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Synthesis of Pyrazolone Derivatives. XIII.[1] Synthesis of N,N-Dialkyl-N′-substituted-N′-[3(4-substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine[2]

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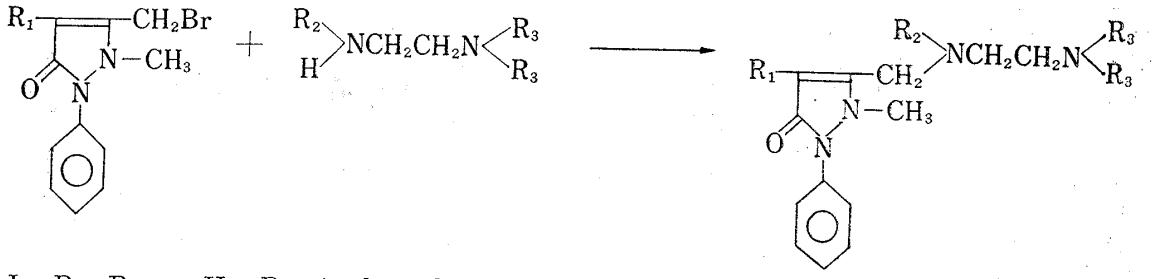
N,N-Dialkyl-N′-substituted-N′-[3(4-substituted-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamines (IIIa—IIIe) were prepared by reacting 3-bromomethyl-3-pyrazolin-5-ones (Ia and Ib) with ethylenediamines (IIa—IIc). Reaction of 4-(N-4-ethoxyphenyl)aminomethyl-3-pyrazolin-5-one (V) with dialkylaminoethylchloride afforded N,N-dialkyl-N′-(4-ethoxyphenyl)ethylenediamines (IIa and VII) or 4-ethoxy-N,N-bis[(2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-yl)methyl]aniline (VIII).

Despite of the widespread use of Aminopyrine and Sulpyrine for the antipyretic and analgestic treatment, an undesired side effect such as anaphylactic shock became the object of public attention recently. This allergic phenomina proves to be caused by internal secretion of histamine.

The majority of potent histamine antagonists are found in N-heterocyclic derivatives of ethylenediamine which include heterocyclic rings such as pyridine, pyrimidine and thiophene in their structure. Therefore the synthesis of new N-pyrazolone derivatives of ethylenediamine which have the antipyretic, analgestic and antihistaminic activities simultaneously are the subject of this paper. The title compounds were synthesized as outlined in Chart 1.



Ia: R_1=Br
Ib: R_1=CH_3

IIa: R_2=4-ethoxyphenyl, R_3=C_2H_5
IIb: R_2=2-pyridyl, R_3=CH_3,
IIc: R_2=2-pyridyl, R_3=C_2H_5

IIIa: R_1=Br, R_2=4-ethoxyphenyl, R_3=C_2H_5
IIIb: R_1=H, R_2=4-ethoxyphenyl, R_3=C_2H_5
IIIc: R_1=Br, R_2=2-pyridyl, R_3=CH_3
IIId: R_1=CH_3, R_2=2-pyridyl, R_3=CH_3
IIIe: R_1=CH_3, R_2=2-pyridyl, R_3=C_2H_5

Chart 1

Starting compound, 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (Ia) obtained by the method of Graef, *et al.*[4] was condensed with N,N-diethyl-N′-(4-ethoxyphenyl)ethylenediamine (IIa)[5] in the presence of anhydrous potassium carbonate and cupper powder to give N,N-diethyl-N′-4-ethoxyphenyl-N′-[3(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIIa) as a yellow viscous oil. This compound IIIa

1) Part XII: I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **14**, 1237 (1966).
2) Presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *3-1 Tanabe-dori, Mizuho-ku, Nagoya.*
4) H. Graef, J. Ledrut and G. Combes, *Bull. Soc. Chim. Belges*, **61**, 331 (1952) [*C.A.*, **47**, 12363 (1953)].
5) H. Nogami, J. Hasegawa and A. Tanaka, *Yakugaku Zasshi*, **71**, 1496 (1951).

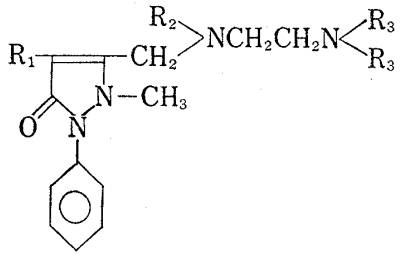
was characterized by convertion to the corresponding chloroplatinate. Catalytic hydrogenation of IIIa over Raney nickel afforded dehalogenated N,N-diethyl-N′-4-ethoxyphenyl-N′-[3(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIIb) as colorless needles. The structure of IIIb was confirmed by infrared spectrum (IR), elementary analysis and nuclear magnetic resonance spectrum.

Condensation of Ia and 3-bromomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (Ib)[6] with N,N-dimethyl-N′-(2-pyridyl)ethylenediamine (IIb)[7] in toluene in the presence of lithium hydride afforded corresponding N,N-dimethyl-N′-2-pyridyl-N′-[3(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIIc) and N,N-dimethyl-N′-2-pyridyl-N′-[3-(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIId) respectively.

In a similar manner, N,N-diethyl-N′-2-pyridyl-N′-[3(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIIe) was prepared by the reaction of N,N-diethyl-N′-(2-pyridyl)ethylenediamine (IIc)[7] with Ib in the presence of lithium hydride. The yields in general were about 15—16%. IR spectra of these ethylenediamines showed the absence of NH and the presence of strong CH and C=O stretch absorption.

Condensation of Ia and Ib with N,N-dialkyl-N′-(2-pyrimidyl)ethylenediamine or N,N-dialkyl-N′-(2-thenyl)ethylenediamine with various condensing reagents resulted in failure. The properties and analytical data of the successfully prepared compounds (IIIa—IIIe) are shown in Table I.

Table I.



Compd. No.	R_1	R_2	R_3	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	Br	4-ethoxyphenyl	C_2H_5	69— 71[a]	tan prisms	$C_{25}H_{33}O_2N_4Br \cdot H_2PtCl_6$			6.15			6.54
IIIb	H	4-ethoxyphenyl	C_2H_5	99—100	colorless needles	$C_{25}H_{34}O_2N_4$	71.09	8.11	13.26	71.38	8.35	13.44
IIIc	Br	2-pyridyl	CH_3	147—149	colorless needles	$C_{20}H_{24}ON_5Br$	55.81	5.58	16.28	55.78	5.84	16.34
IIId	CH_3	2-pyridyl	CH_3	86— 87	colorless prisms	$C_{21}H_{27}ON_5$	69.01	7.45	19.16	68.83	7.69	19.29
IIIe	CH_3	2-pyridyl	C_2H_5	121—122	colorless needles	$C_{23}H_{31}ON_5$	70.19	7.94	17.80	70.43	8.25	17.86

a) chloroplatinate

On the other hand, an attempt to prepare N,N-dialkyl-N′-substituted-N′-[4(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)]ethylenediamines by the reaction of 4-bromo-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[4] with IIa, IIb and IIc in the same manner used for the preparation of the title compound was unsuccessful. An alternative method for the desired compound (IX) was investigated as outlined in Chart 2.

6) H. Farbwerke, *Chem. Zntr.*, **80**, 806 (1909).
7) F.C. Whitemore, H.S. Mosher, D. Goldsmith and A.W. Rythina, *J. Am. Chem. Soc.*, **67**, 393 (1945).
8) I. Ito, *Yakugaku Zasshi*, **76**, 167 (1956).
9) J. Ledrut, U.S. Patent 2650219 (1953) [*C.A.*, **48**, 12181 (1954)].

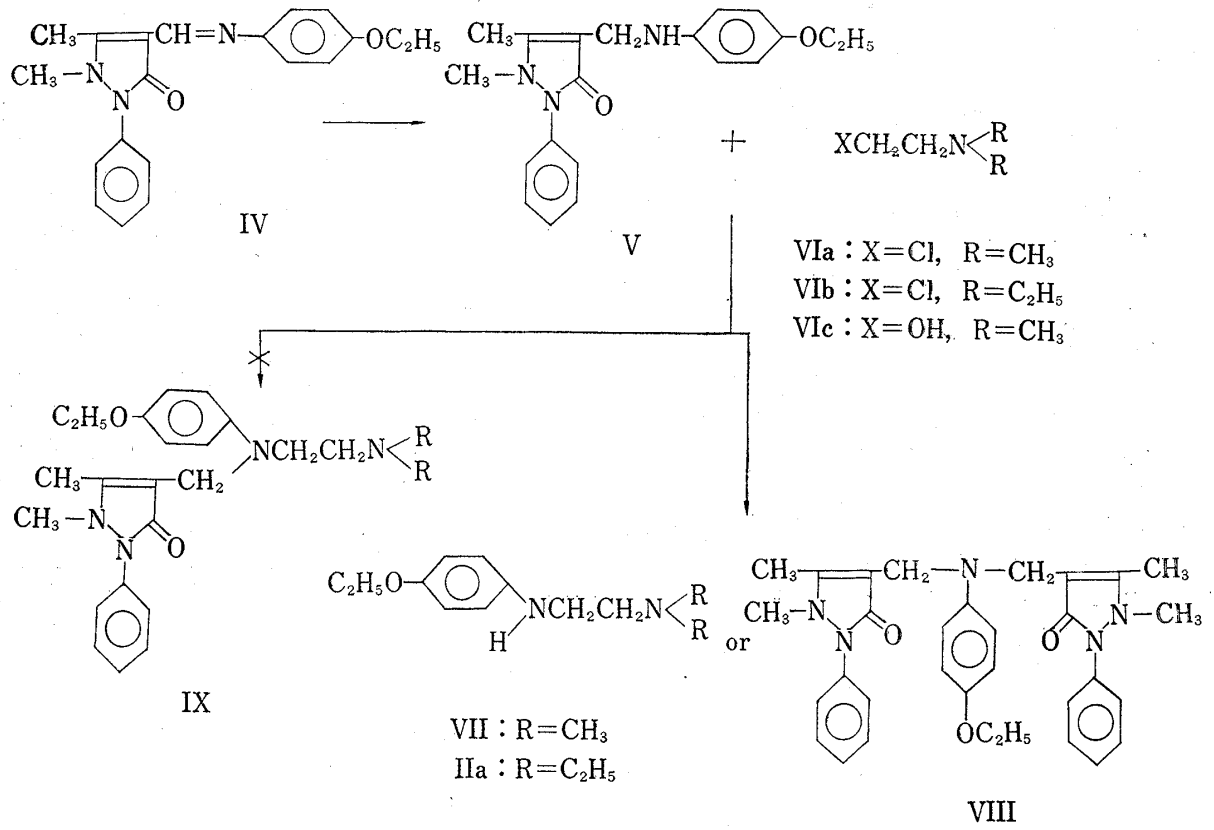


Chart 2

When 4-formyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[8] was treated with *p*-phenetidine in ethanol, Schiff base (IV)[9] was obtained easily. IV was catalytically reduced over Raney nickel under pressure to give 2,3-dimethyl-4-(N-4-ethoxyphenyl)aminomethyl-1-phenyl-3-pyrazolin-5-one (V) in fairly good yield. Condensation of V with dialkylaminoethylchloride (VIa and VIb) or dimethylaminoethanol (VIc) in the presence of various condensing reagents resulted in formation of by-products N,N-dimethyl-N′-(4-ethoxyphenyl)ethylenediamine (VII), N,N-diethyl-N′-(4-ethoxyphenyl)ethylenediamine (IIa) and 4-ethoxy-N,N-bis[(2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-yl)methyl]aniline (VIII) respectively. For example, treatment of V with dimethylaminoethylchloride (VIa) in toluene under reflux for three hours gave VII, isolated as the monohydrochloride. The IR spectrum of VII was identical with that of an authentic sample.[10]

In a similar manner, sodium salt of V prepared by the reaction of V with sodium hydride in toluene was condensed with diethylaminoethylchloride (VIb) and chromatographed on aluminum oxide to give IIa. The structure of IIa was confirmed by comparison of IR spectrum with that of an authentic sample.[5] From these results, it is assumed that these reactions involve either cleavage of C–N bond of IX or V followed by condensation with dialkylaminoethylchloride. Since it was believed at this time that more mild reaction conditions would result in formation of the desired compound IX, attention was turned to attempt the same reaction under the reduced reaction time. However the starting compound V was recovered unchange without formation of VII and IIa.

Treatment of V with VIa or VIb in the presence of lithium hydride afforded VIII as colorless prisms, mp 182—183°. The structure of VIII was confirmed by IR spectrum, elementary analysis and mass spectrum which showed the parention peak at *m/e* 537.

When V was treated with VIa or VIb in the presence of sodium amide or Grignard reagent, this compound VIII was also obtained in 30 or 40% yield respectively. Furthermore the

10) S.G. Fridman, Z. *Obshch. Khim.*, **23**, 278 (1953) [*C.A.*, **48**, 3344 (1954)].

reaction between V and dimethylaminoethanol (VIc) in polyphosphate ester gave VIII in 25% yield. Therefore in the reaction using lithium amide, sodium amide, Grignard reagent and polyphosphate ester, compound VIII was an only product and the formation of VII and IIa was not observed. In view of these result, it is seemed that the formation of VIII is due to condensation of V with 4-methyl-3-pyrazolin-5-one group, liberated by cleavage of C–N bond of V during the reaction.

The pharmacological investigation of the compounds so far described is now being carried out.

Experimental[11]

N,N-Diethyl-N′-4-ethoxyphenyl-N′-[3(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl) methyl]ethylenediamine (IIIa)——A mixture of 4 g (0.017 mole) of N,N-diethyl-N′-(4-ethoxyphenyl)ethylenediamine (IIa),[5] 5.9 g (0.017 mole) of 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (Ia),[4] 2.8 g (0.02 mole) of anhydrous potassium carbonate, 0.2 g of cupper powder and 100 ml of dry benzene was refluxed with stirring for 16 hr. After cooling, the mixture was poured into water. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined extracts were extracted with 100 ml of 10% hydrochloric acid. The acid extract was slowly basified with 10% sodium hydroxide solution until separation of oil was complete. The oil was extracted with chloroform, dried over sodium sulfate and evaporated to dryness. The residual red oil was chromatographed on aluminum oxide to give yellow viscous oil. Yield 2.5 g (30%). This compound moved as a single spot in *n*-butanol saturated with 1N aqueous ammonia on TLC. An aliquot was dissolved in 10% hydrochloric acid and treated with 25% aqueous solution of chloroplatinate. The resulting precipitate was washed with 10% hydrochloric acid and recrystallized from 1% hydrochloric acid to give tan prisms of the chloroplatinate. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1668 (C=O).

N,N-Diethyl-N′-4-ethoxyphenyl-N′-[3(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl) methyl] ethylenediamine (IIIb)——A solution of 1.5 g (0.003 mole) of IIIa and 0.75 g of sodium bicarbonate in 50% ethanol was hydrogenated with 3 g of Raney nickel catalyst. The theoretical quantity of hydrogen was absorbed in 3 hr. After filtration of catalyst, the filtrate was evaporated *in vacuo*. The residue was extracted with benzene. The extract was dried over sodium sulfate and evaporated to give a tan oil which was chromatographed on aluminum oxide. Elution with benzene gave crystals which were recrystallized from petroleum ether–ether (1:1). Yield 0.7 g (60%). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O); 1045, 1240 (=C–O–C). NMR[12] τ: 7.53 (2H, triplet, $J=7$ cps, CH_2-C<u>H</u>$_2$-N$(C_2H_5)_2$), 6.62 (2H, triplet, $J=7$ cps, NC<u>H</u>$_2CH_2N(C_2H_5)_2$), 5.68 (2H, singlet, =C-C<u>H</u>$_2$N), 4.53 (1H, singlet, 4-position proton).

N,N-Dimethyl-N′-2-pyridyl-N′-[3(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl) methyl]ethylenediamine (IIIc)——A mixture of 0.8 g (0.0048 mole) of N,N-dimethyl-N′-(2-pyridyl)ethylenediamine (IIb),[7] 0.04 g (0.005 mole) of lithium hydride and 30 ml of dry toluene was heated under reflux for 4 hr. The mixture was cooled to room temperature and 1.65 g (0.0048 mole) of Ia was added. Reflux was continued for 5 hr. After cooling, the mixture was poured into cold water. The layers were separated and the aqueous layer was extracted with chloroform. The combined organic solutions were evaporated *in vacuo* to give red oil which was extracted with 10% hydrochloric acid. After treating with activated carbon, the acidic solution was basified with 10% sodium hydroxide solution. The oil liberated was extracted with chloroform, dried over sodium sulfate and evaporated to dryness. The residual red oil was chromatographed on silicagel. Elution with chloroform gave crystals which were recrystallized from ether. Yield 0.3 g (15%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=O).

N,N-Dimethyl-N′-2-pyridyl-N′-[3(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl) methyl] ethylenediamine (IIId)——To a suspension of 0.05 g (0.007 mole) of lithium hydride in 30 ml of dry toluene was added a solution of 1 g (0.005 mole) of IIb in 10 ml of dry toluene. The mixture was stirred under reflux for 9 hr and 1.7 g (0.005 mole) of 3-bromomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (Ib)[6] was added at room temperature. The mixture was refluxed with stirring for 28 hr, allowed to cool and poured into cold water. The layers were separated and the aqueous layer was extracted with benzene. The toluene and benzene layers were combined and extracted with 70 ml of 10% hydrochloric acid. The acid extract was basified with 10% sodium hydroxide solution and extracted with chloroform. Concentration of the chloroform solution afforded a viscous red oil which was chromatographed on silica gel. Elution with chloroform yielded crystals. Recrystallization from petroleum ether–ether (1:1) provided an analytical sample. Yield 0.3 g (15%). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O).

11) Melting points were determined on a Yanagimoto Micro Melting Pointo Apparatus and uncorrected. All reactions were carried out under dry nitrogen.

12) NMR spectrum was taken on Varian A–60 Spectrometer in $CDCl_3$ with tetramethylsilane as internal standard.

N,N-Diethyl-N′-2-pyridyl-N′-[3(2,4-dimethyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]ethylenediamine (IIIe)——This reaction was carried out and worked up as in the procedure for IIId to give an acid soluble viscous oil which was extracted with hot petroleum benzin. The petroleum benzin extract was allowed to stand to precipitate yellow crystals. Repeated recrystallization from petroleum benzin gave an analytical sample. Yield 16%. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O).

2,3-Dimethyl-4-(N-ethoxyphenyl)aminomethyl-1-phenyl-3-pyrazolin-5-one (V)——To a solution of 1 g (0.0046 mole) of 4-formyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[8] in 10 ml of ethanol was added 0.63 g (0.0046 mole) of *p*-phenetidine. The mixture was reduced in the hydrogenation autoclave with 2 g of Raney nickel catalyst under a pressure of 55 kg/cm^2 for 6 hr. The catalyst was removed by filtration and the filtrate was evaporated to give a viscous oil which was triturated with ether. The resulting white solid was recrystallized from ether to afford colorless prisms, mp 112.5—113.5°. *Anal.* Calcd. for $C_{20}H_{23}O_2N_3$: C, 71.19; H, 6.89; N, 12.45. Found: C, 71.11; H, 6.83; N, 12.69. Yield 1.2 g (80%). IR ν_{max}^{KBr} cm^{-1}: 3346 (NH); 1047, 1243 (=C–O–C).

Reaction of Compound V with Dimethylaminoethylchloride (VIa)——A mixture of 1 g (0.003 mole) of V, 0.34 g (0.003 mole) of VIa and 20 ml of dry toluene was heated under reflux for 3 hr. The white precipitate was filtered, dissolved in water and basified with 10% potassium carbonate solution. The alkaline aqueous solution was extracted with ether. The extract was evaporated to give a yellow oil whose IR spectrum was identical with that of an authentic N,N-dimethyl-N′-(4-ethoxyphenyl)ethylenediamine. Yield 0.64 g (30%). IR ν_{max}^{liq} cm^{-1}: 3346 (NH).

Reaction of Compound V with Diethylaminoethylchloride (VIb)——Sodium salt of V prepared from 1.1 g (0.003 mole) of V and 0.15 g (0.003 mole) of sodium hydride (54.5% dispersion in mineral oil) was reacted with 0.4 g (0.003 mole) of VIb. After heating for 4 hr, the mixture was allowed to stand at room temperature and hydrolyzed. The toluene layer was separated, dried over sodium sulfate and evaporated. The resulting oil was chromatographed on aluminum oxide. Elution with benzene yielded a pale yellow oil whose IR spectrum was identical with that of an authentic N,N-diethyl-N′-(4-ethoxyphenyl)ethylenediamine. Yield 0.28 g (40%). IR ν_{max}^{liq} cm^{-1}: 3345 (NH).

4-Ethoxy-N,N-bis[(2,3-dimethyl-1-phenyl-5-oxo-3-phrazolin-4-yl)methyl]aniline (VIII)——a) A mixture of 2 g (0.006 mole) of V and 0.05 g (0.006 mole) of lithium hydride in 50 ml of dry toluene was heated under reflux for 4 hr. A solution of 0.65 g (0.006 mole) of VIa in 10 ml of dry toluene was then added dropwise and heating continued for 3 hr. The reaction mixture was cooled and hydrolyzed. The toluene layer was separated and dried over sodium sulfate. Concentration of the toluene solution gave a red oil which was chromatographed on aluminum oxide. Elution with chloroform–benzene (1:1) yielded white solid. Recrystallization from acetone afforded colorless prisms, mp 182—183°. Yield 0.4 g (25%). *Anal.* Calcd. for $C_{32}H_{35}O_3N_5$: C, 71.48; H, 6.56; N, 13.03. Found: C, 71 65; H, 6.38; N, 12.71. Mass spectrum[13] *m/e*: 537 (M^+), IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O); 1047, 1245 (=C–O–C).

b) One and half grams (0.0045 mole) of V was converted to its sodium salt in liquid ammonia by treatment with sodium amide freshly prepared from 0.2 g (0.009 mole) of sodium. The ammonia was displaced by 50 ml of dry toluene and 0.8 g (0.0045 mole) of VIb hydrochloride was added. The reaction mixture was stirred, heated for 7 hr and poured into iced water. The toluene layer was separated, dried over sodium sulfate and evaporated *in vacuo*. The resulting red oil was triturated with ether to give white crystals. Recrystallization from benzene gave colorless prisms, mp 182—183°. Yield 0.35 g (30%). This material was identified by IR spectrum and mixed melting point with the sample prepared by procedure a).

c) To a mixture of methylmagnesium iodide, prepared from 0.2 g (0.008 mole) of magnesium, 1.1 g (0.008 mole) of methyl iodide and 10 ml of dry ether, was added a solution of 2 g (0.006 mole) of V and 150 ml of dry ether on an ice bath. The stirring was continued and the ice bath replaced by a hot water bath, and the mixture refluxed gently for 2 hr. The mixture was cooled and a solution of 1.0 g (0.007 mole) of VIb in 15 ml of dry ether was added. After being refluxed for 6 hr, the reaction mixture was hydrolyzed with concentrated ammonium chloride solution. The ether layer was separaed, dried over sodium sulfate and evaporated. The resulting yellow oil was triturated with ether to give white solid. Recrystallization from acetone afforded colorless prisms, mp 182—183°. Yield 0.7 g (40%). This material was identified by IR spectrum and mixed melting point with the sample prepared by procedure a).

d) A mixture of 1 g (0.003 mole) of V, 0.4 g (0.004 mole) of dimethylaminoethanol (VIc) and 3.5 g of polyphosphate ester was heated at 120° for 30 min, poured into iced water and neutralized with sodium bicarbonate. An oil liberated was extracted with benzene, dried over sodium sulfate and evaporated *in vacuo*. The resulting red oil was chromatographed on silica gel. Elution with chloroform afforded white crystals. Recrystallization from acetone gave colorless prisms, mp 182—183°. Yield 0.2 g (25%). This material was identified by IR spectrum and mixed melting point with the sample prepared by procedure a).

Acknowledgement The authors are indebted to Miss T. Yamagishi of the analysis laboratory of Faculty of Pharmaceutical Sciences, Nagoya City University, for elemental analyses.

13) Mass spectrum was taken on Hitachi Mass Spectrometer, Model RMU-6E equipped with double forcusing system.