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Studies on Isopyrazole Derivatives and Related Compounds. I.[1] Structure of Condensation Product of Nitrobenzylideneacetylacetone with Hydrazine Dihydrochloride

Takushi Kurihara

Osaka College of Pharmacy[2]

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Condensation of nitrobenzylideneacetylacetone (Ia, b), which have double bond on 3 position of acetylacetone, with hydrazine dihydrochloride in several alcoholic solvents afforded 3,5-dimethyl-4-nitrobenzylideneisopyrazolium alkyl chlorides.

On the other hand, reaction of Ia, b with hydrazine dihydrochloride in acetonitrile gave 3,5-dimethyl-4-nitrobenzylideneisopyrazole (IIa, b). These structures and chemical natures were examined.

The condensation of 1,3-dicarbonyl compounds which have at least one reactive hydrogen such as 3-alkylacetylacetone with hydrazine to form pyrazole is general reaction.[3]

On the other hand, Auwers[4] reported that 3,3-dialkylacetylacetone and hydrazine hydrate react spontaneously to give 4,4-dialkyl-3,5-dimethylisopyrazole. However, a reaction of derivatives possessing double bond on the 3 position of acetylacetone, such as benzylideneacetylacetone, with hydrazine to yield isopyrazole type compound has not yet been reported. Recently, Hecht[5] has reported that any isopyrazole type compound was not observed when 1,2-diphenyl-3-diacetylmethylenecyclopropene was allowed to react with hydrazine in absolute ethanol, because of the conjugation of methylenecyclopropene functionality with carbonyl groups.

In the present paper were tried the condensations of *o*- and *p*-nitrobenzylideneacetylacetone (Ia, Ib), which were prepared by the method of Courts,[6] with hydrazine dihydrochloride in aqueous alcoholic solvents.

Attempt to prepare 3,5-dimethyl-4-(2-nitrobenzylidene)isopyrazole (IIa) from the condensation of Ia with 100% hydrazine hydrate in ethanol failed. Instead, when an equivalent amount of hydrazine dihydrochloride was used in aqueous ethanol, only one crystalline product, which has positive Beilstein test, was isolated in fairly good yield.

The infrared (IR) spectrum of this compound showed a characteristic absorption band[7] assignable to quaternary ammonium salt. Hence, this compound was expected to be the hydrochloride of IIa, but the nuclear magnetic resonance (NMR) spectrum exhibited a quartet at 6.50 τ and triplet at 8.75 τ attributable to $>N-CH_2CH_3$ group, in addition to the following data which are likely assignable to structure IIa: 2.0—2.6 τ (4H, multiplet, aromatic), 3.90 τ (1H, singlet, vinyl), and 7.68 τ (6H, singlet, $2\times CH_3$). The elemental analysis of this product supported a molecular structure $C_{14}H_{16}O_2N_3Cl$. The chemical structure, therefore, tentatively assigned to be the chloroethylate of IIa, which has two possible isomers IIIa and III'a.

1) The part of this work was presented at The 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, Apr. 1973.
2) Location: *2-10-65, Kawai, Matsubara, Osaka.*
3) R.C. Elderfield, *Heterocyclic Compounds*, **5**, 45 (1957).
4) V. Auwers, *Ann.*, **472**, 287 (1929).
5) S.T. Hecht, *Tetrahedron Letters*, **1972**, 3371.
6) A. Courts and V. Petrow, *J. Chem. Soc.*, **1953**, 1.
7) L.J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley & Sons, Inc. New York, 1954, p. 200.

Secondly, the chemical nature of this salt was examined. Unexpectedly, IIIa was easily converted to corresponding quaternary ammonium hydroxide (IVa or IV'a), which showed the signal of C_3- and C_5-methyl proton at 7.89 τ as singlet shifted upfield, by treatment with sodium bicarbonate solution or even just water, on the contrary to the general rule that the ordinary quaternary salt is forced to transform to corresponding hydroxide by treatment with basic silver oxide. The hydroxide (IVa) could be recovered to IIIa by warming with hydrochloric acid in ethanol.

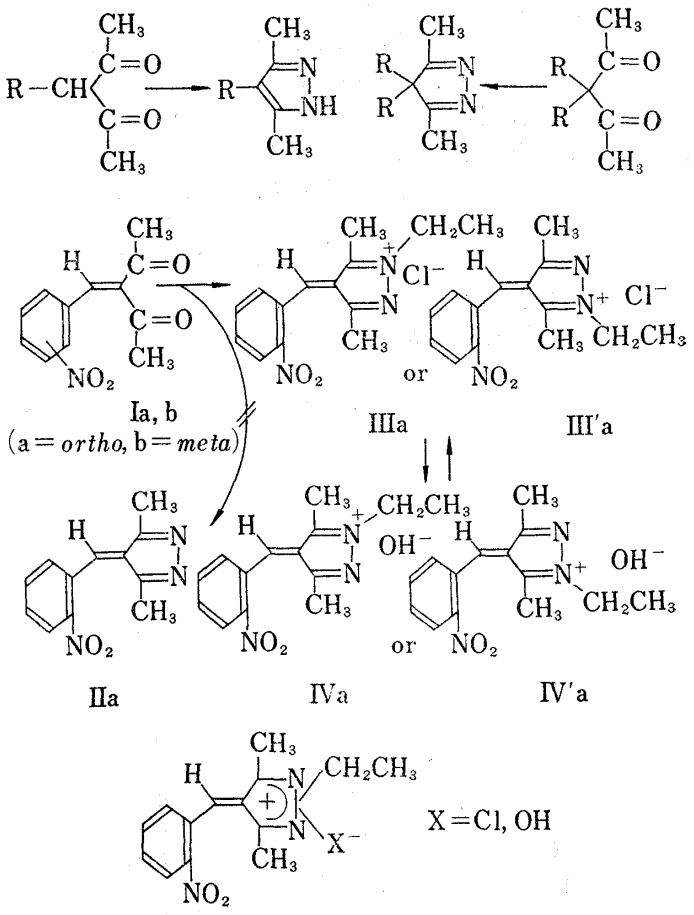


Chart 1

The most interesting and incomprehensible point found on NMR spectra of IIIa and IVa was the magnetical equivalency of two C_3- and C_5-methyl group. Bale and his co-worker[8] have reported that on the NMR spectrum (D_2O) of the mixture of 3-methylpyridazine-1-methiodide and 3-methylpyridazine-2-methiodide, C_3-methyl group appears as two distinct peaks at 7.15 τ and 6.97 τ. Further, the different signals of C_3- and C_5-methyl group of 3,4,4,5-tetramethylisopyrazole-1-methiodide[4] were observed in NMR spectrum. From these results, the tentative structure (IIIa or III'a) was neglected and it might be considered that the delocallized form of quaternary salt and hydroxide would be more appropriate structure for IIIa and IVa as shown in Chart 1.

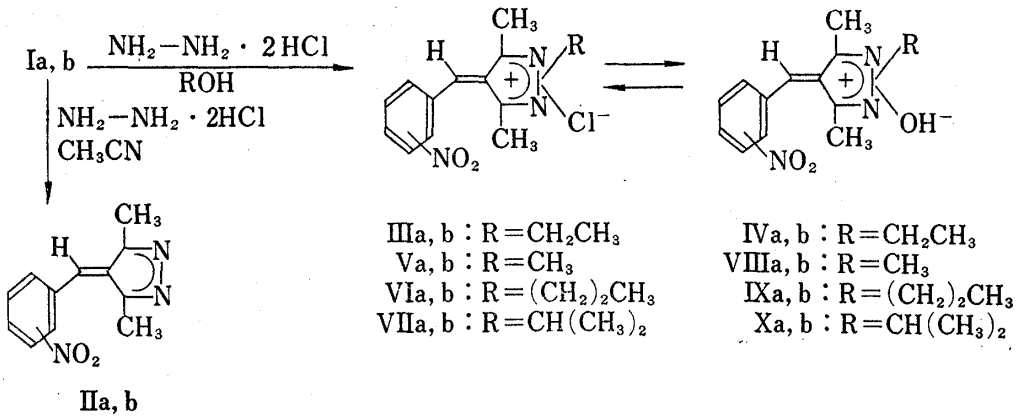
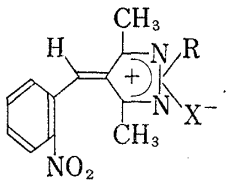


Chart 2

8) M.S. Bale, A.S. Simmonde, and W.F. Trager, *J. Chem. Soc.*, 1966, 867.

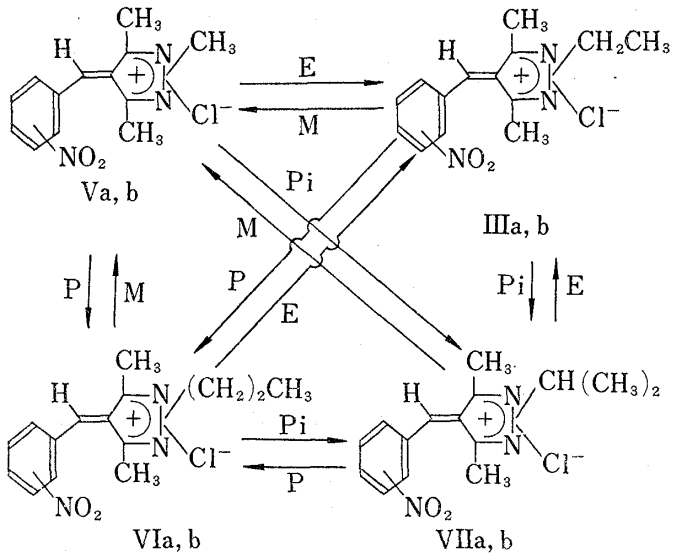
In addition, the attempt for the synthesis of IIa was carried out to confirm the structure of IIIa and IVa. In the case of reaction of Ia with hydrazine dihydrochloride, it was proved that ethanol for reaction solvent had served as alkylating agent. In order to avoid this quaternization, Ia was allowed to react with hydrazine dihydrochloride in acetonitrile contained enough water to make the solution homogeneous, followed by neutralization with ammonium hydroxide, to give IIa of mp 229—230° in yield of 82%, the structure of which was confirmed by microanalysis and NMR spectrum (DMSO-d_6). The NMR spectrum of IIa also showed the signal for C_3- and C_5-methyl proton as singlet at 8.15 τ. Benzylideneisopyrazole (IIa) was readily converted to salt (IIIa) by heating with hydrochloric acid in ethanol, which was identical with an authentic sample by comparison of IR spectrum.

Table I. NMR Data on 3,5-Dimethyl-4-(2-nitrobenzylidene)-isopyrazolium Alkyl Chlorides and Hydroxides



R	X	Chemical shift (τ in $CDCl_3$)		
		C_3- and C_5-C<u>H</u>$_3$	vinyl-<u>H</u>	R
CH_3	Cl	7.67 (6H, s)	4.00	6.63 (s, C<u>H</u>$_3$)
CH_3	OH	7.93 (6H, s)	4.05	6.67 (s, C<u>H</u>$_3$)
CH_2CH_3	Cl	7.68 (6H, s)	3.95	6.50 (q, C<u>H</u>$_2$CH$_3$)
CH_2CH_3	OH	7.89 (6H, s)	3.95	6.50 (q, C<u>H</u>$_2$CH$_3$)
$(CH_2)_2CH_3$	Cl	7.67 (6H, s)	3.95	6.64 (t, C<u>H</u>$_2$CH$_2$CH$_3$)
$(CH_2)_2CH_3$	OH	7.90 (6H, s)	3.95	6.63 (t, C<u>H</u>$_2$CH$_2$CH$_3$)
$CH(CH_3)_2$	Cl	7.68 (6H, s)	3.80	6.38 (m, C<u>H</u>(CH$_3$)$_2$)
$CH(CH_3)_2$	OH	7.90 (6H, s)	3.85	6.37 (m, C<u>H</u>H(CH$_3$)$_2$)

The following abbreviations are used, m=multiplet, q=quartet, s=singlet, t=triplet.



E=CH_3CH_2OH/HCl M=CH_3OH/HCl
P=$CH_3(CH_2)_2OH$/HCl Pi=$(CH_3)_2CHOH$/HCl

Chart 3

Heating of Ia with hydrazine dihydrochloride in methanol, 1-propanol and 2-propanol afforded the quaternary salts (Va, VIa and VIIa), which were reconvertible with the hydroxides (VIIIa, IXa and Xa) as in the case of IIIa and IVa shown in Chart 2. The details of these NMR data were summerized in Table I.

As shown in Chart 3, alkyl interconversion of these quaternary salts took place by warming with a trace of hydrochloric acid in appropriate alcoholic solvents at 40—45°.

Analogously, same results were obtained in *meta*-series starting from Ib.

By these considerations, it is reasonable to conclude that isopyrazole possessing double bond at C_4-position has delocallized structure, which is the interesting five membered diaza ring system.

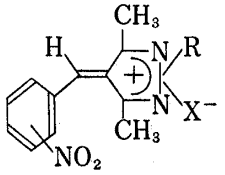
Experimental[9]

General Procedure for the Synthesis of 3,5-Dimethyl-4-(2- or 3-nitrobenzylidene)isopyrazolium Alkyl Chlorides——A solution of *o*- or *m*-nitrobenzylideneacetylacetone (Ia, or Ib) (0.02 mole) and hydrazine dihydrochloride (0.02 mole) in 150 ml of 90% ROH was heated at 60° for 2—3 hr.

After evaporation of the solvent under reduced pressure, the residue was recrystallized from suitable solvent. Details of the chemical data are listed in Table II.

General Procedure for the Synthesis of 3,5-Dimethyl-4-(2- or 3-nitrobenzylidene)isopyrazolium Alkyl Hydroxides——Crude isopyrazolium alkyl chlorides dissolved in $CHCl_3$ were shaken vigorously with 10% Na_2CO_3 solution. The $CHCl_3$ layer was separated and dried over anhyd. $MgSO_4$. After evaporation of the

TABLE II. Quaternized Salts and Hydroxides of 3,5-Dimethyl-4-(2- or 3-nitrobenzylidene)isopyrazole



Compd.	R	X	mp (C°)	Rec. Solv.	Formula		*Anal.* (%) C	H	N
IIIa	CH_2CH_3	Cl	145—147	E-B	$C_{14}H_{16}O_2N_3Cl$	Calcd.	57.24	5.49	14.30
						Found	57.15	5.48	14.16
IIIb	CH_2CH_3	Cl	131—133	E-B	$C_{14}H_{16}O_2N_3Cl$	Calcd.	57.24	5.49	14.30
						Found	57.08	5.25	14.25
IVa	CH_2CH_3	OH	109—110	B-L	$C_{14}H_{17}O_3N_3$	Calcd.	61.08	6.23	15.26
						Found	60.95	6.20	15.17
IVb	CH_2CH_3	OH	100—101	L-P	$C_{14}H_{17}O_3N_3$	Calcd.	61.08	6.23	15.26
						Found	61.24	6.27	15.20
Va	CH_3	Cl	213—216	M-B	$C_{13}H_{14}O_2N_3Cl$	Calcd.	55.82	5.04	15.02
						Found	55.56	4.98	14.87
Vb	CH_3	Cl	148—150	M-B	$C_{13}H_{14}O_2N_3Cl$	Calcd.	55.82	5.04	15.02
						Found	55.80	5.00	14.92
VIIIa	CH_3	OH	54—55	L	$C_{13}H_{15}O_3N_3$	Calcd.	59.75	5.79	16.08
						Found	59.66	5.54	16.15
VIIIb	CH_3	OH	139—140	L	$C_{13}H_{15}O_3N_3$	Calcd.	59.75	5.79	16.08
						Found	59.66	5.80	16.10
VIa	$(CH_2)_2CH_3$	Cl	141—142	B-L	$C_{15}H_{18}O_2N_3Cl$	Calcd.	58.53	5.89	13.65
						Found	58.25	5.61	13.44
VIb	$(CH_2)_2CH_3$	Cl	105—107	B	$C_{15}H_{18}O_2N_3Cl$	Calcd.	58.53	5.89	13.65
						Found	58.46	5.77	13.56
IXa	$(CH_2)_2CH_3$	OH	118—120	L	$C_{15}H_{19}O_3N_3$	Calcd.	62.26	6.61	14.52
						Found	62.24	6.59	14.47
IXb	$(CH_2)_2CH_3$	OH	80—82	P	$C_{15}H_{19}O_3N_3$	Calcd.	62.26	6.61	14.52
						Found	62.35	6.67	14.48
VIIa	$CH(CH_3)_2$	Cl	133—136	B-L	$C_{15}H_{18}O_2N_3Cl$	Calcd.	62.26	6.61	14.52
						Found	62.20	6.49	14.32
VIIb	$CH(CH_3)_2$	Cl	160—162	L-P	$C_{15}H_{18}O_2N_3Cl$	Calcd.	62.26	6.61	14.52
						Found	62.06	6.30	14.25
Xa	$CH(CH_3)_2$	OH	119—122	L	$C_{15}H_{19}O_3N_3$	Calcd.	62.26	6.61	14.52
						Found	62.24	6.55	16.48
Xb	$CH(CH_3)_2$	OH	107—108	P	$C_{15}H_{19}O_3N_3$	Calcd.	62.26	6.61	14.52
						Found	62.33	6.72	14.39

B=benzene, E=ethanol, L=ligroin, M=methanol, P=petr. ether

9) All melting points were uncorrected. NMR spectra were taken with a Varian A-60 spectrometer using TMS as an internal standard.

solvent, the residue was submitted to column chromatography, eluted with benzene–EtOH (9: 1) to give pure products, which were recrystallized from suitable solvent listed in Table II.

3,5-Dimethyl-4-(2-nitrobenzylidene)isopyrazole (IIa)——To a stirred mixture of nitrobenzylideneacetylacetone (0.02 mole) (Ia) and hydrazine dihydrochloride (0.02 mole) in 150 ml of acetonitrile was added water to get a homogeneous solution. A solution was heated at 60° under stirring for 2 hr. After evaporation of the solvent to dryness under reduced pressure, the crystalline residue was dissolved in water. After filtration of aqueous solution with celite, the clear filtrate was made alkaline with NH_4OH. The separated precipitate was collected by filtration and recrystallized from $CHCl_3$–acetone to yield IIa (82%) as colorless needles, mp 229—230°. IR ν_{max}^{KBr} cm^{-1}: 1530, 1365 (NO_2). NMR τ (DMSO-d_6): 2.0—2.5 (4H, m, aromatic proton), 3.82 (1H, s, –C<u>H</u>=C), 8.15 (6H, s, $2\times C\underline{H}_3$). *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.63; H, 4.65; N, 18.20.

3,5-Dimethyl-4-(3-nitrobenzylidene)isopyrazole (IIb)——Under the same procedure described for the synthesis of IIa, colorless needles of IIb (85%), mp 205—206°, recrystallized from $CHCl_3$ was obtained. IR ν_{max}^{KBr} cm^{-1}: 1535, 1360 (NO_2). NMR τ (DMSO-d_6): 1.8—2.5 (4H, m, aromatic proton), 4.15 (1H, s, –C<u>H</u>=C), 7.95 (6H, s, $2\times CH_3$). *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.59; H, 4.58; N, 18.26.

Conversion of IIa, b to Isopyrazolium Alkyl Chlorides——To a stirred solution of IIa, b (0.1 g) in ROH (10 ml) were added two drops of conc. HCl. After stirring for 30 min at 40—45°, the reaction mixture was evaporated to dryness under reduced pressure. The resulting residue was recrystallized from suitable solvent and each alkyl chlorides were identical with authentic samples by comparison of IR spectra.

3,4,4,5-Tetramethylisopyrazole-1-methiodide——3,4,4,5-Tetramethylisopyrazole[4] (0.5 g) and methyl iodide (2 g) were heated in benzene (20 ml) under reflux for 1 hr. The precipitate was collected by filtration and recrystallized from EtOH–ether to give pure sample as pale yellow needles, mp 181—182° (decomp.), (lit.[4] mp 182°). NMR τ ($CDCl_3$): 5.82 (3H, broad s, $=\overset{\oplus}{N}-C\underline{H}_3$), 7.05 (3H, broad s, C_5-C<u>H</u>$_3$), 7.65 (3H, s, C_3-C<u>H</u>$_3$), 8.35 (6H, s, C_4-$2\times C\underline{H}_3$).

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