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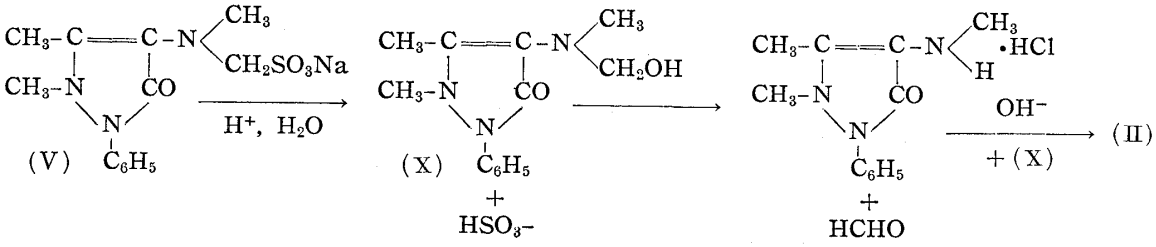
Torizo Takahashi and Ken Kanematsu : Syntheses of Analgesics. XVII.[1] Antipyrine Derivatives. (4)[2]

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

In one of the previous papers[2] of this series, we reported that the decomposition of sulpyrine [sodium (N-4-antipyrinyl-N-methyl)aminomethanesulfonate] (V) with conc. hydrochloric acid yielded 4-methylaminoantipyrine (I) and aminopyrine (4-dimethylaminoantipyrine) (IV), and that with dil. hydrochloric acid, (V) gave (I) and an unknown substance (II), m.p. 175°, which was found from its analytical values to be bis[(N-4-antipyrinyl-N-methyl)amino]methane.

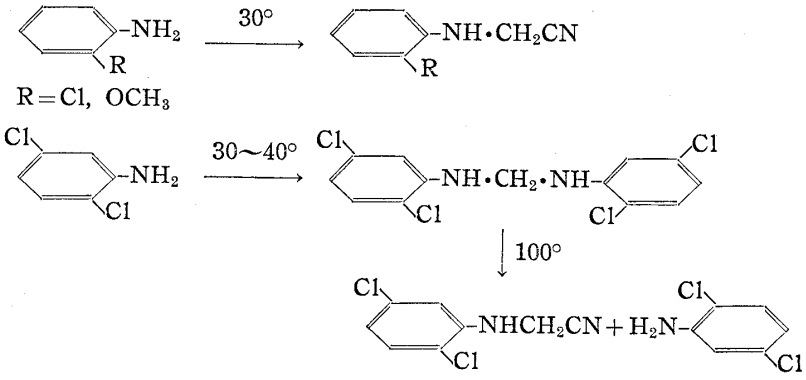
Mechanism of the formation of (II) was also interpreted as follows :



Recently, Wagner[3] showed that the degradation of (V) by means of paper chromatographic and paper electrophoretic experiments gave (II) as a final product, but he did not mention the hydrolysis of (V) with conc. hydrochloric acid.

The present paper is concerned with the so-called transjointing reaction[4] on the degradation product of (V)-formaldehyde-potassium cyanide system, and with the various syntheses of (II).

In 1954, Marxer[5] described a modified synthesis of arylaminoacetonitriles and diarylaminoacetonitriles, observing in some cases the formation of a crystalline intermediate, bis(arylamino)methane instead of the expected nitrile.



In view of the above fact, the decomposition of (II) was attempted. The decomposition of 1 mol. equiv. of (II) with 1 mol. equiv. of paraformaldehyde and 2.5 mol. equiv. of potassium cyanide was effected by heating in glacial acetic acid for 10

* Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 兼松 顕).

1) Part XVI : Yakugaku Zasshi, **77**, (1957),
2) Part (3) : *Ibid.*, **76**, 1180(1956).
3) G. Wagner : Arch. Pharm., **289**, 121(1956).
4) R. Oda : Kagaku no Ryoiki, **6**, 661(1952); **7**, 161, 678(1953); Kagaku (Chemistry), **11**, 118, 712(1956).
5) A. Marxer : Helv. Chim. Acta, **37**, 166(1954).

hours, and afforded (N-4-antipyrinyl-N-methyl)aminoacetonitrile (VI), m.p. 75~76°, and 4-methylaminoantipyrine (I). The identity of the latter was confirmed by the fact that it changed to N-4-antipyrinyl-N-methylbenzenesulfonamide (IX), m.p. 136°, by the application of benzenesulfonyl chloride in chloroform, in the presence of potassium carbonate. However, in the experiment where 2 mol. equiv. of paraformaldehyde was employed, (VI) was obtained in a very good yield (cf. Experimental Section).

On the other hand, the condensation of 4-methylaminoantipyrine (I) with paraformaldehyde and potassium cyanide on being warmed in glacial acetic acid for about 10 hours proceeded to form (VI). The respective action of an excess of paraformaldehyde on (I) and (III) in dil. hydrochloric acid easily yielded (II) as pale yellow crystals, m.p. 175°. However, in conc. hydrochloric acid, the respective action of an excess of paraformaldehyde on (I), (II), (III), and (VII) yielded (IV) as colorless needles, m.p. 108°.

This interesting methylation by paraformaldehyde and conc. hydrochloric acid, which was partly described in our preceding report,[1] seems to be useful for the preparation of aminopyrine, although the methylation of 4-aminoantipyrine using dimethyl sulfate, methyl iodide, or Eshweiler-Clarke's reaction[6] has been accomplished.

The results of these reactions are summarized in Chart 1.

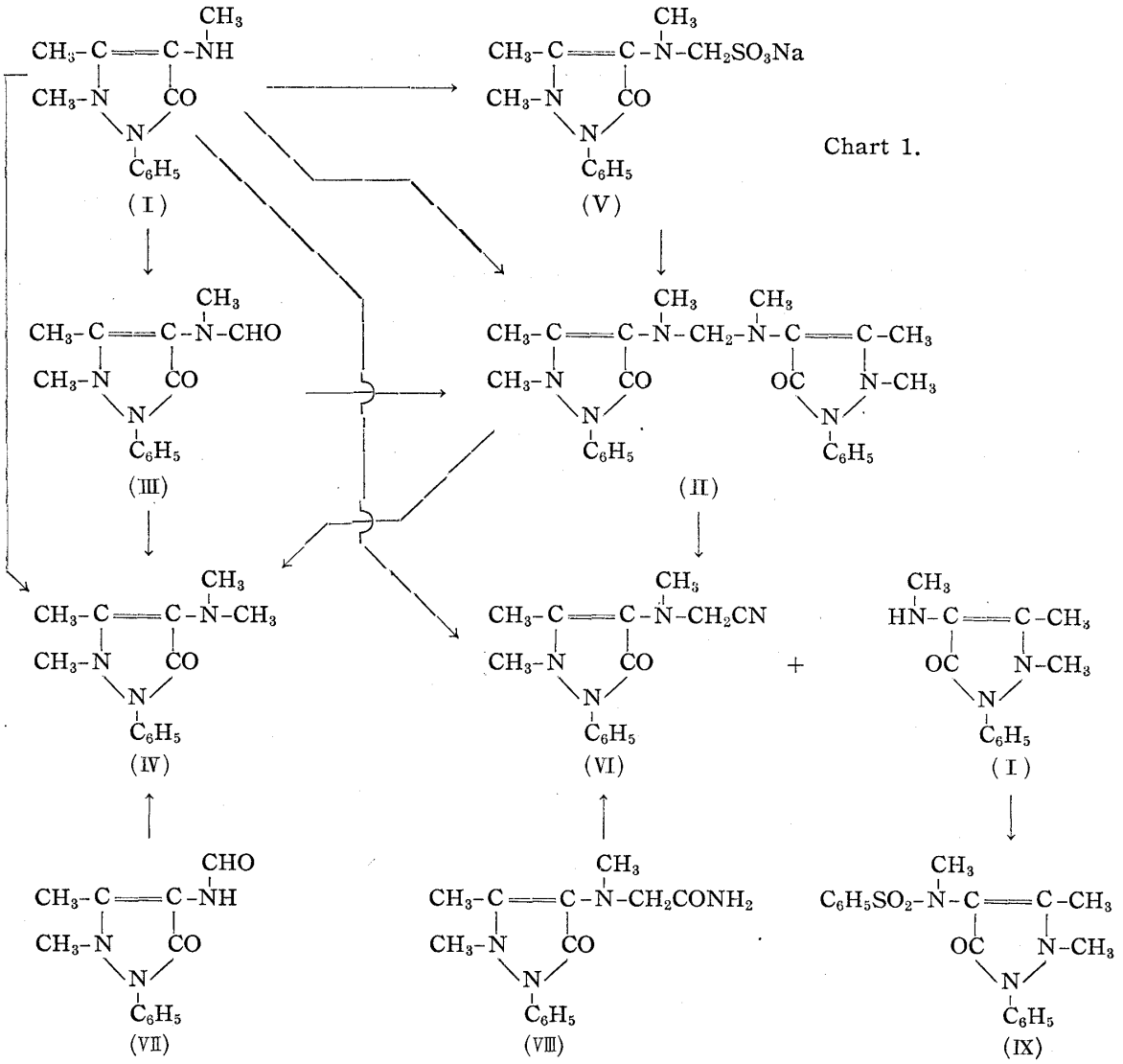


Chart 1.

6) Org. Reactions, 5, 303(1949).

The anthor's thanks are due to the members of the Microanalytical Laboratory of this Institute for the microanalyses.

Experimental

Decomposition of Bis[(N-4-antipyrinyl-N-methyl)amino]methane (II) by HCHO and KCN—i) A solution of (II) (3.4 g.), paraformaldehyde (0.24 g.), and KCN (1.24 g.) dissolved in glacial AcOH (50 cc.) was heated in an oil bath (100~120°) for about 10 hrs. The solution was evaporated *in vacuo*. The residue was rendered alkaline with 10% NaOH solution and extracted with ether. The ether extract was dried over anhyd. K_2CO_3. After removal of the solvent, a small amount of dehyd. ether was added. Crystals thereby separated out were collected by filtration and recrystallized from ether to colorless needles, m.p. 75~76°. Yield, 1.5 g. *Anal.* Calcd. for $C_{14}H_{16}ON_4$ (VI): C, 65.60; H, 6.29. Found: C, 65.32; H, 6.10.

The filtrate was evaporated *in vacuo*. The oily substance (I) thereby obtained was derived to N-4-antipyrinyl-N-methylbenzenesulfonamide (IX) by the application of benzenesulfonyl chloride in $CHCl_3$ at its boiling temperature, in the presence of anhyd. K_2CO_3. (IX) was purified from benzene, forming colorless prisms, m.p. 136°. *Anal.* Calcd. for $C_{18}H_{19}O_3N_3S$: C, 60.49; H, 5.36. Found: C, 60.55; H, 5.41.

ii) Under the same conditions as above, (VI) was obtained by the condensation of (II) (3.4 g.), paraformaldehyde (0.5 g.), and KCN (2.5 g.) in glacial AcOH (50 cc.). Purified from ether, forming colorless needles, m.p. 76°. Yield, 3.2 g. *Anal.* Calcd. for $C_{14}H_{16}ON_4$ (VI): N, 21.86. Found: N, 21.73.

Condensation of 4-Methylaminoantipyrine (I) with HCHO and KCN—To a solution of 4-methylaminoantipyrine (II) (4.34 g.) in glacial AcOH (15 cc.), H_2O (30 cc.), paraformaldehyde (0.63 g.), and KCN (1.7 g.) were added and the mixture was warmed on a water bath at 40~50° for about 10 hrs. The resultant solution was evaporated *in vacuo*. The residue was worked up as usual and purified from ether to colorless needles (VI), m.p. 75°, showing no depression on admixture with (VI) prepared by the reaction of (N-4-antipyrinyl-N-methyl)aminoacetamide (0.5 g.) with P_2O_5 (1 g.) in an oli bath at 150~160° for 2 hrs. Yield, 3.2 g. *Anal.* Calcd. for $C_{14}H_{16}ON_4$: C, 65.60; H, 6.29; N, 21.86. Found: C, 65.43; H, 6.15; N, 21.64.

Condensation of Sulpyrine (V) with HCHO and KCN—A solution of (V) (10 g.), paraformaldehyde (0.5 g.), and KCN (1.5 g.) dissolved in H_2O (250 cc.) and 10% HCl (155 cc.) was heated at 100° for 5 hrs. and the solution was evaporated *in vacuo*. The residue was dissolved in water, basified with 10% NaOH solution, and repeatedly extracted with $CHCl_3$. $CHCl_3$ solution was washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent gave crude (II), which was purified from ether, forming pale yellow crystals, m.p. 172°. Yield, 5.1 g. *Anal.* Calcd. for $C_{25}H_{30}O_2N_6$ (II): C, 67.24; H, 6.77. Found: C, 67.19; H, 6.90.

Bis[(N-4-antipyrinyl-N-methyl)amino]methane (II)—i) A solution of 4-methylaminoantipyrine (I) (10 g.) and paraformaldehyde (3 g.) dissolved in H_2O (380 cc.) and 10% HCl (230 cc.) was heated on a water bath for 4 hrs. and the reaction mixture was concentrated under reduced pressure to approximately 100 cc. The concentrated solution was basified with 10% NaOH solution, extracted with $CHCl_3$, and the extract dried over anhyd. Na_2SO_4. The solvent was then removed. The residue was purified from ether, forming pale yellow crystals (II), m.p. 175°. Yield, 3.5 g. *Anal.* Calcd. for $C_{25}H_{30}O_2N_6$: C, 67.24; H, 6.77. Found: C, 67.07; H, 7.03.

ii) (II) was also prepared from 4-formylmethylaminoantipyrine (III) (4 g.), paraformaldehyde (1 g.), and dil. HCl (200 cc.) in a similar manner as in i), and purified from benzene, forming pale yellow crystals, m.p. 175°. Yield, 1.3 g. *Anal.* Calcd. for $C_{25}H_{30}O_2N_6$: N, 18.82. Found: N, 18.79.

Preparation of Aminopyrine (IV)—i) A mixture of 4-methylaminoantipyrine (I) (2.5 g.), paraformaldehyde (0.8 g.), and conc. HCl (25 cc.) was refluxed for 5 hrs. The mixture was basified with 10% NaOH solution and repeatedly extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and removal of the solvent furnished crude (IV), which was recrystallized from ligroine to colorless prisms, m.p. 108°, showing no depression on admixture with a sample of (IV) J. P. VI. Yield, 1.9 g.

ii) Prepared from 4-formylmethylaminoantipyrine (III) (2.5 g.), paraformaldehyde (0.8 g.), and conc. HCl (25 cc.) in a like manner. Yield, 1.4 g. of (IV), m.p. 108°.

iii) Prepared from (II) (1 g.), paraformaldehyde (0.5 g.), and conc. HCl (10 cc.) in a like manner. Yield, 0.8 g. of (IV), m.p. 108°. *Anal.* Calcd. for $C_{13}H_{17}ON_3$: N, 18.17. Found: N, 18.08.

Summary

The decomposition of bis[(N-4-antipyrinyl-N-methyl)amino]methane (II) with paraformaldehyde and potassium cyanide was effected by heating in glacial acetic acid, and