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The preparation of ^{2}H and ^{3}H-labelled 7,9-, and 7,10-dimethylbenz[c]acridine by catalytic dehalogenation

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SUMMARY

Deuterated and tritiated 7,9-dimethylbenz[c]acridine, and 7,10-dimethylbenz[c]acridine, labelled at the methyl groups, were prepared by catalytic dehalogenation of bromomethyl compounds. For each aza-aromatic compound three brominated derivatives were prepared and characterized. Incorporation of deuterium occurred more readily at the 9- or 10-methyl groups than the 7-methyl groups suggesting a large isotope effect for catalytic deuteration.

INTRODUCTION

Some methyl derivatives of the angular benzacridines have been known to be highly carcinogenic for many years (1-5), especially those of benz[c]acridine. Amongst them, 7,9-dimethylbenz[c]acridine (7,9-DMBAC) and 7,10-dimethylbenz[c]acridine (7,10-DMBAC) have highest carcinogenic activities (3) and have been identified as environmental pollutants (6). Unfortunately, only synthetic studies (7,8) have appeared for them. In order to facilitate metabolic and DNA binding studies of 7,9-DMBAC (1) and 7,10-DMBAC (2), radioactive labelling of those two compounds is necessary.

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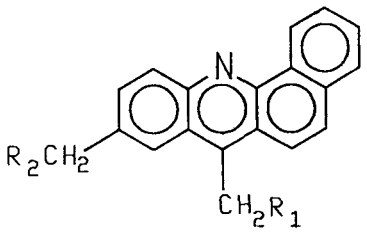

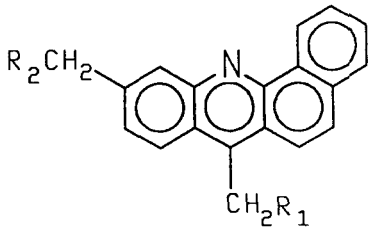

$R_1 = R_2 = H$	1	$R_1 = R_2 = H$	5
$R_1 = Br, R_2 = H$	2	$R_1 = Br, R_2 = H$	6
$R_1 = H, R_2 = Br$	3	$R_1 = H, R_2 = Br$	7
$R_1 = R_2 = Br$	4	$R_1 = R_2 = Br$	8

As a precursor for the tritium labelling, the catalytic dehalogenation of bromo derivatives of the dimethylbenzacridines (4) and (7) was initially investigated in the presence of deuterium. Following this, tritium labelled samples with high radiochemical purity were prepared for dimethylbenz[c]-acridines (1) and (2), with the tritium atom at the 9-and 10-positions respectively.

EXPERIMENTAL

General

Short column vacuum chromatography was performed using 60 mesh silica gel HF_{254},, (E. Merck, Darmstadt, Germany). Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} precoated aluminium sheets with a layer thickness of 0.2mm (E. Merck Darmstadt, Germany). Petroleum spirit refers to that fraction which distils at 70-75°. Deuterium was obtained from Matheson Gas Products (E.Rutherford, N.J., U.S.A.), and tritium from Amersham (Sydney, Australia)

Instrumentation

^{1}H-NMR spectra were measured using a JEOL FX90Q Spectrometer operating at 89.6 MHz in the Fourier-transform mode with a Texas 989B computer Data system using solutions in the deuterochloroform with tetramethylsilane (TMS) as internal reference. High resolution spectra were measured using a Bruker W.M 400 MHz NMR Spectrometer.

Chemical ionisation mass specta (CIMS) were obtained using a Finnigan-Mat TSQ46 GC/MS /MS with an Incos data system. Methane was employed as reagent gas and adduct ions at M + $C_2H_5^+$ and M + $C_3H_5^+$ were seen in all spectra in

which prominent MH^{+} ions were present. GC of deuteration products was performed on an HP-1 capillary column (8.3 m x 0.2 mm i.d., Hewlett Packard, Ryde, N.S.W., Australia) with a temperature gradient, begun after 1.4 min isothermal operation, from 80°C to 250°C at 15 C°/min, and then to 300°C at 20 C°/min using helium (UHP grade) as carrier gas with mass spectral detection.

High Performance Liquid Chromatography (HPLC)

Normal phase HPLC was performed on a dual 110 pump system (Beckman Instrument Inc, Gladesville, Australia) using an NEC PC-8300 controller and a variable wavelength detector (Spectra-Physics, Sydney) at 270 nm. A Lichrosorb 10 μm silica column (250 mm x 4.6 mm i.d., Brownlee Labs, Santa Clara, Ca., U.S.A.) was used with isochratic elution with 1% EtOAc in petroleum spirit and a flowrate of 1 mL/min.

Preparative HPLC was performed using Altex Model 100 pump fitted with preparative heads on a Lichrosorb 5 μm silica column (250 mm x 25 mm i.d., HPLC Technology, Macclesfield, U.K) with an R403 differential refractometer (Waters-Millipore, Ryde, NSW, Australia) and a flow rate of 10 mL/min. Brominated derivatives of 7,9-DMBAC were separated with 1.5% EtOAc in petroleum spirit while those of 7,10-DMBAC were separated with 1% EtOAc in petroleum spirit.

Reversed-phase HPLC was performed on an Altex gradient system (Model 421 solvent programmer) using 110A pumps and a Jasco Uvidec-100-V UV detector at 270 nm. A Lichrospher 100 RP-8 10 μm reversed-phase column (250 mm x 4.6 mm i.d., Merck, Darmstadt, Germany) at 40° with a flowrate of 1 mL/min enabled purification of ^{3}H-labelled 7,9-DMBAC and 7,10-DMBAC and the determination of their radiochemical purities using a linear gradient of methanol-water from 60-100% MeOH over 30 min.

Synthesis of 7,9-dimethylbenz[c]acridine (1)

This compound was synthesized from N-*p*-tolyl-naphthylamine and according to the method of Buu-Hoi (7).

Synthesis of 7,10-dimethylbenz[c]acridine (2)

The same method (7) was employed as for 7,9-DMBAC. A Bernthsen reaction was applied to N-*m*-tolyl-1-naphthylamine, and a mixture of 7,10-DMBAC and 7,8-dimethylbenz[c]acridine (7,8-DMBAC) (8) (85:15) was obtained. Use of the

normal-phase HPLC to analyze this product mixture allowed the relative amounts of 7,10-DMBAC (t_R 8.5 min) and 7,8-DMBAC (t_R 10.4 min) to be obtained from peak areas. Separation of the products by vacuum short column chromatography and repeated recrystallization from EtOAc afforded 7,10-DMBAC, 98% pure by HPLC.

Synthesis of brominated derivatives of 7,9-DMBAC

7,9-DMBAC (200 mg) was refluxed with N-bromosuccinimide (NBS) (135 mg) and dibenzoyl peroxide (30 mg) in CCl_4 (20 mL) for 3 h under N_2. The progress of the reaction was followed by TLC (silica gel) with petroleum spirit (bp 70-75°C):CH_2Cl_2 1:1 and petroleum spirit:EtOAc 9:1, and by normal-phase HPLC. When the reaction was complete, the succinimide was removed from the cold solution by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was subjected to short column chromatography (silica bed: 5 cm i.d. x 3 cm) and gave, on elution with 5% EtOAc in petroleum spirit, 260 mg total products with almost no separation of the brominated compounds. These were separated by preparative HPLC with 1.5% EtOAc in petroleum spirit to afford, in order of emergence, the 7-mono compound, unchanged 7,9-DMBAC, 9-monobromo and dibromo compounds. The products were chromatographically pure on the analytical HPLC column. They were 7-bromomethyl-9-methylbenz[c]acridine (7-CH_2Br-9-MBAC, 3) (72 mg; 27% yield; t_R = 20.8 min.); ^{1}H-NMR (2 mg/0.3 mL, 400 MHz) δ 2.65 (3H, 9-CH_3, s), 5.36 (2H, 7-CH_2Br, s), 7.66 (H_{10}, dd), 7.69-7.88 (H_2-H_4, m), 7.81 (H_5, d), 7.98 (H_8, bs), 7.99 (H_6, d), 8.28 (H_{11}, d), 9.47 (H_1, bd); $J_{5,6}$ = 9.4 Hz, $J_{10,11}$ = 8.8 Hz, $J_{8,10}$ = 1.9 Hz; CIMS m/z (relative intensity): 338 (MH^+ $^{81}Br_1$, 35), 336 (MH^+ $^{79}Br_1$, 35), 256 (58). 9-Bromomethyl-7-methyl-benz[c]-acridine: (9-CH_2Br-7-MBAC, 4) (61.3 mg; 23% yield; t_R = 31.5 min.). ^{1}H-NMR (2 mg/0.3 mL, 400 MHz) δ 3.09 (3H, 7-CH_3, s), 4.77 (2H, 9-CH_2Br, s), 7.70-7.87 (H_2-H_4. m), 7.73 (H_5, d), 7.81(H_{10}, dd), 8.01 (H_6, d), 8.23 (H_8, bs), 8.33 (H_{11}, d), 9.51 (H_1, bd); $J_{5,6}$ = 9.4 Hz, $J_{10,11}$ = 8.8 Hz, $J_{8,10}$ = 1.8 Hz. CIMS m/z (relative intensity): 338 (MH^+ $^{81}Br_1$, 34), 336 (MH^+ $^{79}Br_1$, 34), 256 (58). 7,9-*bis*-Bromomethylbenz[c]acridine (7,9-(CH_2Br)$_2$-BAC, 5) (37 mg; 11% yield; t_R = 37.5 min.): ^{1}H-NMR (2 mg/0.3mL, 400 MHz) δ 4.79 (2H, 9-CH_2Br, s), 5.38 (2H, 7-CH_2Br, s), 7.74-7.91 (H_2-H_4, m), 7.86 (H_{10}, dd), 7.87 (H_5, d), 8.02 (H_6, d), 8.24 (H_8, sd), 8.39 (H_{11}, d), 9.50 (H_1, bd); $J_{5,6}$ = 9.2 Hz, $J_{10,11}$ = 8.8 Hz, $J_{8,10}$ = 1.8 Hz. CIMS m/z (relative intensity): ^{81}Br/^{79}Br cluster; 418 (MH^+ $^{81}Br_2$/$^{79}Br_0$, 37), 416 (MH^+ $^{81}Br_1$/$^{79}Br_1$, 82), 418 (MH^+ $^{81}Br_0$/$^{79}Br_2$, 39) 258 (30), 256 (22).

Synthesis of brominated derivatives of 7,10-DMBAC.

7,10-DMBAC (100 mg) and NBS (100 mg) were mixed in benzene (5 mL). Dibenzoyl peroxide (1 mg) was added as free radical initiator, and the mixture

was refluxed under N_2 for 2.5 h. After removal of the succinimide by filtration, the cold reaction mixture was concentrated under reduced pressure and the residue was then passed through a short column of silica gel (3 cm x 5 cm i.d.) using 5% EtOAc in petroleum spirit to gave total products (140 mg) with little separation. Preparative HPLC with 1% EtOAc in petroleum spirit (10 mL/min) gave pure products. 7-Bromomethyl-10-methylbenz[c]acridine (7-CH_2Br-10MBAC, 6) (40 mg; s0% yield; t_R = 34.2 min.). ^{1}H-NMR (2 mg/0.3 mL,400 MHz) δ 2.67 (3H, 10-CH_3, s), 5.39 (2H, 7-CH_2Br, s), 7.56 (H_9, dd) 7.71-7.90 (H_2-H_4, m), 7.83 (H_5, d), 8.02 (H_6, d), 8.19 (H_{11}, bs), 8.20 (H_8, d), 9.50 (H_1, bd); $J_{5,6}$ = 9.36 Hz, $J_{8,9}$ = 8.8 Hz, $J_{9,11}$ = 1.9 Hz. CIMS m/z (relative intensity): 338 (MH^+ $^{81}Br_1$, 54), 336 (MH^+ $^{79}Br_1$, 54), 256 (18). 10-Bromomethyl-7-methylbenz[c] - acridine (10-CH_2Br-7-MBAC, 7) (13 mg; 10% yield; t_R = 46.1 min.). ^{1}H-NMR (2 mg/0.3 mL, 400 MHz) δ 3.10 (3H, 7-CH_3, s), 4.77 (2H, 10-CH_2Br, s), 7.64 (H_9, dd), 7.71-7.88 (H_2-H_4, m), 7.74 (H_5, d), 8.03 (H_6, d), 8.27 (H_8, d), 8.34 (H_{11}, bs), 9.51 (H_1, bd); $J_{5,6}$ = 9.4 Hz, $J_{8,9}$ = 8.9 Hz, $J_{9,11}$ = 1.75 Hz. CIMS m/z (relative intensity): 338 (MH^+ $^{81}Br_1$, 41), 336 (MH^+ $^{79}Br_1$, 41), 256 (58). 7,10-*bis*-Bromomethybenz[c] - acridine (7,10-(CH_2Br)$_2$-BAC, 8) (41 mg; 25% yield; t_R = 60.2). ^{1}H-NMR (2 mg/0.3 mL, 400 MHz) δ 4.78 (2H, 10-CH_2Br, s), 5.38 (2H, 7-CH_2Br, s), 7.75 (H_9, dd), 7.77-7.91 (H_2-H_4, m), 7.87 (H_5, d), 8.02 (H_6, d), 8.29 (H_8, d), 8.39 (H_{11}, bs), 9.49 (H_1, bd). CIMS m/z (relative intensity) ^{81}Br/^{79}Br cluster; 418 (MH^+ $^{81}Br_2$/$^{79}Br_0$, 16), 416 (MH^+ $^{81}Br_1$/$^{79}Br_1$, 36), 414 (MH^+ $^{81}Br_0$/$^{79}Br_2$, 21), 336 (46), 334 (40), 256 (15).

Deuterium labelled 7,9-DMBAC and 7,10-DMBAC.

5% Pd/$CaCO_3$ (1 mg) in benzene (2 mL) was stirred under D_2 gas for 0.5 h before 10-CH_2Br-7-MBAC (2 mg) or 9-CH_2Br-7-MBAC (2 mg) was added. The reduction was allowed to proceed for 2.5 h until complete (monitored by TLC; EtOAc:petroleum spirit, 1:9). After solvent removal under reduced pressure, the material was dissolved in CH_2Cl_2 (20 mL), and the organic phase was washed with 20% aq. NaOH (2 x 20 mL), dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was then subjected to short column vacuum chromatography on silica gel (3 cm x 3 cm i.d.) eluting with 5% EtOAc in petroleum spirit. The product was a light yellow crystalline solid.

7,9-Dimethylbenz[c]acridine-9-^{2}H,(1). ^{1}H-NMR (1.5 mg/0.3 mL $CDCl_3$): δ (ppm) 2.64 (9-CH_2D, 2H, bs); 3.08 (7-CH_3, 3H, s); 8.31-7.56 (8H, m); 9.52 (H_1, m). GC-CIMS gave a single GC peak at 13.2 min, m/z (relative intensity): 259 (100); 258 (14). Calculations from the relative intensities of the 258 and 259 MH^+ ions showed, after adjustment for natural isotopic abundances, a 90% deuterium incorporation.

7,10-Dimethylbenz[c]acridine-10-^{2}H,(2). ^{1}H-NMR (1.5 mg/0.3 mL $CDCl_3$): δ (ppm) 2.64 (10-CH_2D, 2H, bs); 3.09 (7-CH_3, 3H, s); 7.36-8.17 (8H, m); 9.54 (H_1, m). GC-CIMS showed only one chromatographic peak at 12.7 min, m/z (relative intensity) 259 (100), 258 (17). Calculations from relative intensities of the 258 and 259 MH^+ ions gave an 87% deuterium incorporation.

Tritium labelling of 7,9-DMBAC and 7,10-DMBAC

9-CH_2Br-7-MBAC (6 mg) or 10-CH_2Br-7-MBAC (5 mg) was dissolved in benzene (2 mL) and 5% Pd/$CaCO_3$ (3 mg) was added. Air, and adsorbed gases were removed by a vacuum system using three successive cycles of freezing, evacuation, and thawing of the isolated reaction mixture before tritium gas (2 Ci) was transferred to the reaction flask with a Toepler pump. The flask was isolated, allowed to warm to room temperature and the mixture was stirred 24 h. Reduction occurred but was not complete (shown by TLC; EtOAc : petroleum spirit - 1:9). Benzene was removed by vacuum-line transfer, and the residue was redissolved in benzene (3 mL), another portion of fresh catalyst (1 mg) was added, and reduction was allowed to proceed for another 1 h with H_2. The solvent was removed under reduced pressure and the product was isolated as described above for the deuterated compounds. The product (4 mg) was a light yellow crystalline solid. Radiochemical purities of 94.5% for tritiated 1 and 81.6% for tritiated 2 were obtained by HPLC (gradient shown below).

The products from short column chromatography were further purified on HPLC using a 10 μm Lichrospher 100 RP-8 column. Both 7,9-DMBAC and 7,10 DMBAC eluted at 21 min.

Determination of Radiochemical purity and specific radioactivity

The radiochemical purity was assessed by reverse-phase HPLC by determination of the radioactivity in 40 x 1 min fractions from the column. It was expressed as the percentage radioactivity cochromatographing with added unlabelled aza-arene. The specific radioactivity was calculated from the radioactivity, and the concentration of aza-arene determined by UV spectrophotometry at 281 nm.

Liquid scintillation counting using Emulsifier Scintillator 299 (Packard Instrument Co, Groningen, Netherlands) and a Packard model 1900 Liquid Scintillation Spectrometer were used for radioactivity measurements.

RESULTS and DISCUSSION

As the precursor for ^2H- and ^3H-labelling, the bromomethyl compounds of both 7,9-DMBAC and 7,10-DMBAC were synthesized through bromination of parent compounds 1 and 2 with NBS. In each case two isomeric monobromo compounds were obtained together with the *bis*-bromomethyl derivative. The monobromo compounds bore the bromine atom at the 7-position (3 and 6) or at the 9- (or 10-) position (4 and 7). The structures of the monobromo compounds were determined from the chemical shifts of the remaining methyl protons. In 4 and 7, these signals appeared at about 3.05 ppm, which is in agreement with that of the methyl protons in 9-methylacridine (2.88 ppm) (9). For these compounds the methylene proton signals occurred at 4.77 and 4.78 respectively. In their isomers, the 7-bromomethyl compounds 3 and 6, the methyl proton signals appeared at about 2.65ppm, while the methylene proton signals occurred downfield of those of their isomeric compounds at 5.36 and 5.39 respectively. Both *bis*-bromomethyl compounds (5 and 8) showed the absence of methyl signals, and two methylene signals at about 4.78 and 5.38 ppm.

The preparation of ^2H-labelled 7,9-DMBAC and 7,10-DMBAC were attempted through the dehalogenation of monobromomethyl derivatives of (1) and (2). Table 1 displays the incorporation of deuterium for those reactions. The reduction of two 7-bromo-compounds, 7-CH_2Br-9-MBAC (3) and 7-CH_2Br-10MBAC (6), with D_2 gas over Pd/$CaCO_3$ occurred successfully. However, on observation of GCMS and ^1H-NMR, the major ion was due to the hydrogenated compound (MH^+ at m/z 258) instead of the expected deuterated one (m/z 259).

Table 1. ^2H- and ^3H-labelling of 7,9-DMBAC and 7,10-DMBAC

Compound	precursor	incorporation of deuterium %		specific activity mCi/mmole	radiochemical purity %	
		GCMS	^1H-NMR		- HPLC[a]	+ HPLC
1	7-CH_2Br-9-MBAC (3)	10				
	9-CH_2Br-7-MBAC (4)	90	82	1180	94.6	99.6
	7,9-(CH_2Br)$_2$-BAC (5)	65(1D) 7.3(2D)				
2	7-CH_2Br-10MBAC (6)	12				
	10-CH_2Br-7-MBAC (7)	86	80	202	81.8	98.9
	7,10-(CH_2Br)$_2$-BAC (8)	73(1D) 9(2D)				

[a] Before and after purification by HPLC.

Deuterium incorporation could only be quantitated from CIMS data (and not by ^{1}H-NMR) and only about 10% deuterium content was calculated for each reaction. The possible reasons for this low level of deuterium incorporation were a catalyst-mediated transfer of solvent-hydrogen to the substrate, the presence of $^1H_2$ gas in the catalyst, gas-solvent exchange and the presence of $^1H_2$ gas in the D_2 gas used. According to Oehlke *et al.* (10), the direct transfer of solvent-hydrogen to the substrate was the most probable reason for the exchange of halogen by hydrogen instead of deuterium in their catalytic dehalogenation of N-acetyl-L-4-chloro-and N-acetyl-L-4-iodophenylalanine amide. If this were true in the present case, the competing ^{1}H-incorporation should be diminished by the use of deuterated solvents. When perdeuterated benzene in place of normal benzene was employed, no influence on the extent of hydrogen incorporation was evident. Pretreatment of catalyst with D_2 gas for 0.5 h before introduction of the bromo compounds also failed to produce improvement in deuterium incorporation. The rate of gas-solvent exchange was reported to be in the range of only 3-10 μmol/h (10,11), and such a low rate of exchange cannot account totally for the observed low deuterium incorporation. The D_2 gas used was shown to contain 2 moles % of H_2 gas (by mass spectral analysis), and a catalytic reduction of benzyl bromide in solvent dioxane gave an indication of the magnitude of the isotope effect. GCMS of the the toluene showed a 66% incorporation of deuterium. This suggested that H_2 gas in D_2 gas was the most likely source of the ^{1}H and its incorporation was due to an isotopic effect which was highly variable with different precusors. Deuteration of 9-CH_2Br-7-MBAC (4) and 10-CH_2Br-7-MBAC (7) under the same conditions as for 7-bromomethyl compounds, 3 and 6 proceeded successfully. GCMS data showed a 90% deuterium incorporation for the reduction of 9-CH_2Br-7-MBAC and 86% for that of 10-CH_2Br-7-MBAC in benzene. The percentage deuteration was also calculated from ^{1}H-NMR of the product by assuming that no deuterium was present in the molecule other than on the methyl group, by comparing the integral of 9-CH_3 or 10-CH_3 protons with those of the 7-CH_3 protons. An incorporation of 82% was obtained for 7,9-DMBAC and 80% for 7,10-DMBAC and these were in reasonable agreement with those from the mass spectral data. The *bis*-bromomethyl compounds were also reacted with deuterium gas, and these gave incorporations of 65% and 73% for 1D and only 7.3% and 9% for 2D. These were consistent with results obtained with products from the reduction of the monobromo compounds. It was concluded that H_2 gas in D_2 gas was the source of the introduction of ^{1}H, and that variable isotopic effects were operative with different bromomethyl compounds. The magnitude of the isotope effect cannot be determined under the conditions in the present work (reaction flask volume of about 50 mL), but may be readily determined from the incorporations in

the starting material and products when the extent of product formation is kept low (at about 5%) (12). Clearly quite different kinetic isotope effects are operative for the 7-bromomethyl compounds, the 9-methyl and 10-methyl compounds, and benzyl bromide.

With the deuteration as model, the tritiated 7,9- and 7,10-dimethylbenz-[c]acridine were prepared by tritiation of 9-CH_2Br-7-MBAC (4) and 10-CH_2Br-7-MBAC (7) with tritium gas in benzene respectively. For each reduction, 2 Ci of carrier free tritium gas was used. Because of the low pressure of tritium gas in the reaction vessel, both reactions were allowed to proceed overnight. TLC afforded evidence of incomplete reduction and a further exposure to 5% Pd/$CaCO_3$ and $^{1}H_2$ completed the debromination. After purification by short column chromatography. Small radiochemical impurity peaks appeared at 29 min in the HPLC trace of both 7,9-DMBAC-9-methyl-^{3}H (1) and 7,10-DMBAC-10-methyl-^{3}H (2). The radiochemical purity measured by HPLC was 94.5% for 1 and 81.6% for 2 (table 1)

For the metabolic work, the tritium labelled dimethylbenz[c]acridines 1 and 2 were further purified by HPLC, and then dissolved in toluene containing 2% ethanol. This afforded material of radiochemical purity better than 99% for 1 and 98% for 2. The specific radioactivities were 1.18 Ci/mmol for 1 and 202 mCi/mmol for 2. These are suitable for the metabolic purposes.

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REFERENCES

1. Lacassagne A., Buu-Hoi N.P., Lecocq J. and Rudali G.- Bull. Assoc. Fr. Etude Cancer 33: 48 (1946)

2. Badger G.M.- Brit.J. Cancer 2: 309 (1948).

3. Lacassagne, A., Buu-Hoi N.P., Daudel R. and Zajdela F. - Adv. Cancer Res. 4: 315 (1956)

4. Lieberman C., Lazar P., Chouroulinkov I. and Guerin M. - C.R. Soc. Biol. 162: 835 (1968)

5. Smith I.A. and Seybold P.G. - J. Heterocycl. Chem. 16: 421 (1979).

6. Dipple A. - in Chemical Carcinogens, ed. Searle C.E., American Chemical Society, New York, 1976, pp 145.

7. Buu Hoi N.P. and Lecocq L. - Compt. rend. 218: 792 (1944).

8. Pene C., Lhoste J.M., Markovitz P. and Hubert-Habart M. - J. Chem. Soc. Perkin Trans. I 21: 2277 (1976).

9. Sciacovelli O. and von Philipsborn W. - Org. Magn. Resonance 3: 339 (1971).

10. Oehlke J., Bienert M., Niedrich H., Zopfl H.-J. and Franke P. - J. Labelled Comps Radiopharm. 23: 935 (1986).

11. Cerny B. and Hanus J. - J. Labelled Compds. Radiopharm. 18: 947 (1980)

12. Melander L. and Saunders W.H. Reaction rates of isotopic molecules, John Wiley, New York, 1980, pp 100-102.