# Access to $^{14}C$-Ring Labelled Phenothiazines. Synthesis of 2-Chlorophenothiazine-5a,9-$^{14}C$ (1)



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Through the use of a recently reported ring expansion reaction, a new route to phenothiazines has been developed suitable for the preparation of ring labelled derivatives. As an example, the preparation of 2-chlorophenothiazine-5a,9-$^{14}C$ (**1**) is reported. Condensation of cyclohexanone-2-$^{14}C$ with 2-amino-4-chlorothiophenol gave the spiro-2,3-dihydro-1,3-benzothiazole **4** which was protected by acetylation (**5**). Treatment of **5** with sulfuryl chloride gave the tetrahydrophenothiazine olefin mixture **6** and **7** which was directly converted to labelled **1** *via* treatment with DDQ in refluxing benzene followed by hydrolysis of the acetyl group.

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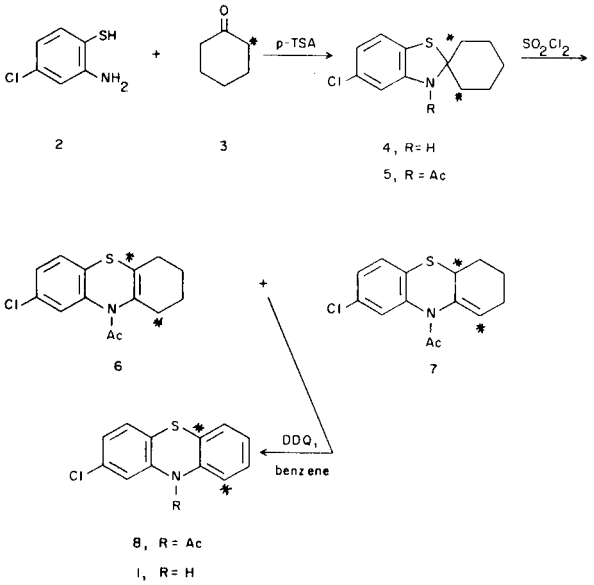
In connection with other studies, we required a general route to ring labelled ($^{14}C$ or $^{13}C$) 2-substituted phenothiazines from which any desired derivative could be prepared. The established synthetic routes to the tricyclic phenothiazine system involve either sulfuration (2-5) or nucleophilic substitution (5-8) reactions on preformed aromatic systems. It was necessary, therefore, to devise a synthetic route which would allow the construction of an aromatic ring from readily available labelled intermediates. Utilizing a recently reported ring expansion reaction (9) and the availability of cyclohexanone labelled in either the 1 (10) or 2 (11) positions, the route in Scheme 1 was chosen. To illustrate the utility of this method, we report the preparation of 2-chlorophenothiazine-5a,9-$^{14}C$ (**1**).

Scheme I




Condensation of 2-amino-4-chlorothiophenol (**2**) (12) with cyclohexanone-2-$^{14}C$ (**3**) (11) gave the spiro-2,3-dihydro-1,3-benzothiazole **4** which was acetylated to give **5**. Ring expansion of **5** *via* treatment with sulfuryl chloride gave the mixture of olefins **6** and **7**, which were used directly in the next reaction (13). Oxidation of mixture **6** and **7** with DDQ in refluxing benzene gave acetate **8** which was hydrolyzed to the desired **1** (similar treatment with *o*-chloranil selectively converted olefin **7** to phenothiazine **8** leaving olefin **6** unchanged).

In summary, we report a procedure for constructing the tricyclic phenothiazine ring system which permits the preparation of ring labelled derivatives and, as a result of using non-aromatic precursors, has the potential for leading to phenothiazine derivatives not readily obtained by existing methods.

## EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Spectra were recorded on standard instruments by the staff of the Physical Chemistry Department and microanalyses were performed by the Microchemical Laboratory, both of Hoffmann-La Roche, Inc. Radiochemical purity was determined on thin layer chromatograms with a Packard Model 7201 Radiochromatogram Scanner System and radioactivity was measured by the liquid scintillation technique with a Packard Tricarb Model 2010 spectrometer. All reactions were carried out in a nitrogen atmosphere and the usual workup refers to ether extraction, washing with dilute acid or base where appropriate, washing with saturated sodium chloride solution, drying over magnesium sulfate and removal of solvent *in vacuo*.

### 3-Acetyl-5-chlorospiro[benzothiazole-2(3*H*)]-1-cyclohexane (**5**).

Cyclohexanone-2-$^{14}C$ (11) (111 mg., 1.13 mmoles, 67 mCi, 59.4 mCi/mmole) and 4-chloro-2-aminothiophenol (12) (200 mg., 1.25 mmoles) were heated to reflux with *p*-toluenesulfonic acid (20 mg.) in benzene (50 ml.) under a DeanStark trap for 2.5 hours. After concentration of the solution *in vacuo*, the residue was chromatographed (silica gel, 100 g, 10% ethyl acetate–hexane elution) to yield 200 mg. (0.83 mmole, 49.3 mCi, 74%) of **4** as a yellow solid, m.p. 90-91°. An unlabelled sample was recrystallized from hexane, m.p. 94-95°; ir (chloroform): 3395 $cm^{-1}$ (NH), 2945 ($CH_2$), 1583 and 1476 (aromatic); nmr

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(chloroform): δ 1.55-1.8 (8H, broad, methylenes), 2.20 (2H, broad doublet, J = 14 Hz, α-equatorial hydrogens), 3.97 (1H, sharp, N*H*), 6.45-6.87 (3H, multiplet, aromatic); ms: m/e 239 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{14}ClNS$: C, 60.11, H, 5.89, N, 5.84; S, 13.37. Found: C, 60.04; H, 5.99; N, 5.83; S, 13.92.

Radiolabelled **4** (200 mg., 0.83 mmole, 49.3 mCi) was diluted with 205 mg. (0.86 mmole) of unlabelled material in acetic anhydride (10 ml.) and heated to reflux for 5 hours. Evaporation of the solvent *in vacuo* gave a residue which was chromatographed (silica gel, 20 g., benzene eluent) to yield 376 mg. (1.34 mmoles, 38.5 mCi, 28.7 mCi/mmole, 79%) as a yellow oil. A non-labelled sample was crystallized from methanol to give m.p. 44-45°; ir (chloroform): 1670 $cm^{-1}$ (tertiary amide); nmr: δ 1.4-1.95 (6H, complex, methylenes), 2.07 (2H, broad doublet, J = 14 Hz, α-equatorial hydrogens), 2.35 (3H, s, acetate), 2.80 (2H, doublet of triplets, J = 4 and 14 Hz, α-axial hydrogens), 6.9-7.1 (3H, complex, aromatic); ms: m/e 281 ($M^+$).

*Anal.* Clacd. for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; N, 4.97; S, 11.38. Found: C, 59.49; H, 5.83; N, 5.01; S, 11.67.

**10-Acetyl-8-chloro-1,2,3,4-tetrahydro-10*H*-phenothiazine (6) and 10-Acetyl-8-chloro-1,2,3,10a-tetrahydro-10*H*-phenothiazine (7).**

Labelled **5** (376 mg., 1.34 mmoles, 38.46 mCi) in methylene chloride (10 ml., dried through an alumina column) was treated with sulfuryl chloride (9) (200 μl., 333 mg., 2.47 mmoles) in methylene chloride (5 ml.) at room temperature over 45 minutes. Stirring was continued 30 minutes, then the reaction was diluted with chloroform, washed with aqueous bicarbonate solution, dried and concentrated. The residue was filtered through a silica gel (10 g.) column in benzene to give 205 mg. (55%) of crude **6** and **7**, which was used directly in the next reaction. A similar reaction with non-labelled material gave a residue, a portion (200 mg.) of which was chromatographed on a preparative plate (10% silver nitrate impregnated on silica gel, 2 mm, 50% ethyl acetate–hexane) to yield 82 mg. (22%) of **6** (Rf = 0.33) as an oil, 38 mg. (10%) of **7** (Rf = 0.29) as an oil and 34 mg. (9%) of a 1:1 mixture of **6** and **7**. The band assigned structure **6** had the following spectral properties: nmr: δ 1.75 (4H, broad, methylenes), 2.07 (3H, sharp, acetate), 2.35 (4H, broad, allylic methylenes), 7.24 (3H, complex, aromatic); ms: m/e 245 (M+). The band assigned structure **7** had the following spectral properties: nmr: δ 1.82 (4H, broad, methylenes), 2.16 (3H, sharp, acetate), 2.44 (2H, broad, allylic methylenes), 4.20 (1H, multiplet, -C*H*-S), 5.98 (1H, sharp, vinyl), 7.30,(complex, aromatic); ms: m/e 245 (M+).

**2-Chloro-10*H*-phenothiazine-5a,9-$^{14}$C (1).**

The crude mixture of **6** and **7** (205 mg.) was heated to reflux overnight in dry benzene (20 ml.) with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Aldrich, 0.5 g., 2.2 mmoles). The solution was concentrated in vacuo, taken up in chloroform and filtered through Celite, then chromatographed (silica gel, 100 g., 10% ethyl acetate/hexane eluent) to yield upon combination of the appropriate fractions, 45 mg. of **8** (0.16 mmole, 4.5 mCi, 23%).

Treatment of **8** (45 mg.) with potassium hydroxide (28 mg., 0.5 mmole) in refluxing ethanol (10 ml., 15 minutes) gave after the usual workup, 37 mg. (~100%, 0.16 mole, 4.5 mCi, 122 μCi/mg, 28.7 mCi/mmole) of **1** in sufficient purity (~96%) for direct use in subsequent reactions. For higher purity, the material can be rechromatographed (silica gel, 10% ethyl acetate in hexane) with ~90% recovery. Overall yield from cyclohexanone-2-$^{14}$C is 7%.

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(13) The olefins were separated from an unlabelled reaction mixture for structure determination purposes, see experimental.