

The Molecular Structure and Chemical Reactivities of the Condensation Products of *o*-Substituted Benzylidenacetone with Hydrazine Dihydrochloride

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Received February 10, 1975

Reaction of *o*-nitrobenzylidenacetone (**1a**) with hydrazine dihydrochloride in methanol gave 4-(α -methoxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole hydrochloride (**4a**), whose structure was unambiguously confirmed by an X-ray crystallographic analysis, via 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazole (**2a**). Compound **2a** was synthesized by condensation of **1a** with hydrazine dihydrochloride in acetonitrile. Analogously the corresponding *o*-chloro derivatives (**2b**, **4b**) were obtained. These were converted to *N*-methyl (**6b**) and *N*-acetyl (**7a,b**) derivatives and the behaviors on bromination and pyrolysis were investigated.

Previously we reported (2) on the tentative structure of the condensation product of *o*-nitrobenzylidenacetone with hydrazine dihydrochloride in methanol as 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazolium methyl chloride (compound A) and also 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazolium methyl hydroxide (compound B), obtained by treatment of compound A with sodium bicarbonate, on the bases of elemental analyses and spectroscopic data. However, no satisfactory explanation of the result of nmr spectra of these compounds showing the equivalency of C₃- and C₅-methyl protons was available for these tentative structures.

As an extension of our work, we reinvestigated the structure of these compounds and hereby wish to report the correct structure of condensation product of *o*-nitrobenzylidenacetone with hydrazine dihydrochloride in methanol and its related compounds and also some chemical reactivities of these derivatives.

The mass spectrum of compound B showed a low intensity of a parent peak at *m/e* 261 corresponding to C₁₃H₁₅N₃O₃ and a fragment ion peak at *m/e* 229 (M⁺-CH₃OH), whereas that of compound A showed peaks at *m/e* 261 and 229 unexpectedly. Repeated recrystallization of compound A from absolute methanol gave big pale yellow needles, m.p. 213-215° dec., whose elementary analysis was in good agreement with the composition of C₁₃H₁₄ClN₃O₂·H₂O or C₁₃H₁₆ClN₃O₃. Since these

ir, nmr, mass and analytical data did not provide the definitive evidence of the structure of compound A and B, an X-ray crystallographic analysis of compound A was carried out and its structure was unambiguously established as 4-(α -methoxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole hydrochloride (**4a**), exhibiting a characteristic ir absorption band at ν max (chloroform) 2600-2850 cm⁻¹ due to a quaternary ammonium salt, nmr signals (deuteriochloroform at δ 2.33 (6H, singlet, C₃- and C₅-CH₃), 3.37 (3H, singlet, OCH₃), 6.00 (1H, singlet, CH).

The crystals are triclinic, space group $\bar{P}1$ with cell constant $a=7.551(5)\text{\AA}$, $b=9.713(5)\text{\AA}$, $c=11.767\text{\AA}$, $\alpha=92.49(2)^\circ$, $\beta=118.55(3)^\circ$, $\gamma=97.71(2)^\circ$. There are two molecules per unit cell corresponding to a calculated crystal density of 1.322 g/cm³. Intensities 2154 independent reflections having the number of counts over three times of standard deviation were measured with the diffractometer using Ni-filtered Cu-K α radiation by means of $\omega/2\theta$ scan technique. The structure was solved by the heavy atom method and refined to an R-factor of 0.05 by a block-diagonal least-squares procedure applying anisotropic temperature factors for all nonhydrogen atoms and isotropic temperature factors for all hydrogen atoms. In structure factor calculation of **4a**, atomic scattering factors cited in "International Tables for X-ray Crystallography" (1962) (3) were used, and all the numerical calculations were carried out on an NEAC-2200-700

Scheme 1

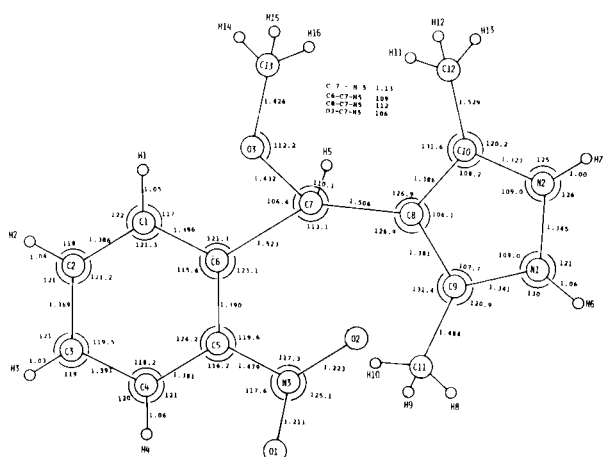
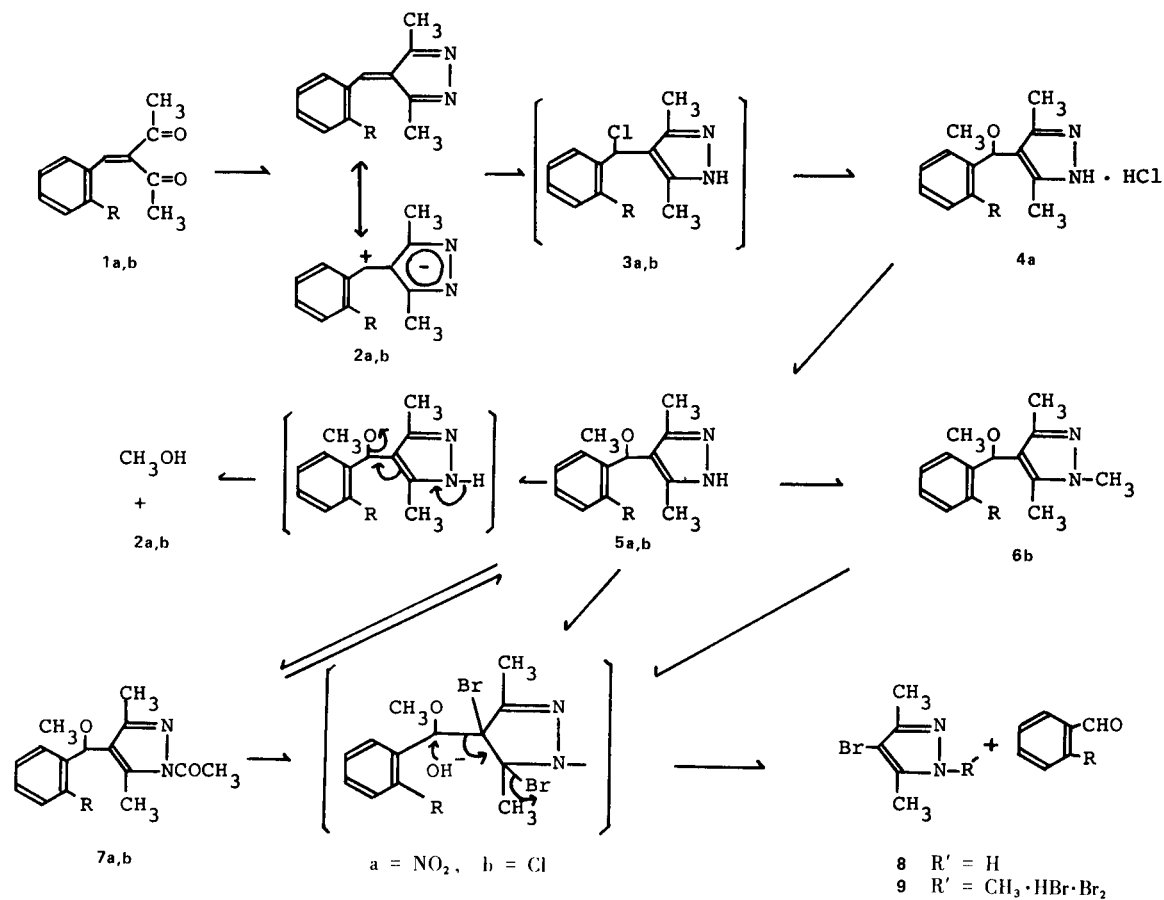


Figure 1

computer of computation center of Osaka University, using the UNICS programs. The bond lengths and angles are shown in Figure 1, where the average standard deviations for non-hydrogen atoms are about 0.005 to 0.008 Å

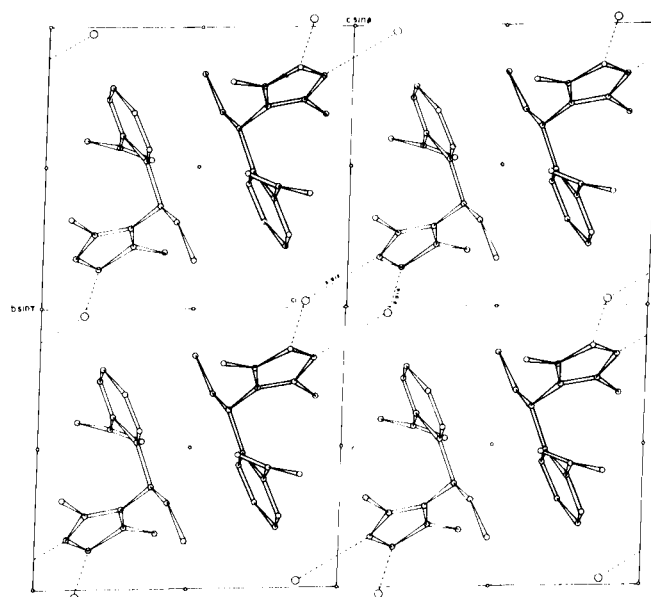


Figure 2

and 0.3 to 0.4°, respectively. The dihedral angle between the two planes, one through benzene ring and the other through pyrazole ring, is 95.0°. The molecular arrangement in crystals viewed along axis is shown in Figure 2. Between the two adjacent molecules related by the symmetry, a dimer was formed at nitrogen atoms of pyrazole ring with N-H . . . -Cl⁻ (3.012, 3.014 Å) hydrogen bond. The detail of the structural features of **4a** will be published elsewhere.

The structure of compound B, therefore, could be assigned as 4-(α -methoxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole (**5a**), exhibiting a ir absorption band at ν max (chloroform) 3460 cm⁻¹ due to the NH group, nmr signals (deuteriochloroform) at δ 2.07 (6H, singlet, C₃- and C₅-CH₃), 3.33 (3H, singlet, OCH₃), 5.95 (1H, singlet, CH), 10.0 (1H, singlet, NH exchanged with deuteriowater). The reaction of **1a** with hydrazine dihydrochloride in acetonitrile followed by neutralization with ammonium hydroxide afforded 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazole (**2a**), m.p. 229-230°, in a yield of 82%, which was isolated for the first time by us. Though only a few papers (4) have been published on isopyrazole, no report on the isopyrazole derivatives possessing an exo-double bond at the C₄-position of the isopyrazole ring has been reported (5). The fact that the nmr spectrum of **2a** in deuteriodimethylsulfoxide showed a signal of the two C₃- and C₅-methyl groups at δ 1.85 as a singlet would strongly support the compound **2a** exists in a betaine form. On treatment of **2a** with hydrochloric acid in methanol, **4a** was obtained in good yield. From these results the mechanism of the formation of **4a** can be reasonably rationalized by the initial formation of **2a** followed by 1,4-addition of hydrogen chloride to the intermediate **3a** and by substitution of chloro group with methanol to produce **4a**.

This type of betaine was also isolated in the corresponding *o*-chloro derivative (**2b**). Treatment of **1b** with hydrazine dihydrochloride in acetonitrile gave 4-(*o*-chlorobenzylidene)-3,5-dimethylisopyrazole (**2b**), m.p. 182-183°, in a yield of 85%, which was derived to **5b** analogously.

Acetylation of **5a,b** with acetic anhydride and pyridine at 50° gave *N*-acetyl derivatives (**7a,b**), whose ir spectrum showed a strong absorption band at 1730 cm⁻¹. It is well known (6) that *N*-acetyl derivatives of five member nitrogen containing heterocycles display a great tendency to hydrolyse readily. In fact, the *N*-acetyl derivatives (**7a,b**) were hydrolysed at pH 10 at 20° in aqueous ethanol.

In order to examine the reactivity of these pyrazole derivatives, the bromination and pyrolysis were investigated. Bromination of **5a** in chloroform with one molar equivalent of bromine at room temperature gave *o*-nitrobenzaldehyde and 4-bromo-3,5-dimethylpyrazole (**8**), pre-

sumably *via* the dibromide (7). Under the same conditions, bromination of the *N*-acetyl derivative (**7a**) and *o*-chloro derivatives (**5b**, **7b**) gave *o*-substituted benzaldehyde and **8**. The carbon-carbon bond cleavage with bromination has been observed in 4-(α -methoxy-*o*-chlorobenzyl)-1,3,5-trimethylpyrazole (**6b**), prepared by treatment of **5b** with methyl iodide. Bromination of **6b** in chloroform at room temperature gave *o*-chlorobenzaldehyde and 4-bromo-1,3,5-trimethylpyrazole hydrobromide perbromide (**9**). Pyrolysis of the methoxypyrazole (**5a,b**) at 200° until the end of foaming afforded methanol and pale brown resinous materials, which were converted to **5a,b**, respectively.

Research is now under way in our laboratory in order to elucidate the reactivity of betaines (**2a,b**).

EXPERIMENTAL

All melting and boiling points were uncorrected. The ir and uv spectra were taken with JASCO Model IRA-1 and Shimadzu UV-200 spectrophotometers. The nmr spectra were measured, using tetramethylsilane as the internal standard, with Varian A-60 spectrometer. The mass spectrometric analyses were determined with Hitachi Mass Spectrometer RMU-7L.

o-Chlorobenzylideneacetylacetone (**1b**)

To a solution of *o*-chlorobenzaldehyde (14 g., 0.1 mole) in acetylacetone (10 g., 0.1 mole), a small amount of piperidine was added. The reaction mixture was allowed to stand for 2 days, and diluted with chloroform. The chloroform solution was washed with 5% hydrochloric acid, water, dried (magnesium sulfate), and evaporated. Distillation of the crude product gave a pale yellow oil (19.5 g.) (90%), b.p. 127-129°/3 mm, which rapidly crystallized, m.p. 42-43°; ir ν max (chloroform): 1705, 1665 cm⁻¹ (CO); uv λ max (99% ethanol): 227 nm (log ϵ 3.95); nmr δ (deuteriochloroform): 2.17 (3H, s, COCH₃), 2.45 (3H, s, COCH₃), 7.88 (1H, s, CH=C).

Anal. Calcd. for C₁₂H₁₁ClO₂: C, 64.72; H, 4.98. Found: C, 64.57; H, 5.09.

4-(α -Methoxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole Hydrochloride (**4a**) and the Free Base (**5a**)

A mixture of *o*-nitrobenzylideneacetylacetone (**1a**) (23.3 g., 0.1 mole) and hydrazine dihydrochloride (10.5 g., 0.1 mole) in 90% methanol (500 ml.) was heated at 60° for 4 hours. Most of the solvent was evaporated *in vacuo* and the residue was poured into ice water. The resulting solid was collected by filtration and dried over phosphorus pentoxide *in vacuo*. The dried solid was recrystallized from absolute methanol three times to give pale yellow needles of **4a** (16.5 g.) (54%), m.p. 213-215° dec.; nmr δ (deuteriochloroform): 2.33 (6H, s, 2 x CH₃), 3.37 (3H, s, OCH₃), 6.00 (1H, s, CH).

Anal. Calcd. for C₁₃H₁₆ClN₃O₃: C, 52.43; H, 5.41; N, 14.11. Found: C, 52.39; H, 5.61; N, 13.94.

The chloroform solution of **4a** was washed with 10% sodium carbonate, water, and dried (magnesium sulfate). The solvent was evaporated and the residue was recrystallized from ligroin to give colorless needles of **5a**, m.p. 54-55°; ir ν max (chloroform): 3460 cm⁻¹ (NH); nmr δ (deuteriochloroform): 2.07 (6H, s, 2 x CH₃), 3.33 (3H, s, OCH₃), 5.95 (1H, s, CH), 10.0 (1H, s, NH

exchanged with deuteriowater); ms: m/e 261 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.75; H, 5.79; N, 16.08. Found: C, 59.66; H, 5.54; N, 16.15.

4-(α -Methoxy-*o*-chlorobenzyl)-3,5-dimethylpyrazole (**5b**).

A mixture of **1b** (4.4 g., 0.02 mole) and hydrazine dihydrochloride (2.1 g., 0.02 mole) in 90% methanol (200 ml.) was heated at 50° for 4 hours. After evaporation of the solvent *in vacuo*, the residue was made alkaline with saturated sodium bicarbonate and extracted with chloroform. The chloroform extract was washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the residual oil was chromatographed on an alumina using benzene as eluent to give colorless viscous oil (4.3 g.) (87%), which rapidly crystallized. It was recrystallized from petroleum ether to give colorless needles, m.p. 112-113°; ν max (chloroform): 3470 cm^{-1} (NH); nmr δ (deuteriochloroform): 2.15 (6H, s, 2 x CH_3), 3.37 (3H, s, OCH_3), 5.50 (1H, s, CH), 10.15 (1H, broad s, NH exchanged with deuterium oxide).

Anal. Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.03; N, 11.17. Found: C, 62.14; H, 6.14; N, 11.30.

4-(*o*-Nitrobenzylidene)-3,5-dimethylisopyrazole (**2a**).

To a suspension of **1a** (4.6 g., 0.02 mole) and hydrazine dihydrochloride (2.3 g., 0.02 mole) in acetonitrile (150 ml.) was added water to make a homogeneous solution. A mixture was heated at 60° for 4 hours and concentrated. The residue was dissolved in hot water (100 ml.) and the insoluble material was filtered off. The filtrate was neutralized with ammonium hydroxide and cooled. The resulting precipitate was collected by filtration and dried (3.8 g.) (82%). It was recrystallized from chloroform-acetone to give colorless powder, m.p. 229-230°; ν max (potassium bromide): 1530, 1365 cm^{-1} (NO_2); nmr δ (deuterio-dimethylsulfoxide): 1.85 (6H, s, 2 x CH_3), 6.18 (1H, s, CH).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.63; H, 4.65; N, 18.20.

4-(*o*-Chlorobenzylidene)-3,5-dimethylisopyrazole (**2b**).

A mixture of **1b** (4.4 g., 0.02 mole) and hydrazine dihydrochloride (2.1 g., 0.02 mole) was worked up in the same manner described for the synthesis of **2a** giving colorless powder (3.7 g.) (85%), m.p. 185-187°, recrystallized from dimethylformamide/ligroin; nmr δ (deuteriodimethylsulfoxide): 2.00 (6H, s, 2 x CH_3), 5.82 (1H, s, CH).

Anal. Calcd. for $C_{12}H_{11}ClN_2 \cdot H_2O$: C, 60.88; H, 5.54; N, 11.84. Found: C, 60.87; H, 5.47; N, 11.73.

Reaction of **2a,b** with Hydrochloric Acid in Methanol.

To a stirred solution of **2a** (0.1 g., 0.43 mmole) or **2b** (0.1 g., 0.46 mmole) in methanol (10 ml.) was added 37% hydrochloric acid (1 ml.). After stirring at 45° for 1 hour, the solvent was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium bicarbonate, water, dried (magnesium sulfate), and then evaporated. The residue was identical with the authentic **5a,b** by comparison of their ir spectra, respectively.

4-(α -Methoxy-*o*-chlorobenzyl)-1,3,5-trimethylpyrazole (**6b**).

A mixture of **5b** (5.0 g., 0.02 mole) and methyl iodide (10 ml.) was refluxed for 2 hours. The excess methyl iodide was evaporated off, and the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium carbonate, water, and dried (magnesium sulfate). The solvent was evaporated and the residual oil was distilled to give colorless viscous oil (3.9 g.) (75%), b.p. 120-130° (bath temperature)/2 mm, which crystallized on

standing in a refrigerator, m.p. 47-48°; nmr δ (deuteriochloroform): 2.11 and 2.12 (each 3H, each s, C_3 - and C_5 - CH_3), 3.35 (3H, s, OCH_3), 3.67 (3H, s, NCH_3), 5.47 (1H, s, CH).

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.50; H, 6.47; N, 10.58. Found: C, 63.77; H, 6.65; N, 10.63.

Acetylation of **5a,b**.

A mixture of **5a** (2.0 g., 7.7 mmoles) or **5b** (2.0 g., 8.05 mmoles) in acetic anhydride (10 ml.) containing three drops of pyridine was warmed at 50° for 10 hours. The mixture was poured into ice water, made alkaline with sodium bicarbonate and extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated *in vacuo*. The residue was purified as follows, respectively.

Distillation of the residue gave pale yellow oil of 1-acetyl-4-(α -methoxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole (**7a**) (1.51 g.) (65%), b.p. 140-150° (bath temperature)/2 mm; ν max (chloroform): 1730 cm^{-1} (CO); ν max (99% ethanol): 246 nm ($\log \epsilon$ 3.46); nmr δ (deuteriochloroform): 2.05 (3H, s, C_3 - CH_3), 2.55 (3H, s, C_5 - CH_3), 2.68 (3H, s, $COCH_3$), 3.40 (3H, s, OCH_3), 6.00 (1H, s, CH).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65. Found: C, 59.60; H, 5.78.

Recrystallization of the residue from petroleum ether gave colorless needles of 1-acetyl-4-(α -methoxy-*o*-chlorobenzyl)-3,5-dimethylpyrazole (**7b**) (1.75 g.), (76%), m.p. 49-50°; ν max (chloroform): 1732 cm^{-1} (CO); ν max (99% ethanol): 242 nm ($\log \epsilon$ 3.35); nmr δ (deuteriochloroform): 2.06 (3H, s, C_3 - CH_3), 2.58 (3H, s, C_5 - CH_3), 2.63 (3H, s, $COCH_3$), 3.38 (3H, s, OCH_3), 5.48 (1H, s, CH).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.53; H, 5.85; N, 9.57. Found: C, 61.72; H, 5.89; N, 9.77.

Bromination of Pyrazole Derivatives (**5a,b** and **7a,b**).

General Procedure.

To a solution of pyrazole derivatives in chloroform was added one molar equivalent of bromine in small portions under stirring at room temperature. After stirring for 0.5 hours, the solution was washed with 10% sodium thiosulfate solution and dried (magnesium sulfate). The resulting oil obtained by concentration of the solvent was submitted to alumina column chromatography using benzene as eluent. From the first fraction was obtained benzaldehyde derivatives in yield of 35-40%. From the second fraction was obtained bromopyrazole (**8**) (25-30%), recrystallized from *n*-hexane, m.p. 121-123° (lit. (8) 123°).

Bromination of **6b**.

To a solution of **6b** (0.5 g., 1.9 mmoles) in chloroform (10 ml.) was added bromine (0.3 g., 5 mmoles) in small portions at room temperature. After standing overnight, the resulting precipitate was collected by filtration and recrystallized from chloroform to give red needles of hydrobromide perbromide of 4-bromo-1,3,5-trimethylpyrazole (**9**) (**9**) (0.14 g.), m.p. 90-92°; nmr δ (deuterio-dimethylsulfoxide): 2.08 and 2.20 (each 3H, each s, C_3 - and C_5 - CH_3), 3.70 (3H, s, NCH_3).

Anal. Calcd. for $C_6H_{10}Br_4N_2$: C, 16.13; H, 2.57; N, 6.50. Found: C, 16.18; H, 2.57; N, 6.50.

The filtrate was condensed and chromatographical separation over an alumina column with benzene as eluent gave *o*-chlorobenzaldehyd (0.1 g.).

Pyrolysis of **5a,b**.

In a 50 ml. flask fitted with a short Liebig condenser was

placed **5a** (5 g., 0.02 mole) or **5b** (5g., 0.021 mole). The flask was heated in an oil bath up to 200° over a period of 1 hour. The liquid which was collected was identified as methanol by comparison of the ir spectra (film) with the authentic methanol. The crystalline residue (4.1 g.) failed to purify, but it was derived to **5a,b** by treatment with hydrochloric acid in methanol, respectively.

Acknowledgement.

We are grateful to Drs. S. Matsunaga and A. Numata for the measurements of mass and nmr spectra and also Mrs. H. Takeda for the elemental analyses.

REFERENCES

- (1) To whom the correspondence should be addressed.
- (2) T. Kurihara, *Chem. Pharm. Bull. (Tokyo)*, **22**, 88 (1974).
- (3) "International Tables for X-ray Crystallography", Vol. III, p. 202.
- (4) K. von Auwers and R. Bergmann, *Ann. Chem.*, **472**, 287 (1929); H. P. Patel and J. M. Tedder, *J. Chem. Soc.*, 4589 (1963); G. Mester and J. Vargha, *Ber.*, **96**, 2334 (1963).
- (5) S. T. Hecht, *Tetrahedron Letters*, 3371, (1972).
- (6) H. A. Staab, *Angew. Chem. Intern. Edit. Engl.*, **1**, 351 (1961).
- (7) A. N. Kost and I. I. Grandberg in "Advances in Heterocyclic Chemistry", Vol., 6, A. R. Katritzky, A. J. Boulton, Eds., Academic Press, New York, N. Y., 1968, p. 393.
- (8) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann. Chem.*, **551**, 80 (1942).
- (9) R. Hüttel and M. E. Schön, *ibid.*, **625**, 55 (1959).