

Preparation of formaldehyde by photochemical condensation of carbon monoxide and tritiated hydrogen, and the synthesis of a tritiated morphine derivative

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SUMMARY

Tritiated formaldehyde, required for labelling 6:14-endo-etheno-7-(2-hydroxy-2-butyl)-tetrahydro-orphavine (M99), was prepared by photochemical condensation of carbon monoxide and tritiated hydrogen. The specific activity of the M99 (48 C/mole) was about one half that of the source of isotope. The loss was traced to undefined secondary decompositions during the photochemical reaction.

INTRODUCTION

M99, or 6:14-endo-etheno-7-(2-hydroxy-2-butyl)-tetrahydro-orphavine, produces morphine-like effects at doses of a few $\mu\text{g}/\text{kg}$. A detailed study of its disposition in animals would require material with a specific activity about 300 C/mole but for exploratory purposes tritiated water (90 C/mole) was the source of isotope for labelling the hydrogen atoms at C₈ by the synthetic route summarized in figure 1. The purified M99 had a specific activity of 48 C/mole, considerably lower than that of the original tritiated water.

EXPERIMENTAL

Tritium was assayed in a coincidence counter by counting scintillations in a solution of naphthalene (5%), PPO (0.7%) and POPOP (0.005%) in dioxan. Activities were related to internal standards of *n*-hexadecane-1:2-T (1.99 $\mu\text{C}/\text{g}$).

Tritiated hydrogen. Tritiated water (90 C/mole) (2 ml) was frozen (liquid nitrogen) in a tube attached to a mercury pump, and air was pumped out before adding clean calcium (200 mg) from a side arm. The generated hydrogen was dried by cooling and its volume measured at room temperature before transfer to a storage bulb. An equal volume of carbon-monoxide, from a cylinder, was admitted to the pump and transferred to the bulb. To recover tritiated water, (to overcome problems of disposal) carbon dioxide was admitted to the calcium

hydroxide slurry. When no more gas was absorbed the solution was frozen at -40°C and excess gas pumped away. The liberated tritiated water was distilled to a second tube for the next cycle. After ten cycles the specific activity of recovered tritiated water had not changed within experimental error.

Tritiated formaldehyde. A closed circuit apparatus, 482 ml capacity, incorporated an automatic mercury pump to circulate gas through a clear silica tube (27×1.5 cm) and a liquid nitrogen cooled trap. Suitable connections were made to a formalde

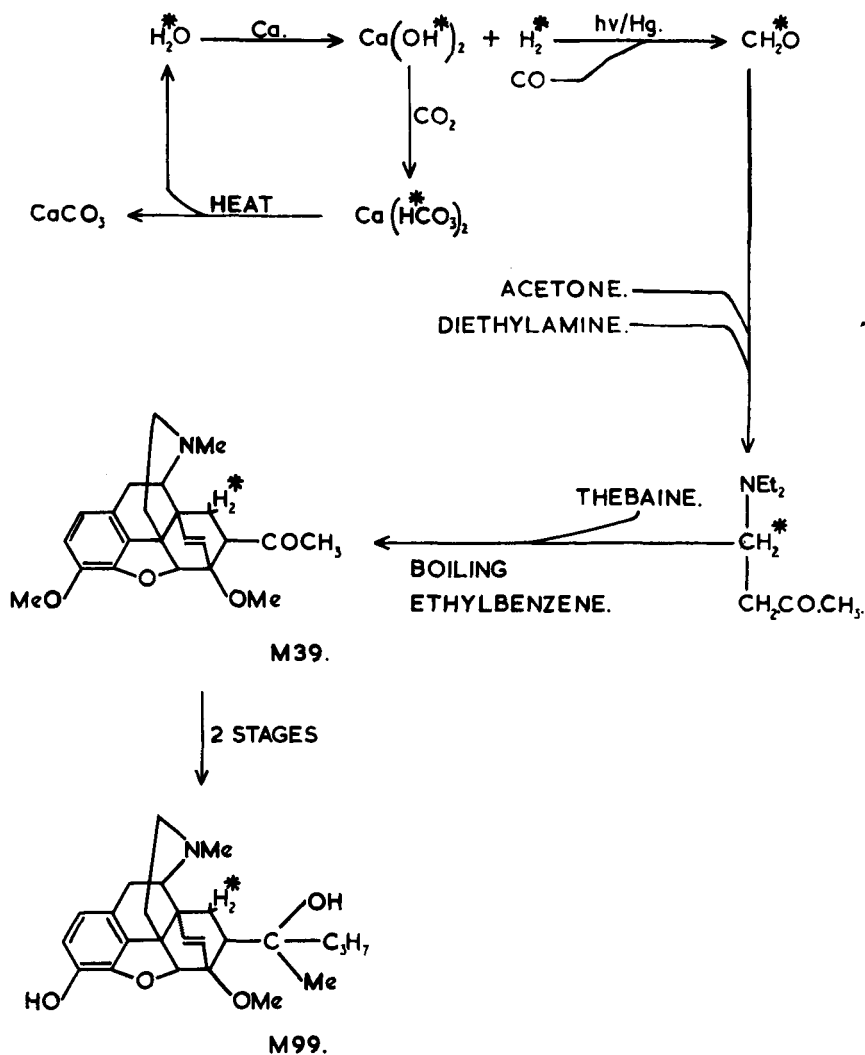


FIG. 1. — Synthetic route to M99.

hyde receiver containing water (1 ml) and a gas storage vessel. Pressures were measured by manometer with respect to a datum on the pump and a fixed level of liquid nitrogen. The silica tube was irradiated (20 cm) by a 25 Watt Chromatolite lamp without filter, emitting mainly at 2537 Å. The average velocity of gas in the irradiated area was estimated to be 10 cm/sec. The initial pressure of mixed gases was 400-500 mm Hg (p_i) and this fell by Δp during 3-7 hr. irradiation. Permanent gases were then returned to the storage bulb. The condensate was expanded into the apparatus to give a pressure p_f , before transfer to the formaldehyde receiver by liquid nitrogen cooling. Residual gas, usually at about 5 mm pressure was pumped to waste.

Table 1 summarises the records of 12 experiments in sequence. The yield of formaldehyde calculated from p_f was greater than found by chemical assay

TABLE 1. Yield of Formaldehyde by Photochemical Union of Carbon Monoxide and Tritiated Hydrogen.

Initial specific activity 90 C/mole. Pressure in mm Hg. 1 mg HCHO = 0.8 mm.
Yield calculated from mg HCHO by chemical assay referred to Δp .

Initial pressure p_i	Fall in pressure Δp	Irradiation time (hr.)	Pressure of products p_f	Yield *	Apparent specific activity (C/mole)
443	86	5.75	26	55 mg (39%)	50.6
417	81	6.75	21		
463	91	5.75	30		
461	95	6.5	39		
407	26	3.5	10	69.5 mg (32%)	68.5
363	65	7	17		
437	67	7	15		
434	90	5.5	27		
456	87	7	36		
396	81	7.25	25		
401	59	7.25	12		
457	65	6	13		

* Polyoxymethylene produced not included.

(chromotropic acid) and in one tested instance the apparent specific activity based on chemical assay was higher (66.2 C/mole) than that of the dimedone derivative (31.4 C/mole). The next crystallisable product in the synthetic sequence (M 39) also had a lower specific activity, e.g. 45.6 C/mole, compared to the formaldehyde used in its preparation (50.6 C/mole).

After 36 preparations the yield of formaldehyde had declined and the residual gas was analysed. Carbon monoxide was absorbed in acid cuprous

chloride. Tritiated hydrogen was oxidized by platinum dioxide. The small volume of residual gas, almost completely absorbed by a potassium hydroxide pellet, appeared to be carbon dioxide and gave no evidence for hydrocarbons by vapour phase chromatography or infrared spectroscopy. The ratio of hydrogen to carbon monoxide was 2.6:1, suggesting a preferential loss of carbon monoxide. Little radioactivity passed into the acid cuprous chloride, and the specific activity of the residual tritiated hydrogen amounted to 81 C/mole.

The plot of $\log(\Delta p)/t$ against $\log p_i$ gave points scattered around a line with a slope suggesting that the rate of combination of the gases varied with the square of the pressure.

The contraction of volume slowed considerably as the pressure fell during an experiment, and the yield of formaldehyde was negligible at low initial pressures, e.g. 0.3 mg/hr. at 140 mm compared to 4.3 mg/hr. at 490 mm. The literature yields for tritio- and deuterio-formaldehyde are much higher^(1, 2), but no comparison is possible due to lack of essential detail. Yields calculated as $(2 \times p_f)/\Delta p$ varied considerably, e.g. at initial pressures about 400 mm the range was 14-84% (mean, 55%). An error arising by the formation of a polyoxymethylene⁽³⁾, in the liquid nitrogen cooled trap did not explain either the loss of product or isotope. While the specific activity of this polymer was high (103 C/mole), possibly by incorporation of tritiated water produced as a by-product in the reaction, it represented very little tritium because of the small amount produced (1-2 mg per experiment).

4-Diethylaminobutan-2-one-4:4T⁽⁴⁾. Tritiated formaldehyde (69.5 mg) in water (1 ml), diethylamine hydrochloride (270 mg), concentrated hydrochloric acid (2 μ l) and acetone (0.5 ml) were heated in a sealed tube at 80-90°C/6 hrs. The mixture was diluted with water (5 ml), saturated with potassium carbonate and liberation of the base completed by a few drops of 50% sodium hydroxide. The base was extracted with ether, dried (K_2CO_3) and distilled, collecting the fraction b.p. 95-100°C/22 mm Hg (air bath temperature). Yield of crude oil, 208 mg. *6:14-endo-etheno-7-acetyl-tetrahydro-thebaine-8:8T*. (M39). The above amino-ketone was heated with thebaine (540 mg) in ethylbenzene (2 ml) at 140°C in a sealed tube for 6 hrs. The solvent was distilled and the residue dissolved in acetone and passed down a column of silica gel (27 \times 1 cm). The required product was eluted rapidly by acetone leaving excess thebaine on the column. (Some grades of silica gel would not give this separation). The eluate gave yellowish crystals, m.p. 106-107°C from aqueous methanol. Yield, 295 mg, specific activity 45.6 C/mole.

Reaction of the above product with *n*-propyl magnesium iodide followed by 3-O-demethylation of the correct isomer as described elsewhere⁽⁵⁾, gave crude M99 (55 mg = 5.5% overall yield from formaldehyde). It was purified by thin layer chromatography (SiO_2 /ether) to give a product m.p. 214-5°C, of specific activity, 48 C/mole.

DISCUSSION

This discussion concerns the fate of the missing tritium and the origin of the adverse isotope effect which reduced the specific activity of the final product by about one half. The effect clearly occurred during the preparation of the formaldehyde.

From Table 1, the discrepancy between Δp and p_f , allowing for a contraction of gas volume to one half during the reaction, shows that about 400 mC of tritium were lost in 12 experiments irrespective of the isotope effect. Other products are produced in the reaction. A primary product seems to be formyl radicles and subsequent formation of glyoxal⁽²⁾ and acetaldehyde⁽⁶⁾ give contractions of 0.33 and 0.4 respectively. These products would appear in the final aqueous solution of formaldehyde and contribute to the discrepancy in specific activity noted. The excess observed was much too small to account for the lost tritium.

Since the specific activity of residual tritiated hydrogen was almost unaltered at 81 C/mole compared to the 90 C/mole started with, the isotope effect must occur in secondary decompositions. To support this, it was observed that doubling the rate of gas flow increased the yield of formaldehyde by 25%. A few products were observed other than formaldehyde. Deliquescent colourless crystals often deposited in the cooled end of the silica tube (glyoxal?). A polyoxymethylene polymerisation due to liquid nitrogen cooling occurred in both the trap and the formaldehyde receiver. A brown stain gradually developed in the silica tube. There were no other deposits in the closed circuit and the only feasible sink for the missing activity was the residual gas pumped out of the apparatus at the end of the experiment. Since this did not condense easily at liquid nitrogen temperature and was insoluble in water, it could be methane. At 5 mm Hg pressure, the 40 ml of methane that could be produced in 12 experiments, would require a specific activity of 150 C/mole to account for the missing activity.

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