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The Metabolism of Arylthioureas— IV. *p*-Chorophenyl- and *p*-Tolyl-thiourea

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The highly toxic phenylthiourea has been shown to be metabolized in rats and rabbits by loss of sulphur and it was suggested that its toxicity was due to metabolic release of hydrogen sulphide.[1,2] *p*-Chlorophenylthiourea and *p*-tolylthiourea are also relatively highly toxic. The metabolism of both these compounds has been investigated in rabbits and it is concluded that they are metabolized in a similar manner to phenylthiourea.

This paper also records the ultraviolet absorption spectra of a number of aryl- and diaryl-ureas and -thioureas.

Materials and Methods

Materials. *p*-Chlorophenylthiourea, m.p. 178°, *p*-chlorophenylurea, m.p. 204–206°, *p*-chlorophenylcyanamide, m.p. 99°, *p*-tolylthiourea, m.p. 188–189°, *p*-tolylurea, m.p. 182–183°, *p*-thioureidobenzoic acid (did not melt below 300°), and *p*-ureidobenzoic (did not melt below 300°) were prepared by standard methods.[3,4]

Determination of thione compounds. Thione compounds in urine were determined with Grote's reagent as described earlier.[5] Preliminary experiments had shown that neither *p*-chlorophenylthiourea nor *p*-tolylthiourea was excreted unchanged. *p*-Tolylthiourea, however, was excreted in part as *p*-thioureidobenzoic acid, which could be estimated satisfactorily by Grote's reagent, the blue colour being read at 590 mμ in a Unicam Spectrophotometer (SP 600).

Determination of p-*chloroaniline.* If *p*-chlorophenylthiourea is metabolized to *p*-chlorophenylcarbamic acid and *p*-chlorophenylurea, then distillation of the urine made strongly alkaline with

NaOH should yield *p*-chloroaniline. *p*-Chloroaniline is readily recovered by steam distillation in amounts of 92–99 per cent. Solutions of *p*-chlorophenylurea (0·8–1·7 mg in 2–5 ml of 25 per cent (v/v) aqueous ethanol) were mixed with 20 ml of 40 per cent (w/v) NaOH. The solutions were steam distilled and 100 ml of distillate was collected. A suitable volume of the distillate (1–5 ml) was diluted to 10 ml with water and treated with 0·5 ml of 4N HCl followed by 1 ml of 0·1 per cent (w/v) aqueous $NaNO_2$. After 10 min, 1 ml of 0·5 per cent (w/v) ammonium sulphamate was added and 2 min later 1 ml of 0·1 per cent aqueous *N*-(1-naphthyl)ethylenediamine, the final volume of solution being 13·5 ml. The red colour was read 3 h later at 535 mμ in a Unicam spectrophotometer (SP 600). The recovery was 95 per cent (range 92–100 per cent). Under the same conditions, *p*-chlorophenylcyanamide was hydrolysed to *p*-chloroaniline only to the extent of 1·7 per cent (range 1·2–2·2 per cent).

Determination of p-*toluidine.* Tolylthiourea could be metabolized to *p*-tolylcarbamic acid and *p*-tolylurea, both of which on alkaline hydrolysis should yield *p*-toluidine. *p*-Tolylurea was treated as above for *p*-chlorophenylurea and the *p*-toluidine formed was measured after diazotization and coupling as above but allowing the colour to develop for 24 h and reading the colour at 545 mμ. The average recovery of 0·6–1·5 mg of *p*-tolylurea as *p*-toluidine was 96·5 per cent. *p*-Tolylthiourea did not yield *p*-toluidine under the same conditions.

Determination of p-*ureidobenzoic acid.* This compound on alkaline hydrolysis yields *p*-aminobenzoic acid which can be estimated by diazotization and coupling to form a dye. A solution of *p*-ureidobenzoic acid (0·5 mg/ml) was made up in 25 per cent (v/v) aqueous ethanol. Appropriate volumes of the solution containing 1·25 mg of the acid were heated under reflux for 2 h with 20 ml of N KOH. The solution was cooled, neutralized with N HCl (20 ml) and made up to 100 ml with water. This solution (1–5 ml) was adjusted to 10 ml with water and diazotized and coupled with *N*-(1-naphthyl)ethylenediamine as above and the intensity of the colour obtained after standing 20 min was measured at 535 mμ. The mean recovery was 87 per cent (range, 86–88 per cent). Hydrolysis for less than 2 h gave much lower yields of *p*-aminobenzoic acid. Under the same conditions,

p-thioureidobenzoic acid was hydrolysed to the extent of 7 per cent (6–9).

Determination of p-*aminobenzoic acid.* An aqueous solution of *p*-aminobenzoic acid (5 μg/ml) was prepared. Now 1–10 ml of this solution was adjusted to 10 ml with water and diazotized and coupled as above. The purplish colour was measured at 535 mμ after standing 20 min.

Isolation and Detection of Metabolites

p-*Chlorophenylthiourea.* The urine of rabbits which had received oral doses of *p*-chlorophenylthiourea (35 mg/kg) was collected for 24 h. It gave a negative Grote's test which suggested that no compound containing a C=S group was present. The urine was chromatographed on Whatman No. 4 paper using solvent systems B, C and E (see Table I.) A large spot giving a positive Tollens test for glucuronic acid and a diazo-coupling reaction was found with R_f 0–0·15 in solvent C and R_f 0·55–0·75 in solvent E. This spot would suggest the presence of *p*-chlorophenylcarbamic acid glucuronide similar to that found in phenylthiourea urine.[1] Ehrlich's reagent revealed a spot corresponding to *p*-chlorophenylurea of R_f values 0·87 in C and 0·41 in E, and on warming the chromatogram a spot corresponding to *p*-chlorophenylcyanamide was also revealed by the same reagent (R_f 0·78 in C and 0·82 in E). Chromatography thus revealed three metabolites of *p*-chlorophenylthiourea.

The bulked urine (of pH 7·8) of five rabbits which had each received 35 mg/kg of *p*-chlorophenylthiourea (total dose, 420 mg) was continuously extracted with ether for 24 h. The extract was evaporated and the residue was taken up in a little hot water (charcoal) and allowed to stand at 0° for 2 days. The crystals (2·2 mg or 0·5 per cent of dose) which separated were identified as *p*-chlorophenylurea, m.p. and mixed m.p. 204–206°, by their R_f values in three solvents (B, C and E, Table I) and by absorption spectra which were the same in ethanol, 0·01N KOH and 0·01N HCl (λ_{max} 244 and 283 mμ and ϵ_{max} about 21,000 and 1100) (see Table III).

The presence of *p*-chlorophenylcyanamide in the urine was shown by paper chromatography in two solvents (C and E,

Table I. R_f values and colour reactions of *p*-chlorophenyl- and *p*-tolyl-thiourea and their metabolites. Whatman No. 4 paper and the descending method were used. Solvents (proportions by vol.) and times of running were: A, benzene–acetic acid–water, 1 : 1 : 2 (2 h); B, butanol–acetic acid–water, 4 : 1 : 5 (4 h); C, butanol–ethanol–ammonium carbonate buffer (equal vols. of 3N ammonia and 3N $(NH_4)_2CO_3$), 40 : 11 : 19 (4–5 h); D, benzene–butanol–pyridine–water, 3 : 5 : 3 : 1 (4–5 h); E, benzene saturated with 98 per cent formic acid (2 h). Sprays as described in the preceding papers[1, 2]

Compound	R_f in solvent					Colour reactions[a]			
	A	B	C	D	E	Grote's	Iodine–Na azide	Ehrlich's test	Diazo test
p-Chlorophenylthiourea	—	0·88	0·90	—	—	blue	white[b]	—	—
p-Chlorophenylurea	—	0·82	0·87	—	0·41	—	—	yellow	—
p-Chlorophenylcyanamide	—	—	0·78	—	0·82	—	—	yellow slowly	—
p-Tolylthiourea	Streaked to 0·78	0·90	0·88	0·88	—	blue	white[b]	weak yellow	—
p-Tolylurea	0·74	0·85	0·90	0·90	—	—	—	yellow	—
p-Thioureidobenzoic acid	0	0·85	0·12	0·20–0·30	—	blue	white[b]	very weak yellow	—
p-Ureidobenzoic acid	0	0·86	0·15	0·30–0·40	—	—	—	yellow	—
p-Aminobenzoic acid	—	—	0·05–0·10	—	—	—	—	yellow	red

[a] — means no colour reaction.
[b] White spot on brown background.

Table I). The spot found with solvent E was eluted with ethanol and the absorption spectrum determined. The eluate showed a large peak at 239 mμ and a small one at 275 mμ. This was replaced by a single band at 270 mμ in 0·01N KOH in 90 per cent ethanol. This behaviour was similar to that of synthetic *p*-chlorophenylcyanamide.

p-*Chlorophenylcyanamide.* This compound (100 mg/kg) was given by mouth suspended in water to three rabbits and a 24-h urine specimen collected. The urine was normal in appearance and odour. It gave no colour with ferric chloride and very weak colour with Gibb's reagent which suggested the presence of little, if any, non-*para*-substituted phenols. The naphthoresorcinol test for glucuronic acid was strongly positive and the urine reduced Benedict's reagent thus suggesting the presence of a labile glucuronide. The diazo test for aromatic amines was strong and became very intense if the urine was first warmed with 10 per cent HCl or 10 per cent NaOH. A compound which could be expected to give these tests would be the unknown ester-glucuronide of *p*-chlorophenylcarbamic acid. Chromatography of the urine in solvent C (see Table I) showed the presence of a polar metabolite of R_f 0–0·2, which gave a positive naphthoresorcinol test, and a positive diazo test for aromatic amines which increased if the paper was first sprayed with 10 per cent HCl and warmed. This spot was similar to one found in *p*-chlorophenylthiourea urine. In solvent E, small spots corresponding to the original compound (R_f 0·72–0·78) and to *p*-chlorophenylurea (0·25–0·3) were found using Ehrlich's reagent for spraying. Colour tests and paper chromatography thus suggested that the urine contained one major metabolite, probably *p*-chlorophenylcarbamic acid glucuronide, and two minor ones, *p*-chlorophenylurea and the original compound.

The combined 48-h urines were made 2N with respect to NaOH and steam distilled. *p*-Chloroaniline (benzoyl derivative, m.p. and mixed m.p. 191–192°) was recovered from the distillate amounting to 70 per cent of the dose. *p*-Chlorophenylcyanamide is not hydrolysed to *p*-chloroaniline under these conditions, and paper chromatography showed *p*-chlorophenylurea to be a minor metabolite. The chloroaniline was probably derived mainly from '*p*-chlorophenylcarbamic acid glucuronide'.

p-*Tolylthiourea*. The urine of rabbits given *p*-tolylthiourea gave a strongly positive Grote's test and a positive diazo-coupling reaction with *N*-(1-naphthyl)ethylenediamine. This suggested the presence of a thione compound and an aromatic amine or a compound readily yielding an aromatic amine. Chromatography of the urine on Whatman No. 4 paper in solvent C (Table I) revealed one spot, R_f 0·08–0·14, reacting for C=S compounds. This spot corresponded to *p*-thioureidobenzoic acid; no spot corresponding to *p*-tolylthiourea was found (both findings were confirmed with solvent D). Using Ehrlich's reagent as a spray, four spots were found, namely R_f, 0·05–0·1 (*p*-aminobenzoic acid), 0·15–0·2 (*p*-ureidobenzoic acid), 0·3–0·4 (urea) and 0·85 (weak; *p*-tolylurea). These were confirmed with solvent D. The paper was sprayed with 10 per cent HCl and warmed at 100° for a few minutes. It was then sprayed with diazotizing and coupling [*N*-(1-naphthyl)ethylenediamine] reagents for aromatic amines. Two spots came up immediately, R_f 0–0·1 (*p*-aminobenzoic acid) and 0·15–0·2 (giving the same red colour as *p*-aminobenzoic, and derived from a compound, possibly *p*-carboxyphenylcarbamic acid, yielding *p*-aminobenzoic acid on heating with acid). A third diazo spot, purple in colour, developed slowly (maximum colour in 24 h) at R_f 0·4 and this suggested a substance yielding *p*-toluidine with acid, possibly *p*-tolylcarbamic acid. Spraying the paper with naphthoresorcinol solution for glucuronic acid, positive reactions were obtained at R_f 0·4, possibly due to *p*-tolylcarbamic acid glucuronide, and at R_f 0·15 (weak), which could be due to *p*-carboxyphenylcarbamic acid glucuronide.

Chromatography thus suggested the presence of *p*-thioureidobenzoic acid, *p*-tolylurea, *p*-aminobenzoic acid and a precursor of *p*-aminobenzoic acid which was also a glucuronide, *p*-ureidobenzoic acid, and a precursor of *p*-toluidine which is also a glucuronide.

Isolation of p-*tolylurea*. *p*-Tolylthiourea (200 mg) was fed to each of six rabbits. The 24-h urine specimen was brought to pH 9 with aqueous $NaHCO_3$ (5 per cent w/v) and continuously extracted with ether for 6 h. The extract was evaporated and the aqueous residue was chromatographed as a band on Whatman No. 4 paper in solvent C (Table I). The *p*-tolylurea band was cut out and soaked overnight in absolute ethanol. On concentration of the ethanol, 15 mg of *p*-tolylurea was obtained, from which the pure compound

(6 mg) was obtained by recrystallization from water. It had m.p. 182–183°.

Anal. Calcd. for $C_8H_{10}N_2O$: toluidine (C_7H_9N), 64·5. Found: C_7H_9N, by hydrolysis, 63·8. Its spectra were identical with authentic *p*-tolylurea (see Table III).

Isolation of p-*thioureidobenzoic acid.* *p*-Tolylthiourea (200 mg) was fed to each of five rabbits. The 24-h urine specimen was brought to pH 2 with 10 per cent H_2SO_4 and continuously extracted with ether for 8 h. Crystalline material (120 mg) separated. A further 8-h extraction yielded another 40 mg (total yield, 16 per cent of dose). Both samples gave Grote's test and their chromatographic mobilities suggested that they were *p*-thioureidobenzoic acid. The combined samples were recrystallized from ethanol, and the crystals shrank at 235° but did not melt on heating at 300°. They behaved like authentic *p*-thioureidobenzoic acid and gave identical absorption spectra. The ether mother liquor from which the compound had been separated from the urine was shown by paper chromatography to contain *p*-ureidobenzoic acid, but none of it was isolated.

The toxicity of p-*chlorophenyl- and* p-*tolyl-thiourea.* It was observed that with *p*-chlorophenylthiourea administered orally to rabbits, 1/6 died at 35 mg/kg and 2/2 at 50 mg/kg.

It was observed with *p*-tolylthiourea that 2/2 rabbits died when given 160 mg/kg orally; 0/4 died at 70 mg/kg and 1/6 died at 40 mg/kg. The LD_{50} of *p*-tolylthiourea is thus much greater than that of phenylthiourea and is of the order of 100 mg/kg.

Results and Discussion

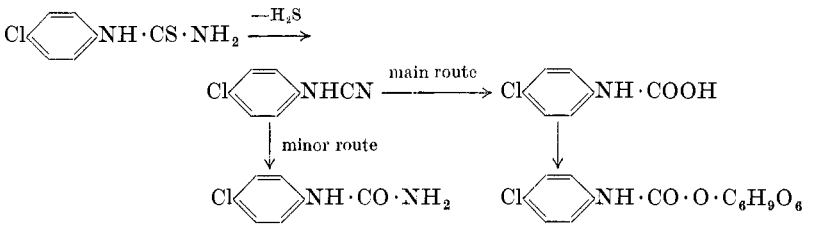
p-Chlorophenylthiourea appears to be slightly more toxic than phenylthiourea and observations on its metabolism suggest that it is metabolized by desulphuration in a similar manner to phenylthiourea.[1] Chromatography of the urine of rabbits dosed with *p*-chlorophenylthiourea suggests that the main metabolite is the labile glucuronide of *p*-chlorophenylcarbamic acid and that *p*-chlorophenylurea and *p*-chlorophenylcyanamide are minor metabolites. There is no unchanged *p*-chlorophenylthiourea. When *p*-chlorophenylcyanamide is fed to rabbits, the urine contains the same major metabolite as when *p*-chlorophenylthiourea is fed, that is *p*-chlorophenylcarbamic acid glucuronide,

Table II. *Quantitative aspects of excretion of metabolites by rabbits given p-chlorophenylthiourea and p-tolylthiourea.* Compounds administered orally; the figures given are mean values, the ranges being in parentheses and the number of animals indicated by superscripts

Compound	Dose, mg/kg	% of dose excreted in 2 days as				
		Thione compounds	Substituted phenylurea + phenylcarbamic acid[a]	*p*-Amino-benzoic acid	*p*-Ureido-benzoic acid	Total
p-Chlorophenylthiourea	35	0	56[b] (43–68)[5]	—	—	56 (43–68)[5]
p-Tolylthiourea	60	38[d] (32–47)[3]	16[c] (14–19)[3]	1·8 (1·5–2·1)[3]	9 (7–14)[3]	65 (55–82)[3]
p-Chlorophenylcyanamide	100	—	81 (77–88)[3]	—	—	81

[a] i.e. compounds yielding *p*-substituted anilines by alkaline hydrolysis.
[b] *p*-Chlorophenylurea + *p*-chlorophenylcarbamic acid.
[c] *p*-Tolylurea + *p*-tolylcarbamic acid.
[d] *p*-Thioureidobenzoic acid.

and small amounts of *p*-chlorophenylurea. The quantitative data given in Table II show also that *p*-chlorophenylcarbamic acid is probably the major metabolite of both *p*-chlorophenylthiourea and *p*-chlorophenylcyanamide, for the contribution of *p*-chlorophenylurea to the figures given in column 4 of this Table is small, judging from paper chromatography. The route of metabolism of *p*-chlorophenylthiourea is thus as follows:—

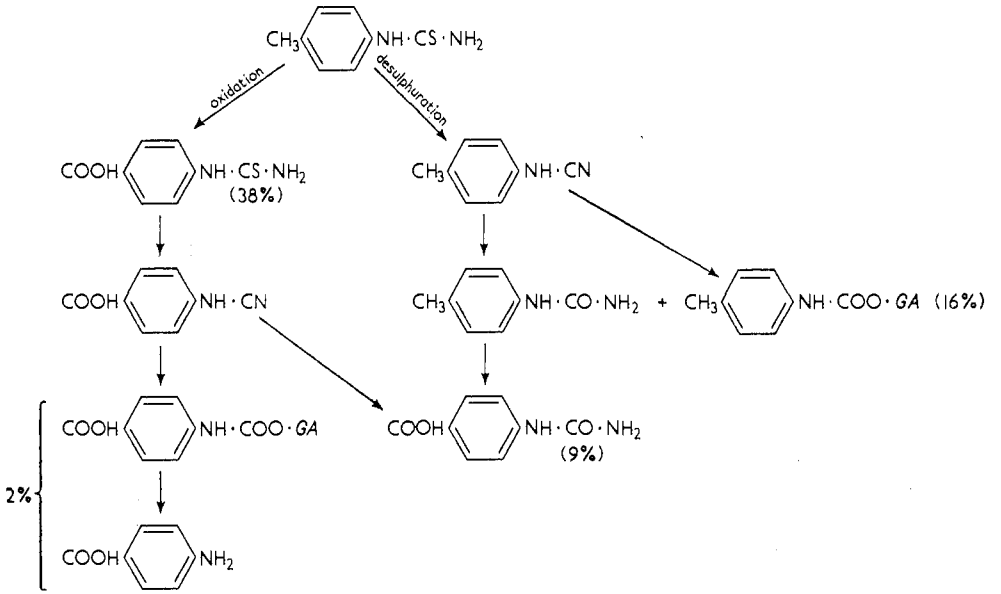


No hydroxylation of *p*-chlorophenylthiourea was detected although it will be recalled that hydroxylation is a minor route of metabolism of phenylthiourea.[1]

p-Tolylthiourea is less toxic than phenylthiourea and its *p*-chloro derivative. This can be explained in terms of metabolism for *p*-tolylthiourea is not completely desulphurized. Table II shows that 38 per cent of the dose of tolylthiourea is excreted as a thione compound. However, the thione compound excreted is not the original compound but an oxidation product, *p*-thioureidobenzoic acid (*p*-carboxyphenylthiourea). Two routes of metabolism of *p*-tolylthiourea are possible, namely oxidation to *p*-thioureidobenzoic acid and desulphuration. Now paper chromatography of the urine showed the presence of six metabolites (see also Table II) which were identified as *p*-thioureidobenzoic acid (38 per cent), *p*-ureidobenzoic acid (9 per cent), *p*-tolylurea and a labile glucuronide precursor of *p*-toluidine (together amounting to 16 per cent of the dose), and *p*-aminobenzoic acid and a labile glucuronide precursor of *p*-aminobenzoic acid (both amounting to about 2 per cent of the dose) in two days. These metabolites can be fitted into the scheme shown on p. 156. The lesser toxicity of *p*-tolylthiourea may be due to the fact that it can be oxidized to *p*-thioureidobenzoic and that it is not as extensively desulphurized as are phenylthiourea and *p*-chlorophenylthiourea.

It is assumed that the sulphur appears in the tissues as H_2S, the toxic agent.[1, 2]

One can now compare the three monoarylthioureas. The most toxic to rabbits is *p*-chlorophenylthiourea which is completely desulphurized in these animals. Phenylthiourea is almost as



$GA = C_6H_9O_6$, the glucuronyl residue

The figures in parentheses are the amounts of these compounds found in the urine in 2 days.

toxic as the *p*-chloro compound, and it is largely desulphurized (80 per cent) *in vivo*, although some 15–20 per cent is hydroxylated to *p*-hydroxyphenylthiourea.[1] The least toxic of the three is *p*-tolylthiourea; in this case about 40 per cent of the dose is not desulphurized, but is oxidized to *p*-thioureidobenzoic acid. These findings with *p*-chloro- and *p*-tolylthiourea support the suggestion that toxicity in these compounds is related to desulphuration *in vivo*.

The Absorption Spectra of Arylureas and Arylthioureas

The wavelength maxima and molecular extinction coefficients ($\epsilon_{max.}$) of five pairs of monoarylureas and monoarylthioureas in

neutral, acid and alkaline media are given in Table III, and typical curves in Figs. 1 and 2. It is to be noted that, apart from *p*-hydroxyphenylurea, the nature of the medium has little effect on the spectra. However, on comparing the ureas with the

Table III. Absorption spectra of arylureas and arylthioureas. General formula: $R \cdot C_6H_4 \cdot NH \cdot CX \cdot NH_2$. Solvents: A, ethanol–water, 9 : 1; B, ethanol–N HCl, 9 : 1; C, ethanol–0·1N KOH, 9 : 1 by vol.

R	X	Spectra in solvent			
		A and B		C	
		$\lambda_{max.}$	$\epsilon_{max.} \times 10^{-3}$	$\lambda_{max.}$	$\epsilon_{max.} \times 10^{-3}$
H	O	238	16·8	238	16·8
H	S	265	13·2	266·5	13·8
4-OH	O	241 (290)	14·0 (1·7)	250 (298)	14·8 (3·3)
4-OH	S	254	14·3	253	17·9
4-CH_3	O	240 (280)	17·6 (1·2)	240 (280)	17·6 (1·2)
4-CH_3	S	264	13·4	[a]	[a]
4-Cl	O	244 (283)	22·2 (1·05)	244 283	20·7 (1·05)
4-Cl	S	240 272	13·1 14·2	234 272	13·7 11·0
4-CO_2H	O	268 in A 272 in B	19·8 20·9	263	20·4
4-CO_2H	S	252, 285 in A	12·7 15·6	248 279	13·0 17·2
		252, 295 in B	13·9 17·7		

[a] Solutions were cloudy.
Figures in parentheses are for minor peaks.

thioureas, it will be noted that the replacement of O by S causes a bathochromic shift of about 20 mμ. This shift is to be expected on comparison with previous data on chromophores containing sulphur.[6] The chromophoric power of the C═S group is reported to be greater than that of the C═O group,[6] but a perusal of Table III shows that this is not true when the monoarylthioureas are

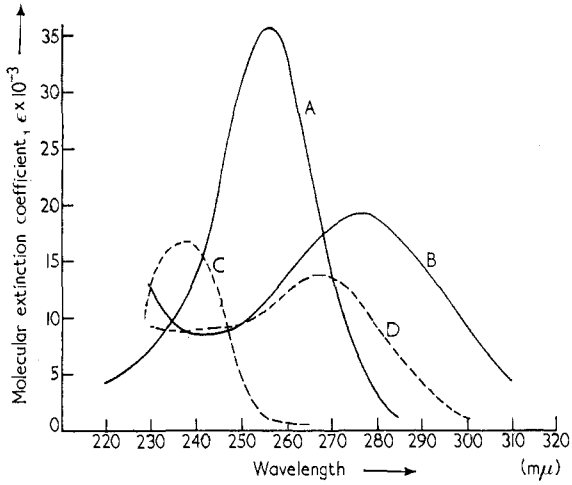


Fig. 1. The absorption spectra of 1,3-diphenylurea (A, $\lambda_{max.}$ 256·5 mμ, $\epsilon_{max.}$ 35,700), 1,3-diphenylthiourea (B, $\lambda_{max.}$ 277 mμ, $\epsilon_{max.}$ 19,200), 1-phenylurea (C, $\lambda_{max.}$ 238 mμ, $\epsilon_{max.}$ 16,700) and 1-phenylthiourea (D, $\lambda_{max.}$ 267·5 mμ, $\epsilon_{max.}$ 13,700) in absolute ethanol.

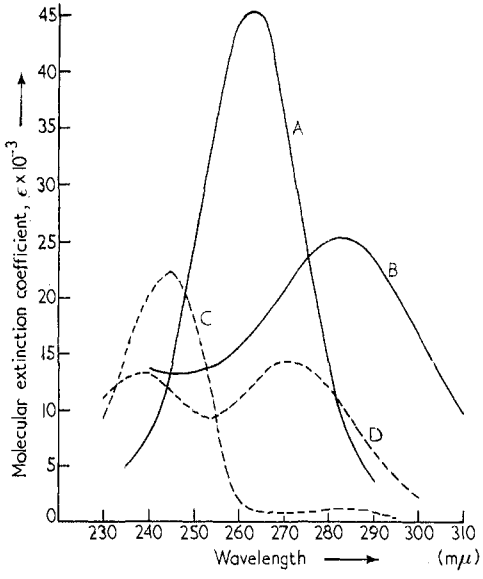
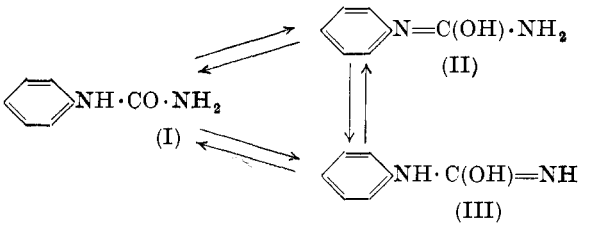
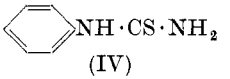


Fig. 2. The absorption spectra of 1,3-di(*p*-chlorophenyl)urea (A, $\lambda_{max.}$ 263 mμ, $\epsilon_{max.}$ 46,000), 1,3-di(*p*-chlorophenyl)-2-thiourea (B, $\lambda_{max.}$ 282·5 mμ, $\epsilon_{max.}$ 25,450), 1-*p*-chlorophenylurea (C, $\lambda_{max.}$, 244 and 283 mμ, $\epsilon_{max.}$ 22,400 and 1,050) and 1-*p*-chlorophenylthiourea (D, $\lambda_{max.}$ 240 and 272 mμ, $\epsilon_{max.}$ 13,300 and 14,500) in absolute ethanol.

compared with the corresponding arylureas, for in these compounds the replacement of O by S results in a fall in the extinction coefficients (a hypochromic effect) of 4000–8000, except in the case of *p*-hydroxyphenylthiourea. A possible explanation is that the arylureas have a greater tendency to occur in the enolic form than the arylthioureas. Two enolic forms are possible, thus:



In the enolic form II, the side-chain double bond is conjugated with the aromatic ring and would enhance the extinction. These observations support the conclusions of Clow and Helmrich[7] who deduced, from their studies on the magnetic susceptibilities of ureas and thioureas, that phenylthiourea approached the structure of a true thiocarbamide (IV) whereas with phenylurea



the presence of an enolic form (II and III) was indicated.

The spectra of the 1,3-diaryl-ureas and -thioureas are given in Table IV, and typical examples are shown in Figs. 1 and 2. Again replacement of O by S produces a bathochromic shift (about 15 mμ), but now the hypochromic effect is very marked and ranges from 11,000 to 20,000 in four pairs of 1,3-diaryl-ureas and -thioureas. In Table V there are quoted the ratios of the $\epsilon_{max.}$ values of 1,3-diarylureas to those of 1-arylureas, and of 1,3-diarylthioureas to those of 1-arylthioureas in solvents A and B of Tables III and IV. It is to be noted that the $\epsilon_{max.}$ values of 1,3-diphenylurea, 1,3-di-(*p*-hydroxyphenyl)urea and 1,3-di-(*p*-chlorophenyl)urea are twice those of 1-phenylurea, 1-*p*-hydroxyphenylurea and 1-*p*-chlorophenylurea, respectively. Doubling of the $\epsilon_{max.}$ value does not occur with the corresponding thioureas. These results suggest that the diarylureas occur to a greater extent in the

Table IV. Absorption spectra of diarylureas and diarylthioureas. General formula: $R \cdot C_6H_4 \cdot NH \cdot CX \cdot NH \cdot C_6H_4 \cdot R'$ (solvents as in Table III)

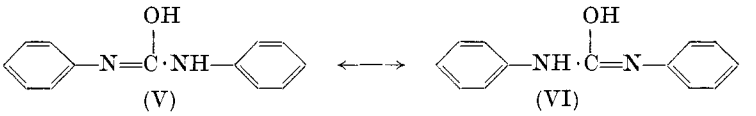
R	R′	X	Spectra in solvent			
			A and B		C	
			$\lambda_{max.}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}$	$\epsilon \times 10^{-3}$
H	H	O	257	35·2	257	36·4
H	H	S	277	18·8	273	20·9
H	4-OH	O	257	31·0	257 ~265	20·6 19·7
H	4-OH	S	274	18·4	257	17·4
H	4-$C_6H_9O_7$[c]	S	272	18·6	270	17·9
4-OH	4-OH	O	258	28·7	257 ~265	26·3 24·4
4-OH	4-OH	S	270	17·7	[a]	[a]
4-OH	4-$C_6H_9O_7$[c]	S	272	18·6	254 ~285	20·8 15·5
4-Cl	4-Cl	O	263	45·0	264	47·2
4-Cl	4-Cl	S	282	25·0	275	25·7
4-$(CH_3)_2N$[b]	4-C_4H_9O	S	272 in A 280 in B	23·2 22·7	271	23·0

[a] Decomposition occurred.
[b] Ciba-1906.
[c] Glucuronides.

Table V. Ratio of molecular extinction coefficients ($\epsilon_{max.}$) of di- and mono-arylureas and di- and mono-arylthioureas

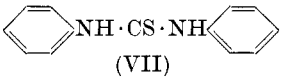
Substituent	$\epsilon_{di}/\epsilon_{mono}$	
	Ureas	Thioureas
C_6H_5	2·1	1·4
p-$HO \cdot C_6H_4$	2·05	1·2
p-$Cl \cdot C_6H_4$	2·0	1·7

conjugated enolic forms (V and VI) than do the corresponding diarylthioureas.



(V) (VI)

This suggestion agrees with the results of magnetic susceptibility studies of Clow and Helmrich[7] who concluded that diphenylthiourea was more nearly a true thiocarbamide (VII)



(VII)

than phenylthiourea, whereas diphenylurea was even more enolic than phenylurea.

Summary. The metabolism of *p*-chlorophenylthiourea and *p*-tolylthiourea has been studied in rabbits. The *p*-chloro derivative is highly toxic. It is metabolized mainly to, and excreted as, a compound which appears to be the glucuronide of *p*-chlorophenylcarbamic acid. It is completely desulphurized. Minor urinary metabolites are *p*-chlorophenylurea and *p*-chlorophenylcyanamide. The latter compound is metabolized mainly to the glucuronide of *p*-chlorophenylcarbamic acid together with small amount of *p*-chlorophenylurea.

p-Tolylthiourea is not as toxic as phenylthiourea and it is only partly desulphurized *in vivo*. Nearly 40 per cent of the dose is oxidized and excreted as *p*-thioureidobenzoic acid. *p*-Tolylurea and probably the glucuronide of *p*-tolylcarbamic acid are also found in the urine. *p*-Aminobenzoic acid, a labile precursor of *p*-aminobenzoic acid (probably the glucuronide of *p*-carboxyphenylcarbamic acid) and *p*-ureidobenzoic acid are also present in the urine.

Observations have also been made on the ultraviolet absorption spectra of a number of aryl-ureas and -thioureas.

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