Metabolism of Polycyclic Compounds

17. THE REACTION OF 1:2-DIHYDRONAPHTHALENE AND 1:2-EPOXY-1:2:3:4-TETRAHYDRONAPHTHALENE WITH GLUTATHIONE CATALYSED BY TISSUE PREPARATIONS

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Naphthalene is converted into *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione by rat-liver slices (Booth, Boyland & Sims, 1960). When 1:2-dihydronaphthalene or 1:2-epoxy-1:2:3:4-tetrahydronaphthalene is administered to rabbits, a mercapturic acid, *N*-acetyl-*S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (III), is excreted in the urine (Boyland & Sims, 1960); this product is closely related in structure to the mercapturic acid, *N*-acetyl-*S*-(1:2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine found in the urine of rabbits treated with naphthalene (Boyland & Sims, 1958). The present work has shown that rat-liver slices convert 1:2-dihydronaphthalene into *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I), which is converted into *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (II) by rat-kidney homogenates and to the mercapturic acid (III) by kidney slices. The action of a rat-liver microsomal system on 1:2-dihydronaphthalene and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene is also described. Evidence

is presented that glutathione is activated by an enzyme or enzyme system, but that cysteine and *N*-acetylcysteine are not.

EXPERIMENTAL

Materials. 1:2-Dihydronaphthalene, 1:2-epoxy-1:2:3:4-tetrahydronaphthalene, *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene, *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (II) and *N*-acetyl-*S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (III) were prepared as described by Boyland & Sims (1960). Reduced glutathione was obtained from Schwarz Laboratories Inc.

The glutathione derivative (I) was prepared as follows: 1:2-epoxy-1:2:3:4-tetrahydronaphthalene (1 g.), glutathione (2.1 g.) and NaHCO₃ (0.6 g.), in water (100 ml.), were kept at 60° with stirring for 2 hr. The solution was cooled, acidified to pH 4 with acetic acid and activated charcoal (10 g.) was added. The charcoal was filtered off and washed with water (1 l.) and the adsorbed material eluted with methanol (500 ml.) containing 5% (v/v) of aq. NH₃ soln. (sp.gr. 0.88). The methanol was removed under reduced pressure to give a clear gum which was chromatographed on a cellulose-powder column (100 g., Whatman standard grade) with butanol-cyclohexane-water (18:1:3, by vol.) as developing solvent. Fractions of 200 ml. were collected,

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evaporated to dryness under reduced pressure and the residue were examined for the glutathione derivative (I) on paper chromatograms. Some of the fractions containing the glutathione derivative (I) formed encrystallizable gums, whereas others yielded colourless solids. These solids were combined, dissolved in methanol and precipitated with ether to give a product which was presumably a mixture of the isomeric forms of *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I) as a colourless powder, melting over the range 130–165° (Found: N, 9.6; S, 6.9. Calc. for $C_{20}H_{27}O_7N_3S$: N, 9.3; S, 7.1%). A little of the derivative was heated to 100° for 5 min. with 2*N*-HCl (1 ml.) and the solution cooled and an excess of 10*N*-NaOH, ethanol (0.5 ml.) and ether (0.5 ml.) were added. On shaking, a blue colour developed in the ether layer, characteristic of 2-tetralone (Straus & Rohrbacker, 1921). A little of the derivative was heated with an excess of HBr (sp.gr. 1.7) for 4 hr. at 100°. The solution was evaporated to dryness and the residue examined on paper chromatograms for amino acids, both directly with solvent 1 described below, and, after treatment with 2:4-dinitrofluorobenzene (Sanger, 1945), with the solvents of Phillips (1958). Compounds indistinguishable from glycine, glutamic acid and cysteine (and cystine) were detected. Hydrogenolysis of the derivative (I) with Raney nickel catalyst as described by Boyland & Sims (1960) led to the detection of compounds indistinguishable from 2-naphthol, glycine, alanine and glutamic acid.

Paper chromatography. This was carried out by downward development for 18 hr. on Whatman no. 1 paper with either solvent 1, butanol-acetic acid-water (12:3:5, by vol.), or solvent 2, butanol-propan-1-ol-water (2:1:1, by vol.), as developing solvent. The properties on paper chromatograms of most of the compounds encountered in the present work have been described by Boyland & Sims (1960). *S*-(2-Hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I) had R_F 0.38 and 0.25 on paper chromatograms in solvents 1 and 2 respectively and gave a purple colour with ninhydrin and a positive reaction with the $K_2Cr_2O_7$ -AgNO₃ reagent of Knight & Young (1958). 2-Naphthol was detected as described by Sims (1959).

Tissue experiments. Slices of liver (approx. 2.5 g. wet wt.) from male adult rats were incubated in Krebs-Ringer phosphate (pH 7.4) (Umbreit, Burris & Stauffer, 1949) (30 ml.), containing a suspension of 1:2-dihydronaphthalene, for 2 hr. at 37° with shaking. At the end of the incubation period, the reaction mixture was decanted from the slices, which were washed once with water (15 ml.). The washings and the reaction mixture were combined and adjusted to pH 4 with acetic acid. The mixture was centrifuged for 20 min. at 600 g, the supernatant was treated with activated charcoal (0.5 g.) and the charcoal filtered off and washed with water. The material, obtained by the subsequent elution of the charcoal with methanol containing 0.2% (v/v) of aq. NH₃ soln. (sp.gr. 0.88) and evaporation under reduced pressure, was examined on paper chromatograms. The kidney-slice experiments were carried out in the same way with slices (approx. 5 g. wet wt.) from the kidneys of male adult rats. Livers and kidneys from male adult rats were homogenized in 3 vol. of Krebs-Ringer phosphate (pH 7.5) with a homogenizer as described by Potter & Elvehjem (1936) with a Teflon pestle.

Rat-liver microsomes were prepared as described by (Booth & Boyland, 1958) except that the livers were

homogenized in 4 vol. of 0.1*M*-phosphate buffer (pH 7.4), prepared from Na₂HPO₄ and KH₂PO₄. The microsomes were suspended in the original volume of iso-osmotic NaCl and reprecipitated by spinning for 30 min. at 90 000 *g* in a Spinco model L preparative ultracentrifuge with rotor no. 40. The microsomal pellets were stored at -20°. The supernatant obtained after the separation of the microsomes was adjusted to pH 5 with acetic acid, spun at 1000 *g* for 15 min. and the pH of the resulting supernatant re-adjusted to 7.4 by the addition, first of 5*N*-NaOH and finally of 0.1*N*-NaOH. Immediately before use a microsomal pellet was suspended in 0.1*M*-phosphate buffer, pH 7.4, with a Potter & Elvehjem homogenizer so that 1 ml. of suspension corresponded to 800 mg. of liver. The complete microsome system used in these experiments contained 1 ml. of microsomal suspension, 1 ml. of supernatant, 1.2 mm-nicotinamide, 0.12 mm-triphosphopyridine nucleotide (TPN), 1.2 mm-glucose 6-phosphate (G 6-P) and 0.01% of G 6-P dehydrogenase in a total volume of 10 ml. of 0.1*M*-phosphate buffer, pH 7.4. The solutions were saturated with 1:2-dihydroxynaphthalene or 1:2-epoxy-1:2:3:4-tetrahydronaphthalene and glutathione (0.02 mm) or cysteine HCl (0.02 mm) for 1:2-dihydronaphthalene, and glutathione (0.01 mm) or cysteine HCl (0.01 mm) for 1:2-epoxy-1:2:3:4-tetrahydronaphthalene, added as indicated below. Other experiments were carried out in the absence of supernatant and in the absence of TPN and its reducing system. The mixtures were incubated for 15 min. at 37° with shaking, the pH of the solution was adjusted to 4.5 with acetic acid and the solutions were centrifuged at 600 *g*. The supernatants were treated with charcoal as described above, the methanolic extracts evaporated and approximately equal amounts of the residue were spotted on to paper chromatograms.

RESULTS

Preliminary experiments, in which either glutathione or cysteine in 0.1*M*-phosphate buffer, pH 7.4, was shaken with 1:2-dihydronaphthalene at 37° for 2 hr., showed that the glutathione derivative (I) and the cysteine derivative (II) respectively were formed in sufficient quantity to be detected on paper chromatograms. In all the tissue experiments involving 1:2-dihydronaphthalene described below, therefore, control experiments with 1:2-dihydronaphthalene and boiled tissue in 0.1*M*-phosphate buffer were performed at the same time and under the same conditions as in the experiments with fresh tissue. Chromatographic examination of the products of the incubation of 1:2-dihydronaphthalene with liver slices showed the presence of three metabolites which were indistinguishable from *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I), *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene and 2-naphthol, whereas the control experiments showed none of these compounds. On some occasions, *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione [previously reported as a product of the action of liver slices on naphthalene (Booth *et al.* 1960)] was

also detected. The addition of glutathione to liver slices did not result in an increased formation of the glutathione derivative (I) (presumably because the tissue had sufficient glutathione) and the addition of cysteine did not yield any of the cysteine derivative (II). When the glutathione derivative (I) was itself incubated with liver slices or with liver homogenate, neither the cysteine derivative (II) nor the *N*-acetylcysteine derivative (III) was formed.

The glutathione derivative (I) formed in the incubation of 1:2-dihydronaphthalene with liver slices was eluted from paper chromatograms with methanol. The material obtained by the evaporation of the solvent was hydrolysed by heating with conc. HCl to 100° for 4 hr. and the products of the hydrolysis were treated with 2:4-dinitrofluorobenzene (Sanger, 1945). When the derivatives were examined on paper chromatograms with the solvents of Phillips (1958), compounds indistinguishable from the 2:4-dinitrophenyl derivatives of cystine, glycine and glutamic acid were detected.

The synthetic glutathione derivative (I), on incubation with rat-kidney homogenate, was converted into a substance indistinguishable from the cysteine derivative (II), and, under the same conditions, the *N*-acetylcysteine derivative (III) was also hydrolysed, although less readily, to the same derivative (II). On the other hand, both the glutathione derivative (I) and the cysteine derivative (II) were converted by rat-kidney slices into the acetylated derivative (III), and this compound, together with *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene was also obtained when 1:2-dihydronaphthalene was incubated with kidney slices in the presence of glutathione. When boiled kidney slices were incubated with 1:2-dihydroxynaphthalene and glutathione, the dihydroxy compound, the *N*-acetyl derivative (III) and the glutathione derivative (I) were not detected.

In the experiments with rat-liver microsomes, control experiments were carried out in which 1:2-dihydronaphthalene and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene were incubated with either glutathione or cysteine in the presence of boiled microsomes in 0.1M-phosphate buffer, pH 7.4, and also in 0.1M-phosphate buffer alone. In the experiments with 1:2-dihydronaphthalene, only small amounts of the sulphur compounds and no dihydroxy compound were detected. When 1:2-dihydroxynaphthalene was incubated with the microsomal system with or without the addition of the supernatant fraction, in the absence of SH compounds, the product detected on paper chromatograms was indistinguishable from *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene. The addition of glutathione, cysteine or *N*-acetylcysteine to the system without added supernatant led to the

formation of compounds indistinguishable from the glutathione derivative (I), the cysteine derivative (II) and the *N*-acetylcysteine derivative (III) respectively, together with the dihydroxy compound. When the system was incubated with the addition of the supernatant fraction, there was a large increase in the amount of the glutathione derivative (I) formed, whereas the amounts of the cysteine (II) and *N*-acetylcysteine derivative (III) formed were not increased. There was no increase in the yield of the glutathione derivative, compared with that in the first experiment, when supernatant which had been boiled and cooled was added. When 1:2-dihydronaphthalene and microsomes were incubated in the absence of TPN and a reducing system (G 6-P with G 6-P dehydrogenase) no *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene was formed, and the additions of glutathione or cysteine to this system led only to the formation of the products (I) or (II) respectively in amounts comparable with those found in the controls.

The incubation of 1:2-epoxy-1:2:3:4-tetrahydronaphthalene with glutathione in the presence of (a) the complete microsome system, (b) the system without the supernatant fraction, (c) the supernatant fraction alone or (d) the boiled supernatant fraction, showed that with either the complete system or with the supernatant fraction alone there was a marked increase in the amounts of the glutathione derivative (I) formed as compared with the amount in the reaction of the epoxide with glutathione in 0.1M-phosphate buffer, pH 7.4. With the microsomal system without supernatant or with boiled supernatant there were no such increases. The reaction with cysteine or *N*-acetylcysteine in place of glutathione was unaffected by the presence or absence of any part of the system. In all these reactions, large amounts of *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene were formed whether the glutathione derivative was produced or not.

DISCUSSION

The metabolism of 1:2-dihydronaphthalene by rat-liver slices closely resembles that of naphthalene (Booth *et al.* 1960) in that both dihydroxy compounds and glutathione derivatives are formed. The identification of the glutathione derivative formed from 1:2-dihydronaphthalene as *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I) follows from a comparison of its properties on paper chromatograms with those of the synthetic material and from an examination of its acid-hydrolysis products. Additional evidence is provided by the fact that, in whole animals, the mercapturic acid (III) has been shown to be a metabolite of 1:2-dihydronaphthalene (Boyland & Sims, 1960). This mercapturic acid is related to the glu-

tathione derivative (I) in the same way that the mercapturic acid, *N*-acetyl-*S*-(1:2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine, formed by animals treated with naphthalene, is related to *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione formed from naphthalene by liver slices. The glutathione derivative (I) from 1:2-dihydronaphthalene resembles that formed from naphthalene in that it is not hydrolysed by rat-liver slices or homogenates, whereas it is rapidly converted into the cysteine derivative (II) by rat-kidney homogenates. In the metabolism of 1:2-dihydronaphthalene by rat-kidney slices in the presence of glutathione, the glutathione derivative was not detected, presumably because it was rapidly converted into the mercapturic acid (III).

The formation of 2-naphthol from 1:2-dihydronaphthalene by rat-liver slices is difficult to explain. Possibly there is a hydroxylation at carbon atom 2, followed by dehydrogenation of the product to 2-naphthol. This dehydrogenation is not unexpected since 1:2-dihydronaphthalene itself is apparently dehydrogenated to naphthalene, which is then converted by slices into *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione. Moreover, it has been shown by Ayengar, Hayaishi, Nakajima & Tomida (1959) that there is an enzyme present in rabbit liver capable of converting *trans*-1:2-dihydro-1:2-dihydroxynaphthalene into the catechol (1:2-dihydroxynaphthalene). The postulated initial product, 1:2-dihydro-2-hydroxynaphthalene, is easily converted into naphthalene by acid (Bamberger & Lodter, 1895) and could be the source of the naphthalene precursor detected in the urine of animals treated with 1:2-dihydronaphthalene (Pohl & Rawicz, 1919; Boyland & Solomon, 1955).

The results of the action of the microsomal system on 1:2-dihydronaphthalene suggest that an intermediate is formed, which, in the absence of glutathione, cysteine or *N*-acetylcysteine, reacts with water to form *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene, whereas in the presence of these SH compounds the derivatives (I), (II) or (III) are also formed. The formation of the intermediate, as detected by its reaction with water or SH compounds to form these products, is dependent on the presence of reduced triphosphopyridine nucleotide. The most likely structure for the intermediate is 1:2-epoxy-1:2:3:4-tetrahydronaphthalene, which has been shown to react with water, glutathione, cysteine and *N*-acetylcysteine at pH 7.4 to give products indistinguishable from those formed in the microsomal system from 1:2-dihydronaphthalene.

The results obtained when the supernatant fraction was added to the system suggest that the supernatant contains an enzyme capable of causing glutathione, but not cysteine or *N*-acetylcysteine,

to react with the epoxide. More evidence for this was provided by the experiments in which the epoxide was used: only systems containing supernatant caused an increase in the amount of the glutathione derivative (I) formed, and there was no increase in the amounts of the cysteine and *N*-acetylcysteine derivatives (I and II). Support for the epoxide hypothesis also comes from experiments *in vivo* (Boyland & Sims, 1960), where it was shown that 1:2-dihydronaphthalene and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene yield the same products when administered to rabbits. Moreover, both compounds yielded only one of the two possible stereoisomeric forms of the mercapturic acid (III), which provides additional evidence that the original reaction of glutathione with the epoxy derivative is enzymic. On the other hand, some evidence suggests that the opening of the oxiran ring with water to form *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene is non-enzymic since, in experiments *in vivo*, both optically active forms of the dihydroxy compound have been obtained (either as the free compounds or as conjugates with glucuronic acid) as metabolites of both 1:2-dihydronaphthalene and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene (Boyland & Sims, 1960). It is uncertain, however, whether or not the isomers are present in equal amounts.

In many respects the metabolism of 1:2-dihydronaphthalene and naphthalene are closely related, both *in vitro* and *in vivo*. Both form mixtures of the optically active forms of the *trans*-dihydroxy compounds and both form substituted cysteine derivatives of closely related structures. This suggests that naphthalene is also converted in the body into a hypothetical epoxide which then reacts either with water (to form *trans*-1:2-dihydro-1:2-dihydroxynaphthalene) or with glutathione [to form *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione]. It has been shown (Mitoma, Posner, Reitz & Udenfriend, 1956; Booth & Boyland, 1958) that a rat-liver microsomal system will convert naphthalene into *trans*-1:2-dihydro-1:2-dihydroxynaphthalene (and into 1-naphthol). The microsomal system with the supernatant fraction converts naphthalene in the presence of glutathione into *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)glutathione but not into *S*-(1:2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine in the presence of cysteine (J. Booth, unpublished observations). Thus the results suggest that the enzyme responsible for the reaction between glutathione and epoxide or other intermediate is specific for glutathione but not for the other substrate. One difference in the metabolism of naphthalene and 1:2-dihydronaphthalene is that, with naphthalene, the presence of the supernatant is essential for the formation of the glutathione derivative. If, indeed, naphthalene is

first converted into 1:2-dihydro-1:2-epoxynaphthalene, then this difference may be due to the relative reactivities of this epoxide and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene.

Instances of the formation of epoxides *in vivo* from compounds containing isolated double bonds have been reported previously. Davidow & Radomski (1953), for example, found that the insecticide, Heptachlor, was converted into the epoxide by dogs and rats and the epoxylation of certain steroid double bonds by micro-organisms is also known (Shull & Bloom, 1958). These epoxides are, however, unusually stable.

SUMMARY

1. The preparation of *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)glutathione (I) is described.

2. 1:2-Dihydronaphthalene was converted by rat-liver slices into the glutathione derivative (I), which, with rat-kidney homogenate, yielded *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (II) and with rat-kidney slices yielded *N*-acetyl-*S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl)-L-cysteine (III).

3. *trans*-1:2-Dihydroxy-1:2:3:4-tetrahydronaphthalene and 2-naphthol were also formed by the action of rat-liver slices on 1:2-dihydronaphthalene.

4. A rat-liver microsomal system converted 1:2-dihydronaphthalene into *trans*-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene, and, in the presence of glutathione, cysteine or *N*-acetylcysteine, to the respective *S*-(2-hydroxy-1:2:3:4-tetrahydro-1-naphthyl) derivatives (I), (II) or (III). The formation of the glutathione derivative (I), but not of the derivatives (II) and (III), was increased by the addition of supernatant from the preparation of the microsomes.

5. The addition of glutathione to 1:2-epoxy-

1:2:3:4-tetrahydronaphthalene was increased in the presence of the supernatant fraction of rat liver, whereas the addition of cysteine and *N*-acetylcysteine to the epoxide was not affected.

6. The supernatant fraction of a rat-liver homogenate in 0.1M-phosphate buffer, pH 7.4, appears to contain an enzyme which activates glutathione.

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Biochemical Studies with Methanesulphonyl Esters, Especially β -Chloroethyl Methanesulphonate

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Methanesulphonyl esters are alkylating agents (Ross, 1953), and are used as anti-neoplastic agents. Haddow & Timmis (1951, 1953) reported that

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several $\alpha\omega$ -dimethanesulphonoxy glycols inhibited the growth of the Walker 256 rat carcinoma, 1:4-dimethanesulphonoxy-*n*-butane (Myleran, busulphan) and 1:5-dimethanesulphonoxy-*n*-pentane being most active. Elson (1955, 1957, 1958*a, b*)