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The Metabolism of Glutethimide (Doriden®)[1]

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Studying the fate of drugs in the organism is one important method by which to gain an insight into their mechanism of action. The chief questions which such metabolic studies are designed to answer are the following: At what rate and to what extent is the drug absorbed? How is it distributed through the various tissues and organs and how long does it remain in them? Is the drug transformed in the organism and, if so, what are the pharmacological properties of such biotransformation products? Are they more toxic or less toxic than the original compound? After how long and in what form is the drug excreted from the organism?

These questions are not easy to answer, because to do so one has to follow up through various stages the fate in the organism of an active substance which is generally present in only small amounts and which as a rule is not particularly stable chemically. For investigations of this kind, special isolation techniques and analytical methods have to be devised which consistently take account of the biological changes undergone by the active substance and by which such changes can if possible be determined quantitatively.

The rapid development of drug therapy has led to a corresponding increase in the importance of metabolic studies. The general trend towards greater safety and reliability in human medicinal therapy has created the need for more information on the mode of action and fate of drugs in the organism. There is now reason to hope that by means of detailed metabolic studies it will often be possible to discover in good time those harmful side-effects of a preparation which do not appear until the patient has been under treatment for some considerable period and which in many instances are due to a cumulative action or to the building up of toxic metabolites.

Doriden (α-phenyl-α-ethyl glutarimide) has been widely employed for years as a mild hypnotic. Detailed metabolic studies on this drug have already been published in a number of papers[3–10]. In the present report we propose to review and summarise the results—including some hitherto unpublished ones—which such metabolic studies have yielded.

To investigate the metabolism of Doriden in the organism, two main approaches were adopted:

Firstly, a series of feeding experiments with relatively high doses (averaging 200 mg/kg) was carried out on dogs in order to isolate the excretion products in pure form in quantities large enough to be able to elucidate their structure. Secondly, Doriden was labelled in various positions with radioactive ^{14}C and fed to dogs and rats in therapeutic doses, so as to determine quantitatively, by means of the tracer technique, how this substance, when introduced into the animal body, is transformed, distributed, and excreted. Particular attention was paid to the chronological sequence of the elimination process, since it is a well-known fact that the extent to which a given hypnotic is suitable either for inducing sleep, for maintaining sleep, or for producing prolonged sleep depends primarily upon the time taken by these processes of elimination.

The results of the feeding experiments and of the isolation and structural elucidation of the metabolites will be described first.

To begin with, the urine of dogs which had received a total of 10 g Doriden over the space of ten days was examined. It proved impossible to recover any unaltered Doriden in the urine. Preliminary experiments using the isotope technique and paper chromatography showed that, after oral administration, Doriden is excreted in the urine almost entirely in the form of metabolites; 92–94% of the dose administered is re-

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[3] J. KEBRLE and K. HOFFMANN, Exper. *12*, 21 (1956).

[4] J. KEBRLE and K. HOFFMANN, Helv. chim. Acta *39*, 767 (1956).

[5] K. BERNHARD, M. JUST, J. P. VUILLEUMIER, and G. BRUBACHER, Helv. chim. Acta *39*, 596 (1956).

[6] K. HOFFMANN, J. KEBRLE, and H. J. SCHMID, Helv. chim. Acta *40*, 387 (1957).

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[8] J. KEBRLE, K. SCHMID, K. HOFFMANN, J. P. VUILLEUMIER, and K. BERNHARD, Helv. chim. Acta *42*, 417 (1959).

[9] J. KEBRLE, K. SCHMID, K. HOFFMANN, J. P. VUILLEUMIER, and K. BERNHARD, Chimia *13*, 172 (1959).

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covered in the form of metabolites conjugated with glucuronic acid, and 6–8% in non-conjugated form. In the light of these findings, it was in fact subsequently possible to isolate in pure form two compounds each from the fraction of the glucuronic acid conjugation products and from that of the non-conjugated metabolites. By analysing the structure of these compounds, it was shown that each of the non-conjugated metabolites is genetically related to one of the glucuronides. From this, the first conclusion to be drawn was that Doriden is metabolised via two different biochemical mechanisms.

As α-phenyl-α-ethyl glutarimide has an asymmetrical carbon atom, it was thought that the metabolism of the two optical antipodes might be different. To check this hypothesis, samples of the two optical antipodes were prepared and fed to animals in separate series of tests. Analysis of the excretion products revealed that each of the two antipodes is transformed in a different manner, as outlined in Figure 1.

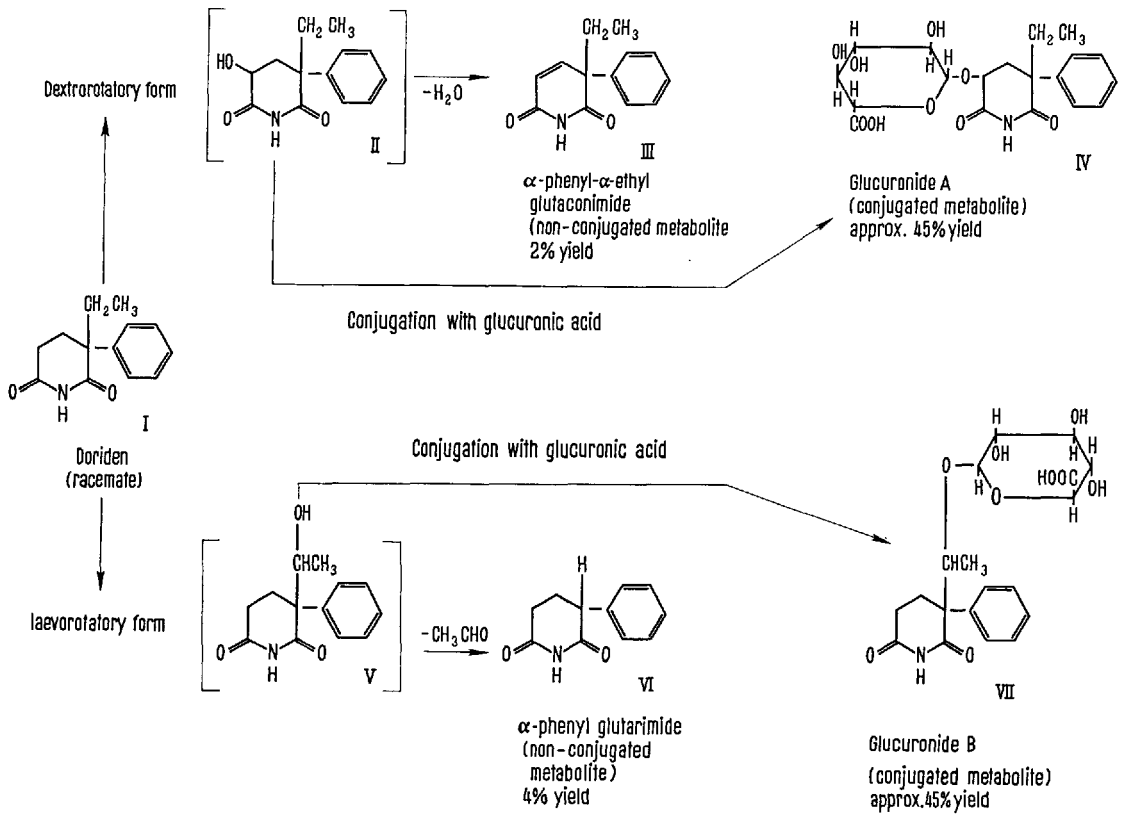
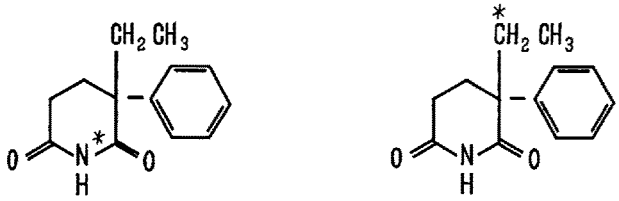


Fig. 1

As can be seen from this Figure, dextrorotatory α-phenyl-α-ethyl glutarimide (50% of Doriden administered is first hydroxylated in the glutarimide ring. A small percentage of the hydroxylated compound II loses water and breaks down into the glutaconimide III, which is excreted in the urine as a non-conjugated metabolite in a yield equivalent to 2% of the dose of Doriden administered. On the other hand, the major portion of compound II combines with glucuronic acid and is excreted in the urine as glucuronide A in a yield equivalent to approx. 45% of the dose of Doriden administered. The laevorotatory form of α-phenyl-α-ethyl glutarimide is hydroxylated at the side chain. Here, too, a small portion of the hydroxylated compound V decomposes into α-phenyl glutarimide VI—although this time the process involves the splitting-off of acetaldehyde instead of water; the resultant metabolite was isolated in the urine in a 4% yield. The rest of the hydroxy compound V also combines with glucuronic acid and appears in the urine as glucuronide B in a yield of some 45%.

Glucuronides A and B, which were recovered in amounts equivalent to over 90% of the dose of Doriden administered, are soluble in water and insoluble in fat; they no longer display any sedative activity and are virtually non-toxic. The non-conjugated metabolite α-phenyl glutarimide VI is also more readily soluble in water than Doriden and possesses no sedative properties; α-phenyl-α-ethyl glutaconimide III has pharmacological properties similar to those of Doriden, but is less active. Since this metabolite occurs in amounts equivalent to only 2% of the dose of Doriden administered, it can have no practical significance as regards the mechanism of action of Doriden.

Now let us return to the results of the tracer studies on the behaviour of Doriden in the animal organism, its distribution in the various organs, and its rate of elimination. Available for these experiments were firstly a compound (VIII) labelled at C atom 2 in the glutarimide ring and, secondly, a preparation (IX) labelled at the C_1 atom of the ethyl chain:



VIII IX

The preparation of the latter compound was considered desirable in view of the fact, already mentioned, that the ethyl chain becomes split off in the form of acetaldehyde (V → VI in Figure 1).

When male rats of medium weight were given an oral dose of Doriden sufficient to induce sleep, the pattern of radioactivity observed after $15^1/_2$ h was as shown in Table I[5].

From Table I it will be seen that, by the end of the period, 65–73% of the uptake of radioactivity had been eliminated. In these experiments the kidneys, brain, spinal cord, and blood showed only a minute content of radioactive substance (0.1–0.3%); the liver still contained a certain amount of radioactive material, indicating that it is in this organ that Doriden is metabolised. To demonstrate the presence of unchanged Doriden in the urine, an isotope-dilution test was performed; from the result it was evident that the amount of unchanged Doriden in the urine must be less than 0.1%. The similar values obtained with the variously labelled compounds I and II showed that elimination of the ethyl chain in the organism plays no significant role.

The relatively high activity retained in the gastro-intestinal tract and in the contents of the latter is due not to the presence of unabsorbed Doriden, but—as we shall see later—to products of conjugation with glucuronic acid, which are secreted with the bile into the intestine, where they are only slowly reabsorbed. That these detoxication products also distort the other values for the percentages of active substances eliminated, and that they interfere particularly with the determination of the biological half-life of the active substance as recorded by the tracer method, can easily be demonstrated. The biological half-life represents the time taken for half of the administered dose of active substance to disappear from the body, irrespective of whether it disappears by direct elimination or by the process of inactivation. Where, however, the metabolites also bear radioactive carbon—which certainly applies to ^{14}C-Doriden (VIII)—and where these are excreted in the urine much more slowly than the rate at which the biological transformation process takes place (owing, for example, to the slow reabsorption of Doriden metabolites from the intestine), the result is that measurements of elimination in the urine yield fictitious half-life values which are far higher than the genuine values.

Table I. Oral administration of ^{14}C-Doriden to rats. Excretion and retention of radioactivity (expressed in % of the dose of radioactivity administered) $15^1/_2$ h after administration

	$^{14}C_{(2)}$ % mean from 2 experiments on rats	$^{14}C_{(1)}$ % mean from 4 experiments on rats
Excretion		
Expired air	1.3	2.7
Urine	37.0	32.1
Faeces	1.6	0.4
Contents of gastro-intestinal tract	35.5	29.7
Total	73.4	64.9
Retention		
Liver	1.5	0.9
Kidneys	0.3	0.2
Brain and spinal cord	0.1	0.1
Gastro-intestinal tract	7.9	16.9
Other parts of the body	7.4	7.0
Total	17.2	24.2
Total traced	90.6	89.1

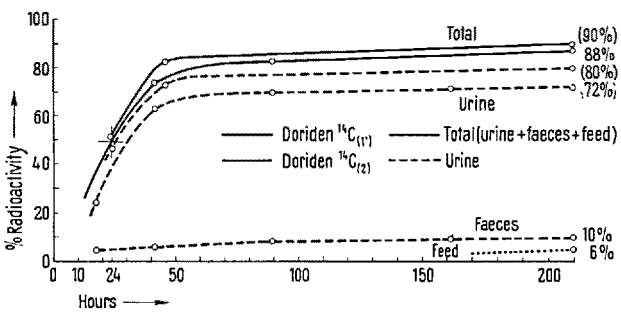


Fig. 2. Rate of elimination of radioactivity in urine and faeces of rats (30–40 mg/kg p. o.) (mean of 2 or 6 tests).

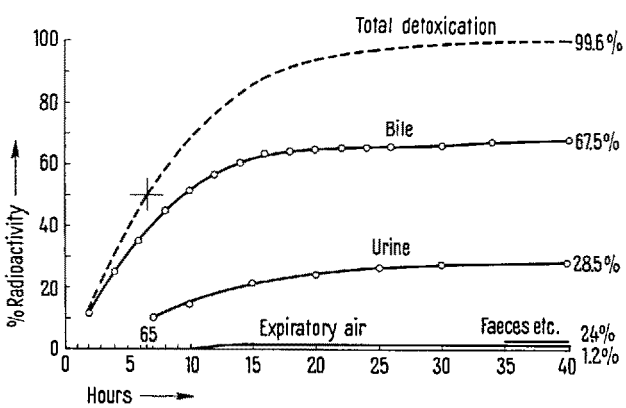


Fig. 3. Determination of biological half-life of Doriden ^{14}C in rats with biliary fistula (30–40 mg/kg p.o.).

Figure 2 shows an example of such a fictitious half-life value[5], which in this instance works out at 24 h (as indicated by the cross). In this experiment, 80–85% of the activity uptake is recovered in the urine after 50 h; after 210 h, the figures have risen to 88–90%. That the missing 10% is not attributable to the retention of Doriden or its metabolites, but is within the margin of error of the method employed, is borne out by the fact that the animals contained no radioactivity when subjected to analysis.

Quite a different impression of the pattern and rate of elimination of Doriden is gained from experiments on rats with a biliary fistula[7]. Two such rats, in which the bile lost was replaced with bile from a donor animal, were given a single dose of radioactive Doriden. The bile flowing from the experimental animals was collected at regular intervals and analysed. Analysis showed that roughly 95% of the radioactivity in the bile is accounted for by glucuronic acid conjugation products and that the latter are excreted with remarkable regularity. At the same time, the urinary excretion was also studied in this experiment, and it was found that in the urine, too, the major portion of the activity was attributable to the conjugation products. As will be seen from Figure 3, 67.5% of the activity uptake is excreted with the bile and 28.5% via the kidneys. In such an experiment, the *half-life works out at 6.5 h*, and the amount of active substance eliminated after 40 h at *99.6%* (the uppermost curve represents the sum of the various values). Although this half-life is much closer to the real figure than the one obtained in the previous experiment, it must likewise be regarded as still too high, since renal excretion can hardly take place at the same speed as metabolism in the liver.

After these experiments on rats with a biliary fistula had proved that the metabolites of Doriden are subject to enterohepatic circulation on quite a considerable scale, the question now arose as to how well the Doriden glucuronides secreted into the intestine are reabsorbed. Labelled glucuronides, which had been isolated for this purpose after feeding animals with radioactive Doriden, were accordingly administrated to rats. Analysis showed that the glucuronides are far less well absorbed than Doriden itself. Once in the blood-stream, they pass easily through the kidneys without spreading into the central nervous system or other lipoid tissues[11].

Table II

Organs	Relative specific activity in terms of dry substance	
	200 mg/kg orally after 16 h	70 mg/kg intraperitoneally after 20 min
Liver	146	736
Kidneys	169	–
Brain and spinal cord	34	985
Stomach and intestine	640	1.241
Fat depots	66	947
Blood (in terms of fresh blood)	15	73

In order to obtain some idea of the distribution of Doriden in the animal organism after a short lapse of time, rats were given a dose of 70 mg/kg, injected intraperitoneally, and sacrificed 20 min later[5]. The right column of Table II lists the relative specific activities measured in the individual organs in terms of dry substance. By way of comparison, the left column shows the corresponding figures measured 16 h after an oral dose of 20 mg/kg.

It may perhaps be interesting at this point to draw attention to the ratio between the specific activity in the blood in relation to that in the lipoid organs (brain, spinal cord, and fat depots). Whereas in experiments of brief duration this ratio works out at 1:13, in the longer experiments it amounts to 1:2 and 1:4, respectively. This suggests that, to begin with, Doriden is accumulated in large quantities in the lipoid organs. (The glucuronides, since they are insoluble in fat, can be ignored here.) This same phenomenon can be observed in the case of most drugs that are liposoluble, including particularly the short-acting barbiturates.

BRODIE et al.[12] have demonstrated that, when administered intravenously, thiopentone (Pentothal) is rapidly distributed in the various tissues and organs via the blood. Shortly after completion of the infusion, the concentration of thiopentone in the blood and organs already begins to diminish as the concentration in the fat depots rises. This process, which is attributable to the fact that thiopentone displays a strong affinity for fats, continues until diffusion equilibrium is established between the various organic phases. As an anaesthetic, thiopentone has an ultrashort action when given in small doses; this is not because the drug is rapidly metabolised, but because the active substance, as already mentioned, quickly penetrates into the fat depots. By the time that diffusion equilibrium has been attained between the tissue and the fat, the drug's plasma concentration is already too low for an anaesthetic effect to be maintained, i.e. the animals soon awake again after an injection of thiopentone. Figure 4[12] shows the distribution of thiopentone in various tissues following an intravenous dose.

Doriden behaves in much the same manner when administered intravenously[13]. Each animal in a group of male rats averaging approx. 250 g in weight was given a 0.25 ml injection of a 5% solution of ^{14}C-Doriden in 70% polyethylene glycol 400, a dose corresponding to 50 mg/kg. The infusion lasted 30 sec in each instance, by the end of which time all the animals were already anaesthetised. The animals awoke again

[11] K. BERNHARD and M. KNECHT, in preparation.
[12] B. B. BRODIE, E. BERNSTEIN, and L. C. MARK, J. Pharmacol. exp. Therap. *105*, 421 (1952).
[13] A. J. PLUMMER, J. SHEPPARD, and B. S. D'ASARO, Fed. Proc. *15*, 415 (1956); personal communication.

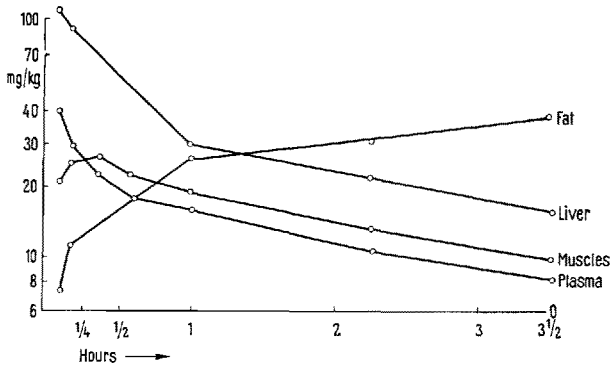


Fig. 4. Concentration of thiopentone in dog tissues after intravenous administration of 25 mg/kg (from BRODIE, BERNSTEIN, and MARK[12]).

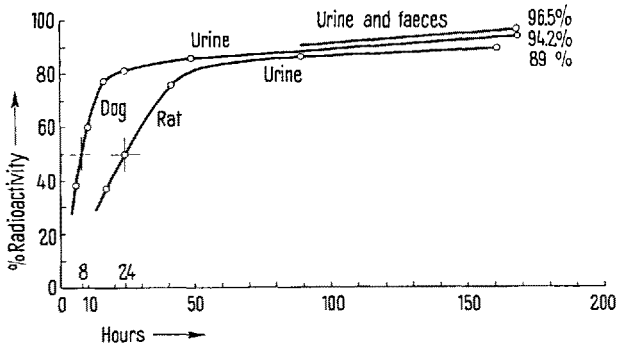


Fig. 5. Rate of elimination of radioactivity in the urine with Doriden ^{14}C. Dog (30 mg/kg p.o.) (mean of 2 tests); rat (30 mg/kg p.o.) (mean of 8 tests)

after about 5 min, although they remained drowsy for some time afterwards. Table III lists the results which tracer analysis of organs, tissues, and body fluids yielded at various intervals of time after the injection. After 24 h, 50% of the activity uptake had already appeared in the urine and 6.12% in the faeces.

As will be seen from Table III, the concentration of Doriden or its metabolites rapidly decreases in the brain, kidneys, lungs, heart, adrenals, plasma, and blood cells 1 min after the injection. In the liver, spleen, muscles, and skin, the concentration rises slightly in the first 5 min and then likewise diminishes. On the other hand, in the fat depots the concentration of Doriden rises appreciably throughout the first 2 h following the injection. In the intestine and its contents, a modest rise in radioactivity is also observed for the first 2 h; this is probably connected with the enterohepatic circulation of the metabolites. After 24 h it is almost impossible to detect any radioactivity in the organs and tissues. The radioactivity still present in the intestine and its contents, as well as in the faeces, can be ascribed to the fact that, as already mentioned earlier, the glucuronic acid conjugation products of Doriden secreted into the intestine with the bile are poorly absorbed.

Table III

Tissue	% of injected ^{14}C determined per g of tissue after			
	1 min	5 min	2 h	24 h
Brain	1.09	0.49	0.17	n.d.[a]
Liver	0.69	0.75	0.34	n.d.
Kidneys	1.60	0.64	0.50	n.d.
Lungs	1.00	0.54	0.16	n.d.
Spleen	0.13	0.34	0.12	n.d.
Heart	1.64	0.51	0.18	n.d.
Adrenals	1.73	0.62	0.56	n.d.
Intestine and contents	0.24	0.27	0.44	0.28
Fat depots	0.17	0.28	0.74	n.d.
Muscles (leg)	0.26	0.33	0.13	0.004
Skin	0.10	0.27	0.26	0.008
Plasma	0.50	0.23	0.15	0.006
Blood cells	0.20	0.04	0.015	n.d.

[a] n.d. = not determinable

We were also interested in determining the distribution of Doriden in various segments of the central nervous system[11]. For this purpose we administered to rats an oral dose of 6 mg labelled Doriden, dissolved in 0.2 ml olive oil, and sacrificed the animals 15, 30, 50, 70, 90, 120, 180, or 240 min afterwards. The central nervous system was then dissected free, from the olfactory bulb to the cauda equina, and divided into different portions, i.e. the cerebrum, diencephalon (thalamus and basal ganglia), and proximal part of the metencephalon, as well as the cerebellum, metencephalon (pons and medulla oblongata) including the caudal portion of the metencephalon, and the spinal cord. Blood samples were also taken and the specific activities measured. It was invariably found that the cerebrum displayed the greater specific activity. The other parts of the brain, as well as the spinal cord, displayed significantly less activity. The specific activities measured after 50 min, for example, were as follows: cerebrum 336, diencephalon 300, cerebellum 281, metencephalon 285, spinal cord 249, and blood 230. In all, 1.05% of the total dose of radioactivity administered was traced in the central nervous system, and 45.2% in the gastro-intestinal tract.

Experience with certain short-acting barbiturates has shown that rats often take longer to metabolise these substances than higher species of animals such as dogs. Figure 5 indicates that the same evidently applies to Doriden as well. The fictitious half-life recorded in the dog amounts to only 8 h, as compared

[14] The break-down and elimination of Doriden and its metabolites are at present being investigated in man with the aid of ^{14}C-labelled substance. Results obtained to date show that the metabolites in man are identical with those found in the dog. The rate of elimination is also similar to that observed in animal experiments. This finding clearly disproves the evidence reported by H. REMMER, G. NEUHAUS, and K. IBE (Arch. exp. Path. Pharmakol. *242*, 90 (1961)). These authors have calculated the elimination rate of Doriden in man by a mathematical method based on the relationship between the size of the dose ingested and the duration of effect in cases of suicide. According to this method, the half-life of Doriden works out at approximately 50 h. A critical commentary on this method, which involves questionable extrapolations and mathematical equations, will be published elsewhere.

with 24 h in the rat (as shown by the cross), and the half-life would no doubt prove even shorter if measured in a dog with a biliary fistula[14].

Figure 6 shows the increase and subsidence of the sedative-hypnotic effect produced in the dog by equipotent doses of Doriden and phenobarbitone[15].

From Figure 6 it may be seen that in fact the effect of Doriden in the dog has already worn off after 3 h, although in this experiment the dose administered was somewhat higher in mg/kg than that which the dogs received in the elimination study described above. The effect of phenobarbitone wears off much more slowly.

This experiment brings us to the end of the studies on the metabolism, distribution in the tissues, and elimination of Doriden that have been carried out to date.

There are two questions which arise from these investigations: how do the results we have described appear in the light of existing theories and known facts concerning the mechanism of action and metabolism of hypnotic agents; and what differences emerge when these results are compared with those of similar studies on other hypnotics?

The concentration of hypnotic in the central nervous system is dependent on the blood concentration. It is the concentration that a given dose of hypnotic attains in the blood and the time it takes to become eliminated from the blood which will always determine whether the drug in question has the effect of merely inducing sleep, of maintaining sleep, or of producing general anaesthesia. The concentration of active substance in the blood depends on the rate at which the drug is absorbed from the gastro-intestinal tract and on the rate at which it is either excreted in the urine or inactivated. Liposoluble substances—and all hypnotics, including Doriden, are readily soluble in fat—are excreted only slowly via the kidneys. Thus, if an hypnotic is to be rapidly eliminated from the blood, it must be converted in the organism into a form which is soluble in water and insoluble in fat. Veronal (diethylbarbituric acid), for example, is not metabolised in the body and is therefore excreted by the kidneys at an extremely slow rate[16]; it can still be traced in the urine 8–12 days after administration of an hypnotic dose. The other long-acting barbiturates are also excreted to a large extent unchanged and are hence only slowly eliminated. On the other hand, the short-acting barbiturates are for the most part detoxicated and rapidly excreted, hardly any of the drug being traceable in the urine in its original form[17]. As already explained earlier, this also applies in particularly marked degree to Doriden. In Figure 7 the rate of elimination of Doriden is compared with that of medium and long-acting barbiturates. It will be seen that Doriden is more rapidly eliminated than the medium-acting barbiturates. Characteristic features of Doriden are its complete inactivation and the rapid and complete elimination of its metabolites. It is this which accounts for the lack of any cumulative effects; and it is also these factors which explain why Doriden displays no after-effects and virtually no side-effects and why the drug is thus well tolerated by the organs and has a low toxicity.

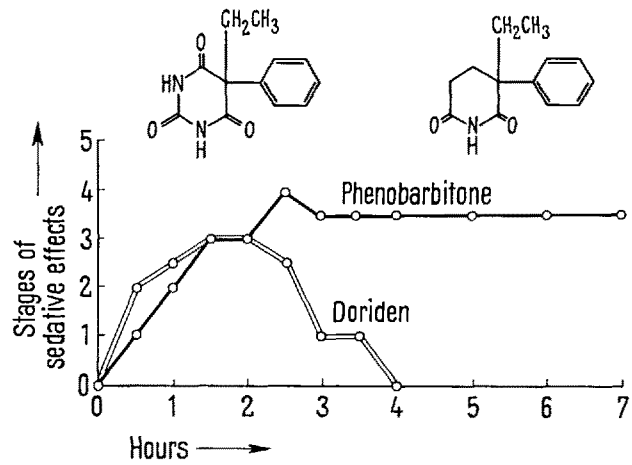


Fig. 6. Sedative-hypnotic effect of Doriden (50 mg/kg p.o.) and of phenobarbitone (40 mg/kg p.o.) in the dog (from GROSS, TRIPOD, and MEIER[15]).

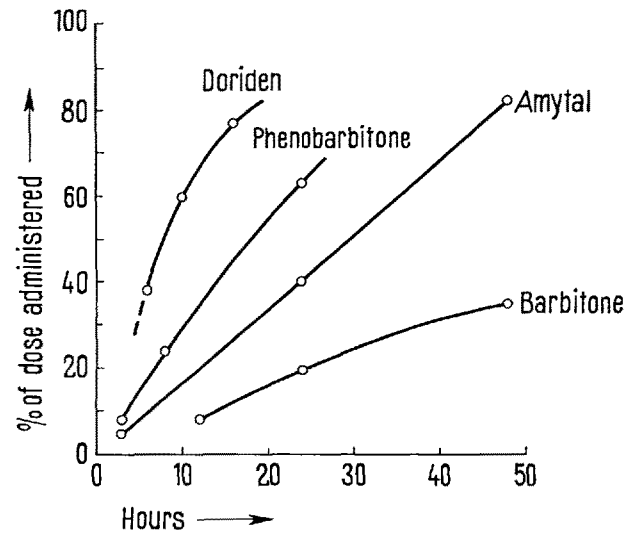


Fig. 7. Rate of elimination of various hypnotics or their metabolites in dog urine following therapeutic doses. Doriden (short-acting hypnotic); Phenobarbitone (medium-acting hypnotic); Amytal (medium-acting hypnotic); Barbitone (long-acting hypnotic).

[15] F. GROSS, J. TRIPOD, and R. MEIER, Schweiz. med. Wschr. *85*, 305 (1955).

[16] E. W. MEYNART and H. B. VANDYKE, J. Pharmacol. exp. Therap. *98*, 184 (1950).

[17] E. W. MEYNART and H. B. VANDYKE, Pharmacol. Rev. *1*, 217 (1949).

Zusammenfassung. In diesem Übersichtsreferat werden die Stoffwechselstudien mit dem Schlafmittel Doriden® (α-Phenyl-α-äthyl-glutarimid) geschildert, wobei alle bisher erzielten, teilweise noch nicht veröffentlichten Resultate zusammengefasst sind. Die Untersuchungen wurden an Ratten und Hunden mit Hilfe von ^{14}C-markierter Substanz durchgeführt, speziell im Hinblick auf die Abklärung der Resorption, Verteilung, Ausscheidung und Struktur der Metaboliten des Wirkstoffes. Es wurde gefunden, dass Doriden nach der Resorption in kurzer Zeit praktisch quantitativ in Form von Metaboliten im Harn ausgeschieden wird. Diese bestehen zu mehr als 90% aus Glucuroniden, welche untoxisch sind und keine sedative Wirkung mehr besitzen. Aus der Strukturaufklärung der isolierten Stoffwechselprodukte ging hervor, dass Doriden nach zwei verschiedenen biochemischen Mechanismen metabolisiert wird, und es konnte gezeigt werden, dass dies auf den verschiedenen Stoffwechsel der beiden Antipoden von α-Phenyl-α-äthyl-glutarimid zurückzuführen ist. Versuche mit Gallenfistelratten liessen erkennen, dass 70% der Glucuronide über die Galle und 30% direkt renal ausgeschieden werden. Bei einer solchen Versuchsanordnung konnte eine biologische Halbwertszeit von Doriden von 6,5 h bestimmt werden. Verteilungsstudien mit ^{14}C-markiertem Doriden und mit markierten Glucuroniden nach oraler und parenteraler Gabe liessen erkennen, dass sich Doriden ähnlich wie die ultrakurzwirksamen Barbiturate verhält, indem es eine ausgesprochene Affinität zu lipoidem Gewebe aufweist. Die Glucuronide dagegen sind aus dem Magen-Darm-Trakt bedeutend schlechter resorbierbar, zeigen keine Affinität zu lipoiden Organen und werden – einmal im Blut angelangt – durch die Niere rasch und vollständig eliminiert.

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

On the Structure of Ryanodol

Ryanodine, $C_{25}H_{35}O_9N$, a constituent of *Ryania speciosa* Vahl., represents a challenging structural problem due to its heavy oxygen substitution and the consequent complexity of its reactions. As reported earlier[1], it is an ester of pyrrol-α-carboxylic acid with ryanodol, $C_{20}H_{32}O_8$.

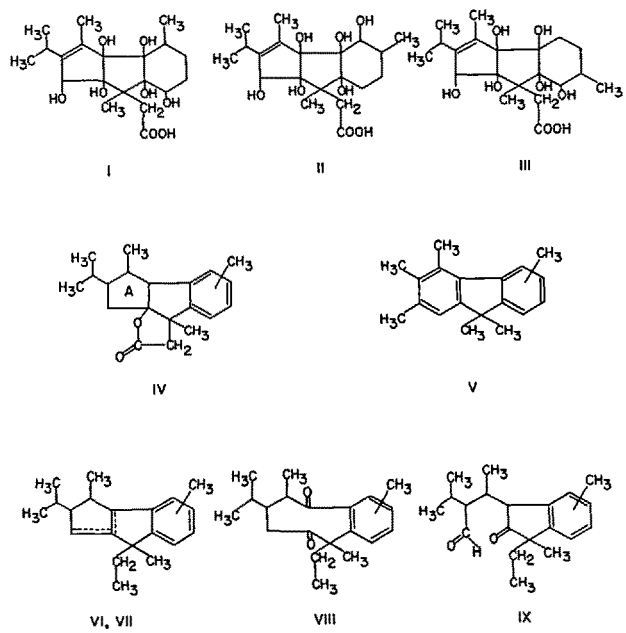
A mild acidic treatment of ryanodol converts it to anhydroryanodol, $C_{20}H_{30}O_7$, which consumes 1 Mol of periodic acid to give oxoanhydroryanodol, $C_{20}H_{28}O_7$[2,3]. In a recent communication[3], we have reported the alkaline cleavage of oxoanhydroryanodol into several fragments of known structure which accounted for all the carbon atoms of this compound.

We have now in principle solved the structure of anhydroryanodol and the mechanism by which it yields the above mentioned fragments. *Anhydroryanodol must be represented as a lactone of one of the three hydroxyacids I–III.*

The most important clue for the skeletal type of anhydroryanodol was provided by the treatment of ryanodol with hydriodic acid and red phosphorus. This reaction gave a mixture of products from which the γ-lactone IV, $C_{20}H_{26}O_2$, m.p. 135–138°, was isolated in a good yield[4].

The clue to the structure of IV came in turn from the selenium dehydrogenation of an amorphous fraction obtained in the same reaction. This dehydrogenation gave an aromatic compound, $C_{19}H_{22}$, m.p. 122–124°, which is clearly a fluorene (UV) and which can be formulated as V on the basis of its NMR spectrum, and of its origin (NMR maxima: singlet (6H) at 8.63 ppm, 2 benzylic methyls; 4 singlets (3H each) at 7.40, 7.60, 7.68, and 7.77 ppm, aromatic methyls; multiplet (4H) at 2.4–3.0 ppm, aromatic hydrogens).

The structural studies performed on IV are too lengthy to describe in a short communication. Suffice it to say



[1] R. B. Kelly, D. J. Whittingham, and K. Wiesner, Can. J. Chem. *29*, 905 (1951).

[2] R. B. Kelly, D. J. Whittingham, and K. Wiesner, Chem. and Ind. *1952*, 857.

[3] D. R. Babin, J. A. Findlay, T. P. Forrest, F. Fried, M. Götz, Z. Valenta, and K. Wiesner, Tetrahedron Letters No. *15*, 31 (1960).

[4] All new compounds reported in this communication gave satisfactory analyses.