Acetylene Compounds of Potential Pharmacological Value. VIII. N-(4-Dialkylamino-2-butynyl)-Substituted Cyclic Imides[1]

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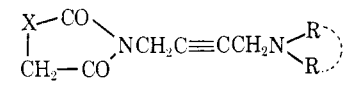
A series of N-(4-dialkylamino-2-butynyl)-substituted cyclic imides has been prepared. These compounds have been investigated for antagonistic activity toward acetylcholine on isolated guinea pig ileal preparations and for mydriatic activity and blockade of the motor effects of oxotremorine in intact mice. While these different activities were significantly correlated, considerable differences were found in the relative central and peripheral anticholinergic effects *in vivo* and one member of the series, N-(4-diethylamino-2-butynyl)succinimide, showed a very high degree of specificity as a central anticholinergic agent.

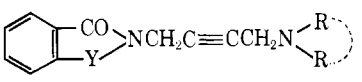
Tremorine[2] (1,4-dipyrrolidino-2-butyne) and oxotremorine[3] [1-(2-oxopyrrolidino)-4-pyrrolidino-2-butyne] have been widely used in the search for compounds of potential value in Parkinson's disease. Both compounds produce in a variety of experimental animals a syndrome characterized by tremor, rigidity, hypokinesia, and parasympathomimetic effects, which are blocked by atropine and many agents of established effectiveness in treating Parkinson's disease. Oxotremorine is preferable to tremorine for screening purposes, since the latter compound owes its effects to biotransformation to oxotremorine, and several unrelated compounds have been shown to block the effects of tremorine by interfering with this metabolic activation.[4,5]

Introduction of large substituents into agonist molecules frequently yields compounds possessing antagonistic properties, and the extreme potency and structural specificity of oxotremorine suggest that analogs may be found with similar potency. The relative specificity of oxotremorine on the central nervous system offers hope that these analogs might also be selectively central in their blocking actions and thus minimize the peripheral parasympatholytic side effects commonly seen in agents used to treat Parkinson's disease.

Of many such analogs which have been examined, the presently described series of cyclic imides of types



I, X = CH_2, CH_3CH, or CH_2CH_2

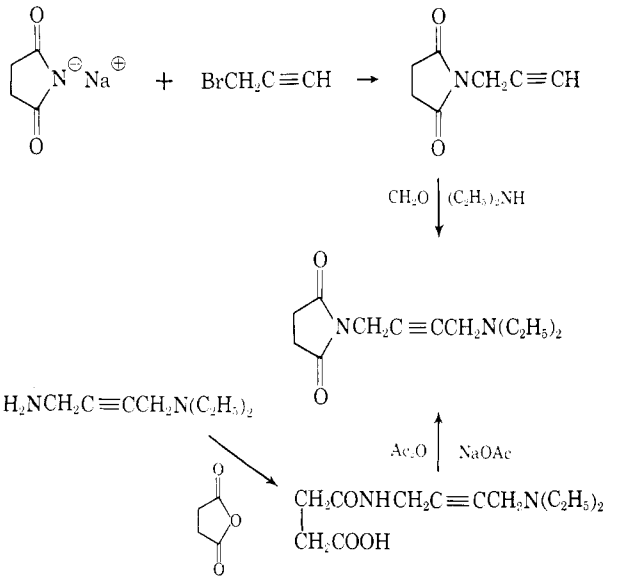


II, Y = CO, SO_2

I and II is of particular interest. The compounds share with oxotremorine the 4-dialkylamino-2-butynyl group, which is attached to substituted cyclic imides rather than to a lactam as in oxotremorine. Several show a pronounced antagonism to oxotremorine which in some cases is evident at much lower dosages than in peripheral parasympatholytic actions.

Chemistry.—In general the compounds listed in Tables I and II were prepared through the Mannich reaction by refluxing a mixture of the N-propargylimide, formaldehyde, and the appropriate amine in dioxane in the presence of a small amount of cuprous chloride. N-(4-Diethylamino-2-butynyl)succinimide was also prepared by ring closure of N-(4-diethylamino-2-butynyl)succinamic acid, obtained from 4-diethylamino-2-butynylamine and succinic anhydride (see Scheme I).

SCHEME I



Pharmacology. A. Methods.—Each compound was administered intraperitoneally in logarithmically spaced doses to groups of five male mice weighing 18–22 g.

(1) Previous paper in this series: R. Dahlbom, B. Karlén, A. Lindquist, R. George, and D. J. Jenden, *Acta Pharm. Suecica*, **3**, 187 (1966).

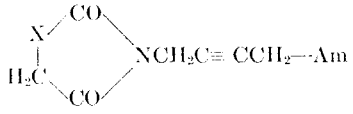
(2) G. M. Everett, L. E. Blockus, and I. M. Shepperd, *Science*, **124**, 79 (1956).

(3) A. K. Cho, W. L. Haslett, and D. J. Jenden, *Biochem. Biophys. Res. Commun.*, **5**, 276 (1961).

(4) F. Sjöqvist and J. Gilette, *Life Sci.*, **4**, 1031 (1965).

(5) G. B. Leslie and D. R. Maxwell, *Nature*, **202**, 97 (1964).

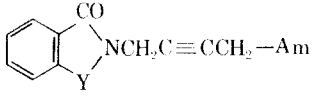
Table I



Compd	X	Am	Yield, %	Derivative	Recrystn solvent[a]	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ia	CH_2	$N(C_2H_5)_2$	59	HCl	Et	183–183.5	$C_{12}H_{18}N_2O_2 \cdot HCl$	55.7	7.40	10.8	55.9	7.47	10.8
Ib[b]	CH_2	NC_4H_8[c]	61	Base	Et–PE	91–92	$C_{12}H_{16}N_2O_2$	65.4	7.32	12.7	65.4	7.40	12.8
Ic	CH_2	NC_5H_{10}[d]	92	Base	Et–PE	76–77	$C_{13}H_{18}N_2O_2$	66.6	7.74	12.0	66.4	7.57	12.1
Id	CH_2	$N(C_3H_7\text{-}n)_2$	54	HCl	Et	167–168	$C_{14}H_{22}N_2O_2 \cdot HCl$	58.6	8.08	9.77	58.5	8.20	9.77
Ie	CH_2	$N(C_3H_7\text{-}i)_2$	42	HCl	Et	159–162	$C_{14}H_{22}N_2O_2 \cdot HCl$	58.6	8.08	9.77	58.6	8.12	9.66
If	CH_2	$NC_5H_8(CH_3)_2$[e]	40	HCl	Et	231.5–233	$C_{15}H_{22}N_2O_2 \cdot HCl$	60.3	7.76	9.38	60.3	7.78	9.43
Ig	CH_3CH	$N(C_2H_5)_2$	26	Base		145–160 (2.5)	$C_{13}H_{20}N_2O_2$	66.1	8.53	11.9	65.6	8.55	11.8
Ih	CH_2CH_2	$N(C_2H_5)_2$	40	Base		190 (1.5)	$C_{13}H_{20}N_2O_2$	66.1	8.53	11.9	66.2	8.45	12.0

[a] Et, ethanol; PE, petroleum ether. [b] After completion of this work this compound was reported by A. Bebbington, R. W. Brimblecombe, and D. Shakeshaft, *Brit. J. Pharmacol.*, **26,** 56 (1966), with mp 89–91°. [c] NC_4H_8 = pyrrolidino. [d] NC_5H_{10} = piperidino. [e] $NC_5H_8(CH_3)_2$ = *cis*-2,6-dimethylpiperidino.

Table II



Compd	Y	Am	Yield, %	Derivative	Recrystn solvent[a]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
IIa	CO	$N(C_2H_5)_2$	68	Base	Et–W	72–73.5	$C_{16}H_{18}N_2O_2$	71.1	6.71	10.4	71.1	6.88	10.4
IIb[b]	CO	NC_4H_8[c]	59	Base	Et–W	110.5–111.5	$C_{16}H_{16}N_2O_2$	71.6	6.02	10.4	71.5	6.19	9.88
IIc	CO	NC_5H_{10}[d]	95	Base	M–W	84.5–86	$C_{17}H_{18}N_2O_2$	72.3	6.43	9.92	72.1	6.76	9.66
IId	SO_2	$N(C_2H_5)_2$	48	HCl	Et–E	188.5–190	$C_{15}H_{18}N_2O_3S \cdot HCl$	52.5	5.59	8.17	52.9	5.32	8.01
IIe	SO_2	NC_5H_{10}[d]	17	HCl	Et–L	195–196 dec	$C_{16}H_{18}N_2O_3S \cdot HCl$	54.2	5.40	7.90	53.9	5.30	7.70

[a] E, ethanol; L, ligroin; M, methanol; W, water. [b] After completion of this work this compound was reported by A. Bebbington, R. W. Brimblecombe, and D. Shakeshaft, *Brit. J. Pharmacol.*, **26,** 56 (1966), with mp 112–114°. [c] NC_4H_8 = pyrrolidino. [d] NC_5H_{10} = piperidino.

After 15–20 min, pupillary diameter was measured under constant lighting conditions with the aid of a binocular microscope fitted with a calibrated eyepiece, and compared to a similar measurement made immediately prior to injection. Oxotremorine was then injected intravenously at a dose of 100 μg/kg, and after a further 15–20 min, the intensity of tremor was graded visually, using a point system previously described.[6] The results were averaged for each group of five mice, and the results were plotted as a function of the dose of antagonist. The "tremorolytic dose" was estimated by visual interpolation as the dose at which the mean tremor response was reduced by one point from the control. This was approximately equivalent to the dose giving twofold protection against oxotremorine. The "mydriatic dose" was also estimated graphically as the dose required to double the pupil size relative to the control. All doses are expressed in moles per kilogram.

Acetylcholine antagonism was measured on isolated guinea pig ileal strips suspended in oxygenated Krebs solution at 38°. Contractions were recorded isotonically at 1-g tension, using a Collins displacement transducer and potentiometric recorder. A series of cumulative dose–response curves was obtained using acetylcholine only; these were then repeated in the presence of a test compound at concentrations increasing in the ratio 1:3:10:30. The preparation was allowed to equilibrate with each new concentration for 30 min before the acetylcholine dose–response curve was obtained.

The antagonism was found to be competitive in every case. The acetylcholine concentration giving a 50% response was estimated at each concentration of antagonist, and the antagonist concentration producing a twofold block of acetylcholine was estimated graphically.

B. Results and Discussion.—Table III summarizes the results obtained and includes atropine as a reference compound treated identically. All compounds except Ig and IIb blocked the central effects of oxotremorine and, in sufficient doses, also produced mydriasis. The relative doses required for these two effects varied widely, and one compound (Ia) appeared to be highly specific in its central actions, causing significant mydriasis only as the lethal dose ($\sim 1.5 \times 10^{-3}$ mole/kg) was approached. Compounds Ig and IIb produced convulsions and death at doses showing no blockade of oxotremorine. Excitement, hyperkinesis, and eventually convulsions were observed after sufficiently large doses of all the compounds; no other consistent effects were seen in mice.

With the exception of Ib, all the compounds behaved as competitive antagonists of acetylcholine on the isolated guinea pig ileum. Ia, Ib, and Ic all produced an increase in tone and motility of the gut at low concentrations ($\sim 10^{-7}$ M), but with Ia and Ic, this effect disappeared as the concentration was increased, being replaced by a competitive anticholinergic action. On the other hand, it became more pronounced with Ib, which thus behaved as an agonist and could be blocked by atropine.

It is evident from Table III that the derivatives of succinimide have higher tremorolytic effect than the corresponding derivatives of phthalimide and benzosulfimide. Introduction of a methyl group into the succinimide ring (Ig) or ring expansion to glutarimide (Ih) lowers the tremorolytic effect considerably.

Table IV summarizes a correlation analysis of the results depicted in Table III, which were first converted to logarithms. The *in vivo* doses of Ig and IIb were both taken as 10^{-3} mole/kg for the purpose of calculating correlation coefficients.[7a] All three types of activity show some correlation with each other in agreement with the view that they depend upon a common, basic pharmacodynamic property. However, the correlation between acetylcholine blockade and oxotremorine antagonism is only suggestive and not statistically significant at the 5% level. Further insight may be obtained by the calculation of partial correlation coefficients[7b] which provide an assessment of the correlation which would be observed between two of the variables if the third could be maintained constant, *i.e.*, the effects of a common correlation with the third variable are eliminated. When the data are examined in this way, the correlation between acetylcholine blockade and oxotremorine antagonism disappears, although mydriatic activity remains significantly correlated with both factors.

The high correlation between atropinic activity *in vitro* and mydriatic activity indicates that blocking

TABLE III

PHARMACOLOGICAL RESULTS

Compd	*In vivo* dose (moles/kg) required to produce in mice: Mydriasis	Oxotremorine blockade	Concn (M) to antagonize acetylcholine on isolated guinea pig ileum
Ia	8.0×10^{-4}	1.6×10^{-5}	1.0×10^{-5} [a]
Ib	2.5×10^{-4}	8.0×10^{-5}	(Agonist)[b]
Ic	2.0×10^{-4}	4.0×10^{-5}	2.7×10^{-6} [a]
Id	$\sim 1.0 \times 10^{-3}$	5.6×10^{-4}	9.6×10^{-5}
Ie	1.4×10^{-3}	1.4×10^{-4}	1.4×10^{-5}
If	1.2×10^{-4}	5.0×10^{-5}	3.8×10^{-5}
Ig	$>1.0 \times 10^{-3}$ [c]	$>1.0 \times 10^{-3}$ [c]	1.1×10^{-4}
Ih	1.0×10^{-3}	2.0×10^{-4}	1.5×10^{-5}
IIa	1.0×10^{-3}	8.0×10^{-4}	3.4×10^{-6}
IIb	$>1.0 \times 10^{-3}$	$>1.0 \times 10^{-3}$	2.4×10^{-6}
IIc	4.0×10^{-4}	3.2×10^{-4}	9.8×10^{-7}
IId	4.0×10^{-4}	2.5×10^{-4}	1.6×10^{-6}
IIe	1.0×10^{-4}	8.0×10^{-5}	1.9×10^{-7}
Atropine	6.4×10^{-7}	3.2×10^{-6}	2.6×10^{-10}

[a] Produced contraction of ileum at $\sim 10^{-7}$ M; this effect disappeared at higher concentrations. [b] Stimulated ileal preparation at all concentrations. [c] No mydriasis or oxotremorine blockade observed at sublethal doses.

TABLE IV

CORRELATION OF PHARMACOLOGICAL ACTIVITIES

	Mydriasis		Oxotremorine blockade	
	r[a]	P	r[a]	P
Mydriasis	...	...	0.720	<0.01
			0.632	<0.05
Acetylcholine antagonism	0.842	<0.001	0.505	<0.1
	0.798	<0.01	−0.268	>0.5

[a] Upper value of "r" is the total correlation coefficient, lower value is the partial correlation coefficient.

(6) A. K. Cho and D. J. Jenden, *Intern. J. Neuropharmacol.*, **3**, 27 (1964).

(7) R. A. Fisher, "Statistical Methods for Research Workers," 11th ed. Hafner Publishing Co., Inc., New York, N. Y., 1950: (a) p 183; (b) p 187,

activity against acetylcholine on the isolated ileum is an excellent predictor of peripheral parasympatholytic activity *in vivo*. However, ability to antagonize the central actions of oxotremorine cannot be reliably predicted from the *in vitro* test; the positive correlation observed can be entirely explained by the correlation of mydriatic activity with both factors. This conclusion is not unexpected, since activity on the central nervous system depends upon distributional factors which bear no necessary relationship to biological activity at the cellular level. Furthermore, although there is an obvious similarity in the structural requirements of central and peripheral anticholinergic agents, there is no logical basis for assuming their identity.

Experimental Section

Melting points were taken in open capillary tubes in an electrically heated metal block using calibrated Anschütz thermometers. Infrared spectra were run on a Perkin-Elmer 237 spectrophotometer equipped with a grating monochromator, using KBr disks. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany.

N-Propargylsuccinimide.—Succinimide (99 g, 1 mole) was added 1 to a solution of sodium (23 g, 1 g-atom) in absolute ethanol (900 ml). Propargyl bromide (119 g, 1 mole) was added to the solution, and the mixture was refluxed for 15 hr. After cooling, the NaBr was filtered and the filtrate was evaporated *in vacuo*. The residue was distilled at 95° (0.5 mm) giving a light yellow oil (117 g, 85%), which solidified upon standing to crystals melting at 51–52°; ν_{max} 3265 (≡CH), 2130 (C≡C), 1780, 1710 cm^{-1} (C=O).

Anal. Calcd for $C_7H_7NO_2$: C, 61.3; H, 5.15; N, 10.2. Found: C, 61.6; H, 5.21; N, 9.99.

N-Propargyl-α-methylsuccinimide was obtained in a similar manner in 74% yield from α-methylsuccinimide[8] and propargyl bromide: bp 93° (0.3 mm); ν_{max} 3280 (≡CH), 2140 (C≡C), 1785, 1730 cm^{-1} (C=O). Although it was not possible to obtain a correct elemental analysis for this compound, the product could be satisfactorily used in the synthesis of compound Ig.

N-Propargylglutarimide.—To a suspension of sodium hydride (2.4 g, 0.1 mole) in dry dimethylformamide (DMF) (30 ml) was added glutarimide (11.3 g, 0.1 mole) dissolved in DMF (35 ml); the mixture was stirred under nitrogen at 100° for 4 hr. Propargyl bromide (14.3 g, 0.12 mole) was added to the hot mixture and stirring without heating was then continued for 1 hr. After filtering, the solvent was removed under vacuum, and the residue was distilled to give an oily product (10.0 g, 66%), bp 113–116° (0.5 mm), n^{25}D 1.5260, which solidified after standing for some days. Recrystallization from ether–petroleum ether afforded a crystalline product: mp 41–42°; ν_{max} 3270 (≡CH), 2130 (C≡C), 1730, 1670 cm^{-1} (C=O).

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.00; N, 9.27. Found: C, 63.8; H, 5.99; N, 9.30.

N-Propargylbenzosulfimide.—A mixture of dry saccharin sodium (103 g, 0.5 mole), propargyl bromide (67 g, 0.56 mole), and DMF (300 ml) was stirred at 100° for 6 hr. The mixture was filtered, and the reaction product was precipitated by the addition of water. The product (104 g, 90%) was almost pure, mp 125–126°. Recrystallization from ethanol raised the melting point to 125.5–126.5°; ν_{max} 3280 (≡CH), 2130 (C≡C), 1745 (C=O), 1340, 1180 cm^{-1} (SO_2).

Anal. Calcd for $C_{10}H_7NO_3S \cdot 0.5H_2O$: C, 52.2; H, 3.50; N, 6.08. Found: C, 52.5; H, 3.02; N, 6.07.

N-Propargylphthalimide was obtained in a similar manner from potassium phthalimide (86% yield); mp 147–150° (lit.[9] mp 150–151.5°, 147–149°).

Preparation of N-(4-Dialkylamino-2-butynyl)-Substituted Cyclic Imides (Tables I and II).—A mixture of the appropriate N-propargylimide (0.1 mole), paraformaldehyde (0.12 mole), the secondary amine (0.11 mole), and cuprous chloride (0.2 g) in peroxide-free dioxane (20 ml) was refluxed for 0.5–1.5 hr. After cooling, water (100 ml) was added, and the mixture was acidified with 5 *N* hydrochloric acid and extracted twice with ether (50 ml). The aqueous phase was made alkaline with 2 *N* Na_2CO_3 under strong cooling and extracted exhaustively with six 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and the solvent was evaporated under vacuum. Compounds Ib and Ie crystallized upon cooling; IIa, IIb, and IIe were obtained crystalline when the acidic, aqueous phase was made alkaline. The other bases could not be obtained in crystalline form; Ig and Ih were purified by distillation *in vacuo* and the remaining bases were converted to the hydrochlorides by addition of ethereal HCl.

The infrared spectra of the succinimides listed in Table I and of the phthalimides in Table II all showed two absorption bands in the C=O stretching region, one sharp of medium strength at 1775–1785 cm^{-1} and one strong and broad, in some cases resolved into two or three minor peaks, at 1700–1735 cm^{-1}. The glutarimide derivative Ih absorbed at lower frequencies, *viz.*, at 1745 and 1695 cm^{-1}. The benzosulfimides IId and IIe showed only one strong, sharp band in this region at 1755 and 1745 cm^{-1}, respectively.

4-Diethylamino-2-butynylamine Dihydrochloride.—A solution of N-(4-diethylamino-2-butynyl)phthalimide (IIa, 64.4 g, 0.24 mole) and hydrazine hydrate (12 g, 0.24 mole) in 96% ethanol (250 ml) was refluxed for 1.5 hr. The solution was acidified with concentrated HCl, and the precipitated phthalhydrazide was filtered and washed with 96% ethanol. The combined filtrate and washings were concentrated, filtered, and evaporated *in vacuo* to give a viscous oil which soon solidified. Recrystallization from ethanol–ether yielded the dihydrochloride, mp 154–154.5° (37 g, 74%).

Anal. Calcd for $C_8H_{16}N_2 \cdot 2HCl$: C, 45.1; H, 8.51; N, 13.1. Found: C, 45.2; H, 7.90; N, 13.0.

The **free base** was obtained from the dihydrochloride by standard methods; bp 62° (2 mm), n^{22}D 1.4740.

Anal. Calcd for $C_8H_{16}N_2$: C, 68.5; H, 11.5; N, 20.0. Found: C, 68.9; H, 11.5; N, 20.2.

4-Pyrrolidino-2-butynylamine dihydrochloride was prepared from IIb by the same procedure as described for the diethylamino analog; mp 180–180.5° after recrystallization from ethanol–ether, yield 86%.

Anal. Calcd for $C_8H_{14}N_2 \cdot 2HCl$: C, 45.5; H, 7.64; N, 13.3. Found: C, 45.5; H, 7.55; N, 13.1.

4-Piperidino-2-butynylamine dihydrochloride was prepared similarly; mp 233–235° dec (from ethanol–ether), yield 70%.

Anal. Calcd for $C_9H_{16}N_2 \cdot 2HCl$: C, 48.0; H, 8.06; N, 12.5. Found: C, 48.3; H, 8.03; N, 12.6.

N-(4-Diethylamino-2-butynyl)succinamic Acid.—A solution of 4-diethylamino-2-butynylamine (6.0 g, 0.043 mole) in acetone (10 ml) was added dropwise to a refluxing solution of succinic anhydride (4.3 g, 0.043 mole) in acetone (40 ml). Stirring and heating were continued for 1 hr after which the reaction mixture was cooled and the precipitated product collected. Two recrystallizations from ethanol–ether gave the pure acid (8.3 g, 81%), mp 94–95°.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.39; N, 11.7. Found: C, 60.2; H, 8.59; N, 11.7.

Cyclization of N-(4-Diethylamino-2-butynyl)succinamic Acid.—A mixture of the acid prepared above (6.2 g, 0.026 mole), anhydrous sodium acetate (1.3 g), and acetic anhydride (13 ml) was stirred at 60–70° for 1 hr and cooled. Ice water (25 ml) was added, and the mixture was left overnight at room temperature. The solution was extracted with ether and the aqueous layer was made alkaline with NaOH under cooling. The mixture was extracted with four 20-ml portions of $CHCl_3$ and the extract was dried over Na_2SO_4. On addition of ethereal HCl, the reaction product crystallized. After recrystallization from ethanol, a product (3.8 g, 57%) was obtained which was identical (mixture melting point and infrared spectrum) with compound Ia prepared above by the Mannich reaction.

1,4-Bis(succinimido)-2-butyne. Sodium (2.3 g, 0.1 mole) was dissolved in ethanol (100 ml) and succinimide (9.9 g, 0.1 mole) was added. 1,4-Dichloro-2-butyne (6.15 g, 0.05 mole) was then added to the solution and the mixture was refluxed for 15 hr. After cooling, the formed precipitate was collected and washed with water to remove NaCl. The residue (3.0 g, 22%) was recrystallized twice from DMF to give crystals of mp 256–257°; ν_{max} 1780, 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.87; N, 11.3. Found: C, 57.7; H, 5.05; N, 11.2.

(8) F. F. Blicke and C. J. Lu, *J. Am. Chem. Soc.*, **74**, 3993 (1952).

(9) (a) K. Sato, *Nippon Kagaku Zasshi*, **76**, 1404 (1955); (b) M. Gaudemar, *Ann. Chim.* (Paris), [13] **1**, 161 (1956).