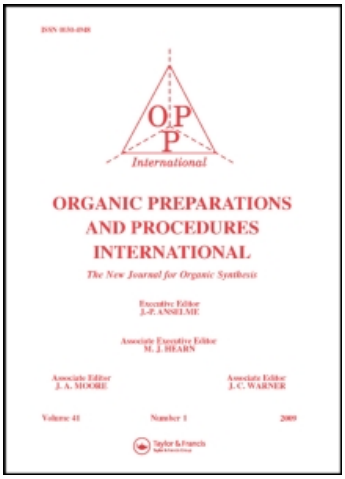


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

β-KETONITROSAMINES AS SYNTHETIC EQUIVALENTS OF α-METHYLENE ALKANOLAMINO ANIONS

Joseph E. Saavedra[a]; David W. Famsworth[a]
[a] NCI-Frederick Cancer Research and Development Center, ABL-Basic Research Program, Frederick, MD

To cite this Article Saavedra, Joseph E. and Famsworth, David W.(1991) 'β-KETONITROSAMINES AS SYNTHETIC EQUIVALENTS OF α-METHYLENE ALKANOLAMINO ANIONS', Organic Preparations and Procedures International, 23: 2, 139 — 146
To link to this Article: DOI: 10.1080/00304949109458300
URL: http://dx.doi.org/10.1080/00304949109458300

ORGANIC PREPARATIONS AND PROCEDURES INT. 23 (2), 139-146 (1991)

β-KETONITROSAMINES AS SYNTHETIC EQUIVALENTS OF α-METHYLENE ALKANOLAMINO ANIONS †

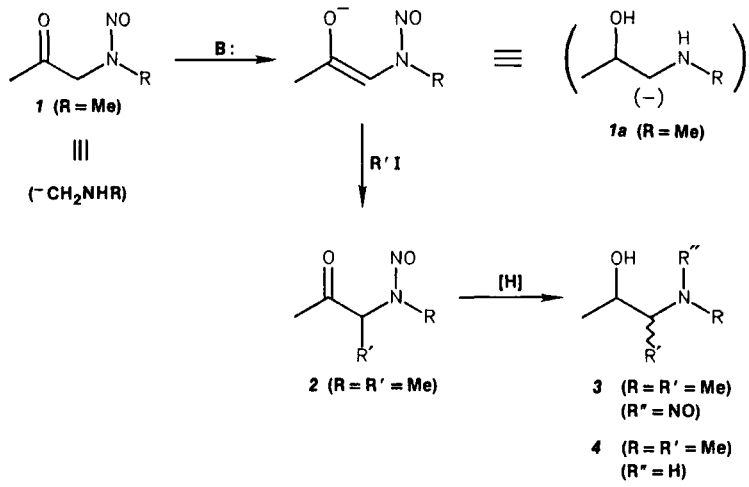
Joseph E. Saavedra* and David W. Farnsworth

NCI-Frederick Cancer Research and Development Center
ABL-Basic Research Program, Frederick, MD 21702

In the course of our investigations into the umpolung reactivity of primary amines and α-heteroatom-substituted carbanionic synthons, it became necessary to search for umpoled synthons of β-alkanolamines.[1] Species of this type are needed for the formation of new carbon-carbon bonds at the α-position between the hydroxyl and the amino groups. Alkanolamines are substances which combine the characteristics of amines and alcohols.[2] These two functionalities make such compounds versatile intermediates in a variety of manufacturing applications; they are useful in the pharmaceutical[3] as well as in the textile and household products industries.[4] Secondary alkyl alkanolamines are also precursors of β-hydroxylated nitrosamines, which are important compounds in the study of nitrosamine exposure, metabolism and carcinogenesis.[5]

We have recently established that β-ketonitrosamines are anionic synthons of the type (RCO^+ $^-CHNHR'$).[6] The enhanced acidity of protons at the α-carbon, as well as the ease of fragmentation of these compounds, established them as synthetic equivalents of α-methylene alkylamino anions($^-CH_2NHR$).[6a] Further investigations established the equivalency of β-ketonitrosamines to α-methinyl alkylamino (R^-CHNHR') anions.[6b] In simpler terms, β-ketonitrosamines can be alkylated or dialkylated at the α-position. Deacylation of the newly formed compounds gives the corresponding dialkylnitrosamines according to the equivalency mentioned above. However, if reduction of the carbonyl group is carried out, instead of a deacylation reaction, the corresponding β-hydroxynitrosamine results. This series of reactions demonstrates the equivalency of a β-ketonitrosamine to an α-(β-alkanolamine) anion [R'(HO)CH ^-CHNHR] (Eq. 1). A specific example is N-nitrosomethyl-N-2-oxopropylamine 1, which upon alkylation with methyl iodide in a slurry of powdered sodium hydroxide-sodium carbonate in THF gives N-nitrosomethyl-N-1-methyl-2-oxopropylamine 2.[6a] Sodium borohydride reduction of 2 produced N-nitrosomethyl-N-1-methyl-2-hydroxypropylamine 3a in 89% yield. Further demasking of 3 by the removal of the nitroso group gave the corresponding alkanolamine 3, establishing this β-ketonitrosamine as synthetically equivalent to the α-(β-alkanolamine) anion 1a. Compound 3 consisted of a 3:1 ratio of threo:erythro isomers 3a and

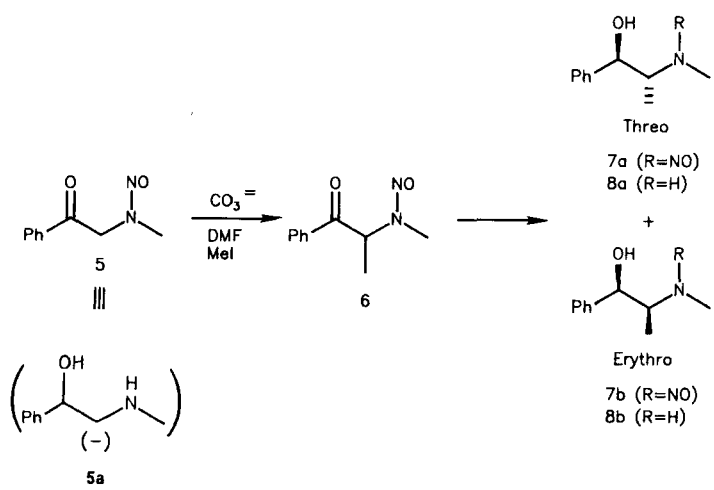
3b. These structures were confirmed by comparing the denitrosated product 4 with authentic samples of threo-3-N-methylamino-2-butanol 4a and erythro-3-N-methylamino-



(1)

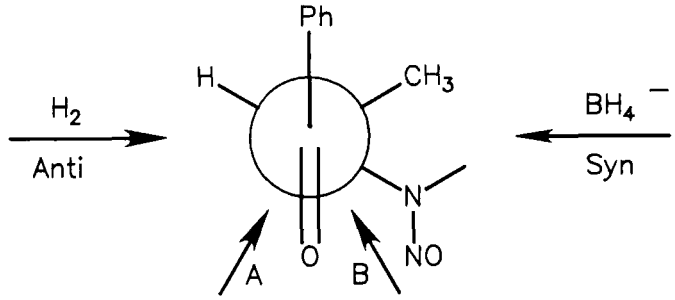
4-butanol 4b. When 2 was treated with aluminum-nickel alloy in aqueous base, reduction of the ketones as well as denitrosation occurred to give a 63% yield. Under these conditions, the ratio of erythro:threo aminoalcohol (4b:4a) was 57:43. None of these reducing agents showed a great deal of diastereoselectivity. However, reduction with sodium borohydride favored the formation of the threo isomer.

We found a more interesting example of an α-methylene alkanolamino anion equivalent in the anion of N-nitrosomethylaminoacetophenone 5. Alkylation of 5 with methyl iodide gave N-nitrosomethylamino-2-propiophenone 6 in 83% yield. Because of the commercial availability of pseudoephedrine (threo, 8a) and ephedrine (erythro, 8b), it was convenient to follow the diastereochemical outcome of the reduction of 6 under different reaction conditions. Sodium



(2)

borohydride reduction of 6 gave mostly the threo isomer 7a (syn-β-nitrosamino alcohol)[7] which was the exclusive isomer obtained (95% yield) by reduction with L-selectride. On the other hand, aluminum-copper catalysts favored (96:4) the formation of the anti (erythro amino alcohol 8b) over the syn isomer 8a. The yields obtained with other reducing agents are listed in Table 1. The results of these reductions may be explained by comparison with the hydride indicated below. When a catalytic hydrogenation is carried out, the metal catalyst approaches the molecule preferentially from the less hindered side, A-attack,[3] giving the anti product 8b. A B-attack of 6 is greatly favored when L-selectride or sodium borohydride are used, affording the syn product 7a. This is consistent with the stereochemical behavior of tertiary aminoketones,[3] where the preference for B-attack increases with increasing steric hindrance exerted by groups attached to



(3)

6

the amino nitrogen. In our case, the nitroso moiety seems to be responsible for the stereochemical outcome of the reaction. Table 1 gives a summary of the alkylation and subsequent reduction of β-ketonitrosamines depicting their equivalency to alkanolamino anions. The difference in reactivity between the Z and the E rotamers in the reduction of N-nitrosomethyl-N-methyl-2-oxopropylamine 2 with sodium borohydride is under investigation. Preliminary studies indicate that the E rotamer is reduced at a faster rate than the Z isomer. However, the diastereomeric outcome of the reaction is the same for both rotamers.

EXPERIMENTAL SECTION

Proton NMR spectra were recorded using a Nicolet NT-300 or a Varian XL-200 spectrometer. Mass spectral measurements were carried out on a VG-Micromass model 7070 spectrometer. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Gas Chromatographic analyses were carried out on a Shimadzu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. A 3% OV-210 on 80/100 Supelcoport 1-1956 column was used. Melting points were determined on an Electrothermal capillary melting point apparatus and were not corrected.

WARNING: All the nitroso compounds herein described are carcinogenic and/or mutagenic.[5]

TABLE 1. Methylation and Reduction of β-Ketonitrosamines

Equivalence	Source	Alkylation Product(%yield)	Demasking Conditions	Product (%)yield	threo/erythro Ratio
1a	1	2 (65%)	$NaBH_4$	3a/3b (89%)	3/1
			Al-Ni/OH^-	4a/4b (63%)	0.75/1
5a	5	6 (83%)	$NaBH_4$	7a/7b (97%)	7.3/1
			L-Selectride	7a (95%)	
			$NaBH_3CN$	7a/7b (82%)	1.97/1
			Al-Ni/OH^-	8a/8b (72%)	0.37/1
			Al-Cu/OH^-	8a/8b (83%)	0.04/1

Reduction of N-Nitrosomethyl-N-1-Methyl-2-oxopropylamine (2) with Sodium Borohydride.- To a solution of 203 mg (1.56 mmol) of N-nitrosomethyl-N-1-methyl-2-oxopropylamine 2[6a] in 2.5 ml of ethanol was added 59 mg (1.58 mmol) of sodium borohydride. The mixture was stirred at 25° overnight. The reaction mixture was treated with 5% aqueous hydrochloric acid, and extracted with methylene chloride. The organic layer was dried over sodium sulfate, filtered through a layer of magnesium sulfate and evaporated in vacuo. Purification of the product was accomplished on dry-packed silica gel, eluted with 2:1 methylene chloride:ethyl acetate to give 184 mg (89%) of a 3:1 mixture of threo-nitrosomethyl-N-methyl-2-hydroxypropylamine 3a and the erythro isomer 3b. The physical and spectral properties of these compounds were identical to standards synthesized by unequivocal methods (vide infra).

Reduction of 2 with Aluminum-Nickel Alloy in Basic Medium.- To a solution of 100 mg (0.77 mmol) of N-nitrosomethyl-N-1-methyl-2-oxopropylamine 2 in 11 ml of water was added 1 g of aluminum-nickel alloy. To the well stirred slurry, was added 5 ml of 10% aqueous potassium hydroxide over a 30 minute period. The cooling bath was removed and the reaction mixture was stirred at 25° for 3.5 hrs. The mixture was filtered, the filtrate extracted with methylene chloride and dried over anhydrous sodium sulfate. The solution was filtered and evaporated to give 50 mg (63%) of a 1.3:1 mixture of erythro-3-methylamino-2-butanol 4b and threo-3-methylamino-2-butanol 4a. The spectral and physical properties of these alkanolamines were identical to those of authentic samples (vide infra).

threo-3-Methylamino-2-butanol (4a).- A solution of 2.0 g (28 mmol) of cis-2,3-epoxybutane in 50 ml of methanol at 0°, was saturated with methylamine gas, allowed to warm up to room temperature, and stirred for 18 hrs. The reaction mixture was evaporated in vacuo, and the resulting oil was distilled in vacuo to give 348 mg (12%) of threo-3-methylamino-2-butanol (4a), bp 24°/0.9 mmHg. IR(film): 3320, 2979, 2880, 2804, 1446, 1381, 1329, 1200, 1173, 1115, 1100, 1075, 1030, 1006 cm^{-1}; ^1H NMR: δ 1.05 (d, 3H), 1.18 (d, 3H), 2.10-2.33 (m, 1H), 2.44 (s, 3H),

2.51 (s, 1H), 3.25-3.42 (m, 1H); MS m/z (relative intensity): 104 (M^{+1}, 1), 88(4), 70(6), 60(22), 59(6), 58(100), 56(7), 51(6), 49(18), 45(34), 44(7), 43(40), 42(10); exact mass (M^{+1}): 104.1075, required for $C_5H_{14}NO$ (M^{+1}): 104.1063.

Anal. Calcd for $C_5H_{13}NO \cdot HCl$: C, 43.03; H, 10.04; N, 10.79

Found: C, 41.38; H, 9.80; N, 9.83

The urea, mp. 99-100° (EtOH), was prepared by reaction with phenylisocyanate.[8]

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60

Found: C, 64.83; H, 8.57; N, 12.58

erythro-3-Methylamino-2-butanol (4b).- A solution of 0.50 g (7.0 mmol) of trans-2,3-epoxybutane in methanol was treated with methylamine gas as described above. Crystallization of the product gave 43 mg (6%) erythro-3-methylamino-2-butanol 4b, mp 30-31°. IR(film): 3317, 2980, 2803, 1650, 1448, 1377, 1151, 1116, 1088, 1053, 1009 cm^{-1}; ^1H NMR: δ 1.01 (d, 3H), 1.11 (d, 3H), 2.34 (s, 1H), 2.45 (s, 3H), 2.5-2.62 (m, 1H), 3.82-3.94 (m, 1H); MS m/z (relative intensity): 103(M^+, 1), 88(4), 73(4), 59(9), 58(100), 57(4), 56(10), 45(4), 44(7), 43(9), 42(14), 41(4); exact mass (M^+): 103.0997; required for $C_5H_{13}NO$ (M^+): 103.1015.

Anal. Calcd for $C_5H_{13}NO \cdot HCl$: C, 43.03; H, 10.04; N, 10.79

Found: C, 42.13; H, 10.28; N, 9.56

The urea, mp. 84-86° (EtOH), was prepared by reaction with phenylisocyanate.[8]

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60

Found: C, 64.85; H, 8.08; N, 12.63

threo-3-N-Nitrosaminomethyl-2-butanol (3a).- To a solution of 100 mg (0.97 mmol) of threo-3-methylamino-2-butanol (4a) in 4 ml of water was added 0.8 ml of 10% aqueous hydrochloric acid. The resulting solution was treated with 167 mg (2.4 mmol) of sodium nitrite, and stirred at room temperature for 2 hr. The mixture was extracted with methylene chloride, dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified on a dry-packed silica gel column, eluted with 2:1 methylene chloride:ethyl acetate to give 36 mg (28%) of threo-3-N-nitrosaminomethyl-2-butanol 3a. IR(film): 3380, 2982, 2940, 2883, 1458, 1427, 1381, 1343, 1277, 1238, 1159, 1122, 1083, 1053, 1022 cm^{-1}; ^1H NMR: E isomer (91.4%): 1.29 (d, 3H), 1.44 (d, 3H), 1.76 (s, 1H), 3.07 (s, 3H), 3.98-4.10 (m, 1H), 4.42-4.56 (m, 1H); Z isomer (8.6%): δ 1.17 (d, 3H), 1.44 (d, 3H), 1.76 (s, 1H), 3.76 (s, 3H), 3.80-3.87 (m, 1H), 4.93-5.00 (m, 1H); MS m/z (relative intensity) 132 (M^+, 2), 102(1), 87(16), 72(7), 71(4), 58(100), 57(42), 56(36), 55(6), 45(88), 44(4), 43(18), 42(55); exact mass (M^+): 132.08989, required for $C_5H_{12}N_2O_2$ (M^+): 132.08997.

Anal. Calcd for $C_5H_{12}N_2O_2$: C, 45.45; H, 9.09; N, 21.21

Found: C, 44.19; H, 9.14; N, 21.04

erythro-3-N-Nitrosaminomethyl-2-butanol (3b).- Nitrosation of erythro-3-methylamino-2-butanol (4b) was carried out as described above for the threo analog. IR (film) 3400, 2986, 2942,

1466, 1430, 1380, 1338, 1279, 1234, 1157, 1118, 1070, 1045, 1010 cm^{-1}; ^1H NMR: E isomer (93%): δ 1.25 (d, 3H), 1.73 (d, 3H), 1.99 (s, 1H), 3.06 (s, 3H), 4.106-4.22 (m, 1H); MS m/z (relative intensity): 132 (M^+, 2), 102(1), 87(18), 85(20), 84(30), 72(7), 58(100), 57(44), 56(37), 55(6), 51(14), 49(45), 47(8), 45(89), 43(20), 42(56); exact mass (M^+): 132.08999, required for $C_5H_{12}N_2O_2$ (M^+): 132.08997.

Anal. Calcd for $C_5H_{12}N_2O_2$: C, 45.45; H, 9.09; N, 21.21
Found: C, 45.12; H, 9.12; N, 21.11

N-Nitrosomethylaminoacetophenone (5).- To a solution of 5 g. (0.033 mol) of d,l-α-(methylaminomethyl)benzyl alcohol[9] in 38 ml. of distilled water was added 10 ml of concentrated sulfuric acid. To the resulting solution was added a solution of 4.97 g. (0.05 mol) of chromium trioxide in 30 ml of water over a 2 hr period at 40°. The solution was cooled to 0°, and 100 ml of methylene chloride were added. To the two-phase mixture was added a 2M aqueous solution of 4.6 g. (0.066 mol) of sodium nitrite. The mixture was stirred at room temperature overnight. The organic layer was separated, and the aqueous layer extracted three times with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered through a layer of magnesium sulfate and the solvent removed on a rotary evaporator to give a crystalline product. The crude product was recrystallized from ether:petroleum ether to give 3.66 g (62%) of 5, mp 112-114°. IR(film): 3032, 2934, 1674, 1598, 1581, 1440, 1326, 1228, 1170, 1050 cm^{-1}; ^1H NMR E isomer (68%): δ 3.17 (s, 3H), 5.65 (s, 2H), 7.46-7.59 (m, 3H), 7.99-8.04 (m, 2H); Z isomer (32%): δ 3.94 (s, 3H), 4.99 (s, 2H), 7.60-7.72 (m, 2H), 7.91-7.96 (m, 2H); MS: m/z(relative intensity) 179 (M^{+1}, 100), 148(5), 129(4), 105(6), 91(4), 89(5), 85(9), 81(4); exact mass (M^+): 178.0736, required for $C_9H_{10}N_2O_2$ (M^+): 178.072.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.62; N, 15.73
Found: C, 60.62; H, 5.63; N, 15.46

N-Nitrosomethylamino-2-propiophenone (6).- To a solution of 337 mg (8.4 mmol) of powdered sodium hydroxide and 337 mg (3.18 mmol) of powdered sodium carbonate in 3 ml of N,N-dimethylformamide (DMF) was added 1 g (5.6 mmol) of N-nitrosomethylaminoacetophenone 5 in 3 ml of DMF. To the resulting slurry was added 0.52 ml (8.4 mmol) of methyl iodide. The mixture was stirred at 25° for 1.25 hr. The reaction mixture was taken up in ether and filtered. The filtrate was washed with water, dried over anhydrous sodium carbonate and filtered through a layer of magnesium sulfate. The solvent was removed on a rotary evaporator, the residual oil chromatographed through dry-packed silica gel and eluted with methylene chloride to give 903 mg (84%) of pure N-nitrosomethylamino-2-propiophenone 6. IR(film): 3068, 2993, 2941, 1968, 1910, 1821, 1687, 1600, 1443, 1220, 1077, 1028 cm^{-1}; ^1H NMR E isomer (64%): δ 1.17 (d, 3H), 2.98 (s, 3H), 6.44 (q, 1H), 7.49 (m, 3H), 7.97 (m, 2H); Z isomer (36%): δ 1.41 (d, 3H), 3.71 (s, 3H), 6.36 (q, 1H), 7.64 (m, 3H), 7.83 (m, 2H); MS: m/z(relative intensity) 192 (M^+, 2), 176(17), 163(8), 162(61), 146(3), 133(3), 128(2), 121(11), 117(2), 107(6), 106(93), 105(100) 104 (5);

Exact mass (M^+): 192.0887, required for $C_{10}H_{12}N_2O_2$ (M^+): 192.0898.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58

Found: C, 62.71; H, 6.33; N, 14.37

Reduction of N-Nitrosomethylamino-2-propiophenone (6)

a) Sodium Borohydride.- To 200 mg (1.04 mmol) of 6 in 4 ml of methanol was added 80 mg (2.11 mmol) of sodium borohydride at 0° and the mixture was stirred in the cold for 24 hrs. Work-up of the reaction mixture and isolation of the products gave 195 mg (97%) of N-nitrosopseudoephedrine (7a)[10] and N-nitrosoephedrine (7b)[11] in 7.3:1 ratio.

b) L-Selectride (Lithium tri-sec-butylborohydride).- Reduction of 6 in THF was carried out at 0° with a 1M THF solution of L-Selectride (see Table 1).

c) Sodium Cyanoborohydride.- Reduction of 6 with this reagent was carried out in methanol as described above for the sodium borohydride reduction. No diastereoselectivity was observed (Table 1).

d) Aluminum-Nickel Alloy.- To a slurry of 250 mg of the alloy in 2 ml of 1:1 methanol-water was added 24 mg (0.13 mmol) of 6. To the stirred mixture was added 1 ml of 10% aqueous potassium hydroxide dropwise, and stirred a 25° to give, after work-up, 72% yield of a 2.7:1 mixture of (±)-ephedrine 8b: (±)-pseudoephedrine 8a.

e) Aluminum-Copper Alloy.- Nitrosoketone 6 was reduced over aluminum-copper alloy as described above for the Al-Ni analog. An 83% yield of amino alcohol was obtained. Analysis of the product indicated that it was predominantly (±)-ephedrine, the erythro isomer 8b (Table 1).

Acknowledgements.- Research sponsored by the National Cancer Institute, DHHS, under contract No. NO1-CO-74101 with ABL. We are indebted to Mr. J. Klose for the NMR spectra and Mr. J. Roman for the mass spectral measurements.

REFERENCES

1. J. E. Saavedra, in "Umpoled Synthons: A Survey of Sources in Synthesis", T. Hase, Ed., J. Wiley & Sons, Inc., New York, NY, 101 (1987).

2. J. E. Saavedra, J. Org. Chem., 50, 2271 (1985).

3. M. Tramentini, Synthesis, 605 (1982) and references therein.

4. "The Alkanolamines Handbook", The Dow Chemical Company (1989).

5. W. Lijinsky, "Genotoxicology of N-Nitroso Compounds", T. K. Rao, W. Lijinsky and

J. L. Epler, Eds., Plenum Press, New York, NY, Ch 10 (1984).

6. a) J. E. Saavedra, D. W. Farnsworth and J. G. Farrelly, Syn. Comm., 19, 1147 (1989). b) D. W. Farnsworth and J. E. Saavedra, ibid., 19, 2375 (1989).

7. G. P. Menshikov and G. M. Borodina, J. Gen. Chem. USSR, 17, 1569 (1947); Chem. Abs., 42, 2245a (1948).

8. R. L. Shriner, R. C. Fuson, D. Y. Curtin and T. C. Morrill, "The Systematic Identification of Organic Compounds", J. Wiley & Sons, 6th Ed., New York, NY, 1980.

9. A. Kamimura and N. Ono, Tetrahedron Lett., 30, 731 (1989).

10. S. N. Alwan, M. K. Al-Hindawi, S. K. Abdul-Rahman and S. Al-Sarraj, Cancer Lett., 31, 221 (1986).

11. S. N. Wogan, S. Paglialunga, M. C. Archer and S. R. Tannenbaum, Cancer Res., 35, 1981 (1975).

(Received March 29, 1990; in revised form December 7, 1990)