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Synthesis of Adamantane Derivatives. III.[1] Synthesis of Adamantane Heterocycles

Tadashi SASAKI, Shoji EGUCHI and Takeshi TORU

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya

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Preparation of 1-adamantyl and adamantane-1-carbonyl derivatives having benzimidazole, 1,3,5-oxadiazole, oxazoline-2, quinoxaline, 2-aminothiazole, thiazolone, 2-methylthiazole, 1,2,3-thiadiazole, pyrazole or pyrazoline ring is described.

The unique structure of adamantane and the pharmaceutical effects of 1-adamantylamine hydrochloride on virus[2] have attracted many chemists and pharmacologists to do considerable work on the syntheses of adamantane derivatives,[3] although the biological activities of adamantane-containing agents are known in general to be quite reduced as the result of seemingly minor structural changes in the adamantane moiety.[4]

However, only a few 1-adamantyl heterocycles have been reported,[5] in which interesting interactions between adamantane and heterocyclic moiety could be anticipated from the pharmacological and also chemical viewpoints. Our present paper is concerned with the preparation of some 1-adamantane derivatives having a five- or six-membered heterocyclic ring.

Results and Discussion

Adamantane-1-carboxylic acid (I) was heated with *o*-phenylenediamine in the presence of hydrochloric acid or polyphosphoric acid, according to the general procedure for the preparation of benzimidazoles from aliphatic acids and *o*-phenylenediamine,[6] but these attempts were unsuccessful; in the former reaction, only the starting materials were recovered, and in the latter, adamantane was formed. The imidazole was obtained by the following stepwise method: *N*-(adamantane-1-carbonyl)-*o*-phenylenediamine (III) was prepared from adamantane-1-carbonyl chloride (II, Ad= adamantyl)[7,8] and *o*-phenylendiamine and III were refluxed with polyphosphoric acid ester (ppe) in chloroform to yield a benzimidazole derivative (IV).

1) Part II of this series; T. Sasaki, S. Eguchi and T. Toru, This Bulletin, **41**, 238 (1968).

2) W. L. Davis, R. R. Grunert, R. F. Hoff, J. W. McGahen, E. M. Neumayer, M. Paulschock, J. W. Watts, T. R. Wood, E. C. Herman and C. E. Hoffmann, *Science*, **144**, 862 (1964).

3) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Revs.*, **64**, 277 (1964).

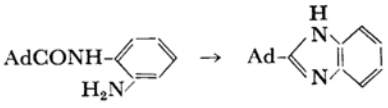
4) K. Gerzon, D. J. Tobias, Jr., R. E. Hilmes, R. E. Rathbun and R. W. Kattau, *J. Med. Chem.*, **10**, 603 (1967), and references cited therein.

5) H. Stetter and E. Rauscher, *Chem. Ber.*, **93**, 2054 (1960).

6) J. B. Wright, *Chem. Revs.*, **48**, 397 (1951).

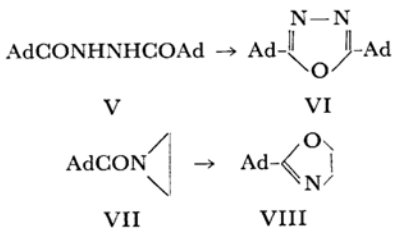
7) H. Stetter, M. Schwartz and A. Hirschhorn, *Angew. Chem.*, **71**, 429 (1959); *Chem. Ber.*, **92**, 1629 (1959); H. Stetter and E. Rauscher, *ibid.*, **93**, 1161 (1960).

8) The crude acid, obtained from 1-adamantyl bromide and formic acid, should be purified by the alkaline extraction, followed by acidification with hydrochloric acid. The purified I was dissolved in a mixture of dry benzene and thionyl chloride and the reaction mixture was kept standing at around 50°C for 2 hr. If the crude acid was used for the preparation of the acid chloride II, a large amount of 1-adamantyl chloride was formed besides the desired acid chloride, as was pointed out by a recent report: L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berberian and R. G. Slighter, *J. Med. Chem.*, **10**, 517 (1967).



III IV

N,N'-Bis(adamantane-1-carbonyl)hydrazine (V), prepared from II, was treated with perchloric acid in acetic anhydride[9] to afford 2,5-di(1-adamantyl)-1,3,4-oxadiazole (VI) in 50% yield. VI was also prepared in a 40% yield from the reaction between V and ppe in chloroform, but treatment of V with concd. sulfuric acid was unsuccessful and gave only adamantane-1-carboxylic acid I. Acylaziridine is known to be rearranged by heating with sodium iodide to oxazoline derivative.[10] Thus, 2-(1-adamantyl)-2-oxazoline (VIII), isolated as its picrate, was prepared from adamantane-1-carbonylaziridine (VII) which was obtained from II and ethyleneimine.

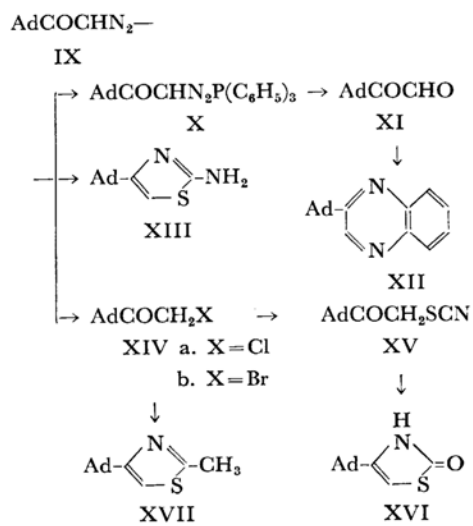


V VI

VII VIII

Adamantane-1-carbonyldizaomethane (IX)[11] could be an excellent precursor for the preparation of adamantane heterocycles. Treatment of II with excess diazomethane in ether gave the diazoketone IX in a good yield. Although reaction of IX with triphenylphosphine proceeded rather slowly (1 day) at room temperature, the triphenylphosphazine (X)[11] was obtained in a good yield of 88%. Phosphazine X was decomposed with nitrous acid to give 1-adamantylglyoxal (XI)[11-12] which, without isolation, was condensed with *o*-phenylenediamine to afford a quinoxaline derivative (XII) in 35% yield. Condensation of IX with thiourea in refluxing ethanol for 5 days afforded 4-(1-adamantyl)-2-aminothiazole (XIII) only in 8% yield after purification on a silica gel column, while heating a mixture of an ethanolic solution of IX and thiourea in a sealed tube at 100°C for 5 days afforded XIII in 20% yield, accompanied by a large amount of untractable decomposition products. The yield was improved up to 65% by using condensation reaction of thiourea with the haloketone (XIV)[11-12] which was easily prepared from IX and concd. hydrochloric or hydrobromic acid.

Reaction of the chloroketone (XIVa) with potassium thiocyanate gave oily adamantane-1-carbonylmethyl thiocyanate (XV) which was hydrolyzed to afford 4-(1-adamantyl)thiazol-2-one (XVI), whereas attempts to cyclize IX with potassium cyanide to the triazine in an aqueous medium were unsuccessful. A thiazole derivative (XVII) was also prepared by the cyclization of the haloketone (XIV) with thioacetamide.



IX

X XI

XIII XII

XIV a. X=Cl b. X=Br XV

XVII XVI

Though 1,3-dipolar cycloaddition reaction of diazoalkanes is well known to afford some heterocycles, the reactivity of most diazoketones in the cycloaddition reaction has been pointed out to be low.[13] Compound IX was also not expected to be very reactive, so drastic conditions were applied to the 1,3-dipolar cycloaddition of IX. Treatment of IX with cyanoacetylene in dioxane at 100°C gave 3(5)-(adamantane-1-carbonyl)-5(3)-cyanopyrazole (XVIII) in 92% yield, while IX did not react with it at room temperature. The structure of XVIII was confirmed from analytical and spectral data; the NMR spectrum of XVIII showed a singlet at 2.72 τ due to a ring proton and a broad singlet at -4.2 τ due to an NH proton which disappeared on deuteration. Cycloaddition of IX with acrylamide gave 3-(adamantane-1-carbonyl)-5-carbamoyl-2-pyrazoline (XIX), the structure of which was confirmed from analytical and spectral data.[14] The cycloaddition of diazoalkane with isocyanate has been reported by

9) G. V. Boyd, *Chem. Commun.*, **1967**, 954.

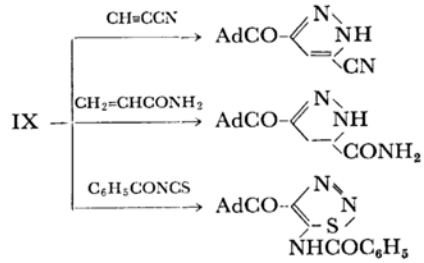
10) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967), and references cited therein.

11) H. Stetter, M. Schwartz and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959); *Neth. Appl.*, **6**, 404, 856 (1965); *Chem. Abstr.*, **64**, 12569f (1966).

12) M. Kuchar, *Collection Czech. Chem. Commun.*, **33**, 880 (1968).

13) See the excellent review, R. Huisgen, R. Grashey and J. Sauer, "Cycloaddition Reactions of Alkene" in "The Chemistry of Alkene," ed. by S. Patai, Interscience Publishers, New York, N. Y. (1964), p. 806—878.

14) R. Sustmann, R. Huisgen and H. Huber, *Chem. Ber.*, **100**, 1802 (1967).



several workers.[15] The reaction of IX with benzoylisothiocyanate in dioxane at 100°C gave a thiadiazole derivative (XX) in 47% yield. This structure was confirmed from infrared and ultraviolet spectrum[16] which had the maxima at 238 mμ (ε 18200) and 299 mμ (ε 15700) in ethanol.

The infrared, NMR and ultraviolet spectral data of the reaction products are summarized in Table 1.

TABLE 1. SPECTROSCOPIC DATA OF THE REACTION PRODUCTS

Compound	Infrared spectrum cm^{-1} (KBr)	NMR spectrum[a] τ ($CDCl_3$)	Ultraviolet spectrum $\lambda_{max}^{ethanol}$, mμ (ε)
III	3500, 3400, 3300, 3040, 1645, 1615, 1520, 740		
IV	3040, 1620, 1590, 1530, 740		281(10450), 275(9400), 243(7150)
VI	1590, 1560, 1050		250(23)
VIII[b]	1625, 1610	8.28(6H, s), 8.06(6H, s), 8.00(3H, br. s), 6.00(2H, m), 5.09(2H, m), 5.0(1H, br. s), 1.44(2H, s)	
IX	2110, 1620	8.29, 8.25, 8.20(12H, os), 7.98(3H, br. s) 4.61(1H, s)	340(320), 250(7310)
X	3060, 1627, 1590, 1530		
XII	3020, 1610, 1553, 762	8.16(6H, s), 7.85(9H, s), 2.08(4H, m), 1.00(1H, s)	319(7450), 309(6670) 235(2980)
XIII	3480, 3310, 3180, 1640, 1625, 1607, 1530, 1520[c]	8.25, 8.22(6H, os), 8.13, 8.09(6H, os), 7.99(3H, br. s) 3.98(1H, s), 4.95(2H, br. s)	253(5790)
XVIa	1710		
XIVb	1702		
XVI	3000, 1650, 1600	8.27, 8.20, 8.15(12H, os), 7.97(3H, br. s), 4.45(1H, d, J=2.1 Hz)[f]	217(6580)
XVII	3100, 1513[d]	8.18(6H, s), 7.98(9H, s), 7.33(3H, s), 3.38(1H, s)	242(4050)
XVIII	3250, 3140, 2270, 1655, 1575, 1537	8.20(6H, s), 7.96(6H, s) 7.88(3H, br. s), 2.72(1H, s), −4.2(1H, br. s)[g]	237(8710)
XIX	3350, 3250, 3220, 1685, 1670, 1640, 1605[e]	8.22(6H, s), 7.94(9H, s), 6.9(2H, m), 5.8(1H, m), 3.25(2H, br. s), 2.37(1H, s)[h,g]	209(16400), 234(7710)
XX	3250, 3050, 1665, 1630, 1600, 1580, 1510		299(15700), 238(18200)

a) br.=broad, s=singlet, d=doublet, m=multiplet, os=overlapped singlet.
b) 2-(1-adamantyl)-2-oxazoline picrate
c) 3480, 3310(ν_{NH}), 3180($\nu_{ring\ CH}$), 1640, 1625, 1607, 1530 (ring vibration), 1520 (δ_{NH}); P. J. Chouteau, G. Davidovics, J. Metzger, M. Azzaro and M. Poite, *Bull. Soc. Chim. France*, **1962**, 1794.
d) 3100 ($\nu_{ring\ CH}$), 1513 (ring vibration).
e) 3350, 3250, 3220 (ν_{NH}), 1685, 1670, 1605 (amide I and II), 1640 ($\nu_{C=N}$).
f) The doublet is due to the interaction with NH proton.
g) The NMR measurement was carried out in deuterated chloroform-deuterated dimethylsulfoxide.
h) The coupling constants could not be ascertained, see R. Sustmann, R. Huisgen and H. Huber, *Chem. Ber.*, **100**, 1802 (1967).

15) W. Ried and B. M. Beck, *Ann.*, **673**, 128 (1964); D. Martin and W. Mucke, *ibid.*, **682**, 90 (1965); J. C. Sheehan and P. T. Izzo, *J. Am. Chem. Soc.*, **71**, 4059 (1949).

16) 4-Nitrofuryl-5-benzoylamino-1,2,3-thiadiazole had the ultraviolet absorptions at 233 mμ (ε 29700), 306 mμ (ε 17800) and 374 mμ (ε 17800) and the infrared absorptions at 3430, 3340, 1675, 1630, 1603 and 1585 cm^{-1}; unpublished data of our laboratory.

Experimental

The microanalyses were performed on a Yanagimoto C. H. N. Corder, Model MT-1, while the IR spectra and the UV spectra were obtained on a JASCO Model IR-S infrared spectrophotometer and a JASCO Model ORD/UV-5 ultraviolet spectrophotometer, respectively. All the melting points were measured on a Yanagimoto micromeltingpoint apparatus and are uncorrected.

***N*-(Adamantane-1-carbonyl)-*o*-phenylenediamine (III).** To a solution of *o*-phenylenediamine (0.3 g) and triethylamine (0.3 g) in dry ether was added a solution of II, obtained from 0.5 g of I, in the same solvent. The reaction mixture was stirred overnight at room temperature and filtered. The precipitates were washed with water and recrystallized from aqueous methanol to give 470 mg (63%) of III as colorless plates, mp 229—231°C.

Found: C, 74.99; H, 8.53; N, 10.42%. Calcd for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36%.

2-(1-Adamantyl)benzimidazole (IV). The compound III (200 mg) was refluxed in chloroform added with 5 drops of ppe. The mixture was poured into water and the organic layer was washed with aqueous sodium bicarbonate, dried over sodium sulfate and evaporated to dryness. Recrystallization of the residue from chloroform afforded 180 mg (96%) of IV as colorless needles, mp>300°C.

Found: C, 80.82; H, 8.06; N, 11.20%. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10%.

2,5-Di(1-adamantyl)-1,3,4-oxadiazole (VI). *N,N'*-Bis(adamantane-1-carbonyl)hydrazine (V)[6] (400 mg) was dissolved in hot acetic anhydride (15 m*l*), added with 4 drops of 60% perchloric acid. After 10 min, the mixture was cooled and filtered. Water was added to the filtrate and the separated crystals were collected. The combined crystals were washed with water and recrystallized from aqueous acetone affording the oxadiazole (VI) (190 mg, 50%) as colorless plates, mp >300°C in a sealed tube.

Found: C, 78.26; H, 9.21; N, 8.38%. Calcd for $C_{22}H_{30}ON_2$: C, 78.06; H, 8.93; N, 8.28%.

2-(1-Adamantyl)-2-oxazoline (VIII). A mixture of ethyleneimine (0.13 g) and triethylamine (0.3 g) in dry ether was added dropwise to a solution of II, obtained from 0.5 g of I, in dry ether. The reaction mixture was stirred for 30 min under ice-cooling and then for 10 min at room temperature. The solution was filtered and the precipitates were washed with dry ether. The filtrate was dried over sodium sulfate and evaporated *in vacuo* affording a brownish oil (VII); the infrared spectrum showed absorptions at 3050 (ν_{CH}) and 1680 (ν_{CO}) cm^{-1}. The oil VII was refluxed in acetone (15 m*l*) with sodium iodide (0.2 g) for 26 hr. The solution was concentrated *in vacuo* and the residual oil was extracted with ether. The ether extracts were washed with water, dried and condensed *in vacuo*. The residue gave the picrate on treatment with picric acid, which was recrystallized from ethanol to afford yellow needles (0.52 g, 43% based on I), mp 216—218°C.

Found: C, 52.75; H, 5.20; N, 13.24%. Calcd for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90%.

Adamantane-1-carbonyldiazomethane (IX). A solution of II, obtained from 1.0 g of I, in ether was added to a solution of diazomethane in ether under cooling. After standing for 2 days at room temperature, the solvent and excess diazomethane were removed *in vacuo* and residual yellow solid was recrystallized from methanol to give 0.82 g (72% based on I) of IX as yellow plates, mp 69—71°C.

Found: C, 70.85; H, 8.00; N, 13.34%. Calcd for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72%.

α-(Adamantane-1-carbonyl)triphenylphosphazine (X). A mixture of the diazoketone IX (200 mg) and triphenylphosphine (330 mg) in dry ether was stirred for 1 day, cooled and the resulting precipitates were filtered. The precipitates were washed with dry ether and recrystallized from benzene affording 410 mg (88%) of the triphenylphosphazine X as yellow crystals, mp 125—127°C.

Found: C, 76.81; H, 6.20; N, 5.56%. Calcd for $C_{30}H_{31}ON_2P$: C, 77.23; H, 6.70; N, 6.00%.

2-(1-Adamantyl)quinoxaline (XII). An aqueous solution of sodium nitrite (60 mg) was added to a suspension of X (410 mg) in acetone (2 m*l*) and then 20% hydrochloric acid was added to the mixture under ice-cooling. The reaction mixture was stirred for 30 min under ice-cooling and then for 30 min at room temperature. The mixture was extracted with ether and the ether extracts were washed, dried and evaporated *in vacuo* leaving an oil of XI whose infrared spectrum showed absorptions at 2730 (ν_{CHO}), 1700 (ν_{CO}) and 1660 (ν_{CO}) cm^{-1}. A mixture of XI, *o*-phenylenediamine (100 mg) and anhydrous acetic acid (1 drop) was refluxed in ethanol for 4 days. The solvent was evaporated leaving a brownish oil which was dissolved in a small amount of methanol and solidified on cooling. Recrystallization from methanol gave 80 mg (35% from X) of a quinoxaline XII as dark brown plates, mp 119—120°C.

Found: C, 82.04; H, 7.58; N, 10.57%. Calcd for $C_{18}H_{19}N_2$: C, 81.78; H, 7.68; N, 10.60%.

1-Adamantyl chloromethyl ketone (XIVa). Concentrated hydrochloric acid was added to a solution of IX (0.8 g) in dioxane (4 m*l*) under ice-cooling. The reaction mixture was heated at 70°C for 5 min until evolution of nitrogen had ceased completely. The reaction mixture was allowed to cool to room temperature and then water was added to it. The resulting precipitates were collected by filtration, and recrystallized from a mixture of acetone and petroleum ether (bp 40—60°C) to give 0.7 g (84%) of XIVa as colorless plates, mp 106—107°C, which showed a positive Beilstein test.

Found: C, 67.47; H, 8.05%. Calcd for $C_{12}H_{17}OCl$: C, 67.76; H, 8.06%.

1-Adamantyl bromomethyl ketone (XIVb). The work-up as above except using hydrobromic acid instead of hydrochloric acid afforded the precipitates which were recrystallized from methanol giving 220 mg (87.5%) of XIVb as colorless powder, mp 78—79°C, from 200 mg of IX. XIVb showed a positive Beilstein test.

Found: C, 56.17; H, 6.93%. Calcd for $C_{12}H_{17}OBr$: C, 56.04; H, 6.67%.

4-(1-Adamantyl)-2-aminothiazole (XIII). *a) from IX.* A mixture of IX (300 mg) and thiourea (400 mg) was heated at 100°C in ethanol (10 m*l*) in a sealed tube for 5 days. Ethanol was removed and the residue was dissolved in chloroform. The solution was washed with water, dried and chromatographed on a silica gel column, using chloroform as an eluent. Recrystalliza-

tion from acetone gave 70 mg (20%) of XIII as colorless needles.

b) from XIVa. XIVa (80 mg) and thiourea (150 mg) were refluxed in ethanol for 12 hr. The solvent was removed *in vacuo* and the residue was recrystallized from acetone to give 70 mg (65%) of XIII, mp 224—226°C.

Found: C, 66.91; H, 7.82; N, 11.73%. Calcd for $C_{13}H_{18}N_2S$: C, 66.60; H, 7.74; N, 11.95%.

4-(1-Adamantyl)thiazolone (XVI). An acetone solution (15 m*l*) of XIVa (170 mg) and potassium thiocyanate (78 mg) was refluxed for 5 hr. After cooling, the solution was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of methanol (1 m*l*), water (3 m*l*) and concd. hydrochloric acid (0.5 m*l*) and the mixture was maintained at 70°C for 15 hr. After cooling, the precipitates were collected and recrystallized from a mixture of chloroform and *n*-hexane to give 80 mg (42.5%) of XVI as colorless plates, mp 293.5—295.5°C.

Found: C, 65.95; H, 7.24; N, 5.80%. Calcd for $C_{13}H_{17}ONS$: C, 66.36; H, 7.28; N, 5.95%.

4-(1-Adamantyl)-2-methylthiazole (XVII). A solution of thioacetamide (120 mg) in dry benzene (2 m*l*) was added in small portions to a solution of XIVa (200 mg) in the same solvent (2 m*l*). After refluxing for 24 hr, benzene was removed *in vacuo* and the residue was recrystallized from methanol affording 100 mg (45.5%) of XVII as colorless plates, mp 97—98°C.

Found: C, 72.17; H, 8.19; N, 6.00%. Calcd for $C_{14}H_{19}NS$: C, 72.16; H, 8.22; N, 6.01%.

4-(Adamantane-1-carbonyl)-5-benzoylamino-1,2,-3-thiadiazole (XX). A mixture of IX (100 mg) and benzoyl isothiocyanate (0.5 m*l*) was kept at 100°C for 1 day. On addition of *n*-hexane to the cooled reaction mixture, yellowish white crystals were separated and further crops were obtained from the mother liquor giving an overall yield of 85 mg (47%) of XX. Recrystallization from a mixture of acetone and *n*-hexane gave yellowish white needles, mp 225—226°C.

Found: C, 65.46; H, 5.68; N, 11.48%. Calcd for $C_{20}H_{21}O_2N_3S$: C, 65.36; H, 5.76; N, 11.44%.

3(5)-(Adamantane-1-carbonyl)-5(3)-cyanopyrazole (XVIII). IX (200 mg) and cyanoacetylene (100 mg) was heated at 100°C in anhydrous dioxane for 1 day. Water was added to the cooled solution to give colorless crystals. Recrystallization from a mixture of methanol and *n*-hexane afforded 230 mg (92%) of XVII as colorless needles, mp 224.5—225.5°C.

Found: C, 70.53; H, 6.43; N, 16.45%. Calcd for $C_{15}H_{17}ON_3$: C, 70.56; H, 6.71; N, 16.46%.

3-(Adamantane-1-carbonyl)-5-carbamoyl-2-pyrazoline (XIX). IX (270 mg) and acrylamide (120 mg) were heated at 100°C in dioxane in the presence of triethylamine (1 drop) for 1.5 days. Addition of water to the cooled reaction mixture afforded solids which were recrystallized from methanol giving 50 mg (14%) of XIX as yellow needles, mp 275—277.5.5°C.

Found: C, 65.63; H, 7.37; N, 15.25%. Calcd for $C_{15}H_{21}O_2N_2$: C, 65.43; H, 7.69; N, 15.26%.

The authors wish to express their thanks to Takeda Chemical Industries, Ltd., for running the NMR spectra, and especially to Mr. Akiho Ishihara of their laboratories who carried out the microanalyses.