SYNTHESIS OF PICOLINIC-(CARBOXYL-^{14}C) ACID AND 2-[(METHYLSULFINYL) ACETYL-(CARBONYL-^{14}C)] PYRIDINE.

E.J. Merril* and G.G. Vernice**.

Received on February 25, 1972.

SUMMARY

Picolinic-(carboxyl-^{14}C) acid was prepared by carbonation of the lithio derivative obtained from n-butyl lithium and 2-bromopyridine. This was esterified and allowed to react with the anion generated from dimethyl sulfoxide by sodium hydride to give 2-[(methylsulfinyl)acetyl-(carbonyl-^{14}C)]pyridine.

Introduction: 2-[(Methylsulfinyl)acetyl]pyridine[1] (IV) has been shown to be a potent selective immunosuppressant (1). The drug was labeled with ^{14}C in order to more easily investigate the absorption and excretion rates, blood levels, distribution patterns, and to determine its metabolites (2,3). The reaction sequence (4) as shown in Figure 1 was designed to incorporate the radioactive atom into the carbonyl group. This position would assure retention of the label during biotransformation.

Discussion: The incorporation of ^{14}C into this position required the preparation of picolinic-(carboxyl-^{14}C) acid (II).

The carbonation of an organometallic derivative, as used in the preparation of nicotinic-^{14}C acid (5), seemed to offer the most direct approach. Gelman and Spartz (6) and Proost (7) have discussed the lithio and magnesium derivatives of pyridine. The lithio derivative was preferred because it offered a less complicated workup.

*Department of Analytical/Physical Chemistry, Warner-Lambert Research Institute, Morris Plains, N.J. 07950.

**Present address: Hoffmann-La Roche, Inc., Nutley, N.J. 07110.

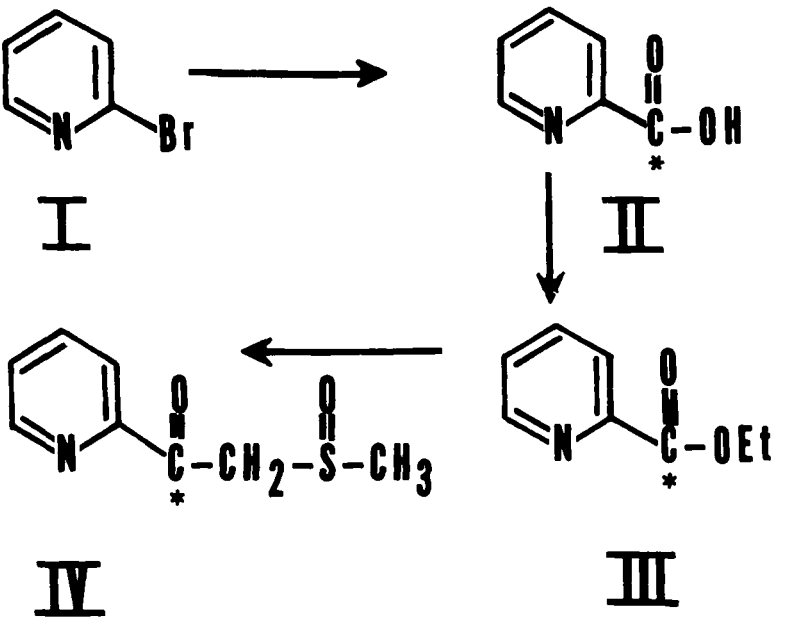
[1]The generic name for this compound is oxisuran.

When n-butyl lithium in hexane was added to an ethereal solution of 2-bromopyridine at -20°C, cooled to -45°C, and then carbonated, a 23% yield of the picolinic acid was obtained. The yield was increased to 28% when the n-BuLi was added at -45°C. No increase in the yield was obtained when the temperature was reduced to -78°C. The CO_2 reacted rapidly with the organolithium complex at these temperatures.

Picolinic-(carboxyl-^{14}C) acid was obtained in 38% chemical and radiochemical conversion from 129 mCi $BaCO_3$-^{14}C, as the unreacted $^{14}CO_2$ was recovered as $BaCO_3$-^{14}C.

Ethyl picolinate-(carboxyl-^{14}C) (III) was obtained in 84% yield by esterification with ethanol.

This ester was then converted into IV by the attack of the anion generated from dimethyl sulfoxide (DMSO) by sodium hydride (8), on III using benzene as the reaction medium, in 62.5% yield. The chemical and radiochemical purity was 99+%. An over-all chemical conversion of 19% from $BaCO_3$-^{14}C was obtained.



Experimental:

Picolinic-(carboxyl-^{14}C) Acid (II): To a magnetically stirred solution under N_2 of 80 ml anhydrous ether and 24 ml of a 15% solution of n-butyl lithium (40 mM) in hexane (9) cooled to -45°C (10), was added 6.33 g (40 mM) of 2-bromopyridine (11) (bp = 75-6°C/13 mm) in 80 ml anhydrous ether over 5 minutes (12). An orange-red color appeared almost instantly. The reaction was then cooled to -78°C and evacuated to 15 mm pressure.

The uptake of $^{14}CO_2$ liberated by the portionwise addition over 1 hour of 200 ml of 5N aqueous perchloric acid to 7.88 g (40 mM) $BaCO_3$-^{14}C (13) (129 mCi, specific activity 3.31 mCi/mM) was rapid. The orange-red color was simultaneously discharged to a steel blue color. The reaction was allowed to stir at -78°C for one hour. The unreacted $^{14}CO_2$ was then pumped (14) into a 3 l flask containing 200 ml of a freshly prepared and filtered saturated aqueous $Ba(OH)_2$ solution.

The reaction was stopped by the addition of 40 ml of a saturated aqueous ammonium sulfate solution, and extracted with four 100-ml portions of diethyl ether. The aqueous phase was put back into the reaction system, sealed, and evacuated. The pH was adjusted to about 7 with 6N hydrochloric acid. The evolved $^{14}CO_2$ was transferred to the $Ba(OH)_2$ containing flask.

The pH of the aqueous solution was adjusted to 3 and was continuously extracted overnight with chloroform. The chloroform extract was dried with $MgSO_4$, filtered, and the solvent removed. The resulting II weighed 1.50 g (31%), melted at 136-138°C, and was satisfactory for the next step.

The recovered $BaCO_3$-^{14}C weighed 1.55 g (21% recovery) and exhibited a specific activity of 3.52 mCi/mM (17.9 mCi/g).

Ethyl Picolinate (carboxyl-^{14}C) (III): To a magnetically stirred solution of 1.50 g (12.2 mM) II in 12.2 ml of absolute ethanol was added 2.65 ml concentrated sulfuric acid at a slow rate. The reaction was refluxed for 7 hours and then cooled to -10°C. Five grams of ice were added and the pH adjusted to 9 by the addition of about 5 ml of 50% aqueous K_2CO_3. The precipitated salts were filtered and washed with 30 ml chloroform. The filtrate was extracted with three 10-ml portions of chloroform. The chloroform extracts were combined, the solvent was removed, and the oily resude was distilled. The fraction boiling at 129-130°C/17 mm was collected and weighed 1.5 g (84%). This was pure III and was used directly to prepare IV.

2-[(Methylsulfinyl)acetyl(carbonyl-^{14}C)]pyridine (IV): To a stirred solution of 1.50 g (9.8 mM) III, and 1.53 g (19.6 mM) dimethylsulfoxide in 8.3 ml dry benzene was added 0.902 g (19.6 mM) of sodium hydride as a 54% dispersion in mineral oil (15) portionwise over 10 minutes. The reaction was left to stir at room

temperature overnight under nitrogen and then poured over 16 g of ice. The solution was washed with four 20-ml portions of ether, which were discarded. The pH of the aqueous phase was adjusted to 6.5 with concentrated hydrochloric acid, and the solution extracted with four 25-ml portions of chloroform. The combined chloroform phases were dried with $MgSO_4$, filtered, and the solvent removed. The residue was dissolved in 10 ml of hot ethyl acetate, boneblacked, and filtered. The filtrate was concentrated to about 3.3 ml and allowed to cool to room temperature. About 3.3 ml of Skellysolve B (16) were added and the mixture left at 5°C overnight. The crystals were filtered to give 1.12 g of IV (62.5%) which melted at 79.0-80.5°C. To this was added 1.9 g of authentic IV, and this mixture was recrystallized again from the same solvents. This gave 2.8 g (94% recovery) of IV, which melted at 80.0-81.3°C.

An infrared spectrum determined as a mull exhibited maxima at 1700, 1585, 1445, 1315, 1290, 1200, 1020, 995 and 790 cm^{-1}. The ultraviolet spectrum determined in ethanol exhibited maxima at 234 and 271 nm(mμ). The absorptivity was 45.4 and 28.1, respectively.

A thin-layer chromatogram (TLC) using a 5 x 20 cm plate coated with a 250 micron thick layer of silica gel GF (17), when irrigated with a mixture of ethyl acetate, methanol, and glacial acetic acid (75/25/5), gave a single spot when viewed under ultraviolet light at an R_f of about 0.6, which was identical with an authentic sample. All of the radioactivity on the plate was contained in this one spot (18). This TLC system was designed to separate the components likely to be present in IV.

The above physical constants, when compared with an authentic sample (19), demonstrated a chemical and radiochemical purity of 99+%.

The specific activity was determined to be 1.12 mCi/mM (6.86 mCi/g) via liquid scintillation spectrometry (20).

Acknowledgements: The authors wish to acknowledge the technical assistance of Mrs. N. Eltvedt. We also are indebted to Mr. A. D. Lewis, Director of Analytical/Physical Chemistry and his associate, Dr. R. C. Greenough, for providing the spectral data.

References:

1. H. H. Freedman, A. E. Fox, G. Morrison, and J. Shavel, Proc. Soc. Exp. Biol. and Med., in press.

2. F. J. DiCarlo, M. C. Crew, L. J. Haynes, and R. L. Gala, Biochem. Pharmacol., in press.

3. M. C. Crew, M. D. Melgar, L. J. Haynes, R. L. Gala, and F. J. DiCarlo, European J. of Pharmacol., in press.

4. G. Morrison and J. Shavel, Jr., German Pat. 1,955,682 (6/4/70).

5. A. Murray, W. W. Foreman, and W. Langham, "Organic Syntheses With Isotopes" Vol. I, A. Murray and D. L. Williams, Ed., Interscience Publishing Co., N.Y., 1958, p. 392.

6. H. Gilman and S. M. Spartz, J. Org. Chem. 16, 1485 (1951).

7. J. Overhoff and W. Proost, Recu. trav. chim. 57, 179 (1938).

8. E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc. 87, 1345 (1965).

9. This solution is available from Matheson, Coleman, and Bell, East Rutherford, N.J. 07073.

10. C. J. Collins, J. Amer. Chem. Soc., 73, 1038 (1951).

11. This compound is available from Nepera Chemical Co., Harriman, N.Y. 10926.

12. W. G. Douben, J. C. Reid, and P. E. Yankwich, Anal. Chem. 19, 828 (1947).

13. Purchased from Mallinckrodt/Nuclear, St. Louis, Missouri.

14. Purchased from Rodder Instruments, Los Altos, California 94022.

15. This mixture is available from Metal Hydrides, Beverly, Mass.

16. Skellysolve B is principally n-hexane and is available from Skelly Oil Co., El Dorado, Kansas.

17. These plates are available from Analtech, Inc., Wilmington, Del. 19801.

18. A Packard Model 7200 Radiochromatogram Scanner was used.

19. The authentic sample was supplied by M. Goodenough of these laboratories.

20. A Packard Model 3310 Tri Carb Liquid Scintillation Spectrometer equipped with external standardization was used. A cocktail composed of 7.0 g PPO (2,5-diphenyloxazole), 0.3 g dimethyl POPOP [1,4-bis-2-(4-methyl-5-phenyloxazolyl)benzene] and 100 g naphthalene in 1 l 1,4-dioxane was used throughout. See F. N. Hayes, Packard Technical Bulletin #1, (1963) p. 4.