Synthesis and Identification of 2-Dimethylamino-5-(phenyl-2'-^{3}H)-2-oxazolin-4-one

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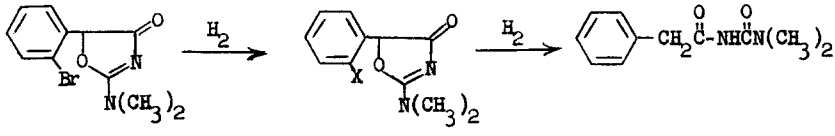
SUMMARY

The title compound **1b** *was prepared by tritiolysis of 5-(o-bromophenyl)-2-dimethylamino-2-oxazolin-4-one,* **2**, *with 10 Ci of tritium and diluted with unlabelled* **1a**. *The mass spectrum of the 2'-deutero derivative* **1c**, *prepared similarly, showed that 92.9 % of labelled compound was D_1 with only 3.1 % D_2 and that > 95 % of the isotope was in the aromatic ring.*

INTRODUCTION.

2-Dimethylamino-5-phenyl-2-oxazolin-4-one, thozalinone, **1a** [1], is a mild stimulant and anorexic agent which differs importantly from the amphetamines both chemically and pharmacologically [2]. It is currently in clinical evaluation.

To facilitate pharmacokinetic and metabolic studies, radiolabelled thozalinone was required. From among several synthetic methods, tritiolysis of the *o*-bromo analogue of **1** was selected since it involved one step with radioactive materials, employed inexpensive tritium gas, and would provide material with high specific activity at a known position. The label in the



2 **1a**, X = H; **1b**, X = T; **1c**, X = D **3**

aromatic nucleus was expected to be non-exchangeable under physiological conditions and the *ortho*-position to be less susceptible to metabolic oxidation than the *para*-position*.

Discussion.

Hydrogenolysis of **1a** to the base-soluble phenylacetylurea **3** was expected to complicate the preparation of **1** from **2**. Indeed hydrogenolysis of **1a** with an excess of H_2 readily gave 80 % of **3**, but in model experiments the rate of hydrogenolysis of **2** was greater. When hydrogenolysis of **2** was stopped after one equivalent of hydrogen had been absorbed, 83 % of **1a**, mp 129-137°, (lit. [1] 133-135°) was isolated.

In the tritiolysis of **2** to **1b**, any tritiated **3** formed would be removed during purification by dissolving **1b** in acid followed by precipitation with potassium carbonate. Unreacted **2** would be unlabelled and go undetected during the metabolic studies.

Subsequently 48 mg (0.17 mmole) of **2** was reduced with 10 Ci (0.17 mmole) of carrier-free tritium, the reduction mixture was immediately diluted with 2 g of **1a** and then worked up to give 1.6 g of **1b** containing 2.95 Ci (370 mCi/mmole). This corresponds to a 74 % of theoretical incorporation of tritium into the reduction product. Dilution of an aliquot with 13.6 parts of unlabelled material gave product with a specific activity of 22.1 mCi/mmole, (87 % of expected specific activity) and radiochemical purity 98 % by countercurrent distribution.

To establish unequivocally the position of the tritium in **1b**, the deutero derivative **1c** was prepared by the same procedure. Scrambling of the label is a problem in the catalytic hydrogenation of aliphatic compounds [6] but not in the hydrogenolysis of haloaromatics [3,7], *e.g.* the preparation of 4-deuterophenylalanine [8]. Unfortunately the pmr spectrum of **1a** exhibits a singlet for the aromatic protons at δ 7.35 ppm [1c] so it was not possible to establish the *ortho* orientation of deuterium in **1c**.

However a comparison of the mass spectra of **1a** and **1c** showed that the $>$ 95 % label was in the aromatic nucleus. The molecular ion region in the mass spectra of **1c** indicated the isotopic composition of the sample was 4.0 % D_0, 92.9 % D_1 and 3.1 % D_2**. Proof that the deuterium label was located in the aromatic ring, and not in any other position of the molecule, was established by comparison of ion intensities in the mass spectra of **1a**

* *Ortho* hydroxylation of aromatic substrates by liver microsomes is usually less than 10 % of the *para* hydroxylation reaction, though equal amounts have been observed with toluene [3]. Oxidation of *p*-hydroxyphenylpyruvic acid to homogentisic acid, which results in 50 % loss of the *ortho* label [4], seems largely confined to various phenylpyruvic acids [5] and would not be expected to affect **1**.

** Error is estimated to be $\pm$ 1 % in this determination.

and **1c** (see Table 1). The C_6H_5 ion at m/e 77 in the mass spectrum of **1a** was quantitatively shifted (> 95 %) to m/e 78 (C_6H_4D) in the spectrum of **1c**. The ion at m/e 78 in the spectrum of **1a** was found to be a doublet of ions C_6H_6 and C_5H_4N (ratio ~ 3 : 1, respectively)*. The apparent greater than quantitative shift of m/e 77 to m/e 78 in the two spectra is accounted for by the C_5H_4N ion remaining at m/e 78 in the spectrum of **1c**.

TABLE 1. Relative ion abundance (%) in the m/e 74-80 region [a]

	Isotopic purity	m/e 74	75	76	77	78	79	80
1a	—	4.3	4.8	6.8	72.1	9.0	3.0	—
1c	3.1 % D_2 92.9 % D_1 4.0 % D_0	2.0	3.4	3.9	6.5	74.6	7.0	2.6

[a] 1. All mass spectra were obtained on an AEI MS-9 mass spectrometer. Isotopic purity measurements were made at ionizing voltage, 18 ev; the m/e 74-80 ion intensities were measured at 70 ev.
2. Corrections for isotopic contaminants and naturally occurring isotopes have been made in all instances.
3. Relative ion abundances reported are averages of at least 3 scans.
4. Errors are estimated to be ± 3 %.

EXPERIMENTAL**.

2-Dimethylamino-5-(phenyl-2'-^{3}H)-2-oxazolin-4-one, **1b**.

A suspension of 48 mg (0.17 mmole) of 5-(*o*-bromophenyl)-2-dimethylamino-2-oxazolin-4-one in 1 ml of ethanol containing 0.03 ml (0.23 mmole) of triethylamine and 5 mg of 10 % palladium on charcoal was hydrogenolyzed under reduced pressure (*ca* 0.5 to *ca* 0 atm.) with 10 Ci (0.17 mmole or 10 cc at 322.7 mm pressure) of carrier-free tritium (Oak Ridge National Lab.) in a Toeppler-type gas burette. Uptake of tritium began immediately and was estimated to be complete after about 20 min. After 105 min the reduction was discontinued and the catalyst was collected by filtration on Celite and washed with a solution of 2.0 g of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (**1a**) in 30 ml of ethanol. The radioactive ethanol was removed and collected by distillation *in vacuo* and the residue was dissolved in 10 ml of 10 % hydrochloric

* High resolution mass measurements were conducted at 10,000 resolution.
** Melting points are uncorrected.

acid, washed with 5 ml of benzene and reprecipitated with potassium carbonate. The product was collected and dried over Drierite® overnight *in vacuo* during which period it became slightly pink in color, 1.617 g (79 %).

A solution of this product in 40 ml of methylene chloride was diluted to 100 ml with benzene. Counting duplicate aliquots of this solution indicated the product contained 2.96 and 2.93 Ci of tritium (59 % of theoretical incorporation, 74 % in original reaction mixture). Presumably, the remainder of the tritium was in the benzene washings which should contain any tritiated **3** and the aqueous filtrate which were not counted. Six milliliters (97 mg, 177 mCi) of the product solution was diluted with 1.303 g of **1a** in 15 ml of benzene, was extracted into two 5 ml portions of 10 % hydrochloric acid, precipitated with potassium carbonate, collected and dried over Drierite® *in vacuo*. This product, 0.948 g (68 % recovery), had mp 133-135° (lit. [1a] mp 133-136°), 22 mCi/mmole.

After storage at room temperature for 5.8 years this sample had mp 119-130° and contained radioactive impurities detectable by countercurrent distribution and by partition chromatography (pc). A sample (526 mg) subjected to pc on Celite® (650 g) eluted with the upper phase of a 75 : 25 : 12 : 8 mixture of heptane, dichloroethane, methanol and water yielded, in the third hold-back volume, 431 mg (82 % chemical recovery) of **1b**, mp 133-135°, 17 mCi/mmole (16 mCi/mmole expected).

Dimethylamino-5-(phenyl-2'-^2H)-2-oxazolin-4-one, **1c**.

Reduction of 5 mg of **2** as above using deuterium resulted in absorption of 1 equivalent of D_2 during 20 min and yielded 2 mg of the 2'-deutero compound **1c** characterized by ms as described above.

5-(o-Bromophenyl)-2-dimethylamino-2-oxazolin-4-one, **2**.

Treatment of ethyl *o*-bromomandelate [bp 131-136° (4 mm) prepared from *o*-bromobenzaldehyde] with dimethyl cyanamide [1a] gave (73 %) of crude 5-(*o*-bromophenyl)-2-dimethylamino-2-oxazolin-4-one, mp 131-133°. A sample recrystallized from ethyl acetate and from benzene-petroleum ether had mp 140-142°.

Anal. Calcd for $C_{11}H_{11}BrN_2O_2$; C, 46.7; H, 3.9; Br, 28.2; N, 9.8. Found : C, 46.35; H, 4.05; Br, 28.5; N, 10.0.

1,1-Dimethyl-3-phenylacetylurea, **3**.

To a suspension of 204 mg (1 mmole) of **1a** in 5 ml of ethanol containing 0.1 ml of triethylamine (distilled from acetic anhydride and stored over barium oxide) was added 20 mg of 10 % Pd/C (Englehard). The mixture was hydro-

genated at atmospheric pressure and absorbed 26.8 ml of hydrogen (112 %) during 12 minutes.

The product crystallized and therefore was diluted with 10 ml of ethanol, warmed and filtered on Celite® to remove the catalyst. Cooling yielded the product which was collected and recrystallized from ethanol to give 164 mg (80 %) of 1,1-dimethyl-3-phenylacetylurea, mp 158-160°, soluble in 1 *N* sodium hydroxide.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.9; N, 13.6. Found : C, 63.9; H, 6.9; N, 13.4

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