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On Radioactive Drugs

B. M. Tolbert

March 29, 1950

Berkeley, California

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ON RADIOACTIVE DRUGS (*)

by

B. M. Tolbert

Radiation Laboratory and Department of Chemistry,
University of California, Berkeley (**)

March 29, 1950

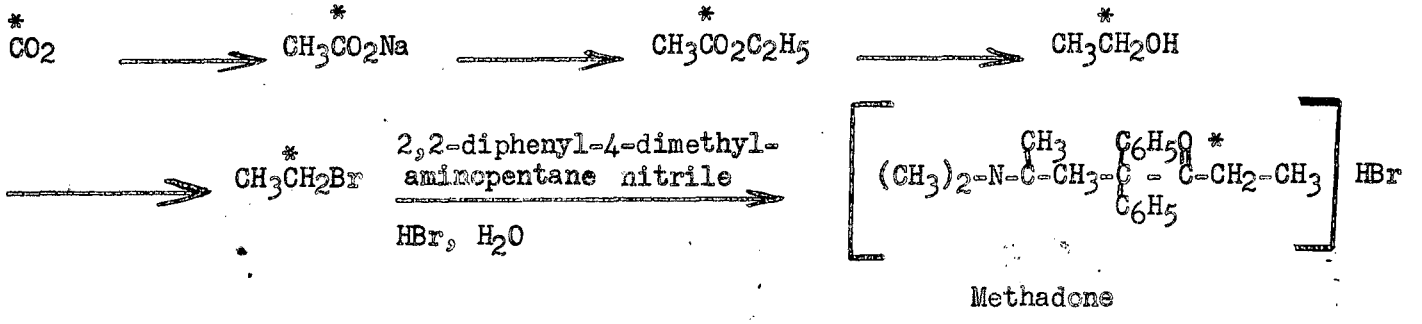
(*) Abstract of an address by Dr. B. M. Tolbert before the Biochemical and Organic Group meeting of the California Section of the American Chemical Society, February 13, 1950.

(**) The work described in this paper was sponsored by the Atomic Energy Commission.

The work on radioactive drugs that I am going to discuss is not a single person's work, but rather a collection of research and chemical problems all related by the use of similar techniques. It is the cooperative effort of several organizations which include: Drs. Hamilton Anderson, Peter P. T. Sah and H. W. Elliot, Division of Pharmacology and Experimental Therapeutics of the University of California Medical School, San Francisco; Drs. J. H. Lawrence and John Weaver of the Division of Medical Physics, Berkeley; Dr. H. Rapoport, Chemistry Department, Berkeley, and, of course, the Bio-Organic Group of the Radiation Laboratory in Berkeley.

To date, Methadone, codeine, Demerol, stilbamidine and acetylcholine have been prepared labeled with C^{14} and others are being studied. I would first like to review the synthesis of the labeled compounds. All preparations were carried out on a 20 mmole or less scale.

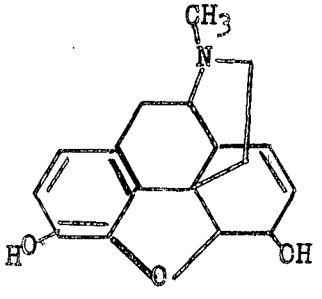
Methadone. Methadone, 4,4-diphenyl-6-dimethylamino-3-heptanone, is an analgesic used in place of morphine as it is less habit forming. It was prepared as follows:



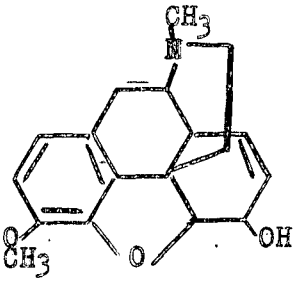
Methadone

The yield based on $^{*}CO_2$ used to begin the synthesis was about 12.5%

Codeine. Codeine is the mono-methyl ether of morphine, and of the opium alkaloids closely related to morphine it is the most important. Morphine and codeine have the following structures:



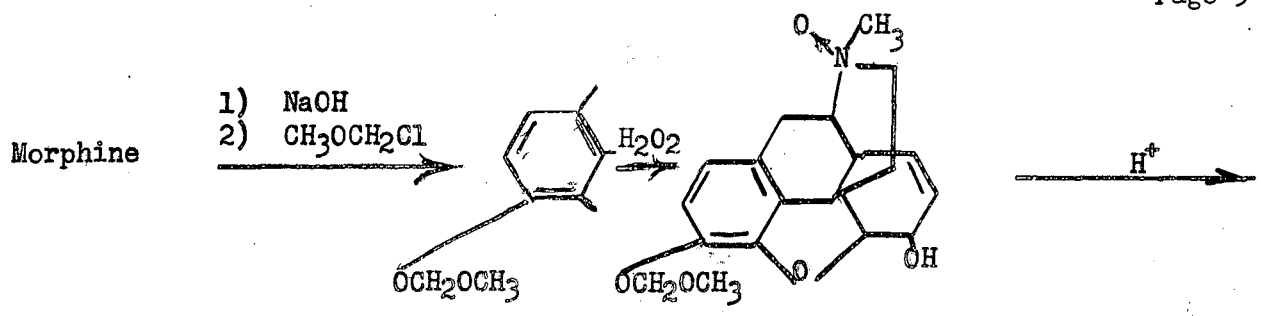
Morphine

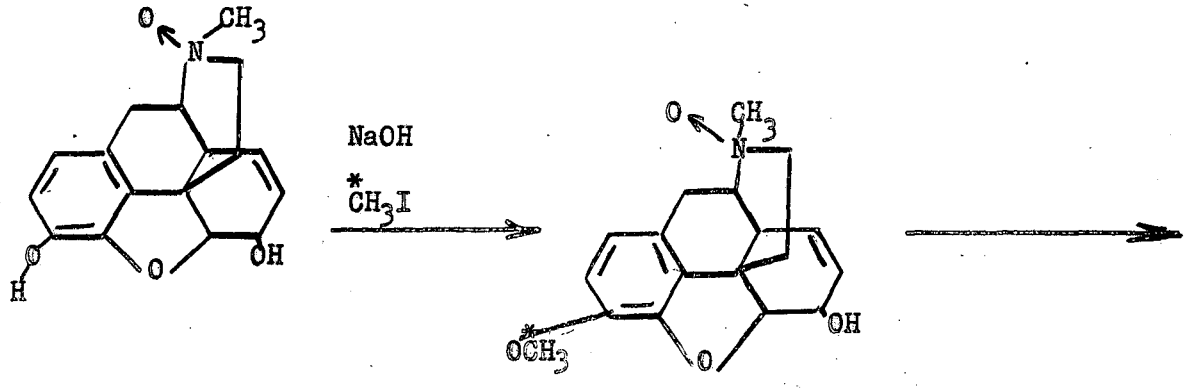


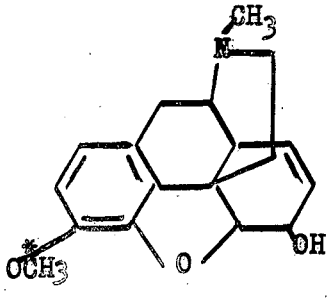
Codeine

The direct methylation of morphine with methyl iodide (which was available tagged with C^{14}) has been previously studied, but the yields are small. This is due to the fact that in the morphine molecule there are three active groups capable of undergoing methylation, namely, a phenolic group, the tertiary amino group and an allylic secondary alcohol. Direct methylation gives a mixture of compounds difficult to purify and low in yield.

Since the group that interferes most in this reaction is the tertiary amino group, the following procedure was developed to prevent reaction with this group:





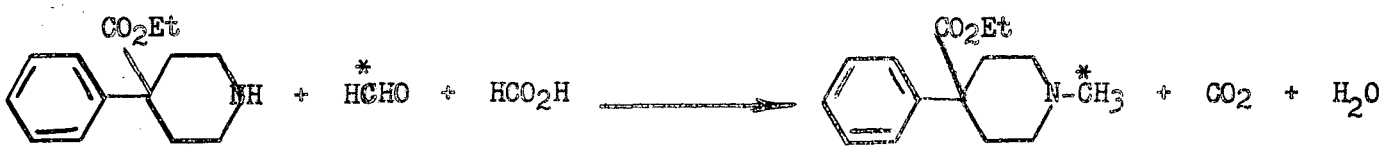


Codeine

The yield was 63% based on methyl iodide-C^{14} or 49.1% based on $^*CO_2$ used to begin the synthesis.

Demerol. Demerol is the hydrochloride salt of N-methyl-4-phenyl-4-carbethoxypiperidine. It is used as an analgesic similarly to morphine and is reported to be less toxic than morphine. The methylation of 4-phenyl-4-carbethoxy-piperidine, which was obtained from the Sterling-Winthrop Research Institute, was

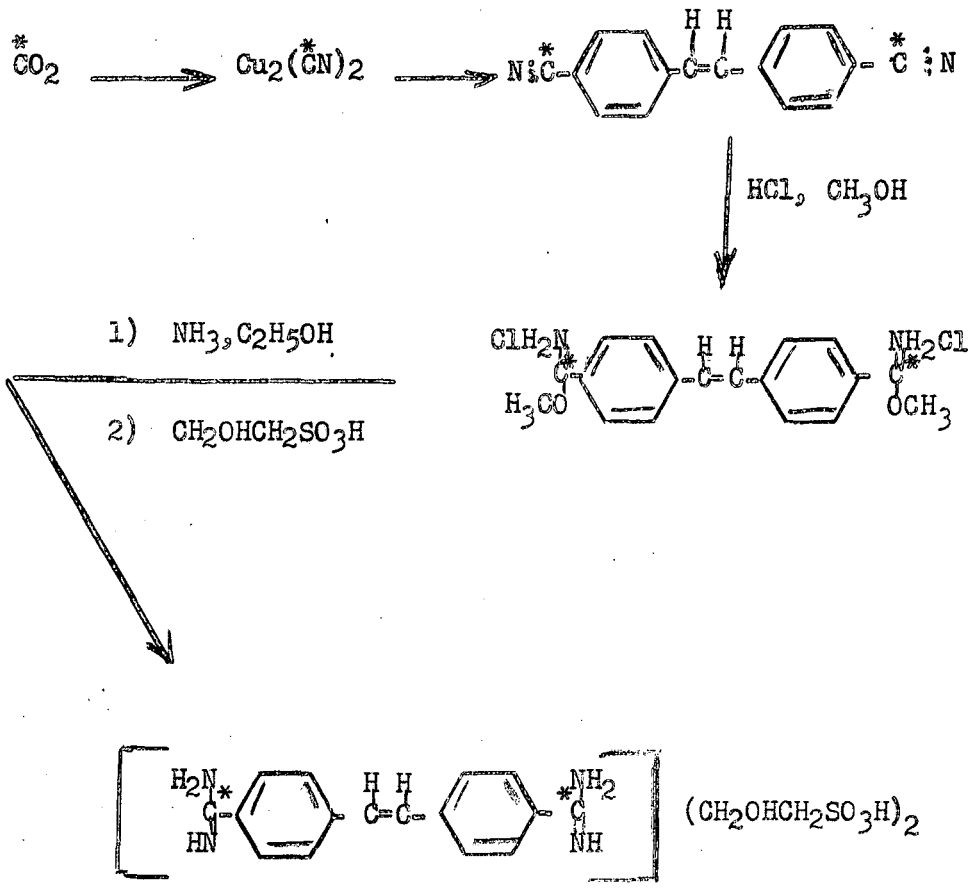
undertaken as a convenient way to label this drug. Preliminary work with methyl iodide showed that the rate of quaternization of the tertiary compound, demerol, was very fast and it was impossible even under best conditions to get much more than 8-9% yield. About this time, formaldehyde-C^{14} became available from the Isotopes Division of the Atomic Energy Commission and the reductive methylation of the intermediate was attempted.



Demerol

It was presumed that the probable source of the reducing power in this reaction would be the formic acid and the aldehyde would be converted to the N-alkyl group. However, there was some question about this for an amine can be alkylated by treatment with formaldehyde alone and previous experimentors have had difficulty in obtaining a satisfactory material balance. The preparation was, therefore, carried out first with labeled formaldehyde and then with labeled formic acid. It was found that the reduction is not appreciably affected by formaldehyde going to carbon dioxide but comes almost exclusively from the formic acid. Using this reaction, the demerol was prepared in 78% yield based on labeled formaldehyde.

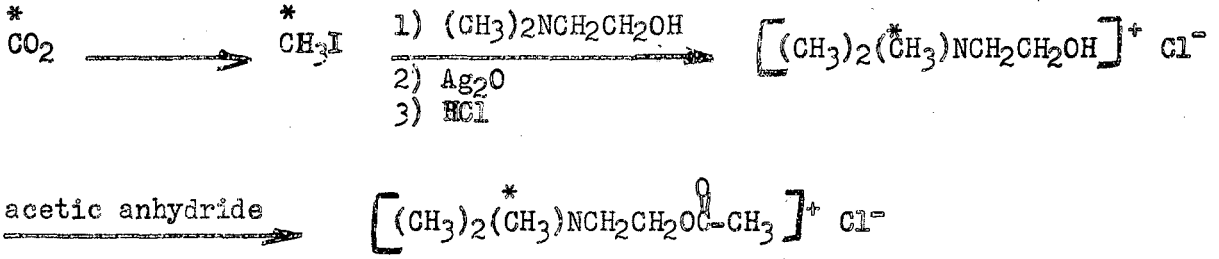
Stilbamidine. The aforementioned drugs have all been analgesics. Stilbamidine, on the other hand, is used in treatment of multiple myeloma, a type of cancer. It was prepared by Dr. J. C. Reid of this laboratory as follows:



Stilbamidine diisothicnate

The yield was 20% based on the cyanide used to begin the synthesis.

Acetylcholine. Acetylcholine was prepared by acetylation of choline as follows:



Acetylcholine chloride

The yield was about 40% based on $^{*}CO_2$ used to begin the synthesis. No biological work has yet been done with this compound.

Biological Work with Radioactive Drugs

Of some interest in a biological study and in the interpretation of data is the mode of excretion of a compound. If a molecule stays intact and is thus excreted, any measurement of activity in the body will represent a real concentration of this molecule or a direct modification of it.

Two of the drugs studied fall in this classification, namely, methadone and stilbamidine. Following intravenous or intramuscular injection no appreciable amount of radioactive carbon dioxide is found in the breath. In the case of the methadone, the kidney excretion is secondary to the intestinal excretion; about 30% of the injected dose is excreted by the kidney and the remaining 70% in the feces. Practically all of the activity of the methadone is excreted in twenty-four hours, mostly by the liver through the bile. Stilbamidine is, as is methadone, excreted without appreciable metabolic oxidation, but the excretion is slow. Approximately equal quantities of activity (and presumably stilbamidine, probably conjugated with a ribose nucleic acid) are excreted in the urine and feces. Again, in this case, the determination of the activity in any tissue is an excellent measure of the stilbamidine present.

In the case of the other two analgesic drugs, codeine and demerol, appreciable amounts of activity appear in expired breath in a short time interval. Thus, in demerol 14% of the activity is expired as $\overset{*}{C}O_2$ in two hours, and in codeine in two hours 20% of the injected dose is eliminated.

An interesting observation made in the study of methadone-C^{14} was that the concentration of activity (and of methadone) is very high in the adrenal, particularly during the period of maximum drug action and decreases as the animal recovers. This is also shown by the thyroid and may be due to vascularity; alternatively, this effect may be of prime importance and the drug may actually be acting by causing the adrenals to release a compound having drug action or the methadone may there be conjugated into some more potent drug. This aspect of the concentration action deserves more study.

The slow rate of expiration of $^{*}CO_2$ in the codeine experiment reopens a very interesting question, namely, the mode of action of codeine. A long time ago it was proposed that this drug operated by being demthoxylated to morphine and that this then produced the anagesia. Since that time the sentiment gradually changed: the demethoxylation of a compound was not a known biological process, codeine is not a very habit forming drug, and the molecule probably has analgesic properties of its own. Thus, it was thought that codeine itself was acting as an analgesic. However, if one takes the rate at which radioactive carbon dioxide is expired from rats given the labeled codeine and estimates from the the rate that morphine would produce by a demethoxylation reaction, the amount of analgesic this morphine would give is about that which the codeine produces. Maybe codeine really goes to morphine. It is hoped this question will be answered eventually with codeine labeled in another position.

Stilbamidine is of interest for use in multiple myeloma, a cancer disease of the marrow. In this disease, the malignant cells in the marrow multiply very rapidly, entending into the adjacent bone and taking over the bone marrow space. It has been observed that stilbamidine tends to localize in the myeloma cells proper, and it is hoped to find something more about the use of the drug in this disease and, if this concentration is a real effect, stilbamidine radiation could be concentrated in the cell itself.