Biochemical Pharmacology, Vol. 18, pp. 633–643. Pergamon Press. 1969. Printed in Great Britain

DISTRIBUTION, EXCRETION METABOLISM AND LOCALIZATION OF A NEW ANTI-INFLAMMATORY DRUG: NIFLUMIC ACID, LABELLED WITH ^{14}C*

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(*Received* 1 *October* 1968; *accepted* 11 *October* 1968)

Abstract—The metabolism of the ^{14}C-niflumic acid† specific activity 16 mc/mM has been studied in the rat, after intraperitoneal administration. With doses of 50 mg/kg, the blood level is of 75 μg/ml at the 1st hr, and of 6 μg/ml at the 24th hr. The product is nearly all bound to the plasma proteins. The liver retains, after 1 hr, 4 per cent of the injected activity and the stomach 0·5 per cent only traces (0·08 per cent) have been detected in the brain. The technique of autoradiography in the mouse, after administration of the product per os and i.p. confirms these results. About 5 per cent of $^{14}CO_2$ is found with respect to the injected activity, after 12 hr. The radioactivity eliminated in the urine is about 2 per cent of the injected activity after 1 hr, reaches 30 per cent at the 12th hr, is practically completed after 24 hr. The radioactivity found in the faeces is generally of the order of 0·01 per cent.

Five catabolites were found by paper chromatography in the urine. Niflumic acid is not eliminated unchanged, and the greatest quantity appears to be conjugated glucuronide. One of the catabolites, after paper chromatographic study in various systems, corresponds to 2-aminonicotinic acid. Possible metabolic pathways of the Niflumic acid discussed.

Niflumic acid: (trifluoro-methyl-3-phenylamino)-2 nicotinic acid was described by Hoffmann and Faure[1] in 1966. It is a pyridic isotere of the flufenamic acid and its anti-inflammatory and analgesic activity has been clearly shown in the rat by Boissier, Fichelle-Pagny and Horakova.[2] This product is now currently used in human therapy.

Synthesis of the labelled molecule

The marking of the Niflumic acid by ^{14}C has been done to carry out the metabolic research. This synthesis is described by Colombini, Deganello, Benakis and Strolin.[3] The following reactions are used in the preparation of this compound from labelled CO_2, according to the five steps of Fig. 1.

A product is obtained having a specific activity of 16 mc/mM. This product is purified by preparative paper chromatography with a *n*-butanol–pyridine–H_2O sat. NaCl system. The structure of the product has been verified by elementary analysis, paper chromatography and i.r. spectrometry. The radiochemical purity is evaluated at 99·9 per cent by paper chromatography.[4]

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* Communication presented at the IUPAC 2nd International Symposium "Pharmaceutical Chemistry", Münster (Germany), 22–26 July, 1968.

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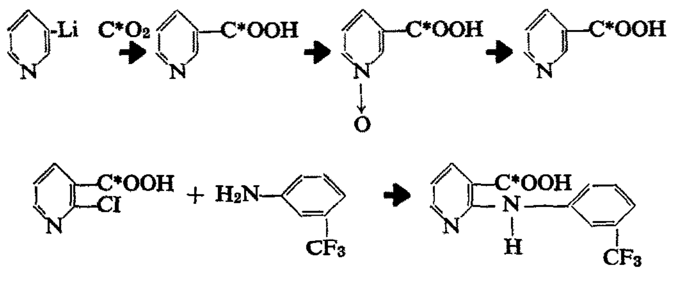

FIG. 1. Synthesis of labelled Niflumic acid.

Experimental techniques

Male Wistar rats of 110 g average weight, received a dose of about 50 mg/kg of ^{14}C-Niflumic acid of roughly 1 mc/mM sp. act., by i.p. injection.

After receiving the dose, the animals are placed in a metabolic cage and the expiratory CO_2 is collected, as well as the faeces and the urines. These last are collected cold and immediately frozen.

To determine the blood rate as a function of time, the blood is taken by puncture of the cavernous sinuses. In order to establish a balance-sheet of drug distribution and excretion, groups of 3 animals are sacrificed under light ether anesthesia by cardiac puncture of the blood at 1-, 3-, 6-, 9-, 12 and 24-hr intervals after administration of the drug. The main organs are removed and the interstitial liquid is collected. The residual of the animal is equally kept, under the denomination "carcass".

The radioactivity is measured by liquid scintillation (spectrometers: Packard Tri-Carb 3002, Beckman LS-200B). According to the nature of the sample, the following techniques for measuring the radioactivity have been adopted:

For *the expiratory* $^{14}CO_2$ the technique of methanolic ethanolamine absorption (20/80 v/v), with an air flow of 500 ml/min during 1 hr through 10 ml of this solution. Sample of 1 ml, measured with 10 ml of toluene, PPO, POPOP. Corrections by the internal standard technique.

The *blood* radioactivity is measured on samples of 10 μl solubilized by 0·1 ml of Hyamine (molar solution in methanol). Scintillation system: toluene, PPO, POPOP.

The *urine* radioactivity is measured by liquid scintillation. Samples of 10 μl; scintillating system: dioxane, ethanol, xylol, naphthalene, PPO, POPOP (ESLA). Corrections by the internal standard technique.

The radioactivity of the *organs* and of the *faeces*, after desiccation and powdering, is measured on 10 mg samples in suspension with Cab-O-Sil; scintillation system: toluene, PPO, POPOP.

For the "*carcass*": combustion of samples of 100 mg by the "oxygen-Flask" technique, absorption of the CO_2 formed by 15 ml ethanolamine/methanol (20/80, v/v), samples of 1 ml measured in 10 ml of toluene, PPO, POPOP. Corrections by the internal standard technique.

For the catabolites separation, the technique of descending chromatography on Whatman No. 1 paper. The chromatographic systems used in this work are:

(a) *n*-butanol–methanol–water (90/10/100, v/v/v): C_1

(b) *n*-butanol–pyridine–H_2O sat.NaCl (40/80/60, v/v/v): X_{61}

The radioactivity of the chromatograms is measured and recorded by a gas-flow windowless GM counter; the counting efficiency is about 10 per cent. Quantitative determination of the active sectors is made by elution and measurement of radioactivity by liquid scintillation.

The catabolites separations are equally carried out by micro-extraction on 0·06 ml urine samples, followed by paper chromatography of the ethereous and chloroformic extracts.

Enzymatic attacks of the glucuro and sulfo-conjugations have been carried out by the gastric juice of Helix Pomatia in an acetic acid-sodium acetate buffer at pH 5·4; incubation at 37°; extraction in an acid medium and chromatography of the hydrolysis products.

Two techniques have been used for the determination of the quantity of drug bound to the plasmatic proteins:

The ammonium sulfate technique is used to precipitate the plasmatic proteins in blood of which the figured elements have been separated by centrifugation at 4000 rpm. The proteins precipitated are then separated by centrifugation at 50,000 rpm (centrifuge Beckman Spinco L 50). The radioactivity of the de-proteinized plasma is measured by liquid scintillation in the ESLA sctintillating system. The plasmatic proteins are put in aqueous solution and their radioactivity is measured in the ESLA scintillating system after addition of Hyamine.

Sephadex G-25 gel has been used in a 9 × 300 mm column containing 5 g of gel equilibrated with a phosphate buffer at pH 7·4. One ml of plasma is used, the elution being done with the phosphate buffer. Two ml fractions are collected; on these, the protein concentration is measured by spectrometry (Biuret technique) and the radioactivity by liquid scintillation.

In the studies of the protein liaisons *in vitro*, 1 ml of plasma is incubated at 37° for 4 hr, with quantities of Niflumic acid between 8 and 30 μg. After incubation the plasma is treated with the same technique as used for experiments *in vivo*. In the case of lyophylized human plasma "Versatol" (albumine 63%, globuline 37%), a solution of 6·9 per cent is prepared.

For the studies by autoradiography, we have used the technique described by Ullberg and his collaborators.[5]

The mice receive doses of 6 mg/kg Niflumic acid. The radioactivity injected is of the order of 4 μc/animal. The product is given i.p., or per os. The animals are then sacrificed by freezing at — 80° in an acetone-carboice mixture. They are then cut up by a microtome (Jung, Hn 40) at 10°, in sections of 30μ thickness, parallel to the sagital plane of the animals. For each animal, at least 30 sections are obtained.

These sections are stuck on an adhesive support and desiccated at — 30° for 3 days. They are put on Kodirex Kodak film and left in contact for 7 days. The blackening of the film corresponds to the localization of the radioactivity.

RESULTS

Localization and distribution in rats after administration of Niflumic acid

Table 1 gives the radioactivity, expressed in μg of ^{14}C-Niflumic acid, found in the organs, in the interstitial liquid and in the "carcass" for 15 animals, sacrificed in groups of three, 1, 3, 6, 9 and 12 hr after i.p. administration of ^{14}C-Niflumic acid.

Table 2 gives the radioactivity found in organs, in expiratory CO_2, in blood, in urines, in faeces and in "carcass" as percentage of the injected radioactivity.

TABLE 1. RADIOACTIVITY, EXPRESSED IN μg OF NIFLUMIC ACID, FOUND IN THE ORGANS OF RATS SACRIFICED 1, 3, 6, 9 AND 12 hr AFTER i.p. ADMINISTRATION OF 50 mg/kg OF NIFLUMIC ACID

Hr	1			3			6			9			12		
Animal No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Radioactivity expressed in μg of Niflumic acid														
Liver	244·14	241·44	159·94	221·35	122·84	80·84	62·83	44·55	54·78	19·29	18·67	26·24	30·85	11·07	50·40
Kidneys	31·75	20·37	19·86	101·08	30·17	8·79	7·98	9·95	9·85	2·10	2·90	1·78	2·86	3·67	7·98
Brain	4·46	4·19	4·51	2·00	2·01	0·81	1·52	1·16	0·72	0·17	4·86	0·63	0·31	0·19	0·59
Stomach	23·55	21·27	29·04	16·03	5·29	16·40	62·03	48·07	46·20	10·84	5·27	18·36	5·44	1·62	7·01
Spleen	16·18	9·28	5·67	4·58	15·32	2·33	3·20	1·93	1·43	0·27	15·73	0·94	1·11	0·54	0·30
Lungs	12·28	9·88	17·99	11·17	11·26	4·29	2·41	2·23	3·19	0·55	0·80	2·04	0·92	0·43	2·92
Heart	5·87	6·89	4·68	9·74	5·53	2·22	1·29	1·93	1·65	0·27	0·06	1·27	0·41	0·23	0·39
Interstitial liquid	52·72	122·82	43·73	191·86	47·81	47·30	34·45	32·07	36·25	2·93	10·62	7·00	20·61	17·02	54·42
Carcass	4795·69	3835·26	3411·65	2911·36	3252·28	2853·03	3443·69	5668·11	2608·43	3184·17	2510·77	2801·77	2084·24	2232·73	2065·35

TABLE 2. BALANCE-SHEET OF THE RADIOACTIVITY FOUND IN THE BLOOD, THE URINES, THE FAECES, THE $^{14}CO_2$, THE ORGANS, THE INTERSTITIAL LIQUID, THE "CARCASS", IN PER CENT OF ^{14}C-NIFLUMIC ACID, AFTER ADMINISTRATION OF A 50 mg/kg DOSE IN THE RAT

Hr	1			3			6			9			12		
Animal No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
% Blood	3·44	6·18	4·50	1·57	2·48	0·92	0·75	0·80	0·74	0·19	0·31	1·21	0·34	0·68	1·12
% Urine	—	1·52	1·69	4·20	0·04	6·59	35·07	13·34	15·93	41·09	35·15	50·94	37·65	30·71	25·97
% Faeces	—	—	—	—	—	0·45	0·01	0·01	0·25	—	0·01	0·75	0·00	—	—
% $^{14}CO_2$	0·18	0·19	0·22	0·38	0·41	0·59	3·36	1·71	1·66	3·58	4·08	1·92	2·82	7·19	5·61
% Liver	4·44	4·39	2·91	4·20	2·23	1·47	1·14	0·81	1·00	0·35	0·34	0·48	0·56	0·20	0·92
% Kidneys	0·58	0·37	0·36	1·84	0·55	0·16	0·15	0·18	0·18	0·04	0·05	0·03	0·01	0·07	0·15
% Brain	0·08	0·08	0·08	0·04	0·04	0·01	0·03	0·02	0·01	0·00	0·09	0·01	0·01	0·00	0·01
% Stomach	0·43	0·39	0·53	0·29	0·10	0·30	1·13	0·87	0·84	0·20	0·10	0·33	0·10	0·03	0·13
% Spleen	0·29	0·17	0·10	0·08	0·28	0·04	0·06	0·04	0·03	0·00	0·29	0·02	0·02	0·01	0·02
% Lungs	0·22	0·18	0·33	0·20	0·20	0·08	0·04	0·04	0·06	0·01	0·01	0·04	0·02	0·01	0·05
% Heart	0·11	0·13	0·08	0·18	0·10	0·04	0·02	0·04	0·03	0·00	0·00	0·02	0·01	0·00	0·03
% Interst. liquid	0·96	2·23	0·79	3·49	0·87	0·86	0·63	0·58	0·66	0·05	0·19	0·13	0·37	0·31	0·99
% Carcass	87·19	69·73	62·03	52·93	59·13	51·87	62·61	70·41	47·43	57·89	45·65	60·94	37·90	40·60	37·55
% Recovered	97·92	85·56	73·62	69·23	66·42	63·38	105·00	88·85	68·82	103·40	86·27	106·95	79·81	79·81	72·55

These results permit a balance to be dressed: injected radioactivity/radioactivity found.

As the radioactivity levels found after 12 hr in the organs were in such small quantities, experiments to establish an evaluation over a longer period were not deemed necessary.

Blood rate

The quantities found in the blood are expressed in μg of ^{14}C-Niflumic acid for 1 ml of blood.

Figure 2 gives the curve of the drug half-life established on the average of the five experiments and for a period of 24 hr. The average is of 75·2 μg/ml at the 1st hr, falling to 32·4 at the 3rd to 14·4 at the 6th, to 9·8 at the 9th, to 8·0 at the 12th and to 5·8 μg/ml at the 24th hr after administration.

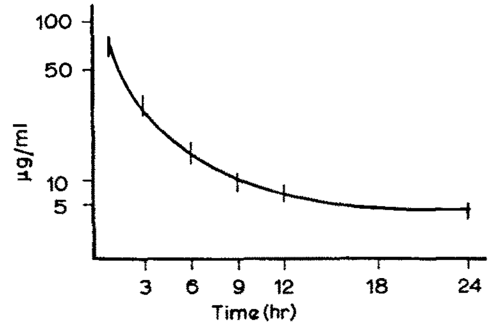

FIG. 2. Blood rate of the ^{14}C-Niflumic acid in the rat, after administration of a single dose of 50 mg/kg.

After separation of the figured elements, the totality of the radioactivity is found in the plasma.

Degree of binding between the Niflumic acid and the plasmatic proteins

The degree of binding between the Niflumic acid and the plasmatic proteins has been studied in the rat *in vivo*, after injection of 50 mg/kg i.p. in animals sacrificed 1, 3, 9 and 12 hr after administration.

The degree of liaison has equally been measured by incubation *in vitro* with rat plasma, guinea pig and rabbit plasma, as well as human plasma and "Versatol" (lyophilized human plasma containing 63% albumine and 37% globuline). Different quantities of Niflumic acid have been incubated with the same plasmatic volume.

Table 3 gives the percentage of Niflumic acid bound to the plasmatic proteins, after passage of 1 ml of plasma on a Sephadex G-25 column.

Figure 3 gives the relation between the radioactivity and the plasmatic proteins recovered in the elution fractions after separation in a Sephadex column.

Radioactivity in the expiratory CO_2

The $^{14}CO_2$ has been measured every hour in the balance establishing experiments up to the 12th hr after administration. For one experiment, measures were taken every hour up to the 60th hr, and equally during 1 hr every day up to the 17th day after administration of the product. The quantity of radioactivity found at the CO_2 level represents, as an average and for an observation of 12 hr, 5 per cent of the injected activity.

TABLE 3. PERCENTAGE OF BINDING OF THE NIFLUMIC ACID WITH THE PLASMA PROTEINS, *in vivo* AFTER ADMINISTRATION OF A SINGLE DOSE OF 50 mg/kg IN THE RAT, AND *in vitro* IN VARIOUS SPECIES

Binding of the Niflumic acid with the plasmatic proteins *in vivo*

Species	hr	Per cent bound	
		Precipitation	Sephadex
Rat	1	86·6	83·6
	3	100·0	—
	9	97·7	—
	12	—	90·5

Binding of the Niflumic acid with the plasmatic proteins *in vitro*

Species	μg incubated	Per cent bound
Man	69	97·6
	119	97·7
	219	97·6
Rabbit	26	98·0
	26	98·1
	26	97·7
Guinea Pig	26	98·2
Rat	8	95·4
	16	94·9
	24	95·4
	195	100·0
	220	100·0
Versatol	9	95·2

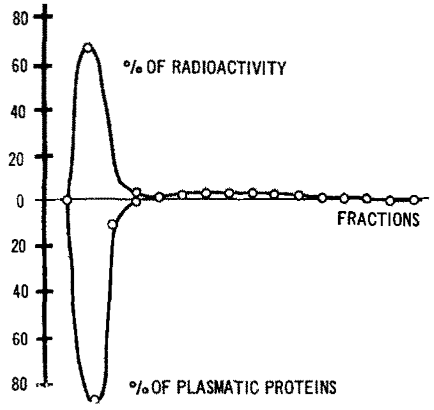

FIG. 3. Percentage of radioactivity and plasmatic proteins found in the fraction, after passage of rat plasma on Sephadex column.

Figure 4 gives the radioactivity of the expiratory $^{14}CO_2$ as a function of time, expressed in percentage of the activity measured over 36 hr, in the rat. Generally, these graphs show a regular repartition of this elimination during the first 12 hr of observation, $^{14}CO_2$ elimination then decreases exponentially up to the 60th hr. At that moment, the radioactivity eliminated by the CO_2 in 1 hr only represents 0·1 per cent of the activity actually injected.

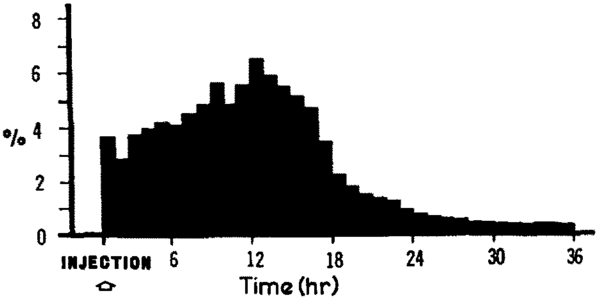

FIG. 4. Expiratory $^{14}CO_2$ in the rat after administration of ^{14}C-Niflumic acid.

The radioactivity eliminated in the CO_2 during 1 hr 17 days after administration is only about 30 ppm of the injected activity.

Urinary elimination

The measure of the radioactivity is carried out on every miction of the animal, the rhythm varying according to individual factors. The radioactivity eliminated this way, with respect to the injected activity, is found to be about 2 per cent at the 1st hr, reaching 10 per cent at the 3rd hr, 15 per cent at the 6th hr and then stabilizing at about 30 per cent for observations between 9 and 12 hr.

Figure 5 gives a typical elimination for an animal whose urinary radioactivity has been measured during 36 hr. These values are expressed as percentage of the total activity measured. For most of the experiments, the maximum radioactivity elimination occurs between the 4th and the 8th hr. After 36 hr, the radioactivity found at the urinary level only represents 0·2 per cent of the injected activity.

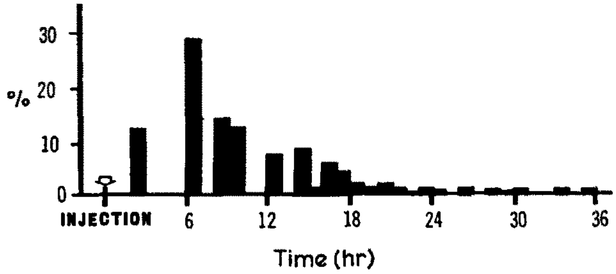

FIG. 5. Urinary radioactivity in the rat after administration of ^{14}C-Niflumic acid.

Faecal elimination

The radioactivity found in the faeces (for 7 rats in the 15 experiments) does not exceed 0·7 per cent of the injected activity. Generally it is in the range of 0·01 per cent.

Catabolites: formation rate

The recording of the urine radioactivity after paper chromatography indicates the presence of three active sectors. Figure 6 represents the recording of the radioactivity on chromatogramme of 0·01 ml of urine eliminated at the 5th hr, for a rat having received 50 mg/kg of Niflumic acid i.p.

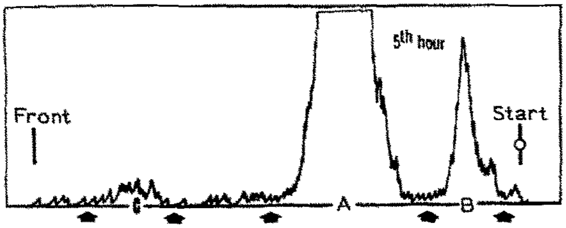

Fig. 6. Radiochromatogram of the rat urine after administration of ^{14}C-Niflumic acid.

For this recording, sector B represents 80 per cent of the radioactivity eliminated at that hour, sector A 10 per cent and sector C about 15 per cent.

Figure 7 gives the formation rate of these three sectors, measured on mictions up to the 12th hr after administration of a single dose of 50 mg/kg of ^{14}C-Niflumic acid in the rat.

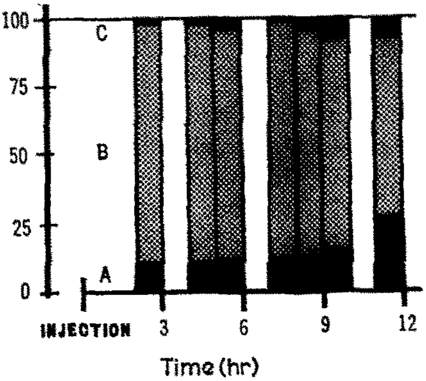

Fig. 7. Ratio of the urinary active sectors, separated by paper chromatography, as a function of time, after administration of ^{14}C-Niflumic acid.

Number and nature of the urinary catabolites

After elution of sectors A, B and C from the chromatogramme shown in Fig. 6, the eluates were again chromatographed in various systems. System X-61 separates sectors A and B into two other sectors. Sector C does not give any new separation. Therefore, one can conclude on the existence of at least 5 radioactive catabolites. None of the R_f on paper chromatography of these 5 sectors corresponds to the R_f of the unchanged Niflumic acid. The attack by glucuronidase and arylsulfatase of the Helix Pomatia gastric juice, or by spontaneous hydrolysis due to the normal presence of glucuronidase in the rat urine, changes sector B in two products; one of these represents the Niflumic acid identified by i.r. spectrometry after chloroform extraction from the urine. The Niflumic acid, therefore, conjugates with the glucuronic acid at the carboxylic group.

In the X–61 system, sector A separates in two active sectors; the R_f of one of these corresponds to the R_f of the 2-aminonicotinic acid in paper chromatography.

Catabolites in the blood

The radioactivity in the blood is entirely due to the Niflumic acid. This has been shown after freeing the Niflumic acid bound to the plasmatic proteins by the urea. Its structure has been confirmed by the R_f values in different systems.

Catabolites in the faeces

The faeces have been extracted by ether in acid medium. The paper chromatography of the ethereous extract indicates the presence of at least 4 catabolites.

Catabolites in the organs

Some of the organs, like liver and stomach, have been extracted by ether and by chloroform equally in acid medium. After chromatography, these two extracts indicate that the greatest amount of radioactivity is not likely to be the unchanged product.

Localization of the ^{14}C-Niflumic acid in the mouse by autoradiography

A first batch of 15 animals received i.p. 6 mg/kg (4 μc) of ^{14}C-Niflumic acid and were sacrificed in groups of three, 30 min, 1, 3, 6 and 9 hr after administration. A second batch of 15 animals received the Niflumic acid per os: the same dose and the same activity as the first batch, and equally as that one, they were sacrificed 30 min, 1, 3, 6 and 9 hr after administration.

Figure 8 shows a representative whole-body autoradiogram of a mouse injected i.p. with ^{14}C-Niflumic acid (6 mg/kg, 4 μc) and sacrificed 30 min later. The dark areas show the localization of the radioactivity in the various organs.

In Fig. 9 one can observe whole-body autoradiograms of mice, sacrificed in groups of three, 30 min, 1, 3, 6 and 9 hr after administration of ^{14}C-Niflumic acid (6 mg/kg, 4 μc) i.p. and per os. One can see the localization of the radioactivity as function of the time, as well as a different time-dependence of localization for different ways of administration.

In the case of an i.p. injection, the localization is fairly uniform during the 1st hr of survival of the animal. From the third hour, the radioactivity decreases and is localized in the liver, the kidneys, the stomach, the bladder and the intestines. These last two organs still present some radioactivity at the 9th hr.

In the case of oral administration, a very strong activity is naturally observed in the stomach and the intestines, radioactivity persisting up to the 9th hr. The other organs, such as the liver, show a radioactivity fairly higher, at the same hour, than for animals treated i.p. It can be said that, at the brain level, the radioactivity is practically null for all our experiments.

DISCUSSION

For the metabolic study of Niflumic acid, we chose to label the carboxylic group. This allowed us to study a certain number of possible pathways, notably the formation of expiratory $^{14}CO_2$. This loss, which represents 5 per cent of the quantity injected during a period of 12 hr, is not very large but is sufficiently significant when one considers that the carboxylic group is common to several anti-inflammatories, such as acetylsa licylic acid, indomethacin, flufenamic and mefenamic acids, Ibufenac which could metabolise in the same way.

For therapeutic doses and i.p. administration, the half-life of the drug in the rat is of 3 hr. This observation agrees with the active pharmaceutical action of the product. Experiments *in vivo* on rats and *in vitro* on other animals show that Niflumic acid is almost completely bound to plasmatic proteins. Thus, this quasi-total link is not in conflict with the therapeutic action.

It is through the urine that most of the radioactivity is eliminated (about 30 per cent during a 12 hr observation period). After the maximum point of elimination is reached —which happens between the 4th and 8th hr, the radioactivity eliminated in this way decreases exponentially, until it reaches a very low level even after 36 hr. As to the faecal level, the radioactivity measured is almost negligible. According to our preliminary results, the one found in the biliary extraction is similarly negligible.

The localization in the organs, observed either by autoradiography in mice or by the balance-sheet experiments in rats (measure of the radioactivity organ by organ as a function of time) confirms that Niflumic acid, like many drugs, accumulates preferentially in the liver. The persistence of its activity at this level indicates that metabolic transformations occur there. The renal distribution is not uniform: one observes a greater concentration in the medullar region as shown by autoradiography. As one could expect, given the pharmaceutical class of the product, we found only slight traces in the brain. A relatively small amount in the other organs can be attributed to the vascularization of the blood. The results obtained in the balance sheet experiments show without doubt a general evolution in the localization and elimination as a function of time. The difference observed between the quantities injected and the quantities recovered must be attributed to the techniques employed in this type of research, without reducing the value of the information to be drawn from the distribution and elimination of the product in the organism.

The study of the chemical structure of the five catabolites found in the urine—a study effected by paper chromatography, by enzymatic attacks and by extractions at different pH, leads us to suggest the following possible schema of metabolic pathways.

The split of the carboxylic group is indicated by the presence of $^{14}CO_2$. It leads as a result to the formation of decarboxylized catabolites, which consequently cannot be followed by tracer techniques. The conjugation in the carboxylic group by glucuronic acid was shown by the formation of the free product either through enzymatic attack *in vitro*, or by a similar reaction by the urinary glucuronidase. The presence of the 2-amino-nicotinic acid is born out by the agreement of the R_f with synthetic 2-amino-nicotinic acid in numerous chromatographic systems. The formation of this 2-amino-nicotinic acid presumes that Niflumic acid divides at the amino stage to give trifluoromethylbenzene. By analogy, the rupture of the amino stage could also lead to the formation of nicotinic acid and trifluoromethylaniline. Hydroxylic products are suggested in the schema since the extractions of catabolites in the urine reveal the presence of components with phenolic characteristics. These are all the more probable, since Williamson *et al.*,[6] working on flufenamic acid, found in the urine both of rats and man hydroxylated products of this acid in ortho of the CF_3 group and in meta of

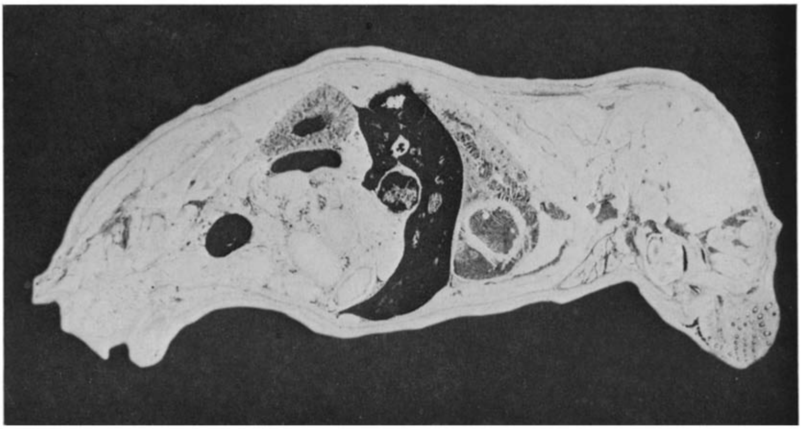

FIG. 8. Representative whole-body autoradiogram of a mouse injected i.p. with ^{14}C-Niflumic acid (6 mg/kg, 4 μc) and sacrificed 30 min later.

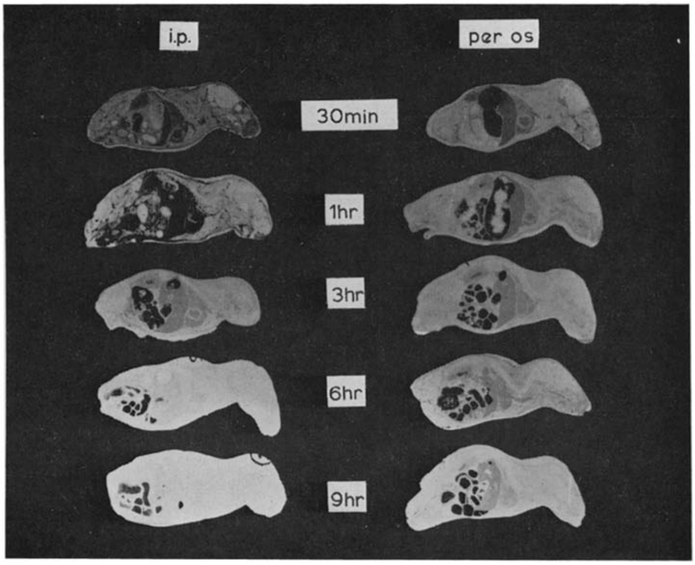

FIG. 9. Whole-body autoradiograms of mice sacrificed in groups of three, 30 min, 1, 3, 6 and 9 hr after administration of ^{14}C-Niflumic acid (6 mg/kg, 4 μc) i.p. and per os. Representative autoradiograms of each group (at least 30 sections/animal).

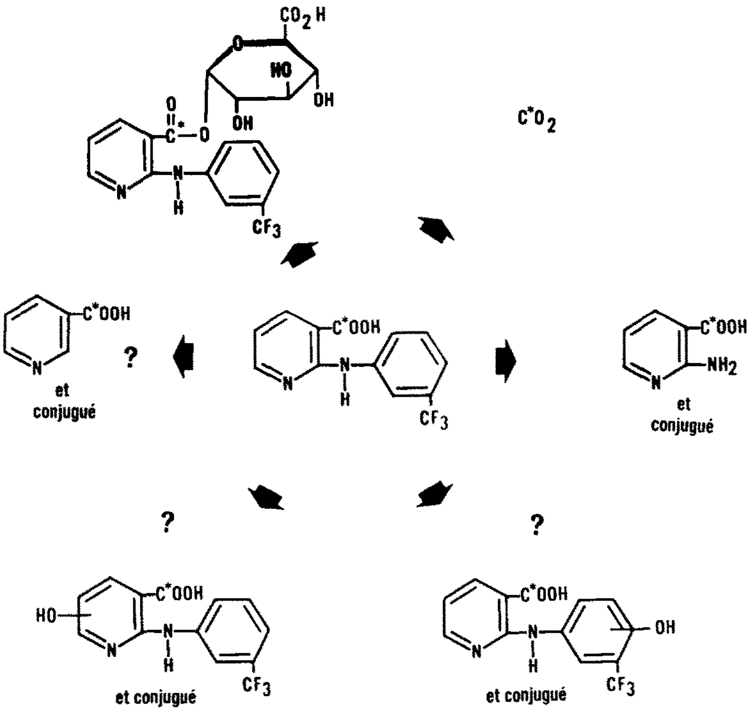

FIG. 10. Possible metabolic pathways of ^{14}C-Niflumic acid.

the carboxylic group. Further work is being undertaken to confirm the schema of metabolic pathways suggested for Niflumic acid.

Acknowledgements—The authors are grateful to Mr. Ch. Plessas, Miss J. Heyman and Miss J. Vitus for their technical assistance.

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