2. Solutions of dehydroascorbic acid spontaneously form pigments under certain conditions.

3. The specificity of these colour reactions is described, and their mechanism discussed.

We are indebted to Messrs Roche Products Ltd., for the gift of ascorbic acid, and to the Medical Research Council of Eire for the grant to one of us (E. K.) to enable this work to be done.

REFERENCES

- Bamberger, E. & Hübner, R. [1903]. *Ber. dtsh. chem. Ges.* **36**, 3803.
 Cox, E. G., Hirst, E. L. & Reynolds, R. W. J. [1932]. *J. chem. Soc.* pp. 130, 888.
 Ekkert, L. [1934]. *Pharm. Zentralh.* **75**, 515.
 Herbert, R. W., Hirst, E. L., Percival, E. G. V., Reynolds, R. W. J. & Smith, F. [1933]. *J. chem. Soc.* p. 1270.
 Kruger, F. [1906]. *Hoppe-Seyl. Z.* **50**, 293.
 Lipschitz, W. [1920]. *Hoppe-Seyl. Z.* **109**, 189.
 Lipschitz, W. & Osterroth, J. [1924]. *Pflüg. Arch. ges. Physiol.* **205**, 354.
 Meisenheimer, J. [1903]. *Ber. dtsh. chem. Ges.* **36**, 4174.
 Patzig, J. M. & Patzig, E. [1906]. *Ber. dtsh. chem. Ges.* **39**, 2526.
 Roe, J. H. [1934]. *Science*, **80**, 561.
 v. Szecseny-Nagy, L. [1935]. *Biochem. Z.* **281**, 175.
 Truhaut, R. [1937]. *J. Pharm. Chim., Paris* (8th ser.), **25**, 216.

Studies in Detoxication

13. THE BIOSYNTHESIS OF AMINOPHENYL- AND SULPHONAMIDOAMINOPHENYL-GLUCURONIDES IN THE RABBIT AND THEIR ACTION ON HAEMOGLOBIN *IN VITRO*

By R. T. WILLIAMS, *From the Department of Biochemistry, University of Liverpool*

(Received 12 February 1943)

Sieberg [1914] fed 'cupferron' (ammonium salt of nitroso- β -phenylhydroxylamine) to dogs and isolated from their urine a crystalline compound, m.p. 179–180°, which he claimed to be the *lactam* form (I) of *p*-aminophenylglucuronide. He isolated the same compound from urine after the administration of β -phenylhydroxylamine. When this substance was neutralized with Na_2CO_3 and the solution kept for a day, it was able to convert a solution of haemoglobin to methaemoglobin. It should be noted that the β -glycosidic link present in this compound is stable to dilute Na_2CO_3 , so that in this case formation of methaemoglobin could not be ascribed to hydrolysis of the glucuronide to *p*-aminophenol, which is a methaemoglobin-former *in vitro* and *in vivo* [Bernheim, Bernheim & Michel, 1937]. From this it would appear that the 'detoxicated' form of *p*-aminophenol could still exert a toxic effect on blood. Therefore, it was important to confirm this observation of Sieberg and to extend it to the study of the properties of the aminophenyl- and sulphonamidoaminophenylglucuronides, none of which has been prepared or described hitherto.

Aminophenylglucuronides

Aminophenylglucuronides are produced in the animal body in response to the administration of the aminophenols themselves, or of certain aromatic amino compounds which are oxidized or converted in some way to aminophenols. When aromatic amino compounds are oxidized *in vivo* to aminophenols, *o*- or *p*-phenols only are produced and in no case studied has *m*-aminophenol been detected.

o-Aminophenol is produced when dimethylaniline or its oxide [Horn, 1936] or acetanilide [Jaffe & Hilbert, 1888] is fed to dogs, or when salvarsan is injected into humans [Sieberg, 1916]. It is excreted in conjugation both with sulphuric and glucuronic acids, and in the rabbit some 26–29% (dose, 0.25 g./kg.) is excreted as an ethereal sulphate [Williams, 1938]. In the present work *o*-aminophenylglucuronide has been isolated from the urine of rabbits fed with *o*-aminophenol. The yield of the crystalline glucuronide was equivalent to 25.5% of the phenol fed and since no free aminophenol was excreted, the remainder, if excreted, must be in

other conjugated forms. *o*-Aminophenyl- β -D-glucuronide ($[\alpha]_D -76.1^\circ$ in *N*/10 HCl) is a white crystalline solid which does not melt, is insoluble in cold water and ordinary organic solvents, but soluble in acid, alkali and boiling water. Its properties indicate that it is probably best formulated as an internal salt (II):

I

II

m-Aminophenylglucuronide ($[\alpha]_D = -94^\circ$ in HCl) was prepared similarly. About 22 % of the *m*-aminophenol fed was isolated as the glucuronide. Williams [1938] had previously shown that 31–36 % (dose, 0.25 g./kg.) is excreted by the rabbit as an ethereal sulphate. The glucuronide is very similar in properties to the *o*-compound and is likewise probably an internal salt (cf. II).

The fate of *p*-aminophenol in the body has received more attention than that of its isomerides, because it is formed *in vivo* from aniline, acetanilide and a number of related compounds, and its formation is claimed to be responsible for the cyanosis, etc., produced by drugs containing these compounds. It has been suggested that the antipyretic action of such substances as acetanilide and *p*-ethoxy-acetanilide (phenacetin) may be due to slow formation *in vivo* of *p*-aminophenol [see Bernheim *et al.* 1937]. *p*-Aminophenol is excreted as an ethereal sulphate in the dog [Baumann & Herter, 1877–8] and in man [Mörner, 1889]. Williams [1938] showed the 19–20 % of *p*-aminophenol (dose, 0.25 g./kg.) was excreted by the rabbit as an ethereal sulphate. On feeding *p*-aminophenol to rabbits the glucuronide isolated was hydrated *p*-aminophenyl- β -D-glucuronide ($C_{12}H_{15}NO_7$, H_2O) and not Sieberg's compound (I). Like Sieberg's compound, however, *p*-aminophenylglucuronide neutralized with Na_2CO_3 converts haemoglobin to methaemoglobin *in vitro*.

p-Aminophenylglucuronide was similar in many properties to its *o*- and *m*-isomers, but differed in that it showed a definite melting-point and con-

tained water of crystallization. The amount of the glucuronide isolated was about 8 % of the phenol fed, and unlike the *o*- and *m*-compounds, free *p*-aminophenol was present in the urine.

Sulphonamidoaminophenylglucuronides

It was suggested [Thorpe, Williams & Shelswell, 1941] that 3-hydroxy-4-aminobenzenesulphonamide might be an oxidation product of sulphanilamide *in vivo*. Shelswell & Williams [1940] showed that sulphanilamide increased the ethereal sulphate output of rabbits, thus indicating the probable formation of a phenol from sulphanilamide in the animal [cf. also Sammons, Shelswell & Williams, 1941; Williams, 1941]. Such an aminophenolsulphonamide could be excreted as a conjugated glucuronide (cf. sulphapyridine which increases the glucuronic acid output in rats [Scudi & Robinson, 1941]). Aminophenolsulphonamides were therefore fed and an attempt was made to isolate the resulting sulphonamidoaminophenylglucuronides. 4-Hydroxy-3-amino-, 6-hydroxy-3-amino- [Williams, 1942] and 3-hydroxy-4-aminobenzenesulphonamide [Thorpe & Williams, 1941] were fed and crystalline glucuronides were isolated in the first two cases, but in the third, although a glucuronide was formed it was not obtained crystalline but as an amorphous Ba salt which has not yet been purified. The crystalline compounds were 4-sulphonamido-2-aminophenylglucuronide (III), M.P. 150° and $[\alpha]_D -67.7^\circ$, and 2-sulphonamido-4-aminophenylglucuronide (IV) which does not melt and shows $[\alpha]_D -76.9^\circ$. Their properties were very similar to those of the aminophenylglucuronides and when neutralized with Na_2CO_3 they converted haemoglobin to methaemoglobin *in vitro*:

III

IV

The action of the above glucuronides on haemoglobin *in vitro*

It was found that the *o*- and *p*-aminophenylglucuronides when neutralized with Na_2CO_3 converted

a solution of oxyhaemoglobin* to methaemoglobin, the change being observed spectroscopically. The tests were carried out for a period up to 6 hr., but as a rule the methaemoglobin-formers produced their effect in 2-3 hr. No change in the spectrum of the control solution occurred in this time. Fairley [1940] found that a concentrated solution of human haemoglobin incubated at 37° began to form methaemoglobin spontaneously within 20 hr., but the present experiments were not long enough for this. The results of the present experiments are shown in Tables 1 and 2.

The *o*-compound appeared to be several times more effective than the *para*-. A slight formation of methaemoglobin was also observed in the case of the *m*-compound, although *m*-aminophenol itself was quite ineffective in this respect. The neutralized solutions of the glucuronides were quite stable since no free aminophenols were obtained from them on continuous extraction with ether, although if present they would readily have been extracted. If red corpuscles contained β -glucuronidase, hydrolysis of these glucuronides might have occurred. Whilst extracts of ox and dog kidney, liver and spleen hydrolysed conjugated glucuronides, the latter were unaffected when incubated with ox or dog blood [Sera, 1915]. Oshima [1934] and Fishman [1940] make no reference to the occurrence of β -glucuronidase in blood. It is unlikely, therefore, that the aminophenylglucuronides would undergo spontaneous or enzymic hydrolysis under the conditions of the present experiments. It is, however, significant that the most effective methaemoglobin-formers are the *o*- and *p*-compounds, i.e. derivatives of *o*- and *p*-aminophenols which themselves can form iminoquinones. The formation of iminoquinones does not appear possible with the aminophenylglucuronides.

The sulphonamidoaminophenylglucuronides (III and IV) were also methaemoglobin-formers, as were also the corresponding aminophenolsulphonamides and particularly the aminophenolsulphonic acids. The *o*-, *m*- and *p*-aminobenzenesulphonamides were ineffective *in vitro*, although it is well known that sulphanilamide forms methaemoglobin *in vivo*, probably due to its conversion to an aminophenolsulphonamide.

The present findings, therefore, confirm and extend Sieberg's original observation. *o*- and *p*-aminophenylglucuronides and the sulphonamido-*o*- and *p*-aminophenylglucuronides convert haemoglobin to methaemoglobin *in vitro*. Discussion of

the significance of these results, and their translation to *in vivo* conditions, however, must await further investigation.

EXPERIMENTAL

Isolation of the aminophenylglucuronides

o-Aminophenylglucuronide. Six rabbits (2.5 kg.) were each given 1 g. of *o*-aminophenol with water by stomach tube. In about 1 hr. the excreted urine showed the presence of conjugated aminophenol and increased amounts of glucuronic acid. In 3.5 hr. 300 ml. of urine collected which gave an intense naphthoresorcinol reaction, a red colour with nitrous acid and dimethyl- α -naphthylamine (diaz reaction), but did not reduce ammoniacal AgNO₃. The urine was acidified with a few drops of glacial acetic acid and treated with saturated normal lead acetate until no further precipitate was formed. The filtrate was neutralized with NH₃ and treated with excess saturated basic lead acetate solution. The precipitate was centrifuged, washed twice on the centrifuge with water, and the lead salt suspended in water and decomposed with H₂S. The filtrate from the PbS was concentrated *in vacuo* at 45-50°, when the *o*-aminophenylglucuronide began to separate as a white crystalline solid, and finally taken to dryness. The white residue was shaken with ethanol and the whole filtered. The glucuronide was then washed with ethanol and ether (yield 3.3 g.). A second portion of urine (210 ml.), collected during the 2 hr. following the first, yielded 0.7 g. of the glucuronide. The total yield for 5 hr. was 4 g. or 25.5% of the aminophenol fed. Later specimens of urine contained very little of the glucuronide.

The glucuronide was recrystallized from a large volume of hot water and formed cigar-shaped platelets which blackened without melting on heating to 300°. It was insoluble in cold water, ethanol, ether and most organic solvents, sparingly soluble in hot water, but soluble in acid and alkali. It showed $[\alpha]_D^{25} - 76.1^\circ$ ($c=1$ in *N*/10 HCl). Found: C, 50.7; H, 5.35; N, 4.9%. C₁₂H₁₅O₇N requires C, 50.5; H, 5.3; N, 4.9%.

m-Aminophenylglucuronide. Six rabbits were each given 1 g. of *m*-aminophenol with water by stomach tube. The urine was worked up in two portions as described above for the *ortho* compound. The first portion (375 ml.), collected during 3 hr., yielded 2.4 g. of *m*-aminophenylglucuronide; the second, collected during the next 4 hr., gave 1.03 g.: total yield 3.45 g. or 21.9% of the aminophenol fed. The urine gave a bluish red diazo reaction, an intense naphthoresorcinol reaction and was non-reducing.

The glucuronide recrystallized from hot water as leaflets, which blackened without melting on heating to 300°. Its solubility was similar to that of the *ortho* compound and it showed $[\alpha]_D^{25} - 94^\circ$ ($c=0.95$ in *N*/12 HCl). Found: C, 50.1; H, 5.3; N, 4.9%. C₁₂H₁₅O₇N requires C, 50.5; H, 5.3; N, 4.9%.

p-Aminophenylglucuronide. *p*-Aminophenol (1 g.) was fed by stomach tube with water to each of six rabbits. The urine was collected in two portions as before. The first (340 ml.), collected after 3½ hr., was dark but clear. It gave a purple diazo reaction and positive indophenol and naphthoresorcinol reactions. It reduced ammoniacal AgNO₃ in the cold, and an ether extract gave the indophenol reaction, indicating the presence of free *p*-aminophenol in the urine (*p*-aminophenylglucuronide is insoluble in ether).

* Lysed human red cells or solutions of Hb washed free from plasma were used in these experiments in order to avoid a possible complication due to methaemalbumin (pseudo-methaemoglobin) formation which may occur when whole human blood is used [see Fairley, 1938; 1940; 1941].

The urine was worked up as in the other two cases and the resulting *p*-aminophenylglucuronide (1.4 g.) was recrystallized from hot water, from which it formed needles, m.p. 213° (decomp.). The second batch of urine was collected up to 24 hr. after feeding the phenol and although some glucuronide was present, it could not be obtained crystalline. The total crystalline material isolated was 1.4 g. or 8.4% of the aminophenol fed. It was insoluble in cold water, ethanol or ether and the analytical figures showed it to contain 1 mol. of water of crystallization, which was not lost at 104° after several hours. It showed $[\alpha]_D^{22} - 82.7^\circ$ ($c=1$ in $N/10$ HCl). Found: C, 47.6; H, 5.55; N, 4.45%. $C_{12}H_{15}O_7N$, H_2O requires C, 47.5; H, 5.6; N, 4.6%.

Isolation of sulphonamidoaminophenylglucuronides

4-Sulphonamido-2-aminophenylglucuronide. Rabbits were given by stomach tube with water, 0.4–0.6 g./kg. of *o*-aminophenol-*p*-sulphonamide. The urine passed within the first hour gave a red colour in the diazo reaction and a positive naphthoresorcinol reaction, thus indicating excretion of the conjugated glucuronide of the phenol. The urine was collected for 24 hr. In one experiment, for example, a total of 4.4 g. of the sulphonamide was fed and 670 ml. urine were collected in 24 hr. The basic lead precipitate was prepared as usual, the lead removed by H_2S , and the filtrate evaporated to dryness *in vacuo*. The residual syrup taken up in ethanol and again concentrated at 45° crystallized only after the addition of crystals prepared from a small portion dissolved in a little ethanol to which an excess of light petroleum had been added. The yield of glucuronide was 0.42 g. from 4.4 g. of the sulphonamide fed (other preparations yielded 0.2 and 0.21 g. from 3 and 4.2 g. of the sulphonamide, respectively).

2-Sulphonamido-4-aminophenylglucuronide. Three rabbits* were each given 1.3 g. (0.75 g./kg.) of *p*-aminophenol-*o*-sulphonamide [Williams, 1942]. The urine (590 ml.), which was blackish in colour, was collected for 24 hr. and worked up as usual. The non-crystalline concentrate from the basic lead precipitate was dissolved in absolute ethanol, charcoaled, filtered and then concentrated *in vacuo* to a syrup. The solution in aqueous ethanol would not crystallize without the addition of a trace of crystalline 4-sulphonamido-2-aminophenylglucuronide, and 0.62 g. of crystalline 2-sulphonamido-4-aminophenylglucuronide was thus obtained. It formed small thick rectangular plates (not notched like its isomeride) from hot water. It did not melt up to 300°, but turned red at 140° and black at 190°. It was almost insoluble in cold water and insoluble in ethanol and ether. It showed $[\alpha]_D^{21} - 76.9^\circ$ ($c=1$ in water as monosodium salt). Found: C, 35.4; H, 5.1; N, 6.35; S, 7.65%. $C_{12}H_{14}O_6N_2S$, $2\frac{1}{2}H_2O$ requires C, 35.2; H, 5.1; N, 6.8; S, 7.8%.

The action of *o*-, *m*- and *p*-aminophenylglucuronides on haemoglobin solutions

Human red cells from the blood bank were used. The blood had been treated with Na citrate and allowed to stand for 7 days at a low temperature. Then the plasma had been poured off and the residual red cells were used in these tests. In the first case, 10 ml. of the red cells as obtained from the blood bank were diluted to 200 ml. with water. In the second case, the red cells were washed three times in the centrifuge with 0.9% NaCl, haemolysed by shaking with asbestos and filtered through a thick layer of cotton-wool. 5 ml. of the filtrate were diluted to 200 ml. The results of the experiments were essentially the same

Table 1. Action of *o*-, *m*- and *p*-aminophenylglucuronides on haemoglobin

Compound	mg. compound ml. Hb solution	Time (hr.)				
		0	0.75	2	3	5–6
Control	0	–	–	–	–	–
<i>o</i> -	3	–	–	+	++	.
<i>m</i> -		–	–	–	–	–
<i>p</i> -		–	–	–	–	+
<i>o</i> -	6	–	+	++	+++	.
<i>m</i> -		–	–	–	–	–
<i>p</i> -		–	.	+	+	+
<i>o</i> -	9	–	+	+++	++++	.
<i>m</i> -		–	–	–	–	+
<i>p</i> -		–	.	+	.	++
<i>o</i> -	12	–	++	++++	++++	.
<i>m</i> -		–	–	–	–	+
<i>p</i> -		–	.	++	.	+++
–	Oxyhaemoglobin spectrum unchanged.			+++	Strong methaemoglobin line in red.	
+	Faint methaemoglobin line in red.			++++	Stronger methaemoglobin line in red.	
++	Definite methaemoglobin line in red.			Blank	No observation at that time.	

4-Sulphonamido-2-aminophenylglucuronide formed small rectangular notched plates from hot water, m.p. 150° (decomp. to an orange froth). It was almost insoluble in cold water, insoluble in ethanol and ether, but soluble in hot water, acid and alkali. It showed $[\alpha]_D^{20} - 67.7^\circ$ ($c=2$ in water containing 1 equiv. Na_2CO_3 , i.e. enough alkali to form a monosodium salt). Found: C, 35.7; H, 5.1; N, 6.6; S, 7.4%. $C_{12}H_{14}O_6N_2S$, $2\frac{1}{2}H_2O$ requires C, 35.2; H, 5.1; N, 6.8; S, 7.8%.

for both solutions of haemoglobin. To each of a series of small test tubes containing 3 ml. of the haemoglobin solution was added the required amount of an aqueous solution

* Two of these rabbits died 2 days later and the third, being obviously ill, was killed. In all these animals the liver was found to be pulpy and friable. One day after administration of the sulphonamide all three animals salivated profusely.

of the Na salt of the aminophenylglucuronide and water to make up to 5 ml. The tests were set up in duplicate and incubated, with the appropriate controls, at 37°. The tubes were periodically examined with a spectroscope for methaemoglobin. Initially all solutions gave a well-marked oxyhaemoglobin absorption spectrum. The results are given in Table 1.

The aqueous solutions of the Na salts of all three aminophenylglucuronides were subjected to continuous extraction with ether for several hours, but in no case could free aminophenols be detected in the extract. Added free aminophenols could easily be extracted under these conditions.

2.6 mg./ml.). To each tube were then added 4 ml. haemoglobin solution. Hence the compounds used were present in amounts equivalent to 1 mg. aminophenol/ml. The tubes were incubated and the spectra observed periodically as before.

SUMMARY

1. The preparation is described of *o*-, *m*- and *p*-aminophenylglucuronide and 2-sulphonamido-4-amino- and 4-sulphonamido-2-aminophenylglucuronides by feeding the corresponding aminophenols to rabbits.

Table 2. On methaemoglobin formation in vitro

Compound	Mg. compound 5 ml. sol.	Time (hr.)				
		1	1.5	2	3	5.5
Control (water)	0	-	-	-	-	-
Control (Na ₂ CO ₃ solution)	0	-	-	-	-	-
Glucurone	8	-	-	-	-	-
Sulphanilamide	8	-	-	-	-	-
Metanilamide	8	-	-	-	-	-
Orthanilamide	8	-	-	-	-	-
Acetylsulphanilamide	10	-	-	-	-	-
<i>l</i> -Menthylglucuronide	17	-	-	-	-	+
Euxanthic acid	18	-	-	+	+	+
<i>o</i> -Aminophenylglucuronide	14	-	++	+++	++++	++++
<i>m</i> -Aminophenylglucuronide	14	-	-	+	+	+
<i>p</i> -Aminophenylglucuronide	15	-	+	+	++	+++
4-Hydroxy-3-aminobenzenesulphonamide	9	-	-	+	+	++
3-Hydroxy-4-aminobenzenesulphonamide	9	-	-	+	+	+
3-Hydroxy-4-aminobenzenesulphonic acid	9	++	++	++++	++++	++++
6-Hydroxy-3-aminobenzenesulphonamide	9	-	+	+	Solution discoloured	
6-Hydroxy-3-aminobenzenesulphonic acid	9	++	++	++++	++++	++++
4-Sulphonamido-2-aminophenylglucuronide	17	-	+	+	+	+
2-Sulphonamido-4-aminophenylglucuronide	17	-	+	+	+	++
<i>o</i> - and <i>p</i> -Aminophenols	5	-	Solutions discoloured			-
<i>m</i> -Aminophenol	5	-	-	-	-	-
-		+++	Methaemoglobin spectrum strong.			
+		++++	Methaemoglobin spectrum very strong.			
++			Methaemoglobin spectrum definite.			

The sulphonamidoaminophenylglucuronides and some other compounds were also tested (Table 2). Each compound, in amount equimolar to that of aminophenol (5 mg.), was weighed into a small test tube, each tube being in duplicate. The compound was dissolved with slight warming, if necessary, in 1 ml. Na₂CO₃ containing 1 equiv. (i.e.

2. It has been shown that the *o*- and *p*-aminophenylglucuronides are methaemoglobin-formers *in vitro*. The sulphonamidoaminophenylglucuronides also caused methaemoglobin-formation, but less powerfully than the aminophenylglucuronides.

REFERENCES

- Baumann, E. & Herter, E. [1877-8]. *Hoppe-Seyl. Z.* **1**, 244.
 Bernheim, F., Bernheim, M. L. C. & Michel, H. D. [1937].
J. Pharmacol. **61**, 311.
 Fairley, N. H. [1938]. *Nature, Lond.*, **142**, 1156.
 — [1940]. *Brit. J. exp. Path.* **21**, 231.
 — [1941]. *Quart. J. Med.* **10** (N.S.), 95, 115.
 Fishman, W. H. [1940]. *J. biol. Chem.* **136**, 229.
 Horn, F. [1936]. *Hoppe-Seyl. Z.* **238**, 84.
 Jaffe, M. & Hilbert, P. [1888]. *Hoppe-Seyl. Z.* **12**, 295.
 Mörner, K. A. H. [1889]. *Hoppe-Seyl. Z.* **13**, 12.
 Oshima, G. [1934]. *J. Biochem., Tokyo*, **20**, 361.
 Sammons, H. G., Shelswell, J. & Williams, R. T. [1941].
Biochem. J. **35**, 557.
 Scudi, J. V. & Robinson, H. J. [1941]. *Amer. J. med. Sci.*
201, 711.
 Sera, Y. [1915]. *Hoppe-Seyl. Z.* **92**, 261.
 Shelswell, J. & Williams, R. T. [1940]. *Biochem. J.* **34**,
 528.
 Sieberg, E. [1914]. *Hoppe-Seyl. Z.* **92**, 331.
 — [1916]. *Hoppe-Seyl. Z.* **97**, 83.
 Thorpe, W. V. & Williams, R. T. [1941]. *Biochem. J.* **35**,
 61.
 — — & Shelswell, J. [1941]. *Biochem. J.* **35**, 52.
 Williams, R. T. [1938]. *Biochem. J.* **32**, 878.
 — [1941]. *Biochem. J.* **35**, 1169.
 — [1942]. *J. chem. Soc.* p. 708.