UDC 547.775.07

68. Torizo Takahashi and Ken Kanematsu: Synthesis of Analgesics. XIX.[1] Antipyrine Derivatives. (6).

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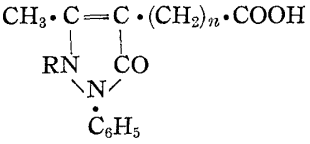
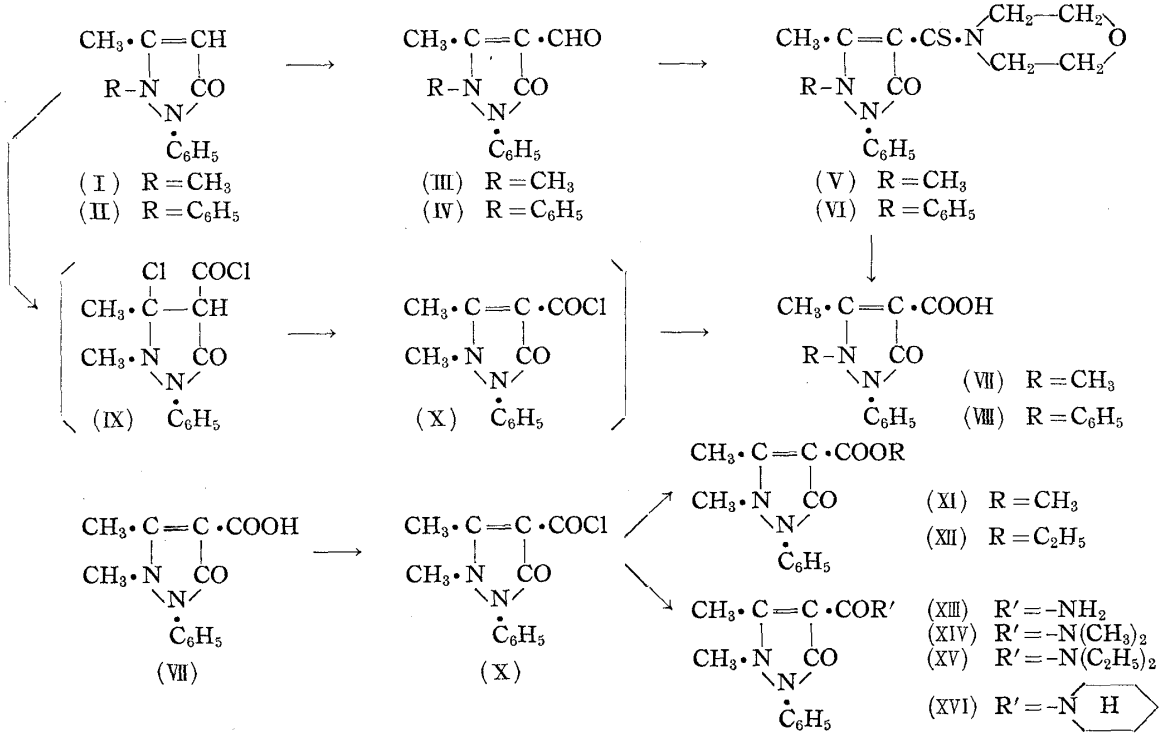
For the purpose of physiological evaluation, synthesis of a series of antipyrinecarboxylic acids was undertaken and the present paper is concerned with the syntheses of 4-antipyrinecarboxylic acid (VII), 1,2-diphenyl-3-methyl-5-pyrazolone-4-carboxylic acid (VIII), 4-antipyrineacetic acid (XXII), and 1,2-diphenyl-3-methyl-5-pyrazolone-4-acetic acid (XXIII) by the Willgerodt-Kindler reaction,[2] and also with the reduction of the derivatives of 4-antipyrinecarboxamides with lithium aluminum hydride.



(VII) $R=CH_3$, $n=0$
(VIII) $R=C_6H_5$, $n=0$
(XXII) $R=CH_3$, $n=1$
(XXIII) $R=C_6H_5$, $n=1$

4-Formylantipyrine (III) and 1,2-diphenyl-3-methyl-4-formyl-5-pyrazolone (IV), when heated with sulfur in morpholine for about 10 hours at 120~130°, yielded the thiomorpholides (V and VI).

These thiomorpholides were submitted to hydrolysis with aqueous or alcoholic alkali and yielded (VII), m.p. 221°(decomp.), and (VIII), m.p. 225~226°, in a good yield. Although the analytical values of (VII) were acceptable, its melting point did not agree with that of the product prepared by condensation of antipyrine with phosgene followed by hydrolysis.[3] For further confirmation, esters (XI~XII) and carboxamides (XIII~XVI) were prepared, and their analytical values agreed well with the theoretical values, as shown in Table I.



(I) $R=CH_3$
(II) $R=C_6H_5$
(III) $R=CH_3$
(IV) $R=C_6H_5$
(V) $R=CH_3$
(VI) $R=C_6H_5$
(VII) $R=CH_3$
(VIII) $R=C_6H_5$
(IX)
(X)
(XI) $R=CH_3$
(XII) $R=C_2H_5$
(XIII) $R'=-NH_2$
(XIV) $R'=-N(CH_3)_2$
(XV) $R'=-N(C_2H_5)_2$
(XVI) $R'=-N\langle H$

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1) Part XVIII. (5): Yakugaku Zasshi, **78**, 787(1958).
2) M. Carmack: Org. Reactions, **3**, 83(1946).
3) H.P. Kaufmann, L.S. Huang, H. Bückmann: Ber., **75**, 1236(1942).

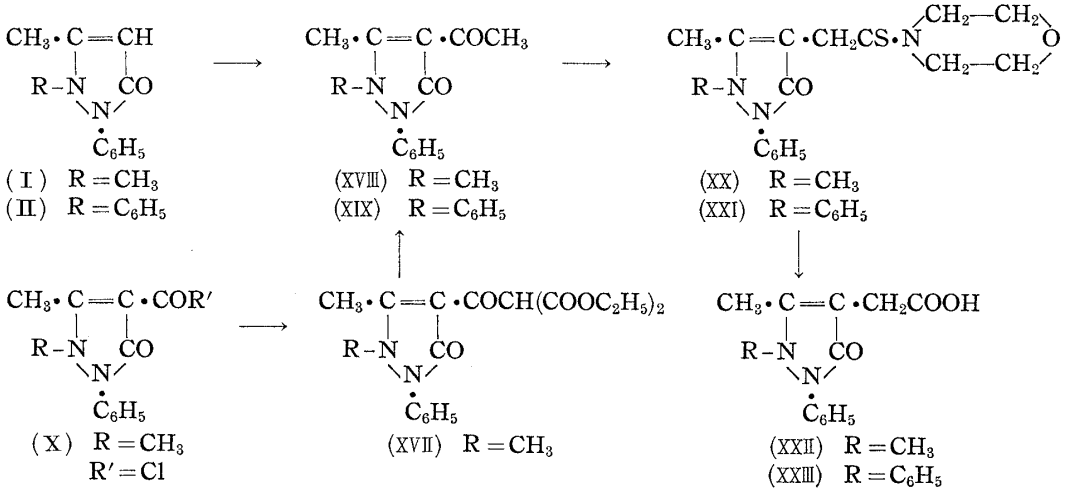
Several works have been recorded in the literature[4] concerning various preparations of 4-formylantipyrine (III). Recently, a convenient method was adopted by Ito,[5] who synthesized (III) by treating antipyrine with dimethylformamide or formylmethylanilide in the presence of phosphoryl chloride. This interesting formylation with dimethylformamide seemed to be useful in the preparation of (IV) and as expected, (IV) was obtained in a good yield.

A method for preparing 4-acetylantipyrine (XVIII) consisted of acylation of the magnesiumethoxy derivative of diethyl malonate with (X), followed by hydrolysis and decarboxylation of the two ester groups of the resulting diethyl acylmalonate in the presence of hydrous acetic and sulfuric acids.

Friedel-Crafts reaction of (I) and (II) with acetic anhydride yielded (XVIII) and 1,2-diphenyl-3-methyl-4-acetyl-5-pyrazolone (XIX), respectively.

The Willgerodt-Kindler reaction was also successfully applied to (XVIII) and (XIX), respectively forming the compounds (XX) and (XXI). Saponification of (XX) and (XXI) with aqueous alkali, followed by neutralization with hydrochloric acid, gave 4-antipyrineacetic acid (XXII), m.p. 181°, and 1,2-diphenyl-3-methyl-5-pyrazolone-4-acetic acid (XXIII), m.p. 192°, respectively.

Their pharmacological properties are now being examined.



Concerning the reduction in pyrazolone series, many investigations have been made. Thoms and Schnupp, and Waser[6] reported that antipyrine was smoothly reduced to dihydroantipyrine by catalytic reduction. Krohs[7] attempted to cleave the pyrazolone ring and to reduce the phenyl group in the 1-position of antipyrine, and found that antipyrine was catalytically reduced to butylanilide in dehydronaphthalene at 180° and 100 atm. in the presence of nickel. Andreocci[8] obtained a compound of pyrazole by heating antipyrine with PS_5 at 200~210°.

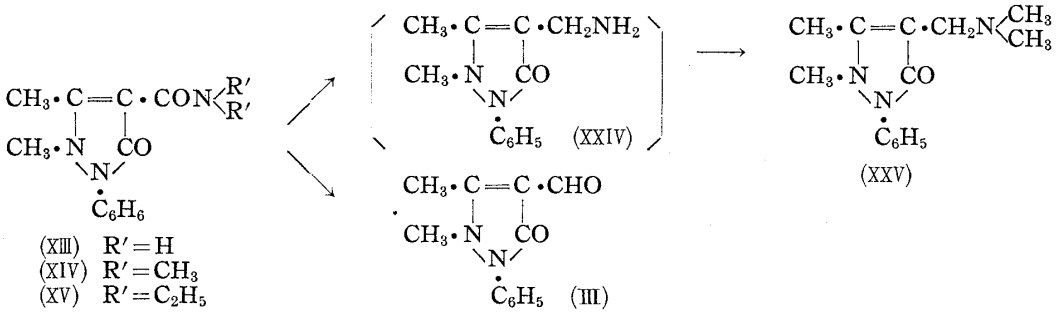
The pyrazolone ring, however, was not reduced with lithium alminum hydride in ether, tetrahydrofuran, or dioxane. In view of above facts, an attempt was made to reduce the compounds (XIII), (XIV), and (XV) with lithium aluminum hydride. As expected, (XIII) was converted to (XXIV) in tetrahydrofuran at 20~30°. The identity of (XXIV) was confirmed by the fact that its methylation changed it to 4-dimethylaminomethyl-antipyrine (XXV), which showed no mixed melting point depression with (XXV)

4) K. Bodendorf, A. Popelak: Ann., **566**, 84(1950); K. Bodendorf, P. Niemeitz: Arch. Pharm., **290**, 494(1957); L. Ledurt, G. Combes: C. A., **47**, 4334(1953); **51**, 10504(1957).
5) I. Ito: Yakugaku Zasshi, **76**, 167(1956).
6) H. Thoms, J. Schnupp: Ann., **434**, 296(1923); E. Waser: Helv. Chim. Acta, **8**, 117(1925).
7) W. Krohs: C. A., **31**, 5795(1937).
8) A. Andreocci: Atti real. accad. Lincei, (4), **7**, **I**, 270.

prepared by the Mannich reaction[9] of antipyrine.

Hydrogenation of N,N-dialkyl-4-antipyrinecarboxamides (XIV) and (XV) under similar conditions described above gave 4-formylantipyrine (III).

As already pointed out by Galinovsky,[10] Wittig,[11] Weygand,[12] and Birkofer,[13] such a usual reduction could be explained by steric interference of the bulky group linked to the nitrogen atom of amide group.



(XIII) $R'=H$
(XIV) $R'=CH_3$
(XV) $R'=C_2H_5$

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

Experimental

1,2-Diphenyl-3-methyl-4-formyl-5-pyrazolone (IV)—A mixture of 1,2-diphenyl-3-methyl-5-pyrazolone (II) (10 g.), dimethylformamide (3 g.), and $POCl_3$ (7 g.) was heated on a steam bath for 3 hrs. The reaction mixture was poured with stirring into a beaker containing cracked ice and the acidic solution was neutralized with AcONa. The oily layer was separated and combined with the $CHCl_3$ extract of the aqueous solution. The $CHCl_3$ solution was washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent gave crude (IV), which was purified by recrystallizing from EtOH to pale yellow crystals (IV), m.p. 155°. *Anal.* Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07. Found: C, 73.36; H, 5.11.

4-Morpholinothiocarbonyl-antipyrine (V)—A mixture of (III) (22 g.), S (5 g.), and morpholine (13 g.), was cautiously heated in an oil bath (120~140°). The first heating had to be moderated to prevent frothing due to evolution of H_2S. After 1 hr. the mixture was heated to vigorous reflux which was continued for 10 hrs. The mixture was evaporated to dryness *in vacuo*. Crystals thereby separated out were collected by filtration and recrystallized from EtOH to pale yellow prisms, m.p. 158°. Yield, 86%. *Anal.* Calcd. for $C_{16}H_{19}O_2N_3S$: C, 60.54; H, 6.03. Found: C, 60.54; H, 6.25.

4-Antipyrinecarboxylic acid (VII)—(V) (10 g.) was refluxed with 20% KOH (20 cc.) for 3 hrs. The solution was acidified with dil. HCl. Crystals thereby separated were collected by filtration and

Table I.

Compd. No.	m.p. (°C)	Lit.[3]	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
(XI)	158~159	158	colorless needles	$C_{13}H_{14}O_3N_2$	63.41	5.69	63.28	5.97
(XII)	152	152	colorless needles	$C_{14}H_{16}O_3N_2$	64.62	6.15	64.95	6.36
(XIII)	242	242	colorless prisms	$C_{12}H_{13}O_2N_3$	62.35	5.63	62.38	5.88
(XIV)	133~134	211	colorless needles	$C_{14}H_{17}O_2N_3$	64.84	6.61	64.55	6.39
(XV)	108	107	colorless needles	$C_{16}H_{21}O_2N_3$	66.87	7.37	66.71	7.52
(XVI)	168	169	colorless needles	$C_{17}H_{21}O_2N_3$	68.20	7.07	68.19	6.59

9) C. Mannich, B. Kather: Arch. Pharm., **257**, 18(1919).
10) F. Galinovsky, A. Wagner, R. Weiser: Monatsh., **82**, 551(1951).
11) G. Wittig, P. Hornberger: Ann., **577**, 11(1952).
12) F. Weygand, *et al.*: Ber., **84**, 625(1951): Angew. Chem., **65**, 525(1953).
13) L. Birkofer, A. Birkofer: Ber., **85**, 286(1952).
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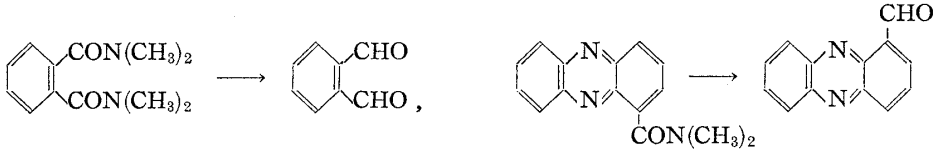

recrystallized from EtOH to colorless needles, m.p. 221°(decomp.). Yield, 95%. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.08; H, 5.34; N, 12.20.

The m.p. of (VII) did not agree with that of the product prepared by the Kaufmann method. For further confirmation, esters (XI～XII) and carboxamides (XIII～XVI) were prepared, and as shown in Table I, their analytical values agreed well with the theoretical values.

1,2-Diphenyl-3-methyl-4-morpholinothiocarbonyl-5-pyrazolone (VI)—A mixture of (IV) (7 g.), S (1.3 g.), and morpholine (3.3 g.) was refluxed for 10～11 hrs. in an oil bath and then poured on ice. (VI) was extracted with $CHCl_3$ and the extract was dried over anhyd. Na_2SO_4. After removal of the solvent, a small amount of dehyd. Et_2O was added. Crystals thereby separated were collected by filtration and recrystallized from EtOH to pale yellow prisms, m.p. 183～184°. Yield, 86.5%. *Anal.* Calcd. for $C_{21}H_{21}O_2N_3S$: C, 66.48; H, 5.58. Found: C, 66.42; H, 5.83.

1,2-Diphenyl-3-methyl-5-pyrazolone-4-carboxylic acid (VIII)—(VI) (3 g.) was boiled with 10% ethanolic KOH for 5 hrs. in an oil bath. The alkaline solution was acidified, extracted with $CHCl_3$, the extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was recrystallized from EtOH to colorless needles, m.p. 225～226°. Yield, 98%. *Anal.* Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.37; H, 4.80. Found: C, 69.15; H, 5.03.

4-Acetylantipyrine (XVIII)—1) Mg turnings (4.3 g.) and a solution of dry CCl_4 (0.8 cc.) in dehyd. EtOH (4 cc.) were placed in a flask. As soon as Mg began to react with EtOH, dry chlorobenzene (50 cc.) was added rapidly, the reaction between Mg and EtOH continuing. A solution of diethyl malonate (28 g.), chlorobenzene (20 cc.), and dehyd. EtOH (16 cc.) was added into the mixture with stirring under cooling at such a rate as to keep the temp. at about 60～65°. When the reaction had proceeded to the extent that removal of the cooling bath did not result in a rise in temp., the mixture was heated slowly to 85° and kept at that temp. until the amount of unreacted Mg became constant. The clear, dark solution was cooled to 25° and a solution of (X) (20 g.) in dry chlorobenzene (100 cc.) was added with stirring and moderate cooling so that the temperature did not exceed 35°. The mixture was stirred for 2 hrs. at 35°, cooled in an ice bath, and a solution of conc. H_2SO_4 (10 cc.) in H_2O (100 cc.) was added immediately, at first slowly and then more rapidly. The mixture was transferred to a separatory funnel and the lower layer, saturated with Na_2SO_4, was discarded.

The chlorobenzene layer was concentrated *in vacuo* and the residue was refluxed with AcOH (50 cc.), conc. H_2SO_4 (60 cc.), and H_2O (30 cc.) for 6 hrs. After being heated, the resulting solution was basified with 10% NaOH solution and extracted repeatedly with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4. Removal of the solvent gave crude (XVIII), which was purified by recrystallization from EtOH or benzene to colorless needles, m.p. 151°. Yield, 83%. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13. Found: C, 67.83; H, 6.28.

2) A mixture of (I) (38 g.) and anhyd. $AlCl_3$ (75 g.) was suspended in CS_2 (50 cc.). Ac_2O (7 g.) was added slowly to this mixture with stirring at 10°. After continued stirring for 8 hrs., the reaction mixture was poured on ice and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and removal of the solvent furnished crude (I), which was recrystallized from EtOH to colorless needles, m.p. 151°. Yield, 76%. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: N, 12.17. Found: N, 12.23.

1,2-Diphenyl-3-methyl-4-acetyl-5-pyrazolone (XIX)—Under the same conditions as above-mentioned 2), (XIX) was obtained by the condensation of (II) (25 g.), anhyd. $AlCl_3$ (37 g.), and Ac_2O (7 g.) in CS_2 (50 cc.), and purified by recrystallizing from EtOH-Et_2O to colorless prisms, m.p. 145°. Yield, 75.3%. *Anal.* Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.95; H, 5.52. Found: C, 74.12; H, 5.76.

4-Morpholinothiocarbonylmethyl-antipyrine (XX)—A mixture of (XVIII) (28 g.), S (6 g.), and morpholine (16 g.) was refluxed for about 10 hrs. in an oil bath and the mixture was evaporated *in vacuo*. Crystals thereby separated were collected by filtration and recrystallized from EtOH to colorless needles, m.p. 143～145°. Yield, 86.5%. *Anal.* Calcd. for $C_{17}H_{21}O_2N_3S$: C, 61.60; H, 6.39; N, 12.68. Found: C, 61.46; H, 6.60; N, 12.91.

1,2-Diphenyl-3-methyl-4-morpholinothiocarbonylmethyl-5-pyrazolone (XXI)—Under the same conditions as above experiment, (XXI) was obtained by the condensation of (XIX) (19 g.), S (3.2 g.), and morpholine (9 g.) in an oil bath (130～140°). This mixture was worked up as before, but did not crystallize.

4-Antipyrineacetic Acid (XXII)—(XX) (10 g.) was refluxed with 20% KOH (20 cc.) for about 10 hrs. The solution was acidified with dil. HCl. Crystals that separated out were collected by filtration and purified by recrystallization from EtOH to colorless needles, m.p. 181～182° Yield, 97%. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73. Found: C, 63.68: H, 5.93.

1,2-Diphenyl-3-methyl-5-pyrazolone-4-acetic Acid (XXIII)—(XXI) (12 g.) was refluxed with 20% KOH (25 cc.) for about 10 hrs. The solution was acidified with dil. HCl, the crystals thereby separated out were collected by filtration, and purified by recrystallization from EtOH to colorless needles, m.p. 192°. Yield, 96.5%. *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23. Found: C, 69.87; H, 5.01.

Reduction of 4-Antipyrinecarboxamides (XIII～XV) with $LiAlH_4$—i) A solution of (XIII) (1 g.) in tetrahydrofuran (20 cc.) was added cautiously to a stirred solution of $LiAlH_4$ (0.1 g.) in tetrahydrofuran (30 cc.). The mixture was warmed for about 15 hrs. followed by careful decomposition of excess of

the hydride with 20% NaOH. The organic solution was dried over anhyd. K_2CO_3, concentrated under reduced pressure, and an oily residue was thereby obtained. This residue was derived to (XXV), m.p. 94°, by its condensation with HCHO (0.5 cc.) and HCOOH (1 cc.) in an oil bath (110~120°), showing no melting point depression on admixture with the same product prepared by the Mannich reaction of antipyrine. (XXV) was recrystallized from Et_2O to colorless needles, m.p. 94°. Yield, 0.09 g. *Anal.* Calcd. for $C_{14}H_{19}ON_3$ (4-Dimethylaminomethylantipyrine): C, 68.57; H, 7.81. Found: C, 68.77; H, 8.08.

ii) A solution of (XIV) (1 g.) in tetrahydrofuran (20 cc.) was added to a stirred solution of $LiAlH_4$ (0.1 g.) in tetrahydrofuran (30 cc.), and the mixture was reacted under the same conditions. This was subsequently worked up as usual and purified by recrystallization from EtOH to pale yellow crystals (III), m.p. 164°, the identity of which was performed by mixed melting point with (III)[5] obtained above. Yield, 0.23 g.

iii) A solution of (XV) (0.9 g.) in tetrahydrofuran (20 cc.) was added to a stirred solution of $LiAlH_4$ (0.1 g.) in tetrahydrofuran (30 cc.), and the mixture was treated under similar conditions. The product was purified by recrystallization from EtOH to pale yellow crystals, m.p. 164°. Yield, 0.2 g. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (4-Formylantipyrine): C, 66.5; H, 5.59. Found: C, 66.52; H, 5.68.

Summary

1) 4-Formylantipyrine (III), 4-acetylantipyrine (XVIII), and 1,2-diphenyl-3-methyl-4-formyl- (IV) and 1,2-diphenyl-3-methyl-4-acetyl-5-pyrazolone (XIX), when heated with sulfur in morpholine, yielded the corresponding compounds of morpholides (V, XX, VI, and XXI).

These morpholides were submitted to hydrolysis with aqueous or alcoholic alkali and respectively gave 4-antipyrinecarboxlic acid (VII), 4-antipyrineacetic acid (XXII), 1,2-diphenyl-3-methyl-5-pyrazolone-4-carboxlic acid (VIII), and 1,2-diphenyl-3-methyl-5-pyrazolone-4-acetic acid (XXIII), each in a good yield.

2) 4-Antipyrinecarboxamide (XIII) was converted to 4-aminomethylantipyrine (XXIV) by lithium aluminum hydride. However, hydrogenation of N,N-dialkyl-4-antipyrinecarboxamides (XIV) and (XV) under similar conditions gave 4-formylantipyrine (III).

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69. Torizo Takahashi und Fumiro Yoneda: Über die Synthese der heterozyklischen Verbindungen mit Stickstoff. CXIII.[1] Synthese der Azaphenoxazinderivate. (2).

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In unserer I. Mitteilung[2] über die Synthese der Derivate des Azaphenoxazins berichteten wir, dass bei der Einwirkung von 2-Chlor-3,5-dinitropyridin auf *o*-Aminophenol in äthanolischer Kalilösung nicht Azaphenoxazin, sondern nur 2-(*o*-Oxyphenylamino)-3,5-dinitropyridin gewonnen wurde, und durch die Einwirkung von *o*-Methylaminophenol dagegen 3-Nitro-10-methylbenz[*e*]pyrido[2,3-*b*]-1,4-oxazin: die von Brady befürwortete Hypothese des chelierten Ringes[3] erklärt nämlich die Möglichkeit dieses Ringschlusses.

Diesmal synthetisierten wir verschiedenartige Azaphenoxazin, indem wir obiger Hypothese folgten; ausserdem gewannen wir bei der Synthese des Zwischenmaterials einige Kenntnisse, worüber hier berichtet werden soll.

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1) CXII. Mitteilung: Dieses Bulletin, **6**, 365(1958).
2) T. Takahashi, F. Yoneda: *Ibid.*, **6**, 46(1958).
3) O. L. Brady, C. Waller: J. Chem. Soc., **1930**, 1218.