydrous media, usually give N-methylated amino acids and not N-unsubstituted esters. The new acid should, accordingly, contain the two additional methyl groups on nitrogen (or on nitrogen and on hydroxyl oxygen, in the case of structure IIIc) and, on hydrolysis, would be expected either to give a mixture of isatin and N-methylisatin or other products (structures IIc and IIIc), or solely N-methylisatin (structure IVc).

The new dimethylated acid has properties similar to those of anhydrobiisatic acid. It is a rather strong acid, pK_1 (ethanol) 3·92, stable only in the solid form and when completely pure. In aqueous solution, upon heating or upon addition of mineral

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* In case of structure III, the hydroxyl group, being activated by the presence of other functional groups, would possibly undergo methylation (to a certain extent) with diazomethane,[11] although the neutralizing effect of anhydrous ether should not be disregarded.[12]

† It may be assumed that a *cis* configuration of structure II would be sterically hindered, thus preventing the usual reactions of the carbonyl and amino groups. Examination of models, however, suggests that under drastic alkaline conditions, such as are used for obtaining the potassium salt of anhydrobiisatic acid, *cis*-II should undergo facile condensation between the carbonyl and amino groups, with elimination of water. For this reason also, an aldehyde-ammonia structure, such as III, is *a priori* highly improbable. Both structures II and III, moreover, should be attacked by sodium borohydride and catalytically activated hydrogen, in contrast to IV, which has no reducible groups.

‡ The identity of both acids was established by conversion of the anhydrous acid, m.p. 154°, to the hydrated acid, m.p. 118°.

[11] O. T. Schmidt and H. Zeiser, *Ber. Dtsch. Chem. Ges.* **67B**, 2120, 2127 (1934).

[12] H. Meerwein and G. Hinz, *Liebigs Ann.* **484**, 1 (1930).

[13] K. Kraut, *Liebigs Ann.* **180**, 172 (1876); G. Körner and A. Menozzi, *Gazz. Chim. Ital.* **13**, 350 (1883); G. Fortmann, *J. Prakt. Chem.* **55**, 123 (1897); R. Willstätter and W. Kahn, *Ber. Dtsch. Chem. Ges.* **37**, 401 (1904); J. Houben and W. Brassert, *Ibid.* **39**, 3233 (1906); J. Novák, *Ibid.* **45**, 834 (1912); T. Imai, *Z. Physiol. Chem.* **136**, 192 (1924).

acids, it is quickly and quantitatively converted to N-methylisatin.* The fact that one mole of acid gives two moles of N-methylisatin (and no isatin) is compatible only with structure IVc.

N:N'-Dimethylanhydrobiisatic acid (IVc) is converted to its dimethyl ester (IVd) by diazomethane, dimethyl sulphate (in aqueous solution) or methyl iodide (using the silver salt of the acid suspended in anhydrous ether). This diester, like that of anhydrobiisatic acid (IVb), is sparingly soluble in ether (although to a somewhat greater extent than the dimethyl ester IVb) and melts higher than the corresponding acid (m.p. 173°). Upon saponification, it gives the original acid (IVc), in 96% yield. Both the acid (IVc) and its dimethyl ester (IVd) are colourless compounds.

Additional evidence for structure IV was obtained by resolving N:N'-dimethylanhydrobiisatic acid (IVc) into its optically active components. The (+)-acid had a specific rotation of +51·3° and the (−)-antipode −50·6° (in ethanol). As can be seen from Fig. 1, the geometry of the molecule of anhydrobiisatic acid and its derivatives is such as to permit the existence of one pair of optically active enantiomers.†

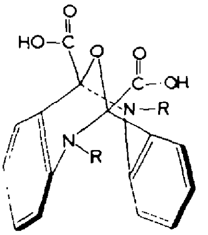

FIG. 1.

The study of the infra-red spectra does not provide much evidence for differentiating between structures II, III and IV, but the spectra are useful for ascertaining the presence of functional groups in the derivatives of anhydrobiisatic acid. Except for the potassium salt of isatic acid, which shows a double band in the 3360–3460 cm^{-1} region (primary amino group), anhydrobiisatic acid and its derivatives (IV) produce only one band, indicating the presence of secondary or tertiary amino groups. A single strong band in the 1130 cm^{-1} region is observed in all compounds of the anhydrobiisatic acid series, which is absent in the spectrum of the potassium salt of isatic acid. This vibration may be due to the presence of an ether linkage.

The ultra-violet spectra are of interest. Considering the potassium salt of isatic acid, it is clear that the ionized carboxyl group cannot participate in the conjugation of the molecule. Its absorption spectrum should, therefore, be similar to those of compounds of the *o*-aminoacetophenone type.[15] This expectation proved to be correct, as can be seen from Table 1. The spectra of the compounds of the anhydrobiisatic acid series are similar to each other but quite different from the spectrum of the potassium salt of isatic acid. Moreover, they resemble the absorption curves of the

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* By treating the yellow silver salt of isatic acid with methyl iodide[8] or the corresponding yellow potassium salt with dimethyl sulphate,[3,14] a mixture of isatin and N-methylisatin is obtained, the latter being the major product.

† Structure II cannot give rise to optically active isomers, whereas structure III contains an asymmetric carbon atom and is theoretically resolvable.

[14] P. Friedländer and S. Kielbasinski, *Ber. Dtsch. Chem. Ges.* **44**, 3098 (1911); W. Borsche and W. Jacobs, *Ibid.* **47**, 354 (1914); M. Kohn and A. Ostersetzer, *Mh. Chem.* **34**, 787 (1913); *Ibid.* **37**, 25 (1916).

[15] P. Grammaticakis, *Bull. Soc. Chim. Fr.* 93, 865 (1953).

[16] R. G. Ault, E. L. Hirst and R. A. Morton, *J. Chem. Soc.* 1653 (1935); L. Marchlewski and A. Moroz, *Bull. Soc. Chim. Fr.* **37**, 404 (1925).

[17] W. C. Sumpter, J. L. Williams, P. H. Wilken and B. L. Willoughby, *J. Org. Chem.* **14**, 713 (1949).

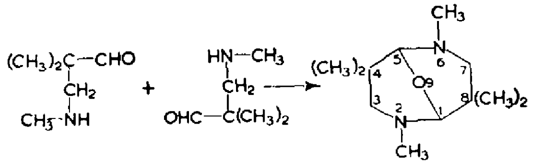
TABLE 1. ULTRA-VIOLET ABSORPTION SPECTRA

Compound	λ_{max} in mμ	(log ε)	λ_{min} in mμ	(log ε)	Solvent
Potassium salt of isatic acid*	229·5	4·25	251	3·74	Water
	264	3·88	290	2·19	
	373	3·64			
o-Aminoacetophenone[15]	228	4·28	248	3·58	Ethanol
	259	3·75	281	2·10	
	365	3·72			
IVa (Potassium salt)	236	4·07	228·2	4·03	Water
	288·5	3·38	270·8	3·20	
IVb	238	4·16	228	4·08	Ethanol
	292	3·56	272	3·36	
IVd	240	4·02 (infl.)	272	3·34	Ethanol
	288	3·43			
(*o*-Aminophenyl)acetic acid (Sodium salt)[18]	234	3·91	260	2·87	Water
	282	3·28			
N-Methyl-*o*-toluidine[19]	242	3·96	267	2·92	Ethanol
	292	3·27			

* Similar spectra have been reported for solutions of isatin in aqueous sodium hydroxide (actually containing the sodium salt of isatic acid).[16] However, Sumpter *et al.*[17] have described a very different spectrum for isatin in a solution buffered at pH 11·6 (which should contain the same anion of isatic acid).

sodium salt of (*o*-aminophenyl)acetic acid[18] and N-methyl-*o*-toluidine[19] (Table 1), suggesting the presence of structure IV, but differ largely from the spectra of compounds of the N-benzalaniline type,[20] possessing the grouping Ar—N=C(R)—Ar, which should be present in the case of structures II or III.

From all the facts, the only possible constitution which can be assigned to anhydrobiisatic acid is the structure of 6:12-*oxa*-5:6:11:12-*tetrahydrophenhomazine*-6:12-*dicarboxylic acid* (IVa; Fig. 1). In one case reported in the literature the substituted 9-oxa-2:6-diazabi*cyclo*(3:3:1)nonane ring system (VI) has been tentatively proposed for the product obtained by self-condensation of 2-dimethyl-3-(methylamino)-1-propionaldehyde (V).[21] In the light of the present work this structure is probable. Compound VI is unstable and, like anhydrobiisatic acid (IVa), is easily converted, by acids, to the starting aminoaldehyde V.



V VI

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[18] P. Ramart-Lucas, *Bull. Soc. Chim. Fr.* **1**, 1133 (1934); P. Ramart-Lucas and D. Biquard, *Ibid.* **2**, 1383 (1935).

[19] A. Wohl, *Bull. Soc. Chim. Fr.* **6**, 1312 (1939); P. Grammaticakis, *Ibid.* 134 (1949); P. Ramart-Lucas and J. Klein, *Ibid.* 454 (1949).

[20] A. v. Kiss and G. Auer, *Z. Phys. Chem.* **A 189**, 344 (1941); E. Hertel and M. Schinzel, *Ibid.* **B 48**, 289 (1941); L. N. Ferguson and G. E. K. Branch, *J. Amer. Chem. Soc.* **66**, 1467 (1944); F. W. Holly and A. C Cope, *Ibid.* **66**, 1875 (1944).

[21] C. Mannich and H. Wieder, *Ber. Dtsch. Chem. Ges.* **65B**, 385 (1932); see also C. Mayer, *Bull. Soc. Chim. Fr.* **7**, 481 (1940).

EXPERIMENTAL

Melting points are not corrected.

The ultra-violet absorption spectra were obtained with a Beckman ultra-violet spectrophotometer, Model DU; and the infra-red absorption spectra with a Perkin-Elmer double-beam infra-red spectrometer, Model 21. Potassium bromide pellets were used for infra-red analysis.

Derivatives of isatic acid [(o-*aminophenyl*)*glyoxylic acid*]

Potassium isatate. 20% Aqueous KOH, containing 0·1 mole of base, was slowly added to 14·7 g (0·1 mole) isatin, the mixture being gently warmed to 40°. The change of colour from dark red-violet to yellow indicated the end of the reaction. The solution was evaporated to dryness under reduced pressure (below 40°) and the yellow *potassium isatate* was recrystallized from ethanol. (Found: K, 19·42; $C_8H_6O_3NK$ requires: K, 19·24%).

Silver isatate. A solution containing 5·1 g (0·025 mole) of potassium isatate in 50 ml water was mixed with 4·7 g silver nitrate dissolved in 50 ml water. The yellow precipitate was filtered and washed with water, and dried. (Found: Ag, 39·52; $C_8H_6O_3NAg$ requires: Ag, 39·66%).

Anhydrobiisatic acid (6:12-*oxa*-5:6:11:12-*tetrahydrophenhomazine*-6:12-*dicarboxylic acid*) *and derivatives*

Potassium anhydrobiisatate. 40% Aqueous KOH (20 ml), was added to 14·7 g (0·1 mole) isatin. The resulting solution was refluxed (30 min) and evaporated (steam-bath). The solid residue, after washing with boiling ethanol (2 × 50 ml), and after recrystallization from ethanol–water, consisted of pure, colourless *potassium anhydrobiisatate* (18·2 g; 93·7%). (Found: N, 7·17; K, 20·42. $C_{16}H_{10}O_6N_2K_2$ requires: N, 7·21; K, 20·13%).

Silver anhydrobiisatate. A solution containing 9·7 g (0·025 mole) potassium anhydrobiisatate in 100 ml water was mixed with 9·4 g silver nitrate dissolved in 100 ml water. The colourless precipitate of the *silver anhydrobiisatate* was washed with water and dried. (Found: Ag, 40·91; $C_{16}H_{10}O_5N_2Ag_2$ requires: Ag, 41·02%).

Anhydrobiisatic acid (IVa). A solution of 3·9 g (0·01 mole) potassium anhydrobiisatate in 10 ml water was cooled (5°) and treated, in portions, with a slight excess of 5% HCl. The precipitate was immediately filtered and washed with ice-cold water to give 2·8 g (89·7%) of colourless *anhydrobiisatic acid* (IVa). It was purified by dissolving it in ether and precipitating with petroleum ether. M.p. 176° (dec). Equivalent, found:* 156·1; calc. 156·1. pK_1 (water) 2·88. (Found: C, 61·37; H, 3·83; N, 9·10; $C_{16}H_{12}O_5N_2$ requires: C, 61·54; H, 3·87; N, 8·97%).

Hydrolysis of anhydrobiisatic acid. A solution of 3·1 g (0·01 mole) acid (IVa) in 20 ml water, on refluxing turned red and, on evaporation, gave quantitatively (2·9 g) pure isatin, m.p. 198° (alone or mixed with authentic sample).

Anhydrobiisatic acid dimethyl ester (IVb). A solution of 12·5 g (0·04 mole) anhydrobiisatic acid (IVa) in 250 ml anhydrous ether was cooled (5°) and treated dropwise with a slight excess of ethereal diazomethane. The *dimethyl ester* (IVb), which precipitated from the solution, was filtered (13 g; 95·6%) and recrystallized from ethanol. M.p. 238°. Saponification value,[22] found: 328·4; calc. 329·7; Mol. wt., found:† 336·1; calc. 340·3. (Found: C, 63·58; H, 4·79; N, 8·21; $C_{18}H_{16}O_5N_2$ requires: C, 63·52; H, 4·74; N, 8·23%).

Saponification of anhydrobiisatic acid dimethyl ester. The ester (IVb) (0·68 g; 0·002 mole) was refluxed (30 min) with 16 ml 0·5 N KOH. The mixture was cooled (5°) and cautiously acidified with 3·64 ml of 2·5 N HCl. Filtration of the precipitate gave 0·514 g (82·3%) of anhydrobiisatic acid (IVa), m.p. 176° (alone or mixed with an authentic sample of the acid).

N:N′-*Dimethylanhydrobiisatic acid* (6:12-*oxa*-5:6:11:12-*tetrahydro*-5:11-*dimethylphenhomazine*-6:12-*dicarboxylic acid*) *and derivatives*

N:N′-*Dimethylanhydrobiisatic acid* (IVc). (a) *Anhydrous.* A mixture of 21 g (0·04 mole) silver anhydrobiisatate, 17 g methyl iodide and 200 ml anhydrous ether was refluxed (6 hr) (excluding atmospheric moisture). Silver iodide, was filtered off and washed with ether (5 × 50 ml). The

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* This and later equivalents were determined in aqueous or ethanolic solution, by titration with 0·1 N aqueous KOH and using phenolphthalein as indicator.

† The molecular weights were determined by the Rast cryoscopic method.

[22] A. Grün, *Analyse der Fette und Wachse* Band I, p. 147. Springer, Berlin (1925); R. T. Hall and W. E. Shaeffer, *Organic Analysis* Vol. 2, pp. 25–27. Interscience, New York (1954).

filtrate and the washings were combined and evaporated to dryness under reduced pressure, and the crude N:N′-*dimethylanhydrobiisatic acid* (IVc) (12·4 g; 91·5%) was recrystallized from ethyl acetate. M.p. 154° (dec.). Equivalent, found: 170·2; calc. 170·2. pK_1 (ethanol) 3·92. (Found: C, 63·12; H, 5·14; N, 8·02; $C_{18}H_{16}O_5N_2$ requires: C, 63·52; H, 4·74; N, 8·23%).

(b) *Hydrated.* A solution of 19·4 g (0·05 mole) potassium anhydrobiisatate in 100 ml water was placed in a three-necked round-bottomed flask equipped with a stirrer, thermometer and dropping funnel, and the contents of the flask were cooled to 10°. Dimethyl sulphate (12·6 g; 0·1 mole) was added in one portion with stirring, followed by 20% aqueous KOH, which was added at such a rate as to maintain the reaction mixture weakly alkaline. When the solution became permanently alkaline, the solution was allowed to stand (30 min) at room temp. It was then cooled (5°) and acidified with a small excess of 5% HCl. The solid which separated (16·7 g; 88·8%) was purified by dissolving in ethanol, at room temp., and precipitating with water. The pure N:N′-*dimethylanhydrobiisatic acid* (IVc) thus obtained was colourless, m.p. 118° (dec.) and crystallized with two molecules of water. Equivalent, found: 188·6; calc.: 188·2 (Found: C, 57·34; H, 5·38; N, 7·68; $C_{18}H_{16}O_5N_2{\cdot}2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

Conversion of anhydrous acid (IVc) *m.p.* 154°, *to the hydrated acid* (IVc) *m.p.* 118°. The anhydrous acid (IVc) (0·34 g; 0·001 mole), m.p. 154°, was dissolved in 10 ml of 3% aqueous sodium bicarbonate. Acidification of the cooled solution (at 5°) with a small excess of 5% HCl gave 0·35 g (93·1%) of hydrated acid IVc, m.p. 118° (alone or on admixture with an authentic sample obtained as described above). Equivalent, found: 186·5; calc. 188·2.

Hydrolysis of N:N′-*dimethylanhydrobiisatic acid.* A solution of 3·8 g (0·01 mole) acid IVc, m.p. 118°, in 20 ml water soon turned red on refluxing and, on evaporation, gave quantitatively (3·2 g) N-*methylisatin*, m.p. 132° (alone or on admixture with an authentic sample, m.p. 132°[23]).

Silver salt of N:N′-*dimethylanhydrobiisatic acid.* A solution of 11·3 g (0·03 mole) of N:N′-dimethylanhydrobiisatic acid (IVc), m.p. 118°, in 60 ml N aqueous KOH was treated with 11·2 g silver nitrate in 100 ml water. The colourless *silver salt* was filtered and washed with water. (Found: Ag, 38·88 and 38·74. $C_{18}H_{14}O_5N_2Ag_2$ requires: Ag, 38·94%).

N:N′-*Dimethylanhydrobiisatic acid dimethyl ester* (IVd). (a) A cold (5°) suspension of 18·8 g (0·05 mole) of acid IVc, m.p. 118°, in 250 ml anhydrous ether was treated, in portions, with a small excess of ethereal diazomethane. After 2 hr at room temp., the solution was evaporated *in vacuo* and the crude *dimethyl ester* IVd (18·4 g) was crystallized from ethanol. m.p. 173°. Saponification value,[22] found: 304·8; calc. 304·6. Mol. wt. found: 362·2; calc. 368·4. (Found: C, 65·44; H, 5·41; N, 7·57; $C_{20}H_{20}O_5N_2$ requires: C, 65·21; H, 5·47; N, 7·61%).

(b) A mixture consisting of 2·77 g (0·005 mole) silver salt of N:N′-dimethylanhydrobiisatic acid, 2·13 g methyl iodide and 20 ml anhydrous ether was refluxed for 6 hr (exclusion of atmospheric moisture). Silver iodide was filtered, washed with ether (4 × 20 ml), and the filtrate and the washings were evaporated to dryness, under reduced pressure. After crystallization from ethanol, the *dimethyl ester* IVd m.p. 172·5°, alone or mixed with a specimen prepared according to (a).

(c) The acid IVc (1·88 g; 0·005 mole), m.p. 118°, was neutralized with 12 ml of 5% aqueous KOH. To the resulting solution, cooled to 10°, 1·26 g (0·01 mole) of purified dimethyl sulphate was added in one portion, followed by 20% aqueous KOH, at such a rate as to keep the reaction mixture weakly alkaline. When the aqueous solution became permanently alkaline, the addition of KOH was stopped and the mixture allowed to stand (30 min) at room temp. The *dimethyl ester* IVd, which separated (1·55 g; 84·2%), was filtered and crystallized from ethanol. It melted at 173°, whether alone or on admixture with samples of esters prepared as described in (a) or (b).

Saponification of ester IVd. The dimethyl ester IVd (0·184 g; 0·0005 mole) was refluxed for one hour with 4 ml 0·5 N aqueous KOH. The mixture was cooled to 5° and cautiously acidified with 0·91 ml 2·5 N HCl. Filtration of the precipitate gave 0·180 g (95·7%) of N:N′-dimethylanhydrobiisatic acid (IVc), m.p. 118° (alone or mixed with an authentic sample).

Resolution of DL-N:N′-*dimethylanhydrobiisatic acid* (IVc) *into optically active components*

(a) *Diastereoisomeric brucine salts of* IVc. N:N′-Dimethylanhydrobiisatic acid (18·8 g; 0·05 mole), m.p. 118°, was dissolved in 700 ml ethanol and mixed with a solution of 19·7 g (0·05 mole) brucine in 700 ml ethanol. After 4 hr at room temp., the precipitate was filtered (20·8 g) and triturated

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[23] M. Kohn and A. Ostersetzer, *Mh. Chem.* 34, 787 (1913); *Ibid.* 37, 25 (1916).

5 times with ethanol (5 × 200 ml) to give 18·2 g of *brucine salt of* (−)-N:N′-*dimethylanhydrobiisatic acid*, m.p. 154°. $[\alpha]_{20}^{D} = -38·3°$ (c = 0·60, water). Further washing with ethanol did not raise the melting point of the product nor change the rotation. Crystallization from ethanol was not possible because the acidic salt, like the acid itself, decomposed readily on heating in ethanol.

The ethanolic filtrate, obtained on filtration of the crude salt (but not the washings), was concentrated to 200 ml, under reduced pressure and at temp. below 40°. After standing at 0°, 8·6 g of *brucine salt of* (+)-N:N′-*dimethylanhydrobiisatic acid*, m.p. 171–172°, was obtained. $[\alpha]_{20}^{D} = +20·8°$ (c = 1·92, ethanol).

(b) *Isolation of* (−)- *and* (+)-N:N′-*dimethylanhydrobiisatic acids*. The diastereoisomer insoluble in ethanol (9·175 g; 0·0125 mole), m.p. 154°, was dissolved in 27·5 ml of N aqueous KOH and the resulting solution was diluted with water to 100 ml. After removal of brucine by chloroform extraction (5 × 50 ml), the aqueous layer was cooled to 5° and acidified with a slight excess of 5% HCl. Crystallization of the precipitate from ethanol–water afforded 2·87 g (62·4%) of (−)-N:N′-*dimethylanhydrobiisatic acid* (IVc), m.p. 115–116°. $[\alpha]_{20}^{D} = -50·6°$ (c = 3·00, ethanol). (Found: C, 57·18; H, 5·33; N, 7·28; $C_{18}H_{16}O_5N_2·2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

The diastereoisomer soluble in ethanol (3·67 g; 0·005 mole), m.p. 171–172°, was dissolved in 11·0 ml of N aqueous KOH. Treatment as above gave 1·08 g (60·4%) of (+)-N:N′-*dimethylanhydrobiisatic acid* (IVc), m.p. 114°. $[\alpha]_{20}^{D} = +51·3°$ (c = 3·00, ethanol). (Found: C, 57·07; H, 5·24; N, 7·46. $C_{18}H_{16}O_5N_2·2H_2O$ requires: C, 57·44; H, 5·36; N, 7·44%).

Both acids crystallized with two molecules of water. They were soluble in 3% aqueous sodium bicarbonate, and could be reprecipitated unchanged from such solutions with dilute acids. By heating their aqueous solution, both acids were converted quantitatively to N-methylisatin.

Acknowledgement—We wish to thank Professor V. Prelog (ETH, Zürich) for his kind permission for the determination of most of the infra-red and ultra-violet spectra at the Department of Organic Chemistry, ETH, Zürich.