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163. Tetsuji Kametani,*1 Kazuo Kigasawa,*2 Noriko Ikari,*2 Takehiko Iwata,*2 Morihiro Saito,*2 and Haruhiko Yagi*1 : Studies on the Syntheses of Heterocyclic Compounds. CXCV.*3 The Structure of a Yellow Substance formed by Mild Oxidation of Aminopyrine.

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A yellow substance, which slightly formed as a by-product in case of preparation of a molecular compound by fusion of aminopyrine (I) with secobarbital or barbital in the presence of air, was also obtained by mild oxidation of I with air in a poor yield. Structural elucidation by physical and chemical methods was carried out, leading eventually to confirm the formula (II) for the yellow substance as above.

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The yellow substance, which slightly formed as a by-product in case of preparation of a molecular compound[1~4] for an analgesic antifebrile by fusion of aminopyrine, namely, 2,3-dimethyl-4-dimethylamino-1-phenylpyrazolin-5-one (I) with secobarbital or barbital in the presence of air, was also obtained by mild oxidation of I with air in a poor yield. Structural elucidation by chemical and physical methods was carried out, leading to confirmation of the formula (II) for the above yellow substance.

At first, a fused mixture of I and secobarbital was kept in a sealed tube in the presence of air and heated on a water-bath, the mixture coloring yellow. On the other hand, the above mixture was treated as above in the presence of nitrogen, giving no colored substance. These facts suggest that the influence of oxygen in the air is one of the important factors for coloration. These results also seem to coincide with the report that the pyrabital prepared in a current of carbon dioxide was colorless.[5] Furthermore, it is well known that the compound (I) is changed to yellow on exposure to the air. With regards to the oxidation products of aminopyrine (I), several studies[6~8] have hitherto been achieved, but all of them were completely different from our yellow substance.

When a mixture of one mole of I and an equivalent molar amount of barbital[8] or secobarbital was heated on a water-bath for one hour, yellowish products were formed. Thin-layer chromatography using ether-ethyl acetate (1:2) as solvent showed a yellow spot of Rf 0.76 besides the spots of I and secobarbital or barbital (Fig. 1). Furthermore, the same treatment of an equivalent molar amount of I and benzoic acid or salicylic acid also afforded the same yellow spot as above at Rf 0.76 on its thin-layer chromatogram, but the yellow substance could not be separated as crystals because of its poor yield.

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8) Japan Pat., 153,365 (1942); Japan Pat., 418,120 (1964).

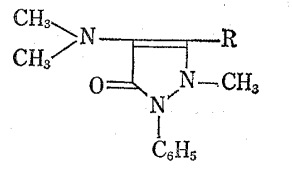
Oxidation of I with potassium permanganate, hydrogen peroxide solution, selenium dioxide, ferric chloride, and chromic anhydride, was examined in order to obtain a large amount of II, but separation of many products by thin-layer chromatography resulted in failure. Therefore, the formation of the yellow substance on introducing the air into a heated solution of I in various solvents without using the above oxidation reagent was investigated. Among them, ethanol, acetic acid, and acetic anhydride were found to be suitable for the formation of yellow substance. In the former two cases, the other yellow spot of Rf 0.54 was detected besides that of Rf 0.76, but the compound showing the former spot could not be elucidated because of very poor yield.

Preparative thin-layer chromatography and recrystallization from ligroin gave the compound (II) as yellow prisms, m.p. 67~69°, which was also characterized as its semicarbazone (III), m.p. 217~219° (decomp.). Furthermore, reduction of II with sodium borohydride gave the alcohol derivative (IV) which was recrystallized from benzene-ligroin to give colorless prisms, m.p. 141~142°.

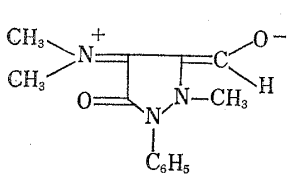
The infrared spectrum (in KBr) of II showed maxima at 1670 (lactam C=O), 1630 (double bond, $>C=C<$), and 1610 cm^{-1} (formyl C=O, broad). The relatively low-frequency band of formyl group at 1610 cm^{-1} is attributed to the resonance structure[9] (IIa) like β-aminoaldehydes of 3-indolecarboxaldehyde[10] and 2-aminobenzaldehyde[11] which also show the formyl group in the low-frequency field. On the other hand, the above characteristic formyl band disappears in case of the alcohol derivative (IV), only the lactam band remains at 1640 cm^{-1}, and a hydroxyl band appears at 3300 cm^{-1}.

The ultraviolet spectrum of II in water showed maxima at 315 mμ (log ε 3.65) and 389 mμ (log ε 4 03), but that of II in 0.1 *N* hydrochloric acid solution showed maxima at 265 mμ (log ε 3.96), the latter of which was closely similar to the spectra of I and IV in water. The high-frequency band at 389 mμ seems to be related to deep yellow color (Fig. 2 and 3).

The nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) of II showed the protons (3H) of 2-methyl group at 2.89 p.p.m., one formyl proton as a broad singlet at 9.95 p.p.m., and the protons (6H) of 4-dimethylamino-group at 3.33 p.p.m.

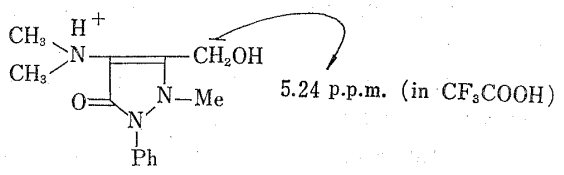


I : R=CH_3
II : R=CHO
III : R=CH=NNHCONH$_2$
IV : R=CH_2OH

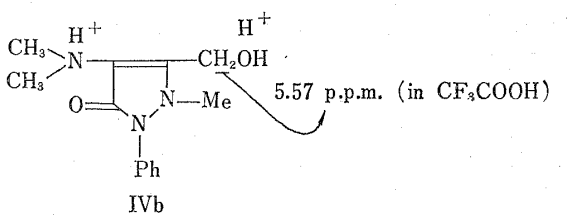


IIa

Chart 1.



IVa



IVb

Chart 2.

9) L. J. Bellamy : "The Infra-red Spectra of Complex Molecules," p. 132, 145. Richard Clay and Company, Ltd., Bungay, Suffolk, 1958.
10) H. Fritz, E. Besch, T. Wieland : Ann., **617**, 177 (1958).
11) M. Scrocco, A. Lieberti : Ricerca Sci., **24**, 1687 (1954); Chem. Abstr., **49**, 7979f (1955).

Furthermore, the NMR spectrum of Ⅱ in benzene was determined in order to recognize the existence of Ⅱa. If the methyl groups would be non-equivalent because free rotation is not possible around the double bond in resonance form (Ⅱa) as in the case of N,N-dimethylformamide,[12] only one of two methyl groups of N,N-dimethyl group lying over the benzene ring would be strongly shielded, but all three methyl groups including N-methyl group at 2-position were equally shielded to give a sharp singlet at 2.75 p.p.m. This fact proves no presence of form Ⅱa at least in bezene solution.

The N,N-dimethyl and N-methyl group resonances of Ⅳ occurred at 2.81 p.p.m. and 2.96p.p.m. in $CDCl_3$ respectively as in the case of Ⅰ in $CDCl_3$ as was shown in Table I, but in CF_3COOH N,N-dimethyl group resonance of Ⅳ occurred at 3.63 p.p.m. and 3.61 p.p.m., whereas N-methyl resonance occurred at 3.56 p.p.m. and 3.40 p.p.m., thus making up four lines of singlets in total. Moreover, the methylene signal, which was resonated as a singlet at 4.73 p.p.m. in $CDCl_3$, occurred as two lines of singlets at 5.75 p.p.m. and 5.24 p.p.m. in the ratio of 5:4, and total patterns did not change greatly even if the NMR spectrum of Ⅳ was measured in CF_3COOH in the range of 34~80°. This fact suggest that the compound (Ⅳ) exists as two forms of Ⅳa and Ⅳb in acidic solvent as CF_3COOH (Chart 2).

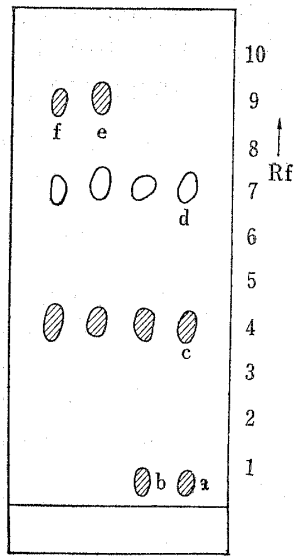


Fig. 1. Thin-layer Chromatography of Compound Ⅰ and Related Compounds

a : Salicylic acid
b : Benzoic acid
c : Aminopyrine
d : Compound (Ⅱ)
e : Secobarbital
f : Barbital

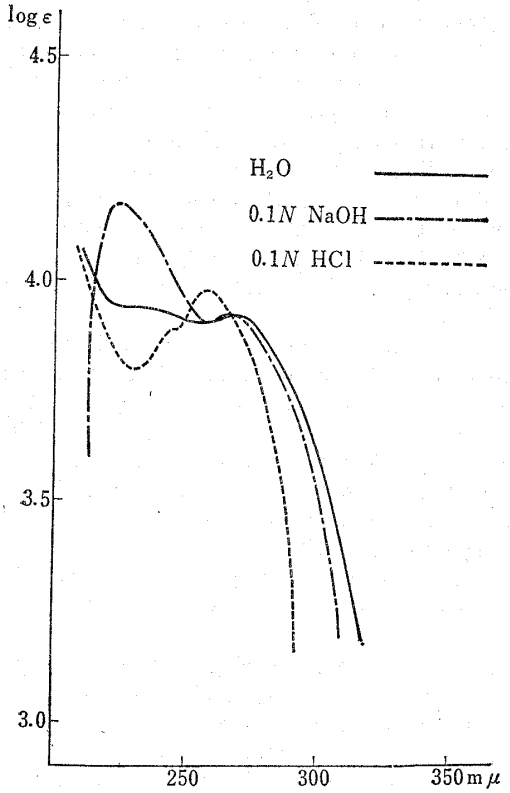


Fig. 2. UV Spectra of Aminopyrine (Ⅰ)

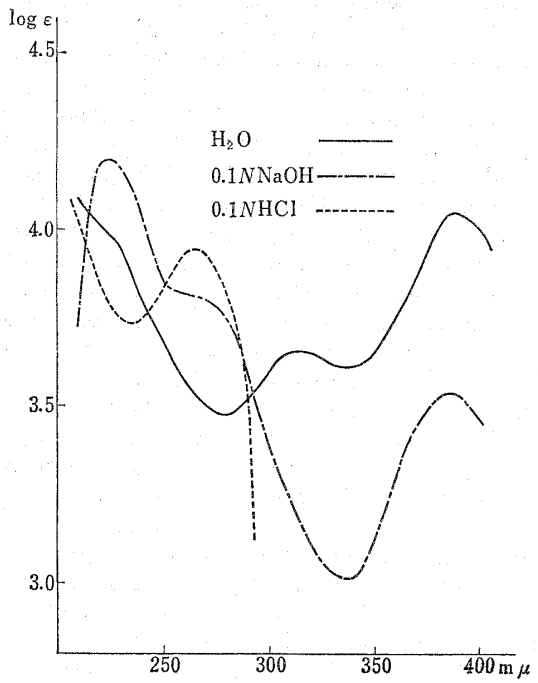


Fig. 3. UV Spectra of 3-Carboxaldehyde-derivative (Ⅱ)

12) N. S. Bhacca, D. H. Williams : "Applications of NMR Spectroscopy in Organic Chemistry," p. 161 (1964). Holden-Day, Inc.

Since oxidation of the methyl group with air to form heterocyclic aldehyde has not yet been described, this reaction seems to be very interesting from the point of purification of aminopyrine (I).

TABLE I. Solvent Effects on N,N-Dimethyl and N-Methyl Resonance in Some Aminopyrine Derivatives in NMR Spectra (δ value in p.p.m.)

	Compound	$\delta^{osb.}_{CDCl_3}$	$\delta^{osb.}_{CF_3COOH}$	$\Delta=\delta^{osb.}_{CDCl_3}-\delta^{osb.}_{CF_3COOH}$
I	N,N-dimethyl	2.81	3.58	−0.77
	N-methyl	2.96	3.51	−0.55
II	N,N-dimethyl	3.33	3.60	−0.27
	N-methyl	2.89	3.86	−0.97
IV	N,N-dimethyl	2.81	3.63(a)	−0.82
			3.61(b)	−0.80
	N-methyl	2.96	3.56(a)	−0.60
			3.40(b)	−0.44

Experimental*4

Oxidation of I by Air——a) A solution of 100 g. of aminopyrine (I) in 200 ml. of AcOH and 50 ml. of EtOH was heated under reflux on a water-bath for 12 hr., during which time the air was violently introduced into the above mixture. After the reaction, removal of the solvent under reduced pressure gave the residue, which was basified with 10% aq. NaOH solution. The mixture was filtered from insoluble substance, and then a yellowish filtrate was extracted with EtOAc.

The preceding extract was chromatographed on Wakogel Q-22 (200 mesh), using EtOAc as solvent. The yellowish band of Wakogel was collected and extracted with EtOAc. The yellowish extract was again chromatographed on Wakogel B-O [depth of layer, 500 mμ; ether-EtOAc (1:2) as solvent], by the result of which two yellowish absorption bands were obtained. Both Rf values were 0.76 (II) and 0.54 (an unknown compound). Since the yield of the latter compound was very poor, its structure has not yet been confirmed. Evaporation of the EtOAc eluate from the former band gave the viscous syrup, which was triturated with benzene to give the solid. Collection by filtration and recrystallization from ligroin afforded 0.7 g. of 5-oxo-2-methyl-4-dimethylamino-1-phenyl-3-pyrazoline carboxaldehyde (II) as yellow prisms, m.p. 67~69°. IR ν^{KBr}_{max} cm^{-1}: 1670 (lactam C=O), 1630 (double bond >C=C<), and 1610 (formyl C=O, broad). UV mμ (log ε): $\lambda^{H_2O}_{max}$ 315 (3.65) and 389 (4.03), $\lambda^{0.1N\ HCl}_{max}$ 265 (3.96). NMR (p.p.m.) (in $CDCl_3$): 9.95 (1H, singlet, -CHO), 7.75~7.27 (5H, aromatic proton), 3.33 (3H, singlet, N-CH_3), and 2.89 (6H, singlet, N-$(CH_3)_2$); NMR (p.p.m.) (in CF_3COOH): 3.60 (6H, singlet, N-$(CH_3)_2$) and 3.86 (3H, singlet, N-CH_3). *Anal.* Calcd. for $C_{13}H_{15}O_2N_3$: C, 63.66; H, 6.16; N, 17.13. Found: C, 64.05; H, 6.36; N, 17.22.

b) A mixture of aminopyrine (100 g.) and Ac_2O (200 ml.) was heated in an oil-bath at 110° for 10 hr., during which time the air was violently introduced with keeping out of the moisture. After the reaction, removal of the solvent under reduced pressure gave the residue, which was basified with 10% aq. Na_2CO_3 solution and extracted with EtOAc. The extract was washed with a small amount of water and dried on K_2CO_3. Removal of almost the solvent gave the mixture containing colorless crystals, which was removed by filtration. After the concentration of the resultant brown filtrate, followed by separation of aminopyrine, the filtrate was chromatographed on Wakogel Q-22 (200 mesh) using EtOAc as solvent. The removal of EtOAc eluate gave the residue, which was crystallized on being triturated with benzene. When the residue was not crystallized, purification by chromatography as above was repeated. Recrystallization from ligroin gave the compound (II) as yellow prisms (2 g.), m.p. 67~69°, which was identical with the above sample (method a) on mixed melting point test and infrared spectrum.

Fusion of Aminopyrine (I) with Secobarbital (or Barbital) and Benzoic Acid (or Salicylic Acid)——A mixture of one mole of I and an equivalent molar amount of secobarbital (or barbital) was heated on a water-bath at 100° for 1 hr., and it melted uniformly, becoming yellow. After cooling, the resultant mixture was dissolved in EtOH. Evaporation of the solvent gave the yellowish substance, which was treated as usual by thin-layer chromatography on silicagel (Wakogel B-5) using ether-EtOAc (1:2) as solvent. The same yellow spot described above was observed at Rf 0.76.

*4 Infrared and nuclear magnetic resonance spectra were measured on type EPI-3 Hitachi recording spectrophotometer and a Varian A-60 spectrophotometer with deuterochloroform and trifluroacetic acid as solvent and tetramethylsilane as an internal reference. Melting points were not corrected.

Secondly, use of 1 mole of I with 1 mole of the benzoic acid (or salicylic acid) at 100° (1 hr.) yielded the yellow substance (II) also in a very poor yield. The formation of II was recongnized by thin-layer chromatography, which showed the yellow spot of Rf 0.76.

The Reaction of Aminopyrine (I) with Benzoic Acid——A mixture of aminopyrine (I) (50 g.) and benzoic acid (26 g.) was mixed, smashed in a mortar and then warmed on a water-bath for 3 hr., a yellowish oily substance forming. The reaction mixture was neutralized with 10% aq. Na_2CO_3 solution and extracted with EtOAc. The extract was washed with a small amount of water, dried on K_2CO_3, and evaporated *in vacuo* until colorless crystals began to separate. After all the crystals of aminopyrine (I) had been removed by filtration, the resultant filtrate was chromatographed on Wakogel Q-22 (200 mesh). The EtOAc eluate was distilled to give the residue, which was again purified by preparative thin-layer chromatography using Wakogel B-5 (thickness, 500 mμ) and ether-EtOAc (1:2) as solvent. The yellowish part showing Rf 0.76 was collected by scratching and extracted with ether-EtOAc. The extract was dried on K_2CO_3 and distilled to give yellow crystals. Recrystallization from ligroin gave the compound (II) as yellow prisms (20 mg.), m.p. 67~69°, which was identical with the above sample (II) on mixed melting point test and infrared spectrum.

Semicarbazone of II——A mixture of 200 mg. of I, 500 mg. of semicarbazide hydrochloride, 500 mg. of Na_2CO_3 and 5 ml. of water was heated at 80~90° on a water-bath for 1 hr., a yellow oil being separated. After being allowed to stand in a refrigerator, it solidified and collected by filtration to give 250 mg. of the solid. Recrystallization from iso-PrOH gave the semicarbazone of II as yellow prisms, m.p. 217~219° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3460 and 3300 (NH and NH_2), 1690 (lactam), and 1640 (amide C=O). *Anal.* Calcd. for $C_{14}H_{18}O_2N_6$: C, 55.61; H, 6.00; N, 27.80. Found: C, 56.09; H, 6.22; N, 27.38.

3-Hydroxymethyl-2-methyl-4-dimethylamino-1-phenylpyrazolin-5-one (III)——$NaBH_4$ (200 mg.) was added in small portions with shaking to a solution of 200 mg. of II in 10 ml. of MeOH containing a few drops of water. After the mixture had been refluxed on a water-bath at 70~80° for 0.5 hr., the solvent was removed by distillation to give the solid, which was admixed with water and extracted with $CHCl_3$. The extract was dried on K_2CO_3 and distilled. Recrystallization of the resultant residue from benzene-ligroin (1:1) gave 140 mg. of 3-hydroxymethyl-2-methyl-4-dimethylamino-1-phenylpyrazolin-5-one (III) as colorless prisms, m.p. 141~142°. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH) and 1640 (C=O). UV mμ (log ε): $\lambda_{max}^{H_2O}$ 262 (3.95). NMR (p.p.m.) (in $CDCl_3$): 7.55~7.35 (5H, aromatic proton), 5.50~5.05 (1H, alcoholic OH, broad), 4.74 (2H, singlet, $-C\underline{H}_2-$), 2.96 (3H, singlet, N-Me), and 2.81 (6H, singlet, N-Me_2). NMR (p.p.m.) (CF_3CO_2H): 3.63, 3.61 (6H, two singlets, N-Me_2), 3.56, 3.40 (3H, two singlets, N-Me) and 5.75, 5.24 (2H, two singlets, $-C\underline{H}_2$). *Anal.* Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.95; H, 6.77; N, 16.98.

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