[Chem. Pharm. Bull. 16(8)1521—1526(1968)]

UDC 547.864.2.04 : 547.461.4.04

Studies on Phenazines. XXX.[1] Bromination of Phenazine Derivatives by N-Bromosuccinimide. (2)[2]

KAN UEDA and ITIRO YOSIOKA

Faculty of Pharmaceutical Sciences, Osaka University[3]

(Received October 9, 1967)

The N-bromosuccinimide (NBS) bromination of six 1-methylphenazine derivatives (I—VI) possessing either a methoxyl or an acetoxyl function at C_4, C_6, or C_9 was studied.

It has been found that a methoxyl group attached at C_4 disturbs the allylic bromination of C_1-methyl by NBS while a methoxyl group at C_6 or C_9 does only partly. An acetoxyl group existing at C_4, C_6, or C_9, however, has been noticed not to disturb the allylic bromination at C_1-methyl function, but the expected product has been secured.

In the previous paper,[4] the allylic bromination of 1-methyl- and 2-methyl-phenazines by means of N-bromosuccinimide (NBS) with a catalytic amount of benzoyl peroxide (BPO) has been reported. In the present paper, we wish to describe the further results on the NBS bromination of six 1-methylphenazine derivatives (I—VI) whose α-positions (*viz.* C_4, C_6, or C_9) are substituted by either a methoxyl or an acetoxyl function and also to discuss the significantly different effect caused by the two kinds of substituents in the NBS bromination reactions.

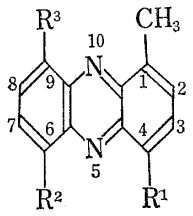

TABLE I

Compounds	R^1	R^2	R^3
I	OCH_3	H	H
II	$OCOCH_3$	H	H
III	H	OCH_3	H
IV	H	$OCOCH_3$	H
V	H	H	OCH_3
VI	H	H	$OCOCH_3$

It has generally been known that an electron attractive group attached on the alkyl-benzene ring facilitates the allylic bromination at the alkyl side chain under the NBS bromination.[5] On the other hand, an electron releasing group such as a methoxyl group has been believed to disturb the aforementioned tendency and enhance the substitution with bromine on the aromatic nucleus.[6]

In the first example, the bromination of 1-methyl-4-methoxyphenazine (I) with NBS and BPO resulted a complex mixture of reaction products, so that all the efforts for isolating the products were in vain. As it is apparently compared with the result obtained by the NBS bromination of 1-methylphenazine,[4] where the allylically brominated derivative was

1) Part XXIX: *Chem. Pharm. Bull.* (Tokyo), **14**, 426 (1966).
2) This work was presented at the 24th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April, 1967.
3) Location: *Toneyama, Toyonaka, Osaka.*
4) I. Yosioka and K. Ueda, *Chem. Pharm. Bull.* (Tokyo), **12**, 1247 (1964).
5) Buu-Hoi, *Ann.*, **556**, 1 (1944).
6) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); L. Horner and E.H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

the sole product, the finding is demonstrating that the methoxyl substituent existing in the same benzene moiety as methyl would bring about an undesirable effect in the bromination of I. While, on the bromination of 1-methyl-4-acetoxyphenazine (II) under the same reaction condition, there was obtained a crystalline bromide, $C_{15}H_{11}O_2N_2Br$, mp 178°. The structure of the product was assigned as 1-bromomethyl-4-acetoxyphenazine (VII) by the evidence below.

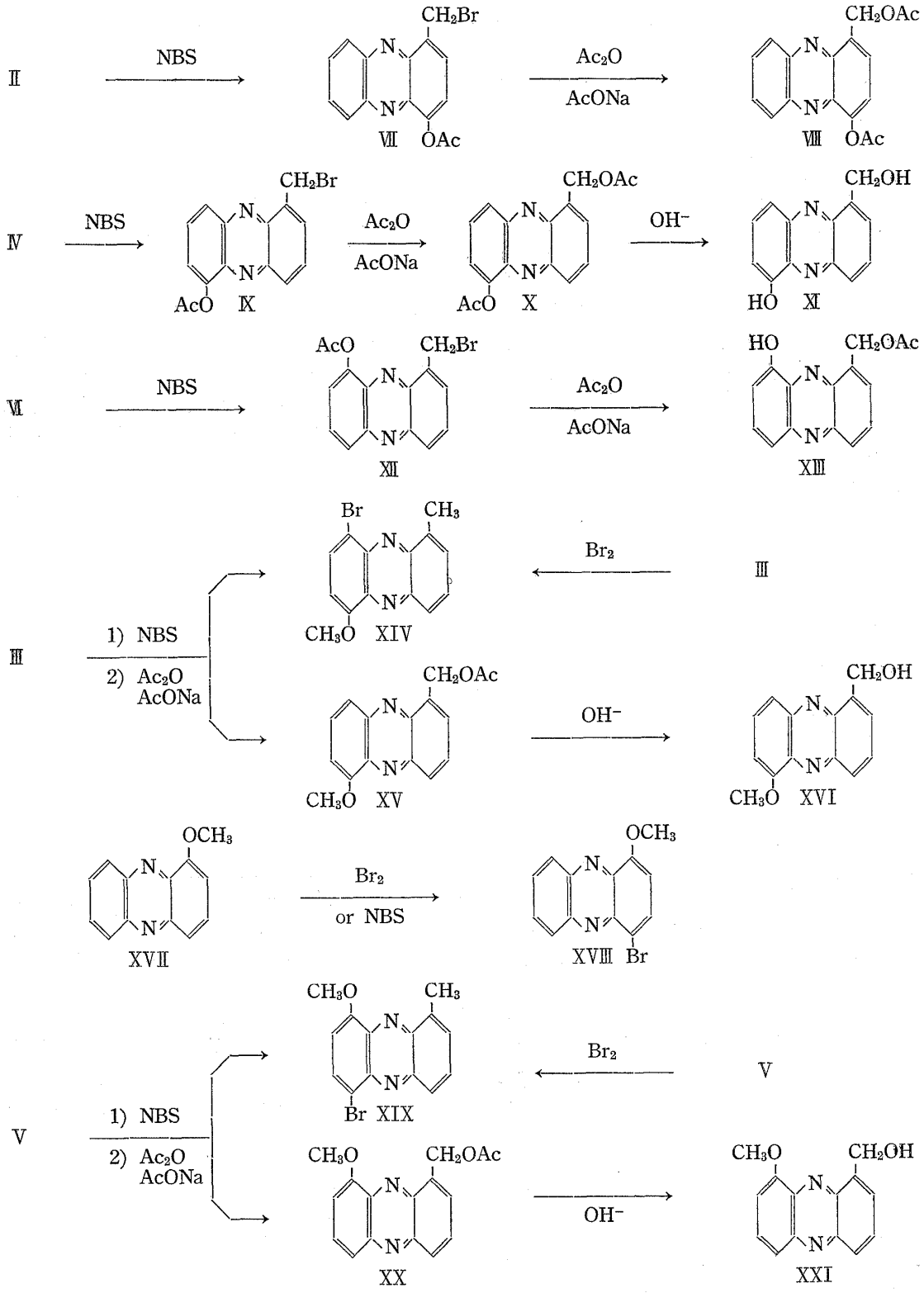

Chart 1

Thus, on acetolysis with acetic anhydride and sodium acetate, VII furnished a diacetate (VIII), $C_{17}H_{14}O_4N_2$, mp 175°, whose infrared absorption bands appearing at 1763 and 1740 cm^{-1} attributable to the phenolic (at C_4) and alcoholic (at C_1–methylene) acetate carbonyls respectively support to formulate the diacetate with 1–acetoxymethyl–4–acetoxyphenazine (VIII). The nuclear magnetic resonance (NMR) spectrum (Table I) of VIII corroborates the formulation by the disappearance of the methyl protons existed in II (τ 7.15) and by the signals due to the methylene protons at τ 4.08 (s.) and acetyl methyl at τ 7.82 (s.). It follows that the acetoxyl function on the same benzene ring as methyl would not provoke the abnormality in the NBS bromination and as the result the usual allylic bromination at the methyl function of II was secured yielding VII.

Table II. The Nuclear Magnetic Resonance Data (in τ values)

Compounds	Ar–C<u>H</u>$_3$	Ar–OCOC<u>H</u>$_3$	Ar–OC<u>H</u>$_3$	Ar–C<u>H</u>$_2$OAc	–CH$_2$OCOC<u>H</u>$_3$	Ring protons
I	7.24 (s.)		5.95 (s.)			3.26—1.63 (m.) (6H)
II*	7.15 (s.)	7.51 (s.)				2.67—1.67 (m.) (6H)
III*	7.20 (s.)		5.99 (s.)			3.13—1.88 (m.) (6H)
IV	7.11 (s.)	7.44 (s.)				2.58—1.72 (m.) (6H)
V*	7.10 (s.)		5.91 (s.)			3.08—1.89 (m.) (6H)
VI	7.14 (s.)	7.44 (s.)				2.60—1.80 (m.) (6H)
VIII		7.43 (s.)		4.08 (s.)	7.82 (s.)	2.56—1.68 (m.) (6H)
X		7.44 (s.)		4.08 (s.)	7.81 (s.)	2.68—1.74 (m.) (6H)
XIII		7.43 (s.)		4.15 (s.)	7.82 (s.)	2.55—1.69 (m.) (6H)
XV			5.87 (s.)	4.06 (s.)	7.81 (s.)	3.04—1.57 (m.) (6H)
XX			5.89 (s.)	3.97 (s.)	7.79 (s.)	3.05—1.74 (m.) (6H)

Each sample was measured with Hitachi H–60 at 60 Mc. All the spectra of the samples except the ones with * (taken in CH_2Cl_2) were measured in $CDCl_3$. The abbreviations s. and m. denote singlet and multiplet respectively.

The similar tendency was true in the cases of 1–methyl–6–acetoxy– and 1–methyl–9–acetoxy–phenazines (IV, VI), which on the NBS bromination, afforded 1–bromomethyl–6–acetoxy– (IX) and 1–bromomethyl–9–acetoxy–phenazines (XII) respectively in good yields (68%, 82%) with a few concomitant side reaction products.[7] The allylic brominations occurring at the methyl functions of IV and VI were substantiated by converting IX and XII through acetolysis as described above to 1–acetoxymethyl–6–acetoxy– (X) and 1–acetoxymethyl–9–acetoxy–phenazines (XIII), whose infrared spectra showing the existence of both phenolic (1765, 1763 cm^{-1}) and alcoholic acetate carbonyls (1733, 1730 cm^{-1}) support the formulae X and XIII being correct. Furthermore the NMR signals of both X and XIII (Table II) appearing at τ 4.08 (s.) (2H), 7.81 (s.) (3H), and 4.15 (s.) (2H), 7.82 (s.) (3H) assignable to Ar–C<u>H</u>$_2$–OAc and –OCOC<u>H</u>$_3$ respectively are also fully consistent with the formulation. The diacetate (X) was then hydrolyzed to give 1–hydroxymethyl–6–hydroxyphenazine (XI).

7) Not yet isolated.

In the case of 1–methyl–6–methoxyphenazine (III), two products were obtained by the NBS bromination. Without isolating the reaction products at this stage, the mixture was subjected to the acetolysis as mentioned before, followed by column chromatography using silicic acid furnishing two products. From the earlier eluted fraction, a nuclear substituted bromide was obtained (15%) and the structure of which was established as 1–methyl–6–methoxy–9–bromophenazine (XIV) based on its positive Beilstein test, no carbonyl absorption band in its infrared spectrum and finally on the direct comparison with the bromide synthesized from III with the aid of bromine. The position C_9 for the bromine of XIV was rationalized by the evidence that 1–methoxyphenazine (XVII) yielded 4–bromo derivative (XVIII) (namely, *para* to the methoxyl group) on the bromination with either bromine[8] or NBS. In addition, it is quite reasonably accepted that the bromine attached on the aromatic nucleus was not affected on acetolysis. The fraction eluted later from the column gave a compound $C_{16}H_{14}O_3N_2$ (62%), showing a negative Beilstein test and having a carbonyl absorption band at 1733 cm^{-1} in its infrared spectrum. The NMR signals of the compound appearing at τ 5.87 (s.) ($C\underline{H}_3O$–), 4.06 (s.) (Ar–$C\underline{H}_2$–OAc), 7.81 (s.) (–O–CO–$C\underline{H}_3$), 3.04—1.57 (m.) (6H) have led us to formulate it by 1–acetoxymethyl–6–methoxyphenazine (XV) and consequently its hydrolysis product can be expressed by 1–hydroxymethyl–6–methoxyphenazine (XVI).

Similarly on the NBS bromination followed by acetolysis, 1–methyl–9–methoxyphenazine (V) yielded two products (9 and 59% respectively), the one is deduced to be a nuclear substituted bromide, 1–methyl–6–bromo–9–methoxyphenazine (XIX) and the other is presumed to be 1–acetoxymethyl–9–methoxyphenazine (XX) in the analogous manner (The NMR data of XX were listed in Table II).

In conclusion, on the NBS bromination, 1–methylphenazine derivatives having an acetoxyl function at C_4, C_6, or C_9 would not disturb the allylic bromination at methyl functions as expected, while the existence of a methoxyl residue at C_4 resulted the complex reaction products. Although a methoxy function at C_6 or C_9 (namely attaching to the different benzene moiety from that bearing methyl function) causes some yield of nuclear brominated product (at C_9 or C_6), the major product is the one allylically brominated at C_1 methyl function.

The fact that the electron releasing effect of the methoxy function could not be extended to another benzene ring in the phenazine molecule could be understood in the analogous sense as in the NMR analyses performed by Morita,[9] where he clarified that most of the methoxyl functions existing at α–position in the phenazine derivatives would not give significant shielding effect on the ring protons of another benzene ring.

The study on the NBS bromination of the more highly substituted 1–methylphenazine derivatives are in progress in this laboratory.

Experimental[10]

1-Bromomethyl-4-acetoxyphenazine (VII)——A mixture of 1–methyl–4–acetoxyphenazine (II) (120 mg), NBS (100 mg) and BPO (10 mg) in CCl_4 (20 ml) was refluxed for 3 hr. During the procedure, the additional amount of NBS (50 mg) was added portionwise to the reaction mixture, so that the starting material was consumed completely (monitored by thin–layer chromatography (TLC)). The residue, obtained by the evaporation of the solvent, was washed with hot water and dried. The product was then purified by column chromatography using silica gel (benzene as an eluant), followed by recrystallization with MeOH to give 80 mg (55%) of VII as yellow needles, mp 178°. *Anal.* Calcd. for $C_{15}H_{11}O_2N_2Br$: C, 54.40; H, 3.35. Found: C, 54.64; H, 3.50.

1-Acetoxymethyl-4-acetoxyphenazine (VIII)——VII (34 mg) was refluxed with Ac_2O and AcONa for 2 hr. After treating in a usual manner, the product was crystallized from MeOH giving 26 mg (82%) of

8) I. Yosioka and S. Arafune, *Chem. Pharm. Bull.* (Tokyo), **7**, 581 (1959).
9) Y. Morita, *Chem. Pharm. Bull.* (Tokyo), **14**, 419, 433 (1966).
10) All the melting points were uncorrected.

VIII, mp 175°. IR ν_{max}^{Nujol} cm^{-1}: 1763, 1740, 1241, 1193. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55. Found: C, 65.71; H, 4.61.

1-Bromomethyl-6-acetoxyphenazine (IX)——A mixture of 1–methyl–6–acetoxy–phenazine (IV) (124 mg), NBS (90 mg), and BPO (10 mg) in CCl_4 (20 ml) was treated as for VII. In this case, additional 70 mg of NBS was added during the procedure. The residue, obtained after the usual treatment, was subjected to column chromatography using silica gel ($CHCl_3$) and the product was recrystallized with AcOEt yielding 110 mg (68%) of IX as yellow needles, mp 178—179°. *Anal.* Calcd. for $C_{15}H_{11}O_2N_2Br$: C, 54.40; H, 3.35; N, 8.46. Found: C, 54.51; H, 3.15; N, 8.76.

1-Acetoxymethyl-6-acetoxyphenazine (X)——IX (107 mg) was treated with Ac_2O and AcONa for 2 hr. After working up as usual, the product (91 mg, 90%), purified through silica gel column ($CHCl_3$), was recrystallized with benzene giving X as yellow needles, mp 199—200°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1733, 1230—1200 (broad), 1186. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.75; H, 4.45; N, 9.22.

1-Hydroxymethyl-6-hydroxyphenazine (XI)——A solution of X (62 mg) in acetone (5 ml) containing 10% aq. KOH (1 ml) was refluxed for 1 hr. After distillating off the acetone, the resulting syrup was diluted with water, acidified with AcOH, extracted with $CHCl_3$. The crude product (42 mg) obtained by the evaporation of the solvent was crystallized from benzene giving XI (30 mg, 67%) as yellow needles mp ,189—190°, IR ν_{max}^{Nujol} cm^{-1}: 3350, and no carbonyl absorption band. *Anal.* Calcd. for $C_{13}H_{10}O_2N_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 69.06; H, 4.46; N, 12.28.

1-Bromomethyl-9-acetoxyphenazine (XII)——1–Methyl–9–acetoxyphenazine (VI) (130 mg) was treated with NBS (100 mg), BPO (10 mg) in CCl_4 (10 ml) for 8 hr as described above. After the ordinary working up, the product was purified with silica gel column ($CHCl_3$) furnishing 140 mg (82%) of crystals, which was recrystallized with benzene to give XII as yellow needles, mp 210.° *Anal.* Calcd. for $C_{15}H_{11}O_2N_2Br$: C, 54.40; H, 3.35; N, 8.46. Found: C, 54.76; H, 3.23; N, 8.44.

1-Acetoxymethyl-9-acetoxyphenazine (XIII)——On treatment of XII (14 mg) with Ac_2O and AcONa in a usual manner, followed by silica gel column chromatography ($CHCl_3$), a quantitative amount of XIII was obtained. Recrystallization with *n*–hexane gave pale yellow needles melting at 132°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1763, 1730, 1245—1185 (broad). *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55. Found: C, 65.44; H, 4.44.

NBS Bromination of 1-Methyl-6-methoxyphenazine (III)——A mixture of III (300 mg), NBS (340 mg) and BPO (30 mg) in CCl_4 (50 ml) was refluxed until III was consumed completely (monitored by TLC). The crude bromide mixture was then subjected to acetolysis by refluxing with Ac_2O and AcONa. After working up as described before, the crude product (370 mg) was chromatographed on silica gel ($CHCl_3$). From the earlier eluate, XIV (60 mg, 15%) mp 172°, was obtained as yellow needles (recrystallized with ligroin), which exhibited a positive Beilstein test. IR: no carbonyl absorption band. *Anal.* Calcd. for $C_{14}H_{11}ON_2Br$: C, 55.46; H, 3.66; N, 9.25. Found: C, 55.39; H, 3.55; N, 9.36.

The later eluate gave XV (250 mg, 62%), mp 197—198°, yellow leaflets from AcOEt. IR ν_{max}^{Nujol} cm^{-1}: 1733, 1220, 1118. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.10; H, 4.85; N, 9.81.

1-Hydroxymethyl-6-methoxyphenazine (XVI)——XV (150 mg) was hydrolyzed with alkali as described for XI. XVI, thus obtained, was recrystallized with acetone–water giving yellow needles (90 mg, 71%), mp 202—203°. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3150, 1075. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 4.85; N, 11.39.

Bromination of 1-Methyl-6-methoxyphenazine (III) with Bromine——To a solution of III (500 mg) in AcOH (10 ml), was added Br_2 (400 mg) in AcOH. Immediately after the addition, yellow precipitates yielded. After keeping at room temperature for 2 days, the mixture was diluted with water and filtered. The collected precipitate was then chromatographed on alumina column (benzene) followed by recrystallization with ligroin giving 360 mg (53%) of yellow needles, mp 174°. *Anal.* Calcd. for $C_{14}H_{11}ON_2Br$: C, 55.46; H, 3.66; N, 9.25. Found: C, 55.31; H, 3.52; N, 9.04. The identity of the product described here with XIV synthesized from III using NBS was achieved by the mixed melting point determination and by com parison of the infrared spectra.

1-Methoxy-4-bromophenazine (XVIII)——A mixture of XVII (200 mg), NBS (170 mg) and BPO (20 mg) in CCl_4 (50 ml) was refluxed for 5 hr. The product was next purified by column chromatography over alumina using benzene as an eluant. XVIII (210 mg, 77%) was obtained by recrystallization with *n*–hexane as yellow needles, mp 155°. *Anal.* Cacld. for $C_{13}H_9N_2OBr$: C, 54.00; H, 3.14; N, 9.69. Found: C, 54.10; H, 3.05; N, 9.50. This compound was proved identical with the authentic sample of 1–methoxy–4–bromophenazine[8] by comparison of their IR spectra and by mixed melting determination.

NBS Bromination of 1-Methyl-9-methoxyphenazine (V)——V (224 mg) was brominated with NBS (260 mg) and BPO (20 mg) in CCl_4 (50 ml) as described for III. The earlier fraction eluted with $CHCl_3$ from the silica gel column furnished the nuclear substituted bromide (XIX) (26 mg, 9%), mp 211° (yellow needles from benzene). The compound was identified with the one prepared by bromination of V with bromine (mp 215°, the yield was 56%) as described for III (mixed mp, IR, and TLC). From the later eluted fraction, 162 mg (58%) of XX was obtained (yellow needles from benzene, mp 201—202°). IR ν_{max}^{Nujol} cm^{-1}: 1736, 1251, 1110. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.20; H, 5.04; N, 9.81.

1-Hydroxymethyl-9-methoxyphenazine (XXI)——XX (73 mg) in acetone (10 ml) was treated with 10% aq. KOH (10 ml) as described for XVI. The crude product (55 mg) thus obtained was recrystallized with AcOEt yielding XXI as yellow needles, mp 213—214°. No carbonyl absorption band is seen in the IR spectrum. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 55.46; H, 3.66; N, 9.24. Found: C, 55.48; H, 3.57; N, 9.28.

Acknowledgement The authors are indebted to Miss M. Suzuki for measuring the NMR spectra and to the members of analytical laboratory of this faculty for the elemental analyses.