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The Metabolism of Arylthioureas— V. The Metabolism of 1-(*p*-Butoxyphenyl)-3-(*p*-Dimethylaminophenyl)-2-Thiourea (Ciba-1906, Thiambutosine)

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4-Butoxy-4′-dimethylamino-*N*,*N*′-diphenylthiourea (Ciba-1906, SU 1906 or thiambutosine) has received clinical trials in leprosy (see Davey[1]). The drug (henceforth referred to as Ciba-1906) has shown promise despite the fact that a substantial portion of an oral dose is excreted in the faeces in the unchanged state by man. This suggested the possibility that the drug might be active through a metabolite. However, Schmid and Tripod[2] have shown, using the ^{35}S- and ^{14}C-labelled drug, that in the dog and the rabbit the drug appears to undergo entero-hepatic circulation, so that any of the original drug appearing in the faeces could have been absorbed and then secreted again into the intestine. In the present paper, we shall show that, in rabbits receiving single 300 mg/kg doses, about 70 per cent of the dose is excreted in the urine mainly as transformation products and about 20 per cent in the faeces mainly as the unchanged drug in 8 days after dosing. The main urinary metabolite has been isolated and identified as 4-(γ-carboxypropoxy)-4′-dimethylamino-*N*,*N*′-diphenylthiourea (hereafter referred to as Ciba-1906 propoxy acid).

Materials and Methods

Materials. Ciba-1906, m.p. 121°, [^{35}S]Ciba-1906, Ciba-1906 propoxy acid, m.p. 148–150°, 4-carboxymethoxy-4′-dimethylamino-*N*,*N*′-diphenylthiourea (Ciba-1906 methoxy acid), m.p. 165–167°, 4,4′-dibutoxy-*N*,*N*′-diphenylthiourea, m.p. 165–167°, and 4-(β,γ-dihydroxypropoxy)-4′-dimethylamino-*N*,*N*′-diphenylthiourea,

m.p. 140–142°, were the gift of Ciba Laboratories Limited, Horsham. The *benzylamine salt* of Ciba-1906 propoxy acid was prepared by adding benzylamine to the acid dissolved in ethyl acetate. The salt was recrystallized from ethyl acetate and had m.p. 131–132°.

Anal. Calcd. for $C_{26}H_{32}N_4O_3S$: N, 11·7. Found, N, 11·8.

Methods. Glucuronic acid in urine was determined according to Mead, Smith and Williams[3] and thione compounds according to Smith and Williams.[4]

Determination of Ciba-1906. This drug is readily oxidized to give a deep blue-green colour by a number of oxidizing agents including ferric chloride, acid permanganate, potassium dichromate and nitrous acid. Using ferric chloride in slightly acid solution, the colour could be used to estimate the drug. Other compounds giving the test are shown in Table I. The qualitative

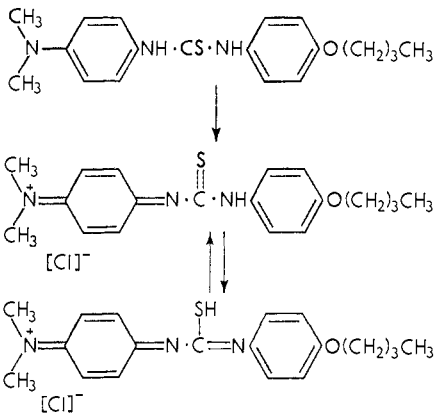
Table I. Colour reaction with ferric chloride of Ciba-1906 and related compounds

R	R′	Colour
(a) Derivatives of thiourea, RNH·CS·NHR′		
C_6H_5	H	none
C_6H_5	C_6H_5	none
p-*n*-$C_4H_9O\cdot C_6H_4$	*p*-*n*-$C_4H_9O\cdot C_6H_4$	pale yellow
p-$NH_2C_6H_4$	*p*-$NH_2C_6H_4$	deep olive green
p-$(CH_3)_2N\cdot C_6H_4$[a]	*p*-*n*-$C_4H_9O\cdot C_6H_4$[a]	deep blue-green
p-$(CH_3)_2N\cdot C_6H_4$[b]	*p*-$HO_2C(CH_2)_3O\cdot C_6H_4$[b]	deep blue-green
(b) *p*-Phenylenediamine derivatives		
p-Phenylenediamine, $NH_2\cdot C_6H_4\cdot NH_2$		magenta, quickly turning yellow
N-Monomethyl-*p*-phenylenediamine, $CH_3NH\cdot C_6H_4NH_2$		brown, turning magenta
N,*N*-Dimethyl-*p*-phenylenediamine, $(CH_3)_2N\cdot C_6H_4\cdot NH_2$		brown

[a] Ciba-1906.
[b] Ciba-1906 propoxy acid.

tests were carried out by dissolving 20 μg of the compound in a millilitre of aqueous acetone and adding two drops of aqueous ferric chloride solution (20 per cent w/v). The table shows that

the colour is dependent upon the *p*-*N*,*N*-dimethylaminophenylthiourea portion of the molecule, and it is possible that the coloured complex (possibly a kind of Wurster's salt) is formed as follows:



A solution of Ciba-1906 in ethanol (0·1 g in 100 ml; the drug is practically insoluble in water) was diluted with 0·5 per cent (v/v) aqueous acetic acid to 2 mg/100 ml. Suitable volumes of the latter containing 4–14 μg/ml of the drug were each made up to 10 ml with 0·5 per cent acetic acid in stoppered tubes, and each tube was treated with 0·1 ml of aqueous ferric chloride (20 per cent w/v). The solutions were mixed by inversion. The blue-green colour was read at 630 mμ (Unicam spectrophotometer) at exactly 1 min after mixing, against a blank solution consisting of 10 ml of 0·5 per cent acetic acid and 0·1 ml of 20 per cent ferric chloride solution. The colour is stable for 4 min, but after 30 min at room temperature it decays to about 80 per cent of its original intensity. A linear relationship was found between colour and concentration of the drug up to 12 μg/ml and Ciba-1906 in pure solution could be measured very accurately by this method. On applying the method to urine, interference by phosphates competing for ferric ions was possible, but this could be overcome by dilution. Solutions of Ciba-1906 in a mixture of equal volumes of rabbit urine and ethanol containing 0·4–1·2 mg of drug/ml were prepared. Four dilutions of 10, 25, 50 and 100 times with 0·5 per cent acetic acid were prepared, so that solutions containing 8–12 μg of drug/ml

were obtained. To 10 ml of these solutions 0·1 ml of 20 per cent ferric chloride was added and the colour measured as above. With dilutions of 50 and 100, the recovery of drug was 96 per cent (range 90–100). At 25 times dilution, the recovery was 84 per cent and at 10 times, 69 per cent. The estimation was therefore satisfactory if the original urine was diluted 100 times and if it contained 40–60 mg of drug/100 ml. If the urine contained less drug than this, the 100-fold dilution could not be carried out, but a 20-fold dilution could be used and then the recovery of added drug was 70 per cent. Ciba-1906 propoxy acid gave the same colour and in pure solution, molecule for molecule, it gave 90 per cent of the colour given by the drug at 630 mμ.

Preliminary experiments had shown that the urine of rabbits given Ciba-1906 contained basic and acidic metabolites. An estimate of these compounds was obtained by determining the total Ciba-1906-like compounds with the ferric chloride reagent and then extracting the basic metabolites with $CHCl_3$ from alkaline urine and determining the compounds in the extract with ferric chloride. The difference gave the acidic metabolites.

Samples of urine were diluted hundred-fold with 0·5 per cent acid and the Ciba-1906-like compounds determined as above. For basic metabolites, the urine (10 ml) was treated with 2N Na_2CO_3 (2 ml) and extracted with 3×20 ml of $CHCl_3$. The extract was washed with 2×20 ml of 5 per cent (w/v) Na_2CO_3, filtered, dried (Na_2SO_4 anhyd.) and evaporated to dryness at room temperature using a stream of nitrogen. The residue was dissolved in absolute ethanol (20 ml) and glacial acetic acid (0·5 ml) added and the solution made up to 100 ml with water. Suitable aliquots of this solution were then analysed with the ferric chloride reagent as above.

Faeces (10 g), which had been homogenized in a Waring blender, were shaken for an hour with 50 ml of ethanol in a stoppered flask on a mechanical shaker. The mixture was centrifuged and the alcohol decanted off. The residue was shaken with more ethanol and centrifuged and decanted as before. The extract was made up to 100 ml with ethanol. Suitable aliquots were then analysed for Ciba-1906 as described for urine.

Determination of radioactivity. ^{35}S in urine and faeces and in urinary inorganic sulphate was determined as already described.[5]

Paper chromatography. R_f values and colour reactions are given in Table II. Ciba-1906 and the acetoxy and propoxy acids were detected on paper as blue spots after spraying with 10 per cent (w/v) aqueous ferric chloride. The naphthoresorcinol, iodine–sodium azide, and silver nitrate tests were as described by Smith and Williams.[4] For the detection of *p*-phenylenediamine and its methyl derivatives, the paper was exposed to nitrous fumes (from 50 per cent (v/v) nitric acid and Cu turnings) or sprayed with bromine water.

Isolation and Detection of Metabolites

In urine. Ciba-1906 (400 mg/kg) was administered by stomach tube. The 24-h urine specimen was cloudy and slightly acid (pH 5·5–7·0). It reduced Benedict's reagent and gave a strong naphthoresorcinol test for glucuronic acid, thus suggesting the presence of a labile glucuronide, possibly of a carboxylic acid. It gave a blue colour with ferric chloride or bromine water and a positive Grote's test, which suggested the presence of Ciba-1906 or a closely related compound. Extraction of the alkalinized urine with chloroform or benzene, solvents in which Ciba-1906 is readily soluble, produced little Ciba-1906-like compounds in the extract. Ether extracts of the urine were often orange-red in colour and on evaporation gave reddish gums. It appears that Ciba-1906 and its derivatives are readily oxidized, possibly to 'Wurster salt'-like compounds. Reddish-orange urines were sometimes passed by the animals, the colour being due to oxidation products of Ciba-1906 or its metabolites.

The urine (0·1 ml) was chromatographed on Whatman No. 4 paper in solvents A, B and C (see Table II). In solvent A, four spots giving positive tests for thione compounds were found. The first spot, R_f 0·05–0·15, was large and gave a positive napthoresorcinol test for glucuronic acid and a blue colour, which faded, with $FeCl_3$. This spot was therefore due to a glucuronide containing a thione group and a *p*-dimethylaminophenylthiourea grouping. On acid hydrolysis, the spot was reduced in intensity but on alkaline hydrolysis it disappeared and was replaced by a spot for Ciba-1906 propoxy acid. It was concluded that this spot was due to the glucuronide of Ciba-1906 propoxy acid. The

Table II. R_f values and colour reactions of Ciba-1906 and related compounds. Descending chromatography, on Whatman No. 4 paper, was used. Solvents: A, ethyl acetate saturated with water, run for 3 h; B, ethyl acetate–benzene (1 : 1 by vol.) saturated with water, run for 5 h; C, ethanol–*n*-butanol–3N- ammonia in 3N- ammonium carbonate (11 : 40 : 19 by vol.)[6] run for 5 h; D, methanol–*n*-pentanol–benzene–water (2 : 1 : 1 : 1 by vol.); E, 2-propanol–ammonia solution, s.g. 0·88 (7 : 3, by vol.); F, 10 per cent ammonia solution made by dissolving 1 vol. ammonia solution, s.g. 0·88, in 9 vols. water

Compound	R_f value in solvent						Colour reactions[a]				
	A	B	C	D	E	F	$FeCl_3$	I/NaN_3	$AgNO_3$	Nitrous fumes	Br water
Ciba-1906	0·98	0·95	0·93	—	—	—	blue	white spot on brown background	brown	—	blue
Ciba-1906 propoxy acid	0·82–0·92	0·78 0·90	0·20–0·35	—	—	—	blue	white spot on brown background	brown	—	blue
Ciba-1906 methoxy acid	0·68–0·78	—	—	—	—	—	blue	—	—	—	blue
p-Phenylenediamine	—	—	0·53	0·67	0·68	0·70	—	—	—	blue	pale yellow-green
N-Monomethyl-*p*-phenylenediamine	—	—	0·77	0·80	0·81	0·79	—	—	—	orange	pale red turning yellow-green
N,*N*-Dimethyl-*p*-phenylenediamine	—	—	0·86	0·89	0·90	0·79	—	—	—	scarlet	crimson

[a] See text.

second large spot, R_f 0·82–0·92, gave with $FeCl_3$ a blue colour which faded, and was identical with Ciba-1906 propoxy acid. The third spot, R_f 0·95, was small and gave with $FeCl_3$ a dark blue colour, which did not fade. This spot was not identified but other evidence suggested it might be Ciba-1906 less one methyl group. The fourth spot, R_f 0·98, was small and corresponded to Ciba-1906. These findings were confirmed with solvents B and C. Chromatographic evidence suggested that rabbits were excreting small amounts of unchanged Ciba-1906, large amounts of Ciba-1906 propoxy acid and its glucuronide, and a small amount of a metabolite running very close to Ciba-1906, possibly nor-Ciba-1906. The latter compound should be basic. Therefore, 10 ml of the urine was brought to pH 10 with 10 per cent $NaHCO_3$ solution and extracted with 2×10 ml of $CHCl_3$. On chromatography of the $CHCl_3$ extract in A, B and C, traces of Ciba-1906 were found and relatively large amounts of the basic metabolite. The urine was then adjusted to pH 7 and again extracted with $CHCl_3$. The residual urine was chromatographed and it showed no spots corresponding to Ciba-1906 or the basic metabolite, but Ciba-1906 propoxy acid and its glucuronide were readily detected.

Isolation of Ciba-1906 propoxy acid. This acid was isolated from rabbit urine with considerable difficulty and after several attempts. Compounds of this type appear to be readily oxidized to coloured complexes (Wurster salts?) and if warmed they dismutate to symmetrical diarylthioureas thus:

$$2\,R\cdot NH\cdot CS\cdot NH\cdot R' \longrightarrow R\cdot NH\cdot CS\cdot NH\cdot R + R'\cdot NH\cdot CS\cdot NH\cdot R'$$

Ciba-1906 (2 g) was fed to each of three rabbits and the urine was collected for 60 h under benzene. The urine was adjusted to pH 7 with 10 per cent (w/v) Na_2CO_3 solution and then saturated with ammonium sulphate. It was then extracted with 5×200 ml portions of a 1 : 1 mixture of acetone and ether. The extracts were filtered and evaporated at reduced pressure in an atmosphere of nitrogen. When the extract had reached a small bulk, a dark red compound separated. This was collected on the centrifuge, washed with a little water and dried in a desiccator (yield 0·65 g or 11 per cent of the dose). The compound had no definite melting point and turned into a gum on warming. It dissolved in bicarbonate and was reprecipitated on acidification. It gave a blue

colour with ferric chloride, bromine water and Grote's reagent, and paper chromatography showed it to contain substantial amounts of Ciba-1906 propoxy acid. The red compound thus appeared to be Ciba-1906 propoxy acid containing coloured oxidation products. The mother liquors from this product were diluted with a little water and on standing a pink precipitate separated. This was purified by dissolving in a little alcohol and precipitating by adding water. This compound gave colour tests and R_f values identical with Ciba-1906 propoxy acid.

Anal. Calcd. for $C_{19}H_{23}N_3O_3S$: C, 61·1; H, 6·2; N, 11·25; S, 8·6. Found: C, 60·6; H, 6·2; N, 11·35; S, 8·2.

It softened above 90°. Its benzylamine salt was prepared from ethyl acetate. It had m.p. of 131° and mixed m.p. of 131–132° with the authentic benzylamine salt of Ciba-1906 propoxy acid, m.p. 131–132°.

A sample of the acid was also prepared by freeze-drying. Two litres of urine were collected over 48 h from six rabbits each given 3 g of Ciba-1906. The urine was filtered through glass-wool, adjusted to pH 4 with glacial acetic acid and then freeze-dried to a volume of 200 ml. On keeping at 0° overnight, a precipitate formed which was separated by centrifugation. This precipitate was almost free from the red oxidation product. However, it decomposed on attempted recrystallization from warm solvents. It was therefore purified as before by dissolving in ethanol and precipitating with water. It was obtained as a greyish-white powder (40 mg) chromatographically identical with Ciba-1906 propoxy acid. The isolated acid shrank a little at 80–90° and then frothed and melted at 148–151°. The synthetic acid frothed and melted at 148–150°, and a mixture of the two shrank a little at 80–90° and frothed and melted at 146°. The benzylamine salt was prepared and it had a m.p. and mixed m.p. of 131–132°, with an authentic sample. The absorption spectrum of the metabolite was identical with that of Ciba-1906 propoxy acid (Table III).

Attempts to isolate the ester glucuronide of the propoxy acid were also made, and although solid material containing glucuronic acid and Ciba-1906 propoxy acid was isolated by extraction of the urine at pH 4 with ethyl methyl ketone, it could not be purified sufficiently for elementary analysis. This solid material had the same R_f values as found for it in the urine. It gave tests for

glucuronic acid and Ciba-1906 propoxy acid, and, on acid or alkaline hydrolysis, it yielded the propoxy acid as shown by paper chromatography.

Table III. Absorption spectra of Ciba-1906 and its metabolite

	Spectra in solvents[a]			
	A, B, C		D	
	$\lambda_{max.}$, mμ	$\epsilon_{max.} \times 10^{-3}$	$\lambda_{max.}$, mμ	$\epsilon_{max.} \times 10^{-3}$
Ciba-1906	271·5	23·0	280	22·7
Ciba-1906 propoxy acid (synthetic and metabolic)	270·5	22·7	280	22·0

[a] Solvents: A, absolute ethanol; B, ethanol–water, 9 : 1; C, ethanol–0·1N HCl, 9 : 1; D, ethanol–0·1N KOH, 9 : 1.

Detection of demethylation of Ciba-1906. Ciba-1906 (1·5 g) was fed to each of four rabbits and the urine collected for 36 h. The urine was adjusted to pH 9 with 10 per cent (w/v) Na_2CO_3 solution and extracted with 200 ml and 2 × 100 ml of chloroform. The extract was washed twice with 50 ml of 5 per cent Na_2CO_3 solution and then with 50 ml of water, and filtered and dried over anhydrous Na_2CO_3. The extract was evaporated under reduced pressure in nitrogen. The residue was dissolved in a little chloroform and an excess of light petroleum (b.p. 40–60°) added whereby a yellow gummy precipitate (200 mg) was produced. This material gave a strong blue colour with ferric chloride and a positive Grote's test. Attempts to crystallize it were unsuccessful. On paper chromatography, it was shown to contain a small amount of Ciba-1906, but the main bulk of it was a compound with R_f values very similar to Ciba-1906. The material was then boiled under reflux with 5N HCl for 2 h. The solution was extracted with ether and the extract chromatographed in solvents C, D and E (see Table II). The chromatograms showed that the hydrolysate contained large amounts of *N*-monomethyl-*p*-phenylenediamine together with small amounts of *N*,*N*-dimethyl-*p*-phenylenediamine. No *p*-phenylenediamine was found. It was therefore concluded that the above yellow gummy precipitate was probably largely nor-Ciba-1906, i.e. 4-butoxy-4′-monomethylamino-*N*,*N*′-diphenylthiourea.

Faecal excretion of Ciba-1906. Paper chromatographic examination of ethanolic extracts of the faeces of rabbits dosed with Ciba-1906 showed the presence of large amounts of the original drug. No other metabolites were detected.

The faeces of 6 rabbits each dosed with 2 g of the drug were collected for 7 days. They were homogenized and made alkaline with 10 per cent ammonia solution. The mixture was extracted with 3×400 ml of benzene. The extracts were filtered and dried (Na_2SO_4 anhyd.). After treatment with charcoal, the extract was evaporated to a small volume at reduced pressure and temperature in an atmosphere of nitrogen. An excess of light petroleum (b.p. 40–60°) was added to the residue and the whole kept at 0°. After 3 h, the precipitate which formed was filtered, washed with ether and twice recrystallized from ethyl acetate (charcoal). The white powder (120 mg) obtained was identified as Ciba-1906, m.p. and mixed m.p. 121–122°, by colour reactions and chromatographic mobility in solvents A, B and C (Table II).

Results and Discussion

The qualitative examination of the urine and faeces of rabbits dosed with Ciba-1906 shows that the urine contains mainly 4-(γ-carboxypropoxy)-4′-dimethylamino-*N*,*N*′-diphenylthiourea (Ciba-1906 propoxy acid) and its glucuronide, whereas the faeces contain only unchanged Ciba-1906. The urine also contains small amounts of a compound which yields *N*-monomethyl-*p*-phenylenediamine on strong acid hydrolysis and this suggests that 4-butoxy-4′-monomethylamino-*N*,*N*′-diphenylthiourea (nor-Ciba-1906) is also a urinary metabolite. Traces of unchanged Ciba-1906 were also found in the urine. Attempts were made to estimate the amounts of these various metabolites and the results are shown in Tables IV and V. Using ^{35}S-labelled Ciba-1906, Table V shows that about 95 per cent of the dose is excreted in 16 days after dosing, 73 per cent of the label appearing in the urine and 22 per cent in the faeces. However, both Tables show that the main bulk of the drug and its metabolites is eliminated in three days after dosing. The amount of Ciba-1906-like compounds excreted in the urine has been assessed in three ways: (*a*) by estimation of C=S compounds with Grote's reagent—this method

Table IV. Quantitative aspects of the metabolism of Ciba-1906 in rabbits. The figures given below are the averages for 3 animals; the ranges are in parentheses

Dose[a], mg/kg	% of dose in: Urine (3 days): glucuronide	ethereal sulphate	C=S compounds (Grote's reagent)	substances reacting with $FeCl_3$[b]: total	basic	acidic (by diff.)	Faeces (6 days)
400	31 (16–42)	0 (0–0)	38 (29–45)	—	—	—	—
300	—	—	—	46 (44–48)	7 (5–8)	39 (36–42)	—
300	—	—	—	—	—	—	24 (18–24)[b,c]

[a] Oral dose.
[b] Estimated by blue colour with $FeCl_3$; see text.
[c] Four animals used.

Table V. Excretion of ^{35}S by rabbits receiving [^{35}S]Ciba-1906. Dose of drug: 300 mg/kg; dose of ^{35}S; 21 μc/animal. The results are the mean for three animals; ranges in parentheses

Day	% of dose of ^{35}S in: Urine: total ^{35}S[a]	^{35}S as SO_4^{2-}[b]	Faeces
1	25 (24–26)	—	—
2	53 (49–58)	—	—
3	61 (57–64)	10 (7–12)	—
8	70 (69–70)	—	16 (12–20)
16	73 (70–74)	—	22 (21–23)

[a] ^{35}S accounted for 95 (93–97) per cent.
[b] Total sulphate.

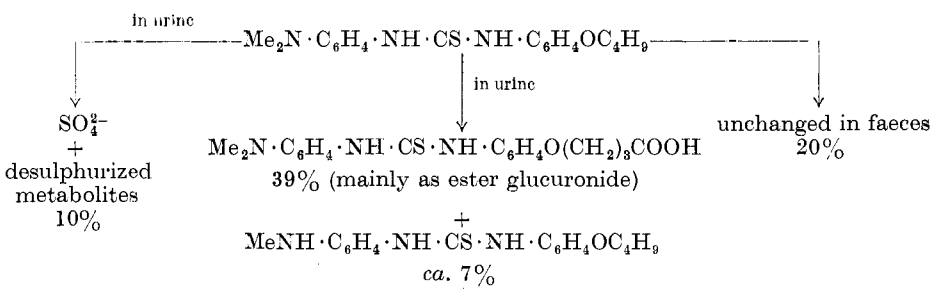
(see Table IV) gives an average value of 38 per cent in 3 days with a dose of 400 mg/kg; (*b*) by estimating the *p*-dimethylaminophenylthiourea grouping with ferric chloride—this method (see Table IV) gives an average value of 46 per cent in 3 days with a dose of

300 mg/kg; and (*c*) by estimating the neutral sulphur output using ^{35}S (see Table IV)—this method gives an average value of 51 per cent (i.e. total ^{35}S – the ^{35}S excreted as sulphate) in 3 days at a dose of 300 mg/kg. It can be concluded therefore that, in 3 days, about 40–50 per cent of the dose of Ciba-1906 is excreted in the urine as compounds closely related to it. The main urinary metabolite is Ciba-1906 propoxy acid, which was isolated, and from Table IV it can be deduced that about 39 per cent of the dose is excreted in the urine as this acid and that about three-quarters of it (see Table IV) is probably excreted as an ester glucuronide. The formation of nor-Ciba-1906 has also been suggested, and in Table IV it can be seen that the basic metabolites amount to about 7 per cent of the dose. This figure could be largely accounted for as nor-Ciba-1906, since the excretion of the unchanged drug is very small.

Both Tables IV and V suggest that the faecal excretion of the drug is about 20 per cent of the dose, and this material is largely the unchanged drug as shown by qualitative tests. Whether this material represents unabsorbed drug, or drug which has undergone entero-hepatic circulation as suggested by Schmid and Tripod,[2] cannot be determined by the present type of experiment.

The experiments with [^{35}S]Ciba-1906 show that a small proportion of the drug must undergo desulphuration, for about 10 per cent of the administered ^{35}S appeared in the urine as sulphate. This would suggest that a small proportion of Ciba-1906 is excreted as the corresponding urea or its derivatives. These compounds, however, were not investigated.

The metabolism of Ciba-1906 (3 days after dosing) in the rabbit, as far as it has been elucidated in this paper, is as follows:



Preliminary experiments on a normal human and on patients suffering from leprosy have shown that neither 4-(γ-carboxypropoxy)-4′-dimethylamino-*N*,*N*′-diphenylthiourea (Ciba-1906 propoxy acid) nor its β-oxidation product, 4-carboxymethoxy-4′-dimethylamino-*N*,*N*′-diphenylthiourea (Ciba-1906 methoxy acid), is a metabolite of Ciba-1906 in man. However, there is excreted in the urine a substance which is very similar to the propoxy acid. This substance is a major metabolite and is readily detectable by paper chromatography and spraying with 10 per cent ferric chloride solution. One gram of Ciba-1906 was taken by mouth and urine was collected for 12 h. Samples (0·05–0·1 ml) of the urine were chromatographed on Whatman No. 2 paper using solvent A of Table II and running the chromatogram for 5 h concurrently with samples of Ciba-1906 propoxy and methoxy acids. After spraying the paper with ferric chloride solution, the major metabolite showed up as a large blue spot of R_f 0·80–0·90. Under the same conditions, Ciba-1906 methoxy acid had R_f 0·68–0·78 and Ciba-1906 propoxy acid R_f 0·95. These results were confirmed with solvent C on Whatman No. 4 paper, when the metabolite showed an R_f of 0·05–0·3 and the propoxy acid R_f 0·35. The metabolite was more polar than the propoxy acid and less polar than the methoxy acid. A possibility is a glycine conjugate of the propoxy acid, and this point is to be further investigated.

Summary. The antileprotic drug Ciba-1906 (Thiambutosine; 4-butoxy-4′-dimethylamino-*N*,*N*′-diphenylthiourea) is metabolized in rabbits mainly to 4-(γ-carboxypropoxy)-4′-dimethylamino-*N*,*N*′-diphenylthiourea and its glucuronide, which are excreted in the urine. Very little of the unchanged drug is found in the urine, but the faeces contain appreciable amounts of the unmetabolized drug. At dose levels of 300 mg/kg, the main bulk of the drug is eliminated in the urine as metabolites in three days. About a fifth of the dose may be excreted unchanged in the faeces in 3–16 days. Experiments with [^{35}S]Ciba-1906 shows that only about 10 per cent of the drug is desulphurized. Evidence has also been obtained of some demethylation, less than 10 per cent of the dose, possibly to 4-butoxy-4′-monomethylamino-*N*,*N*′-diphenylthiourea. Preliminary experiments in man suggest that the carboxypropoxy acid, which is the main metabolite in rabbits, is not excreted by man. However, the main metabolite in man is closely related to this acid, possibly a glycine conjugate.

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