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Synthesis of Melanthioidine Derivative by Double Ullmann Reaction (Studies on the Syntheses of Heterocyclic Compounds. CCXXVI)[1]

Tetsuji Kametani, Seiichi Takano, and Kiyotsugu Haga

Pharmaceutical Institute, Tohoku University School of Medicine[2]

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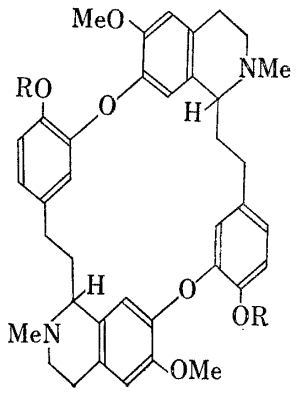
Diastereoisomeric mixture of racemic melanthioidine (I and II), was synthesized by the following procedures. Bischler–Napieralski reaction of the amide (XII), which was obtained by Schotten–Baumann reaction of 4–hydroxy–3–methoxyphenethylamine zinc chloride (IX) with acid chloride (X), followed by ethoxycarbonylation of the amide (XI) with ethyl chlorocarbonate, afforded the 3,4–dihydroisoquinoline (XIII). Reduction with sodium borohydride of the methiodide (XIV), which was obtained by methylation of XIII with methyl iodide, gave a mixture of 1,2,3,4–tetrahydroisoquinolines, (XV) and (XVI), whose hydrolysis with an alkaline solution afforded the latter compound (XVI). Secondly, double Ullmann reaction of the preceding compound (XVI) afforded a diastereoisomeric mixture of O,O–dibenzylmelanthioidine, which was debenzylated to give a diastereoisomeric mixture of I and II. Therefore, it is of particular interest that the twenty–membered ring system as melanthioidine–type compound has been synthesized.

Melanthioidine (II), $C_{38}H_{42}O_4N_2$, occurs in the leaves and corms of *Androcymbium melanthiodies* which grows in Southern and Eastern Africa.[3] The structure studies have already been reported briefly.[4]

The purpose of the present investigation was to study the cyclization of the amide (XII) in order to obtain the corresponding dihydroisoquinoline derivative (XIII), its methiodide (XIV) and tetrahydroisoquinoline (XV) as possible intermediates for the synthesis of racemic melanthioidine (I and II). Furthermore, double Ullmann reaction of the tetrahydroisoquinoline (XVI) was examined to give one of the diastereoisomeric mixture of O,O–dibenzylmelanthioidine (a mixture of III and IV).

Recently, Battersby and coworkers[5] have achieved a total synthesis of (−)–melanthioidine independenlty and revealed that double Ullmann reaction afforded two compounds, namely, (±)–O,O–dibenzylisomelanthioidine (III) and (±)–O,O–dibenzylmelanthioidine (IV). Since our sample was identical with diastereoisomeric mixture of O,O–dibenzylmelanthioidine, a total synthesis of diastereoisomeric mixture of melanthioidine (I and II) has been accomplished by debenzylation of the above compound (a mixture of III and IV).



I: R=H[(+)(−)−form]
II: R=H[(−)(−)−form]
III: R=CH_2Ph[(+)(−)−form]
IV: R=CH_2Ph[(−)(−)−form]

Chart 1

Bromination of 2–(4–methoxyphenyl)propionic acid in chloroform according to the literature[6] was examined, but our expected bromo–compound (V) could not be obtained

1) Part CCXXV: *Yakugaku Zasshi*, **88**, 483 (1968).
2) Location: *Kita–4–bancho, Sendai.*
3) J. Hrbek, jun. and F. Santavy, *Collection Czech. Chem. Commun.*, **27**, 255 (1962).
4) A.R. Battersby, R.B. Herbert, and F. Santavy, *Chem. Comm.*, **1965**, 415.
5) A.R. Battersby, Private communication.
6) H.D. Lossey and J. Judd, *J. Chem. Soc.*, **1965**, 960.

in a good yield. Therefore, acetic acid was used as solvent in case of bromination, by the result of which the compound (V) was obtained in an excellent yield.

Demethylation of the bromo-compound (V) with 48% hydrobromic acid in acetic acid afforded 2-(3-bromo-4-hydroxyphenyl)propionic acid (VI), which was benzylated with benzyl chloride in ethanol in the presence of sodium ethoxide to give the benzyl derivative (VIII). In this case benzyl 2-(4-benzyloxy-3-bromophenyl)propionate (VII) was obtained as a by-product, whose hydrolysis with 10% potassium hydroxide solution gave the above acid (VIII), but the total yield of VIII was not so good. Therefore, a modified benzylation of VI with potassium carbonate in dimethylformamide was investigated to give VII, and its hydrolysis afforded the acid (VIII) in a comparatively good yield.

Schotten-Baumann reaction of 4-hydroxy-3-methoxyphenethylamine zinc chloride (IX)[7] with acid chloride (X), which was prepared by chlorination of VIII with thionyl chloride, gave the amide (XI). Ethoxycarbonylation of the amide (XI) with ethyl chlorocarbonate afforded the amide (XII), whose Bischler-Napieralksi reaction in toluene with phosphoryl chloride gave the 3,4-dihydroisoquinoline (XIII).

Reduction of the methiodide (XIV), which was obtained by methylation of XIII with methyl iodide, with sodium borohydride gave a mixture of 1,2,3,4-tetrahydroisoquinoline (XV) and its hydrolyzed compound (XVI). Therefore, further hydrolysis of the above mixture with 10% potassium hydroxide solution was carried out without the isolation of XV, by the result of which the phenolic base (XVI) was obtained.

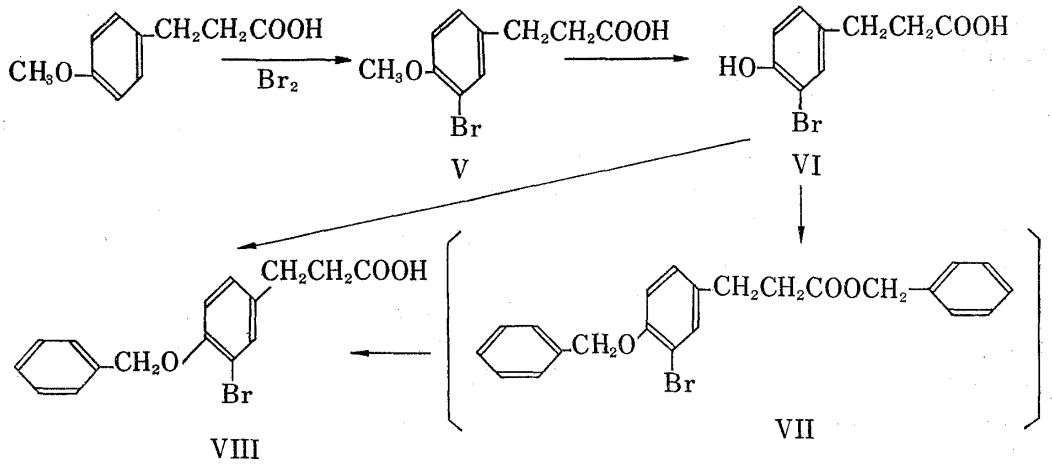


Chart 2

Secondly double Ullmann reaction of XVI afforded the twenty memebered ring compound (a mixture of III and IV), which was chromatographed on alumina to give the compound, mp 219—220°. This showed two spots on its thin-layer chromatogram and proved to be a diastereoisomeric mixture of O,O-dibenzylmelanthioidine.[8] The NMR spectrum of a mixture of III and IV showed the protons of the methylene of benzyloxy groups at 4.98 τ and 4.93 τ, methyl protons of methoxyl groups at 6.18 τ and 6.22 τ, and N-methyl group at 7.57 τ. Debenzylation of the mixture of III and IV afforded diastereoisomeric mixture of I and II.

Although natural melanthioidine could not be available for comparison, our sample was proved to be a diastereoisomeric mixture of O,O-dibenzylmelanthioidine by the identification kindly achieved by Prof. A.R. Battersby.

7) T. Kametani, S. Takano, and E. Karibe, *Yakugaku Zasshi*, **83**, 1035 (1963).
8) Prof. A.R. Battersby kindly performed the comparison of our specimen with his sample.

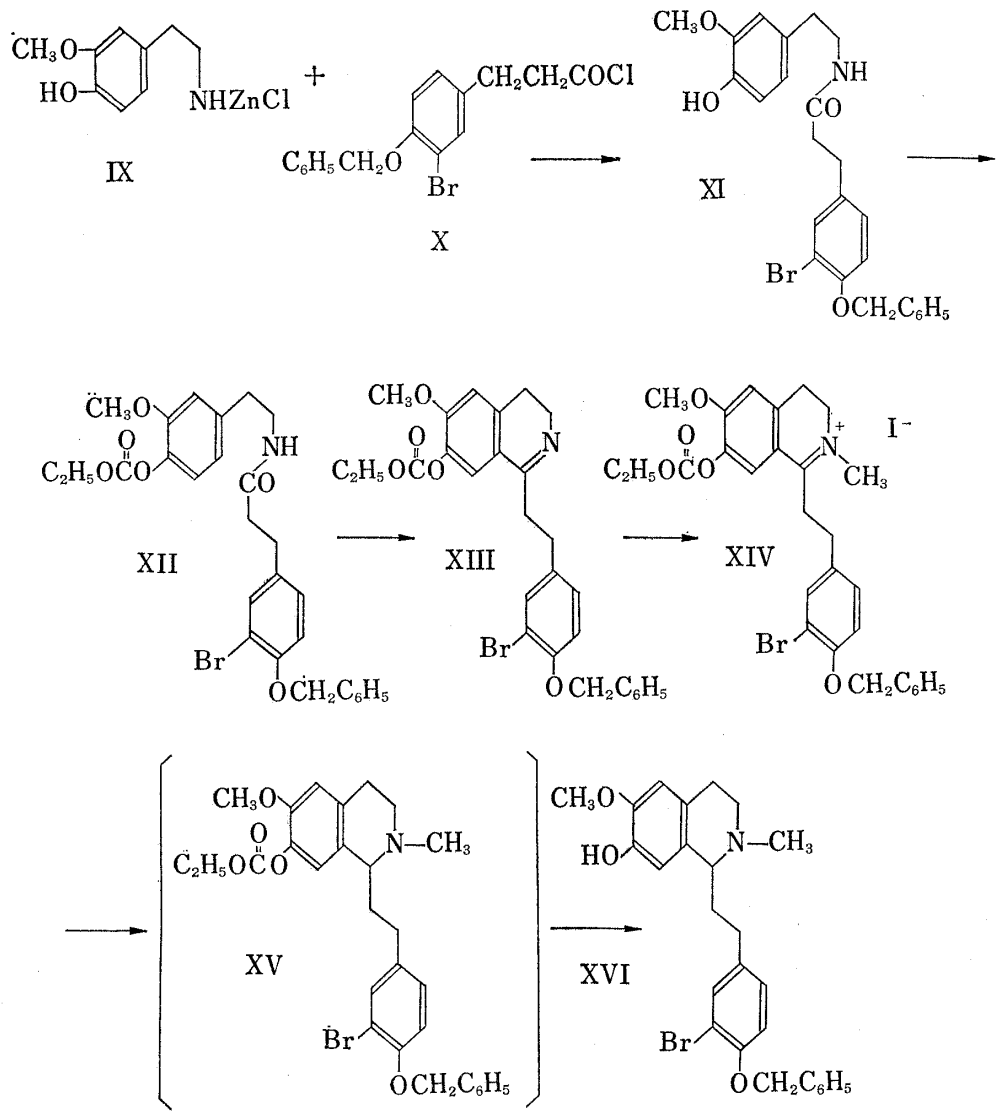


Chart 3

Experimental[9]

2-(3-Bromo-4-methoxyphenyl)propionic Acid (V)——To a solution of 127 g of 2-(4-methoxyphenyl)-propionic acid in 190 ml of AcOH was added dropwise at room temperature with stirring 113 g of Br_2 within 3 hr, and the mixture was then stirred for 1 hr. Removal of AcOH in a current of N_2 under reduced pressure afforded yellow cubes, which were recrystallized from benzene–hexane to give 146 g (89.5%) of the acid (V) as colorless needles, mp 96—97° (lit.,[6] mp 96—97°).[10]

2-(3-Bromo-4-hydroxyphenyl)propionic Acid (VI)——A mixture of 150 g of V, 700 ml of 48% HBr, and 200 ml of Ac_2O was heated under reflux in an oil-bath for 4 hr. Removal of the reagents under reduced pressure in a crurent of N_2 afforded the residue, which was extracted with benzene. The extract was washed with water, dried on Na_2SO_4, and distilled to give a syrup, which was recrystallized from benzene–hexane to give 89.8 g (65.1%) of colorless prisms, mp 78—79°. *Anal.* Calcd. for $C_9H_9O_3Br \cdot H_2O$: C, 41.09; H, 4.22. Found: C, 41.22; H, 3.98. IR cm^{-1} ($CHCl_3$): ν_{OH} 3494, $\nu_{C=O}$ 1702. NMR (τ) ($CDCl_3$): 2.72—3.19 (3H, multiplet, aromatic protons). Beilstein test was positive.

2-(4-Benzyloxy-3-bromophenyl)propionic Acid (VIII). a) Benzylation with NaOEt——To a solution of 4 g of metallic Na and 300 ml of EtOH was added 10 g of VI, whose solution was refluxed together with

9) All melting points were not corrected.
10) According to Lossey, *et al*,[6] bromination of 9 g of the above acid was held in $CHCl_3$ to give 6.1g (45.9%) of V.

15 g of benzyl chloride for 7 hr. After removal of the solvent, the resultant residue was decomposed with water and extracted with benzene. The extract was washed with water, dried on Na_2SO_4, and distilled to give an oil, whose solution in 172 ml of EtOH, 17.2 ml of H_2O, and 17.2 g of KOH was refluxed in a current of N_2 for 16 hr. Removal of the solvent gave the residue, which was dissolved in 160 ml of H_2O and extracted with ether. The resultant aqueous layer was acidified with 10% HCl aq. solution and extracted with ether. The latter ethereal extract was washed with water, dried on Na_2SO_4, and distilled to give the residue, which was recrystallized from benzene–hexane or benzene to give colorless needles, mp 119—120°. Furthermore, the aqueous layer described above in case of extraction with benzene was acidified with 10% HCl aq. solution and extracted with ether. The extract was treated as usual to afford the above sample of VIII. Total yield, 58 g (42.6%). *Anal.* Calcd. for $C_{16}H_{15}O_3Br$: C, 57.33; H, 4.50. Found: C, 57.33; H, 4.37. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1720. NMR (τ) ($CDCl_3$): 2.50—3.25 (3H, multiplet, aromatic protons), 4.90 (2H, singlet, $-C\underline{H}_2Ph$). Beilstein reaction was positive.

b) Benzylation with K_2CO_3——A mixture of 19.8 g of VI, 280 ml of dimethylformamide, 40 g of benzyl chloride, and 20 g of K_2CO_3 was heated under reflux in an oil-bath for 1 hr, and, after cooling, the reaction mixture was mixed with 400 ml of water. The preceding solution was acidified with 10% HCl aq. solution and extracted with benzene. The extract was washed with water, dried on Na_2SO_4, and distilled to give 33.2 g of the ester (VII) as an oil, whose solution in 40 g of KOH and 100 ml of H_2O was refluxed for 12 hr. Removal of the solvent from the reaction mixture gave the residue, which was dissolved in 200 ml of H_2O and extracted with ether. The resultant aqueous solution was acidified with 10% HCl aq. solution, and extracted with benzene. Removal of the extract and recrystallization from benzene afforded 22.7 g (84.4%; calculated from VI) of VIII as colorless needles, mp 119—120°, which were identical with the above sample prepared by method a).

N-(4-Hydroxy-3-methoxyphenethyl)-3-(4-benzyloxy-3-bromophenyl)propionamide (XI)——A mixture of 5 g of the preceding acid (VIII), 4 g of $SOCl_2$, and 20 ml of benzene was refluxed for 1 hr, and the excess of the reagent and solvent was removed from the reaction mixture to give an oily substance, which could not be crystallized and therefore used in the following reaction without purification.

On the other hand, a solution of the above acid choride (X) in dry $CHCl_3$ was added dropwise under cooling to a stirred mixture of 5 g of the amine zinc chloride complex (IX), 16 ml of 10% NaOH aq. solution, and 30 ml of $CHCl_3$, and the mixture was stirred for 2 hr. After the reaction, the mixture was mixed with an excess of H_2O and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ aq. solution and H_2O, dried on Na_2SO_4, and distilled to give a syrup which solidified on being triturated with benzene. Collection by filtration and recrystallization from benzene or benzene–hexane gave 4.2 g (60.3%) of XI as colorless needles, mp 107—108°. *Anal.* Calcd. for $C_{25}H_{26}O_3NBr$: C, 61.99; H, 5.41; N, 2.89. Found: C, 61.68; H, 5.40; N, 3.18. IR cm^{-1} ($CHCl_3$): ν_{OH} 3505, ν_{NH} 3400, $\nu_{C=O}$ 1663. NMR (τ) ($CDCl_3$): 4.49 (1H, singlet, phenolic $O\underline{H}$), 4.89 (2H, singlet, $-C\underline{H}_2Ph$), 6.18 (3H, singlet, $OC\underline{H}_3$).

N-(4-Ethoxycarbonyloxy-3-methoxyphenethyl)-3-(4-benzyloxy-3-bromophenyl)propionamide (XII)——To a cooled solution of 5.9 g of the above amide (XI) and 1.24 g of triethylamine in dry $CHCl_3$ was added gradually with stirring 13.6 g of ethyl chlorocarbonate, and the mixture was stirred for 30 min. After 100 ml of H_2O had been added, the mixture was extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ aq. solution and water, dried on Na_2SO_4, and distilled to give an oil, which solidified on being triturated with benzene. Recrystallization from benzene gave 6.52 g (93%) of XII as colorless needles, mp 99—100°. *Anal.* Calcd. for $C_{28}H_{30}O_6NBr$: C, 60.44; H, 5.43; N, 2.52. Found: C, 60.67; H, 5.78; N, 2.75. IR cm^{-1} ($CHCl_3$): ν_{NH} 3370, $\nu_{C=O}$ 1750 (ester), $\nu_{C=O}$ 1658.

1-(4-Benzyloxy-3-bromophenethyl)-7-ethoxycarbonyloxy-3,4-dihydro-6-methoxyisoquinoline (XIII)——A mixture of 7.6 g of the preceding amide (XII), 50 ml of dry toluene, and 6 g of $POCl_3$ was heated at 92—98° in a current of N_2 for 1.5 hr, and 300 ml of hexane was added to the above reaction mixture. Removal of the excess hexane by decantation gave a syrup, whose solution in $CHCl_3$ was shaken with saturated $NaHCO_3$ aq. solution for 1 hr. The $CHCl_3$ layer separated was dried on Na_2SO_4 and distilled to give 6.6 g of XIII as an oil, which was used in the following reaction without purification due to the difficulties in crystallization. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1710.

1-(4-Benzyloxy-3-bromophenethyl)-7-ethoxycarbonyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolinium Iodide (XIV)——A mixture of 6.1 g of the above 3,4-dihydroisoquinoline (XIII) and 30 ml of MeI was warmed mildly for 30 min and, after cooling, 100 ml of hexane was added to the reaction mixture. Removal of the excess hexane by decantation afforded yellow crystals, whose recrystallization from EtOH gave 7 g (90.9%) of the iodide (XIV) as yellow scales, mp 157—158° (decomp.). *Anal.* Calcd. for $C_{29}H_{31}O_5NBrI$: C, 51.19; H, 4.59; N, 2.06. Found: C, 51.23; H, 4.88; N, 2.25.

1-(4-Benzyloxy-3-bromophenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (XVI)——To a solution of 5.5 g of the methiodide (XIV) in 150 ml of EtOH containing a few drops of H_2O was added in small portions 5.5 g of $NaBH_4$, the yellowish solution becoming colorless after the addition. The mixture was then refluxed for 1 hr and removal of the solvent gave the residue, which was admixed with water and extracted with $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and distilled to give 4.9 g of XV as a pale yellow syrup, which could not be obtained in a crystalline state.

A mixture of 4.9 g of the above syrup (XV), 50 ml of EtOH, 1 g of KOH, and 10 ml of H_2O was heated under reflux for 1 hr and the solvent was removed by distillation. The pH of the resultant alkaline solution was adjusted to pH 9 with saturated NH_4Cl aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and distilled to give 4.5 g of XVI as a yellowish-brown syrup, which was used in the following reaction without purification because of difficulties in its crystallization. IR cm^{-1} ($CHCl_3$): ν_{OH} 3510. NMR (τ) (CCl_4): 4.92 (2H, singlet, $-C\underline{H}_2Ph$), 6.21 (3H, singlet, $OC\underline{H}_3$), 7.65 (3H, singlet, $N-C\underline{H}_3$).

Diastereoisomeric Mixture of O,O-Dibenzylmelanthioidine (III and IV)——A mixture of 3 g of the tetrahydroisoquinoline (XVI), 20 ml of dry pyridine, 2.05 g of K_2CO_3, 375 mg of Cu powder, and 125 mg of KI was heated with stirring at 150—155° for 72 hr in the presence of N_2, and then 20 ml of $CHCl_3$ was added to the above reaction mixture. Filtration and removal of the solvent gave a brownish-black syrup, which was chromatographed on alumina (length, 20 cm, inside diameter, 3.5 cm) using 1300 ml of $CHCl_3$ as solvent to give a brown syrup. The preceding syrup was extracted with hot ether. The extract was washed with 10% NaOH aq. solution and water, dried and distilled to give 500 mg of a yellow viscous syrup, whose Beilstein test was negative. This was again chromatographed on alumina (length, 15 cm, inside diameter 3.5 cm) in benzene and then benzene–$CHCl_3$ (2:1). After removal of 300 ml of the first eluate, 500 ml of the second eluate was distilled to give 100 mg (4.44%) of O,O-dibenzylmelanthioidine (a mixture of III and IV), which crystallized on bing triturated with ether. Recrystallization from MeOH–$CHCl_3$ afforded a colorlees powder, mp 219—220°. *Anal.* Calcd. for $C_{52}H_{54}O_6N_2 \cdot MeOH$: C, 76.23; H, 7.00; N, 3.36. Found: C, 76.08; H, 6.94; N, 3.85. NMR (τ) ($CDCl_3$): 4.89 (2H $-OC\underline{H}_2-Ph$), 4.93 (2H, $-O-C\underline{H}_2-Ph$), 6.18, 6.22 (6H, $2OC\underline{H}_3$), 7.57 (6H, $2NC\underline{H}_3$), which were recognized as a mixture of III and IV by Prof. Battersby.

Diastereoisomeric Mixture of Melanthioidine (a mixture of I and II)——A mixture of 100 mg of the above O,O-dibenzylmelanthioidine (a mixture of III and IV), 10 ml of 35% HCl aq. solution and 10 ml of EtOH was refluxed for 5 hr under a current of N_2. Removal of the solvent gave a pale brown residue which was dissolved in a small amount of H_2O. The resultant solution was basified with conc. NH_4OH aq. solution, and extrated with $CHCl_3$ and then EtOAc. The combined extract was washed with saturated NaCl aq. solution and dried over Na_2SO_4. Filtration and removal of the solvent gave 67 mg of a powder whose recrystallization from EtOAc gave a pale pink powder, mp 202—205°. The following spectral data seem to support that this substance is a diastereoisomeric mixture of melanthioidine solvated by one mole of EtOAc. Further precise elucidation of this mixture is under examination. IR cm^{-1} (KBr); $\nu_{C=O}$(ester) 1735. NMR (τ) ($CDCl_3$): 6.17, 6.21(6H, two singlets, $2OC\underline{H}_3$), 7.57(6H, singlet, 2 $N-C\underline{H}_3$), 3.1—3.5(10H, aromatic protons), 8.76 (3H, triplet, 2 $N-CH_3$), 3.1—3.5 (10H, aromatic protons), 8.76 (3H, triplet, $C\underline{H}_3-CH_2-$, $J=9$ cps), 790 (3H, singlet, $C\underline{H}_3CO-$), 4.89 (2H, quartet, $CH_3-C\underline{H}_2-$, $J=9$cps). MS [*m/e* (%)]: M^+ 622 (29), 485 (22), 312 (93), 310 (100), 295 (100), 192 (10), 107 (11).