Tetrahedron Vol. 44, No. 21, pp. 6723 to 6728, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

THE MECHANISM FOR THE CONVERSION OF URIC ACID INTO UROXANATE AND ALLANTOIN

A NEW BASE-INDUCED 1,2-CARBOXYLATE SHIFT

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(*Received in UK* 22 *August* 1988)

Abstract — Alkaline permanganate oxidation of uric acid (**1**), particularly the late stages of the transformation into uroxanate (**7**) and allantoin (**3**), was studied by means of isotope-position labelling. A clear-cut degradation procedure developed for distinguishing among carbonyl and α-aminal carbon atoms in these products demonstrated conclusively that the carboxylic carbon of **7** and the 4-carbonyl carbon of **3** have their origin in C(5) of uric acid (**1**). None of the mechanisms that have been proposed for this reaction would have predicted this result. Isotope-labelling evidence, in combination with other data, revealed the sequence of events and identities of species involved in oxidative transformation of **1**; the carbon-skeleton rearrangement of the first transient intermediate **4** must occur by a 1,2-carboxylate shift to give allantoin-5-carboxylate (**6**) which either decarboxylates to allantoin (**3**) or else undergoes hydrolytic ring opening to uroxanate (**7**).

Early work on the structure of uroxanic acid (**7**), an unusual product encountered in alkaline oxidation of uric acid (**1**),[1-3] has played a major part in the formulation of the key ring-contracted intermediate **2** in chemical and enzymic breakdown to allantoin (**3**).[4,5] With some modifications,[6,7] this is essentially the pathway that was commonly accepted until recently (Scheme 1, path a). The reaction has a number of further ramifications that leave one in little doubt that something, perhaps a good deal, still remains to be unravelled despite more than a hundred years of study. The timing of oxidation to allantoin (**3**) and the observed location of the label from [2-^{14}C]**1** in the trapped [7-^{14}C]dehydroallantoin presented an apparently insuperable objection to previous concepts and established several fixed points that any projected pathway must traverse.[8] This involves initial formation of the elusive quinonoid dehydro-uric acid, nucleophilic attack to its 5-position, and a base-catalysed ring opening at the 1,6-bond as the salient step (path b). The first capturable intermediate **4** decarboxylates via the enol form of the end-product **3** under acidic conditions, whereas under alkaline conditions it undergoes a further transformation into a second intermediate. The question therefore remains, how is the non-symmetrical species **4** transformed into uroxanate (**7**) or its immediate precursor?

The problem of the uroxanate structure is very interesting in this connection. This product is usually given an acyclic symmetrical formula **7**, and the particular structure **8** which Brandenberger proposed[9] we do not regard as probable. Our decision in favour of **7** for uroxanic acid was made through highly informative NMR patterns of its dipotassium salt and the dimethyl ester, congruent with C_{2v} molecular symmetry. A detailed consideration of the course of remarkable decarboxylative degradation to the next lower homologue, allantoic acid (**9**),[2] pointed in the same direction. The early observations were confirmed and substantiated when we were able to prepare two crystalline derivatives from the resultant hemihydrate of **9**. One of these was the corresponding methyl ester **10**.

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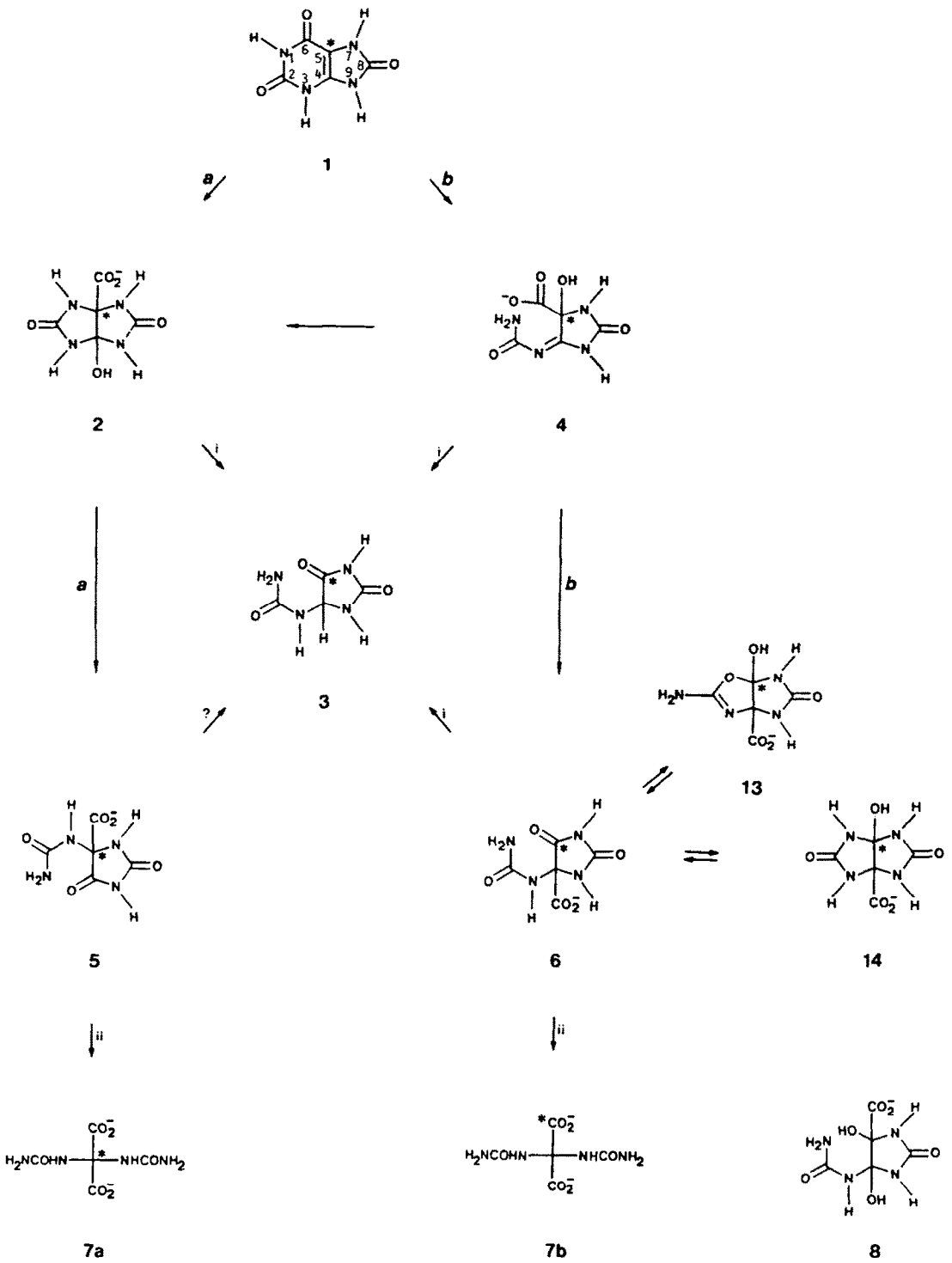
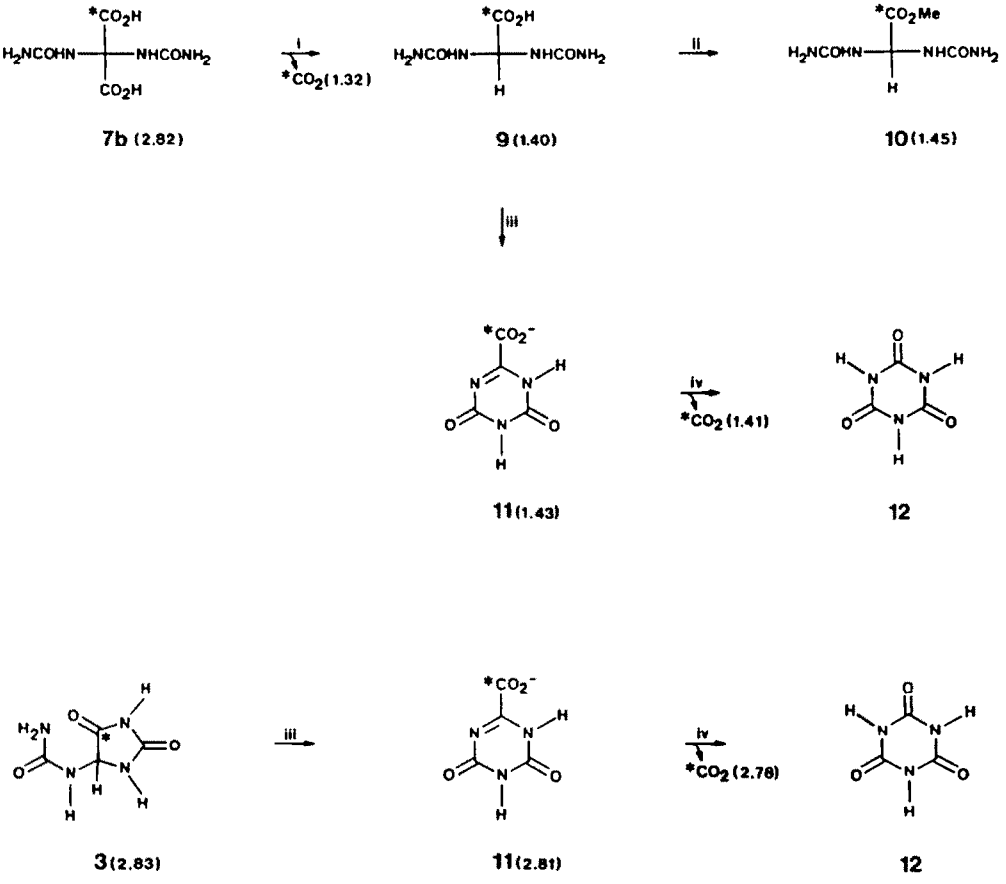


Scheme 1. Alkaline permanganate oxidation of uric acid (1). I, AcOH; ii, KOH; (*) designates ^{14}C-labelled atom.

However, of particular interest was the conversion into oxonate (11), a special circumstance which, in combination with the known oxidation of the latter to cyanuric acid (12),[10] permitted complete degradation of the three-carbon chain of 7. Having established the structures beyond question and with the sequential degradation method in hand, we could deduce the fundamental nature of the carbon skeleton.

There are two extreme a priori mechanisms that might be envisaged. One might involve, at one extreme, the classical case **2** (path a), but the possibility that regiochemical results can be explained on this basis appears to be slight. Alternatively, at the other extreme, one might picture a carbon skeleton rearrangement (Scheme 1, path b) which could nicely account for the observed decarboxylation to allantoin (**3**) and hydrolysis to uroxanate (**7**). Both mechanisms lead to chemically identical products and this particular dilemma may be overcome only by isotope-position labelling.

Accordingly, we chose to model our initial approach after the classical alkaline permanganate oxidation of discretely labelled [5-^{14}C]uric acid (**1**), for the resultant [^{14}C]uroxanates (**7a** and **7b**) will clearly differ in the position in which they carry their label. A hint at the involvement of a common precursor, which incorporates the feature of the allantoin system, is that it can be diverted from its ordinary reaction course. Thus, even after isolation of dipotassium [^{14}C]uroxanate (7,25%), a significant amount of [^{14}C]allantoin (3,13%) was obtained on work-up with acetic acid (Scheme 1). Decarboxylative degradation of the labelled sample of uroxanic acid (**7**) to [^{14}C]allantoic acid (**9**) and [^{14}C]carbon dioxide disclosed a labelling pattern consistent with the derivation of carboxylic carbon from the 5-position of uric acid (**1**). As our suggested pathway would require, a half of the ^{14}C-label is found in allantoic acid (**9**), being converted, for convenience, into the ester **10**, while the other half is contained in the carbon dioxide. There was, in fact, slightly more of the former as a result of the ^{12}C/^{14}C isotope effect.[11] In order to pursue this important finding further, we carried out the oxidation of [^{14}C]allantoic acid (**9**) to [^{14}C]oxonate (**11**). Cyanuric acid (**12**) resulting from the oxidative decarboxylation of ^{14}C-labelled **11** was free of tracer, while the isotope was retained entirely in the



Scheme 2. Decarboxylative degradation of uroxanic acid (**7**) and allantoin (**3**). i, 95%MeOH/Δ; ii, CH_2N_2; iii, $KMnO_4$/KOH, then AcOH; iv, $KMnO_4/H_2SO_4$; (*) designates ^{14}C-labelled atom and specific activities (μCi/mmol) are given in parentheses.

[^{14}C]carbon dioxide. The incorporation of radioactivity into [*carboxy*-^{14}C]uroxanate demonstrates conclusively that the reaction is, indeed, a case of carbon-skeleton rearrangement. The location of the label in allied [4-^{14}C]allantoin (**3**) was unequivocally established by the analogous degradation procedure and by exclusive incorporation of the label into the resultant [^{14}C]carbon dioxide (Scheme 2). Position of the label in the final end-products, coupled with the skeletal array and transient life-time of **4**,[8] were highly revealing about the situation of the labelled carbon in the course of rearrangement. The implication is strong, therefore, that it is allantoin-5-carboxylate (**6**) that arises from the incipient intermediate **4** by a genuine 1,2-carboxylate shift. The presence of the ureide side-chain capable of acting as an ambident neighbouring group[12] raises the possibility that a more satisfactory description may be provided by **13** or by **14**; in view of the supposed accompanying ring-chain tautomeric equilibrium **6** ⇌ **14** under the reaction conditions,[13] the problem of transition state is at once more complex and more subtle.

The formal skeletal change **4** → **6**, regardless of the precise description of the transition state, is analogous to base-induced 1,2-shifts of the ester group. Migrations of this type are relatively rare, one of the oldest examples being indoxyl-oxindole rearrangement,[14] but nevertheless it has been established that in α,β-diketoesters they can be so facile as to take precedence over the possible migrations of the other groups.[15] Each of these systems is characterized by formation of stable hydrates, or a cyclic carbinolamine equivalent, at the migration origin. The present case shows, however, that the electron deficient centre at the migration terminus need not be a ketone carbon. The group also includes movement of carboxylate with its bonding electrons to the adjacent amidine-type carbon, such as the unique rearrangement of **4** in the course of formation of uroxanic acid (**7**). A simple analysis predicts that this 1,2-migration should proceed suprafacially. The defined vicinal stereorelationship in the rearrangement **4** → **6** can point the way for further investigations into the mechanism and stereochemistry of uricase-mediated oxidation of uric acid (**1**) and provide a useful solution of the long-standing problem of creation of the asymmetric centre in the naturally occurring (*S*)-(+)-allantoin.[8]

EXPERIMENTAL

M.ps. were determined on a Tottoli apparatus (Büchi) and are corrected. IR spectra were recorded for KBr disks on a Perkin-Elmer 257 grating instrument. Unless otherwise stated ^{1}H- and ^{13}C-NMR spectra were measured for DMSO-d_6 solns on a JEOL FX-100 spectrometer. Chemical shifts are given in δ units (ppm) relative to internal TMS, and coupling constants are expressed in Hz (b, broad; s, singlet; d, doublet; t, triplet; q, quartet; umc, unresolved multiplet centre). Discretely labelled [5-^{14}C]uric acid was prepared in a 52% overall yield (specific activity 28.40±0.01 μCimmol^{-1}) from diethyl acetamido[2-^{14}C]malonate (1 mCi, The Radiochemical Centre Amersham, U.K.) by four-step synthetic route (0.02 molar scale) according to Cavalieri *et al.*[16] [^{14}C]Carbon dioxide which evolved during decarboxylative degradations was absorbed in a carbonate free 12% solution of ethanolamine in MeOH. N_2 used as the carrier gas was passed through two bubble tubes in series filled with 40% KOH. Specific activities were measured in Aquasol on a Beckman LS-100 liquid scintillation counter, corrected for background, self-absorption, and dilution by non-radioactive carbons. All ^{14}C analyses were determined in triplicate and the average deviation from the mean was less than 1%.

Oxidation of **1** *with alkaline permanganate*

The classical preparative procedure was used on a 0.03 molar scale. A solution of uric acid (**1**, 5.04g) in 10% KOH (120 ml) was vigorously stirred at 0–2° while 5% $KMnO_4$ (65 ml) was added dropwise during 1 hr. After standing for 4 hrs at room temperature, MnO_2 was filtered off and washed well with hot water. The combined filtrates were concentrated to a volume of 20 ml. Traces of MnO_2 were then removed and the clear filtrate was left overnight at +4°. The crystalline product was then collected, washed with cold water (3×1 ml), recrystallized from hot water (10 ml, 80°) and dried to yield colourless plates of the dipotasium salt of **7** as a trihydrate (2.73g, 26%). Two recrytallizations from water gave the analytical sample. (Found: H_2O, 15.76. $C_5H_6K_2N_4O_6 \cdot 3H_2O$ Requires: H_2O, 15.43%). IR: 3400–2400 (NH_2, NH), 1655 (CO), 1540 (CO_2^-) cm^{-1}. ^{13}C-NMR (D_2O), δ 169.4 (CO_2^-), 156.5 (ureide CO), 69.5 (C_2).

The alkaline mother liquor was acidified with glacial acetic acid and the crystalline product which separated after 2 days at +4° was collected. It was recrystallized twice from water to yield pure allantoin (**3**, 0.67g, 14%), m.p. 238–239° dec, identical in all respects with an authentical sample.

The potassium salt of **7** (2.6g) was dissolved in hot water (25 ml, 90°), the solution was then cooled to 30–40° and acidified with hydrochloric acid. Crystalline precipitate was collected, washed with cold water, EtOH, ether, and dried. Uroxanic acid (**7**, 1.58g, 25.1%) cannot be recrystallized unchanged; m.p. 162–163° dec (lit.[2] m.p. 162° dec). (Found: C, 26.96; H, 4.02; N, 25.10. $C_5H_8N_4O_6$ Requires: C, 27.28; H, 3.66; N, 25.45%). IR: 3450, 3350 (NH_2), 3250, 3100–2220 (NH, OH), 1720, 1640 (CO) cm^{-1}.

The free acid **7** was fully characterized by conversion into its dimethyl ester. A suspension of finely powdered **7** (0.22g, 0.001 mol) in MeOH (1 ml) and an excess of ethereal diazomethane (3×30 ml) were allowed to react for 48 hrs. The resulting crude product was stirred with 5% Na_2CO_3 solution (5 ml) to remove unreacted acid. The product was collected, washed well with water, and dried. Two recrystallizations from DMSO-MeOH yielded pure dimethyl ester of **7** (0.13g, 52%); m.p. 213–214° dec. (Found: C, 34.00; H, 4.96;

N, 22.60; $C_7H_{12}N_4O_6$ Requires: C, 33.87; H, 4.87; N, 22.85%). IR: 3470, 3445 (NH_2), 3250, 3200 (NH), 1766, 1732 (CO_2Me), 1688, 1655 (CO) cm^{-1}. H-NMR: δ 7.25 (s, NH), 5.92 (s, NH_2), 3.63 (s, CO_2Me). ^{13}C-NMR: δ 166.6 (CO_2Me), 156.7 (ureide CO), 69.7 (C_2), 53.1 (Me).

Oxidation of [5-^{14}C]uric acid (1)

The foregoing procedure was repeated with a soln of [5-^{14}C]uric acid (1, 5.04g, 2.84 μCimmol^{-1}) to yield [4-^{14}C]allantoin (3, 0.71g, 15%), specific activity 2.83±0.01 μCimmol^{-1}, and [*carboxy*-^{14}C]uroxanic acid (7, 1.32g, 20%), specific activity 2.82±0.02 μCimmol^{-1}, identical in all respects with the unlabelled compounds.

Decarboxylation of 7 *to allantoic acid* (9)

The original procedure was slightly modified.[2] The reaction was carried out in a flask fitted with a N_2 inlet and an outlet at the top of the condenser leading to a half saturated $Ba(OH)_2$ trap. A suspension of finely powdered 7 (1.1g, 0.05 mol) in 95% MeOH (30 ml) was heated under reflux for 1 hr. A stream of N_2 carried the released CO_2 to the $Ba(OH)_2$ trap and the collected $BaCO_3$ (0.987 g) corresponded to quantitative decarboxylation. The reaction mixture was then concentrated to a volume of 10 ml. The product which separated on cooling was collected, washed with ether and dried. It analyses for a hemihydrate of allantoic acid (9, 0.8g, 86%) and cannot be recrystallized unchanged; m. p. 172-3° dec (lit.[2] m. p. 173° dec). (Found: C, 26.23; H, 5.02; N, 30.08. $C_4H_8N_4O_4 \cdot 0.5H_2O$ Requires: C, 25.95; H, 4.90; N, 30.27%). IR: 3470, 3420 (NH_2), 3380, 3330, 3295, 3000-2200 (NH, OH), 1720 (CO_2H), 1685, 1652 (CO) cm^{-1}. This product was characterized by conversion into the corresponding ester 10. A suspension of the pulverized hemihydrate of 9 (0.185 g, 0.001 mol) in MeOH (1 ml) was allowed to react with an excess of ethereal diazomethane (3×20 ml) for 24 hrs. The product was recrystallized twice from DMSO-Me_2CO to yield pure methyl allantoate (10, 0.15 g, 79%); m. p. 212-213° dec. (Found: C, 31.43; H, 5.51; N, 29.30. $C_5H_{10}N_4O_4$ Requires: C, 31.58; H, 5.30; N, 29.47%). IR: 3475, 3378 (NH_2), 3280, 3235 (NH), 1740, 1690, 1655 (CO) cm^{-1}. ^1H-NMR: δ 6.90 (d, 2H, NH, J=8), 5.29 (t, 1H, CH, J=8), 5.80 (s, 4H, NH_2), 3.61 (s, 3H, CO_2Me). ^{13}C-NMR: δ 170.5 (CO_2Me), 157.7 (ureide CO), 57.6 (CH), 51.9 (Me). An identical product was obtained by hydrolysis and esterification of allantoin (3).

Decarboxylation of [carboxy-^{14}C]*uroxanic acid* (7b)

The same procedure as described above for the unlabelled analogues, but this time using a 12% methanolic ethanolamine trap (40 ml), was repeated with [*carboxy*-^{14}C]uroxanic acid (1.1g, 2.82 μCimmol^{-1}) to give [*carboxy*-^{14}C]allantoic acid hemihydrate (1.78g, 84%); m. p. 172-173° dec. Specific activity 1.40±0.01 μCimmol^{-1}. The resultant hemihydrate of 9 (185 mg) was converted into the methyl [*carboxy*-^{14}C]allantoate (10, 0.16g, 84%, 1.45±0.01 μCimmol^{-1}). [^{14}C]Carbon dioxide, specific activity 1.32±0.01 μCimmol^{-1}.

Oxidation of 9 *to oxonate* (11)

To a stirred solution of the hemihydrate of 9 (0.56g, 0.003mol) in cold 12% KOH (3ml) 5% $KMnO_4$ in 0.5 N KOH (7 ml) was added dropwise during 2 hrs at 0-2°. Ammonia was freely evolved and after stirring for 30 min EtOH (1 ml) was added and the precipitation of MnO_2 accelerated by a stream of air bubling through the mixture. After removal of MnO_2, the clear filtrate was acidified with glacial acetic acid. The product which separated on cooling was recrystallized twice from hot water (80-90°) to yield pure potassium oxonate (11, 0.28 g, 48%) as fine needles, m. p. > 300°. It was characterized by conversion to the free oxonic acid, m. p. 261-262° dec, and allantoxaidine, m. p. 276°dec. These products were identical in all respects with those prepared by independent syntheses from allantoin (3) or dehydroallantoin.[8]

Oxidation to potassium [carboxy-^{14}C]*oxonate* (11)

The foregoing procedure was repeated with a soln of the hemihydrate of [*carboxy*-^{14}C]allantoic acid (0.56g, 1.40 μCimmol^{-1}) to yield ^{14}C-labelled potassium oxonate (0.29g, 49%). Specific activity 1.43±0.01 μCimmol^{-1}.

The same procedure as described above for allantoic acid (9) was used in conversion of [4-^{14}C allantoin (3, 0.474g, 0.003 mol, 2.83 μCimmol^{-1}) to the potassium [*carboxy*-^{14}C]oxonate (0.32g, 55%). Specific activity 2.81±0.02 μCimmol^{-1}.

Oxidative decarboxylations of [carboxy-^{14}C]*oxonate* (11)

The oxidative decarboxylation to cyanuric acid (12) was accomplished using a modified method of Biltz and Robl,[10] in a flask equipped with a N_2 inlet. Connected to the flask were two dropping funnels containing 75% H_2SO_4 and 5% $KMnO_4$. While a steady slow stream of N_2 was passed through the system carrying the released CO_2 to a 12% methanolic ethanolamine trap (10ml), H_2SO_4 (3ml) was added to the suspension of oxonate 11 (0.195g, 0.001 mol) in water (1 ml). Addition of 5% $KMnO_4$ (4 ml) to the resultant solution was accompanied by strong effervescence and immediate separation of MnO_2. The reaction mixture was stirred for 15 min and MnO_2 then removed by introduction of SO_2. Cyanuric acid was collected, washed, and recrystallized twice from water. After drying, 12 was obtained as a white powder.

Potassium [*carboxy*-^{14}C]oxonate (11, 1.43 μCimmol^{-1}) derived from the labelled allantoic acid (9) afforded [^{14}C]carbon dioxide, specific activity 1.41±0.01 μCimmol^{-1}, and non-radioactive 12 (0.12g, 93%).

Potassium [*carboxy*-^{14}C]oxonate (11, 2.81 μCimmol^{-1}) derived from the labelled allantoin (3) yielded [^{14}C]carbon dioxide, specific activity 2.78±0.02 μCmmol^{-1}, and non-radioactive cyanuric acid (12, 0.116g).

Acknowledgement—We thank the Research Council of Croatia (Grant SIZZ-203010013) for support of this work.

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