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# Studies on the Erythrina Alkaloids. XII.[1] Conversion of Erysodienone Methiodide and Erysodienol to Dibenzazonine Derivatives

Kazuo Ito and Hitoshi Tanaka

*Faculty of Pharmacy, Meijo University*[2]

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Reaction of erysodienol (**4**) with methyl iodide afforded the corresponding dibenzazonine (**7**), whose structure was confirmed by identification with the authentic specimen, prepared by N-methylation of a known secondary amine (**1**).

On the other hand, erysodienone methiodide (**6**), synthesized by N-methylation of erysodienone (**3**), was treated with alkali reagents in methanol and ethanol to yield dibenzazonines (**8** and **9**), which have newly formed methoxyl and ethoxyl groups at $C_5$-position in dibenzazonine skeleton.

**Keywords**——erythrina alkaloids; synthesis of dibenz(*d*,*f*)azonine derivatives; transformation of erysodienone methiodide; transformation of erysodienol; $^{13}$C-NMR spectra of dibenz(*d*, *f*)azonine derivatives

A key intermediate in biosyntheses[3] of Erythrina alkaloids, 5,6,8,9-tetrahydro-2,12-dimethoxy-7*H*-dibenz(*d*,*f*)azonine-3,11-diol (**1**) plays important roles in their biogenetic syntheses,[4] Kupchan, *et al.* have reported[5] biomimetic synthesis of dibenzazonine (**1**) by vanadium oxytrifluoride oxydation of N-trifluoroacetylnorptorosinomenine, followed by alkali hydrolysis and sodium borohydride reduction. Dibenzazonine (**1**) remains unknown in nature, although the methyl analogue (erybidine (**2**)) has been isolated from leaves of *Erythrina X bidwillii* Lindl.[6]

In our preceding paper,[7] we have reported that erybidne (**2**) was synthesized by photolytic intramolecular cyclization of the bromophenolic compound, followed by reduction with diborane and N-methylation. On treatment of erysodienol (**4**) with Rodinov reagent, we have also found[6] that the dienol (**4**) was easily converted to **2** along with O-methylerybidine having dibenzazonine system.

In this paper, we now wish to report novel transformation of the dienol (**4**) and erysodienone methiodide (**6**) to dibenzazonine derivatives (**7**, **8** and **9**).

The starting material (**3**), prepared by phenol oxidation of bisphenethylamine according to the method of Scott[8] and Mondon, *et al.*,[9] is an effective *in vivo* precursor[3] of dibenzazonine (**1**). Reduction of **3** with sodium borohydride gave erysodienol (**4**) as a known product.[9]

On treatment of the dienol (**4**) with an excess of methyl iodide in methanol at 60°, the hydriodide salt of **7** was isolated as a sole product in excellent yield (93%). The structure of this substance (**7**) was assigned on the basis of the following evidence.

In the mass spectrum of the hydriodide of **7**, the molecular peak ($M^+$—HI) was the base peak, and a fragment ion at *m/e* 272 arised from the loss of $C_3H_7N$ radical from molecular ion

1) Part XI: K. Ito, M. Haruna, Y. Jinno, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 52 (1976).
2) Location: *Yagoto-urayama, Tenpaku-cho, Tenpaku-ku, Nagoya.*
3) D.H.R. Barton, R.B. Boar, and D.A. Widdowson, *J. Chem. Soc.*, (*C*) **1970**, 1213.
4) D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, *J. Chem. Soc.*, (*C*), **1968**, 1529; D.H.R. Barton, R.B. Boar, and D.A. Widdowson, *ibid.*, **1970**, 1208.
5) S.M. Kupchan, C.K. Kim, and J.T. Lynn, *J. Chem. Soc.*, (*D*), **1976**, 86.
6) Part III: K. Ito, H. Furukawa, H. Tanaka, and J.S. Lai, *Yakugaku Zasshi*, **93**, 1218 (1973).
7) Part VIII: K. Ito and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **22**, 2108 (1974).
8) J.E. Gervay, F. McCapra, T. Money, G.M. Sharma, and A.I. Scott, *Chem. Comm.*, **1966**, 142.
9) A. Mondon and M. Ehrhardt, *Tetrahedron Lett.*, **1960**, 2557.

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was observed as a characteristic peak of dibenzazonine system.[10] Infrared (IR) spectrum ($CHCl_3$) of the free base (**7**), mp 220—221° (dec.), showed an absorption at 3550 $cm^{-1}$ due to a hydroxyl group. A characteristic band of double bond for dienol absorption disappeared. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of **7** exhibited the presence of two phenolic hydroxyl protons (broad singlet at 4.42) which disappeared on $D_2O$ treatment, one N-methyl group (7.66) and two aromatic methoxyl groups (6.15). In the aromatic region, four aromatic *para* proton signals appeared as two sharp singlets (3.33 and 3.22).

Therefore, this compound is represented to be 5,6,8,9-tetrahydro-2,12-dimethoxy-7-methyl-dibenz(*d*,*f*)azonine-3,11-diol (**7**), which was identical with the authentic specimen prepared by N-methylation of a known secondary amine (**1**).[4]

On the other hand, a similar treatment of the dienol (**4**) with various alkali reagents (sodium hydroxide, potassium hydroxide and sodium ethoxide) did not give the dibenzazonine derivative, recovering the material (**4**) unchanged completely.

A probable mechanism for the formation of dibenzazonine (**7**) from **4** is shown in Chart 1. The primarily formed intermediate may be an unstable erysodienol methiodide (**5**) which suffers fission of the spiro-dienol ring to afford dibenzazonine (**7**).

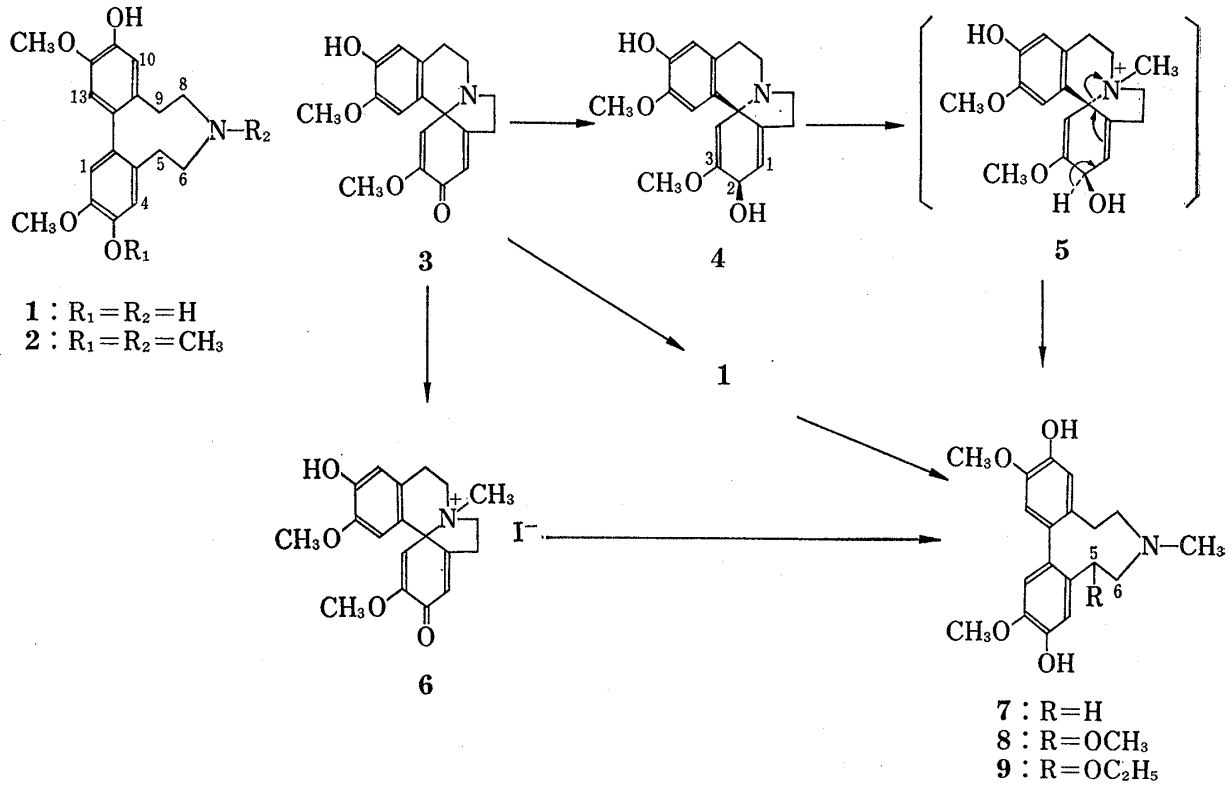


Chart 1

Furthermore, conversion of erysodienone methiodide (**6**) to dibenzazonine system was studied.

The methiodide (**6**), obtained easily by N-methylation of the dienone (**3**), was treated with methanolic alkali solution such as sodium methoxide, sodium hydroxide and potassium

10) H. Pande and D.S. Bhakuni, *J. Chem. Soc., Perkin I*, **1976**, 2197.

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hydroxide to produce colorless prisms, mp 195—196°, as a sole product in high yield. This compound was found to be the molecular formula $C_{20}H_{25}NO_5$ by the elemental analysis and mass spectral (MS) data. Its IR spectrum lacked the characteristic band due to a dienone system (1680, 1660 and 1620 $cm^{-1}$) and showed the presence of hydroxyl group at 3560 $cm^{-1}$. The ultraviolet (UV) spectrum ($\lambda_{max}^{EtOH}$ 222 and 285 nm) displayed the presence of a substituted biphenyl system[7] and underwent a bathochromic shift on addition of alkali, suggesting that the hydroxyl group was phenolic. The NMR spectrum in deuteriochloroform revealed the signals due to one N-methyl group (singlet at 7.67), two aromatic methoxyl group (6.16 and 6.14) and four aromatic protons (3.07, 3.29, 3.37 and 3.39). These chemical shifts were in excellent agreement with the values of dibenzazonine (**7**) described above. In addition, one aliphatic methoxyl group appeared as a singlet at 7.03 and a quartet at 5.88 ($J$=8 and 4 Hz) due to a proton on the methoxy-bearing carbon was, in deuteriobenzene, clearly observed (Fig. 1).

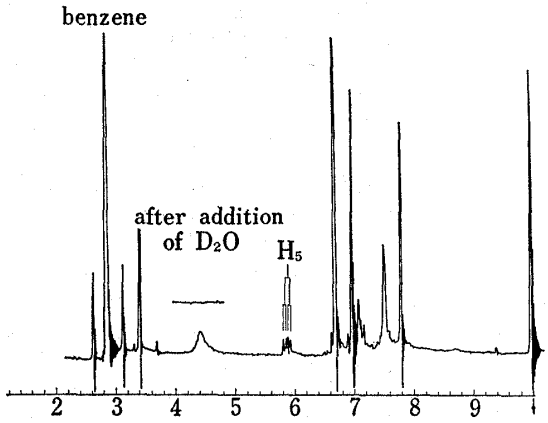


Fig. 1. The NMR Spectrum of Compound (**8**) ($C_6D_6$)

Because of the absence of signal at 5.19—5.21[11] corresponding to methine proton ($C_6$-H or $C_8$-H) of carbinolamine ether moiety, the signal of the methine proton at 5.88 allows to be attributable to a benzylmethine proton ($C_5$-H or $C_9$-H) on the carbon bearing methoxyl group. The evidence of the presence and assignment for the remaining methylene groups ($CH_2\times3$) was obtained by determination of its $^{13}$C-NMR spectrum. The spectrum ($CDCl_3$) revealed three methylene signals due to two aminomethylenes (58.2 and 64.1 $\delta$) and one benzylmethylene (33.5 $\delta$). Furthermore, the observed chemical shift of the benzylmethine (80.1 $\delta$) bearing methoxyl group follows the standard theory.[12]

Therefore, the structure of this substance was supposed to be 5,6,8,9-tetrahydro-3,11-dihydroxy-2,5,12-trimethoxy-7*H*-dibenz(*d*,*f*)azonine (**8**), in which a newly formed aliphatic methoxyl group was ascribable to be at $C_5$-position.

Next, under the same alkali ethanolic condition the methiodide (**6**) produced similarly an ethanol adduct (**9**) as a sole product. As this compound (**9**), mp 208—210°, $C_{21}H_{27}NO_5$, exhibits a similar UV spectrum to that of **8**, it has also a biphenyl system, In its NMR spectrum ($C_6D_6$) and $^{13}$C-NMR ($CDCl_3$) spectrum, the newly formed ethoxyl group was observed and the remainder of those spectra was very similar to that observed for **8**. Quartet signals at 5.78 were similarly assigned to the benzyl proton ($C_5$-H) on the ethoxy-bearing carbon. Therefore, a newly introduced ethoxyl group was located at $C_5$-position and the structure of **9** was supported.

The mechanism leading from methiodide (**6**) to dibenzazonine (**8** and **9**) is not yet clear. The newly introduced alkoxyl group presumably arises from the solvent.

From these results, it became apparent that reaction of dienol (**4**) with methyl iodide underwent dienol-benzene rearrangement to give the corresponding dibenzazonine (**7**) and dienone methiodide (**6**) under alcoholic alkali condition was also converted into dibenzazonine having alkoxyl group at $C_5$-position (**8** and **9**).

11) A.Z. Britten and G.F. Smith, *J. Chem. Soc.*, **1963**, 3851.
12) J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972; G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972.

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## Experimental[13]

**Erysodienol (4)**——To a stirred solution of **3**[9] (150 mg) in MeOH (20 ml) was added $NaBH_4$ (70 mg) portionwise under ice cooling and then stirring was continued for 1 hr at room temperature. After evaporation of MeOH, the oily residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was treated with $H_2O$, dried over $Na_2SO_4$, and evaporated. The resulting residue containing a small amount of $C_2$-epimer,[14] was obtained as white crystals, mp 128—129° (lit,[9] mp 131°). This substance was recrystallized from ligroin to give **4** (120 mg) as colorless needles, mp 187—188° (lit,[6] 187—189°).

**Reaction of Erysodienol (4) with $CH_3I$ (Formation of 7)**——A mixture of **4** (100 mg), MeOH (40 ml) and $CH_3I$ (0.1 ml) was heated at 60° for 2 hr. After evaporation of MeOH, the residue was recrystallized from a mixed solution of EtOH and ether to give hydriodide salt of **7** (135 mg) as yellow needles, mp 270—271°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3560 (OH). NMR ($D_2O$) $\tau$: 7.00 (3H, s, $NCH_3$), 6.17 (6H, s, $2\times OCH_3$), 3.17, 3.02 (4H, $2\times$s, $4\times$arom. H). MS *m/e*: 329 ($M^+$—HI, 100%), 314, 272, 271, 241. *Anal.* Calcd. for $C_{19}H_{24}INO_4\cdot 1/2H_2O$: C, 48.94; H, 5.40; N, 3.00. Found: C, 49.24; H, 5.39; N, 2.78.

The hydriodide was neutralized with $NH_4OH$ and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $Na_2SO_4$ and evaporated. The residue was recrystallized from a mixed solution of *n*-hexane and $CHCl_3$ to give free base of **7** as colorless needles, mp 220—221° (dec.). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3550 (OH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 221 (4.32), 285 (3.96). NMR ($CDCl_3$) $\tau$: 7.66 (3H, s, $NCH_3$), 6.15 (6H, s, $2\times OCH_3$), 4.42 (2H, br. s, $2\times$OH), 3.33, 3.22 (4H, $2\times$s, $4\times$arom. H). NMR ($C_6D_6$) $\tau$: 7.86 (3H, s, $NCH_3$), 6.80 (6H, s, $2\times OCH_3$), 3.41, 3.40, 3.04, 3.02 (4H, $4\times$s, $4\times$arom. H). MS (*m/e*: 329 ($M^+$, 100%), 314, 272, 271, 241.

**Preparation of Dibenzazonine (7) from 1**——To a stirred solution of **1**[3] (60 mg) in MeOH (10 ml) was added dropwise 37% HCHO (0.2 ml). After the resulting mixture was stirred for 30 min at room temperature, $NaBH_4$ (200 mg) was added portionwise and then stirred for 30 min. After evaporation of MeOH, the oily residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was treated with water, dried over $Na_2SO_4$ and evaporated. The residue was recrystallized from EtOH to give **7** (56 mg) as colorless needles, mp 220—221° (dec.).

This compound was completely identical with the substance synthesized above by mixed mp determination and comparison of their spectra (NMR, IR and MS).

**Erysodienone Methiodide (6)**——A mixture of **3** (100 mg), MeOH (30 ml) and $CH_3I$ (0.1 ml) was heated at 50° for 15 min. After evaporation of MeOH, the residue was recrystallized from MeOH to afford **6** (130 mg) as yellow prisms, mp 240—242° (dec.). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3540 (OH), 1680, 1660, 1620 (dienone). NMR ($D_2O$) $\tau$: 6.82 (3H, s, $NCH_3$), 6.64, 6.28 (6H, $2\times$s, $2\times OCH_3$), 3.72 (1H, s, $C_4$–H), 3.54 (1H, s, arom. H), 3.24 (1H, br. s, $C_1$–H), 3.16 (1H, s, arom. H). *Anal.* Calcd. for $C_{19}H_{11}INO_4\cdot 1/2H_2O$: C, 49.15; H, 4.99; N, 3.02. Found: C, 48.86; H, 5.04; N, 2.76.

**Reaction of 6 with $NaOCH_3$, NaOH or KOH in MeOH (Formation of 8)**——To a stirred solution of **6** (130 mg) in MeOH (30 ml) was added $NaOCH_3$, NaOH or KOH (20 mg) at 55—60°, and heating and stirring were continued for 1 hr. After evaporation of MeOH, the residue was dissolved in water, neutralized with HCl and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $Na_2SO_4$ and evaporated. The resulting residue was recrystallized from acetone to give **8** (87 mg) as colorless prisms, mp 195—196° (dec.). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3560 (OH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 222 (4.34), 285 (3.94). NMR ($CDCl_3$) $\tau$: 7.67 (3H, s, $NCH_3$), 7.03 (3H, s, $OCH_3$), 6.16, 6.14 (6H, $2\times$s, $2\times OCH_3$), 4.93 (2H, br. s, $2\times$OH), 3.39, 3.37, 3.29, 3.07 (4H, $4\times$s, $4\times$arom. H). NMR ($C_6D_6$) $\tau$: 7.80 (3H, s, $NCH_3$), 6.99 (3H, s, $OCH_3$), 6.70, 6.68 (6H, $2\times$s, $2\times OCH_3$), 5.88 (1H, d.d, $J=4$, 8 Hz, $C_5$–H), 4.42 (2H, br. s, $2\times$OH), 3.41, 3.40, 3.13, 2.64 (4H, $4\times$s, $4\times$arom. H). $^{13}$C-NMR ($CDCl_3$) $\delta$: 33.5 (Ar$\underline{C}H_2$), 47.4 ($NCH_3$), 56.0 (ArO$\underline{C}H_3$), 58.2 and 64.1 ($\underline{C}H_2NCH_3$), 80.1 (Ar$\underline{C}$HOCH$_3$), 111.2, 111.6 and 115.2 (ArH), 132.1, 133.3, 134.2, 144.7, 145.2 and 145.8 (ArR). MS *m/e*: 359 ($M^+$, 100%), 344, 301, 272, 271, 241. *Anal.* Calcd. for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.67; H, 7.03; N, 3.68.

**Reaction of 6 with $NaOCH_3$, NaOH or KOH in EtOH (Formation of 9)**——To a stirred solution of **6** (150 mg) in EtOH (40 ml) was added portionwise NaOEt, NaOH or KOH (20 mg) at 60—65°, and heating and stirring were continued for 1 hr. The resulting mixture was treated in a similar manner described above. The residue was recrystallized from benzene to give **9** (100 mg) as colorless prisms, mp 208—210° (dec.). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3560 (OH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 222 (4.38), 285 (3.97). NMR ($CDCl_3$) $\tau$: 8.98 (3H, t, $J=7$ Hz, $OCH_2$–

13) All melting points were uncorrected. NMR spectra were obtained in $CDCl_3$, $C_6D_6$ or $D_2O$ with tetramethylsilane as an internal standard on a Nippon Denshi PS-100 spectrometer, and chemical shifts were given in $\tau$-value. Mass spectra were taken with a Hitachi M-52 spectrometer with a heated direct inlet system. UV spectra were obtained in EtOH solution on a Nippon Bunko UVIDEC-I spectrometer. $^{13}$C-NMR spectra were measured with a Nippon Denshi F.X. 100 at 25.1 MHz using tetramethylsilan as an internal standard in $CDCl_3$. The chemical shifts of **8** and **9** were determined from proton-decoupled $^{13}$C-NMR spectra, single-frequency off resonance decoupled $^{13}$C-NMR spectra and from application of standard chemical shift theory.[12]

14) D.H.R. Barton, R.D. Bracho, C.J. Potter, and D.A. Widdowson, *J. Chem. Soc., Perkin I*, **1974**, 2278.

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$C\underline{H}_3$), 7.69 (3H, s, $NCH_3$), 6.87 (2H, *q*, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.18, 6.16 (6H, $2\times$s, $2\times OCH_3$), 4.99 (2H, br. s, $2\times OH$), 3.39 (2H, s, $2\times$arom. H), 3.29, 3.03 (2H, $2\times$s, $2\times$arom. H). NMR ($C_6D_6$) $\tau$: 8.98 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 7.84 (3H, s, $NCH_3$), 7.10 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.76, 6.74 (6H, $2\times$s, $2\times OCH_3$), 5.78 (1H, d.d, $J=8$, 4 Hz, $C_5$–H), 4.88 (2H, br. s, $2\times OH$), 3.44, 3.41, 3.12, 2.58 (4H, $4\times$s, $4\times$arom. H). $^{13}$C-NMR ($CDCl_3$) $\delta$: 15.3 ($OCH_2\underline{C}H_3$), 33.8 ($Ar\underline{C}H_2$), 47.6 ($NCH_3$), 55.9 and 56.1 ($ArO\underline{C}H_3$), 58.4 and 64.6 ($\underline{C}H_2NCH_3$), 63.2 ($O\underline{C}H_2CH_3$), 77.7 ($Ar\underline{C}HOCH_2CH_3$), 111.3, 111.5, 111.7 and 115.3 (ArH), 132.1, 133.1, 133.8, 134.5, 144.6, 145.1, 145.8 and 145.9 (ArR). MS *m/e*: 373 ($M^+$, 100%), 345, 344, 315, 272, 271, 241. *Anal.* Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.67; H, 7.38; N, 3.55.

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