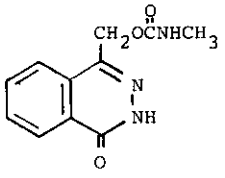
SYNTHESES OF 4-HYDROXYMETHYL-1(2H)-PHTHALAZINONE AND ITS ANALOGS

Masayuki Ishikawa* and Yukuo Eguchi
Institute for Medical and Dental Engineering
Tokyo Medical and Dental University
2-3-10, Surugadai, Kanda, Chiyoda-ku, Tokyo, Japan

Abstract --- 4-Hydroxymethyl-1(2H)-phthalazinone (2) was preferably prepared by reduction of 4-ethoxycarbonyl-1(2H)-phthalazinone with $NaBH_4$ in EtOH in good yield. The synthetic method was applicable for the preparation of 7-ethoxycarbonyl-4-hydroxymethyl-1(2H)-phthalazinone and its 2-phenyl derivative, where the regioselective reduction of the ester at the position 4 was possible, leaving the ester at the position 7 intact. The Grignard reaction of 4-ethoxycarbonyl-1(2H)-phthalazinone was also described.

During the studies on antiathereosclerotic agents, 4-carbamoyloxymethyl-1(2H)-phthalazinone (1) and 4-hydroxymethyl-1(2H)-phthalazinone (2) were found to possess considerably potent inhibitory effects on platelet-aggregation induced by ADP and also on edematous arterial reaction.[1] In order to obtain insights into the structure-activity relationship of the 1(2H)-phthalazinone derivative, it was necessary to explore the more efficient and versatile synthetic methods for the phthalazinone derivative bearing a hydroxy group on the carbon atom attached to the position 4. In the present paper, we describe synthetic methods of (2), its analogs having substituents on the benzene ring, and also phthalazinones carrying a secondary or tertiary alcohol at the position 4.



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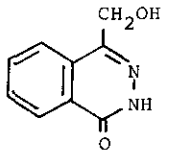

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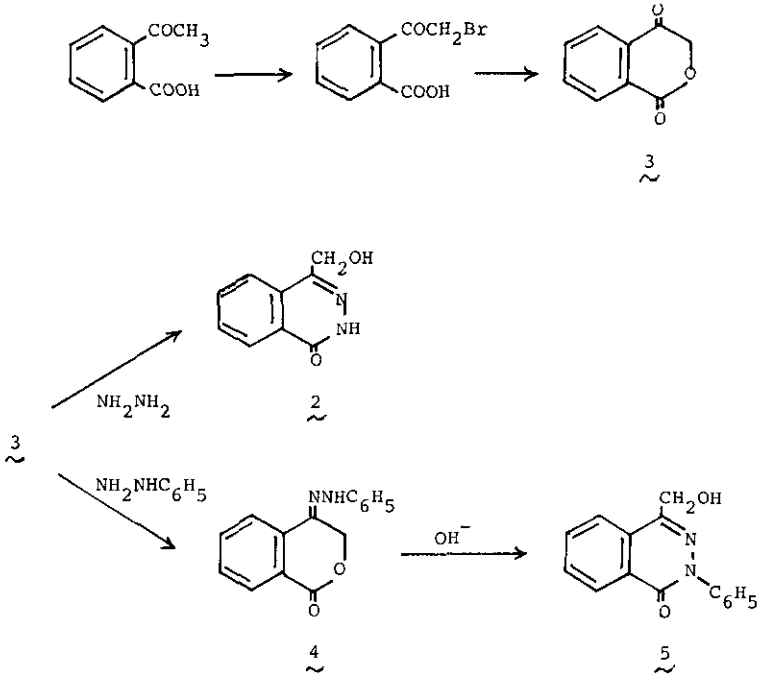
The compound (2) itself was synthesized as early as in 1907 by Gabriel [2] by reaction of o-(ω-hydroxyacetyl)benzoic acid with hydrazine. The benzoic acid,

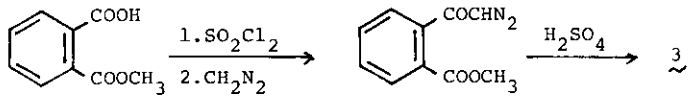
whose structure was later revised by Knott[3] as isochroman 1,4-dione (3), was obtained by bromination of o-acetylbenzoic acid and subsequent hydrolysis with water.[2] The corresponding 2-phenyl derivative was also prepared by treatment of phenylhydrazine and subsequent treatment of the resulting hydrazone (4) with potassium hydroxide, that led to the recyclization of 4 to 5 as depicted in the following scheme.[3]



In the above synthetic route, difficulties were found in controling the reaction condition of bromination on o-acetylbenzoic acid, in which the product was inevitably contaminated with dibromo compound. In addition, in most cases the route can not be applied for derivatives having substituents on the benzene ring, because of the inaccessibility of the starting compound. Under the circumstances, we wished to explore other synthetic pathways which will enable us to develop further modification of the compound (2).

When phthalic anhydride was boiled in absolute MeOH in the presence of catalytic amount of KCN for 2 hr, a half-ester of the phthalic acid was produced. After chlorination of the half-ester with $SOCl_2$, the acyl chloride was treated with excess diazomethane in ether to afford diazoacetyl compound of mp 128-129°,

$C_8H_{10}O_3N_2$ (6), which showed a typical absorption band due to N≡N at 2170 cm^{-1} in the IR spectrum. Stirring with dilute H_2SO_4 converted 6 into 3 under evolution of N_2, whose spectral data were identical with those of a sample obtained by Gabriel's method. However, this procedure was not preferable, because treatment with $SOCl_2$ produced a considerable amount of phthalic anhydride as an undesirable product and the use of diazomethane limited scaling up of the preparation.



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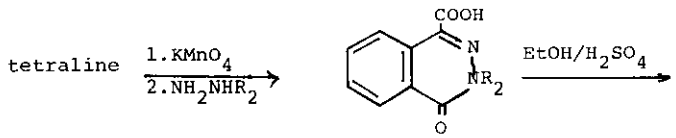
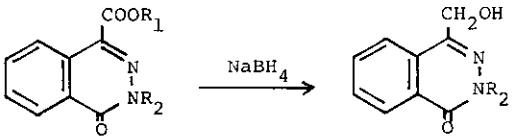
Next, we examined the preparation of 2 from 4-carboxy-1(2H)-phthalazinone (7), since the latter compound could be obtained easily by oxidation of tetraline with $KMnO_4$, followed by treatment of the resulting aqueous filtrate with hydrazine hydrate.[4] 4-Carbonyl-2-phenyl-1(2H)-phthalazinone which melted at 222-223°, $C_{15}H_{10}O_3N_2$ (8) could be synthesized by a similar procedure with 7. Both 7 and 8 were esterified with EtOH in the presence of conc. H_2SO_4 to afford the corresponding ethyl ester 9 and 10. Although no crystalline products were obtained by reduction of 9 or 10 with $LiAlH_4$ in THF, reduction of 9 with $NaBH_4$[5] in EtOH afforded colorless needles of mp 203°, $C_9H_8O_2N_2$ (2) in 93% yield, whose physical properties are the same of those obtained by the Gabriel's method in all respects. The ester (10) was also converted into 5 by the same $NaBH_4$ reduction, mp 166-168°, $C_{15}H_{12}O_2N_2$, whose spectral data were identical with those of a sample obtained by the Knott's method.[3]



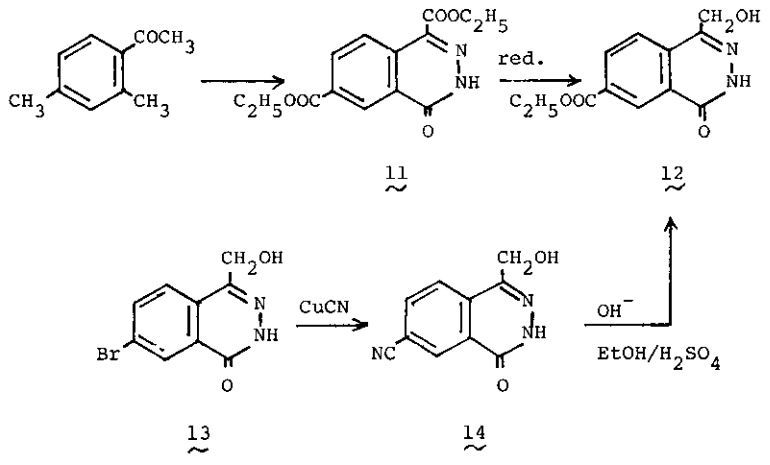


	R_1	R_2
7:	H	H
8:	H	C_6H_5
9:	C_2H_5	H
10:	C_2H_5	C_6H_5

	R_2
2:	H
5:	C_6H_5

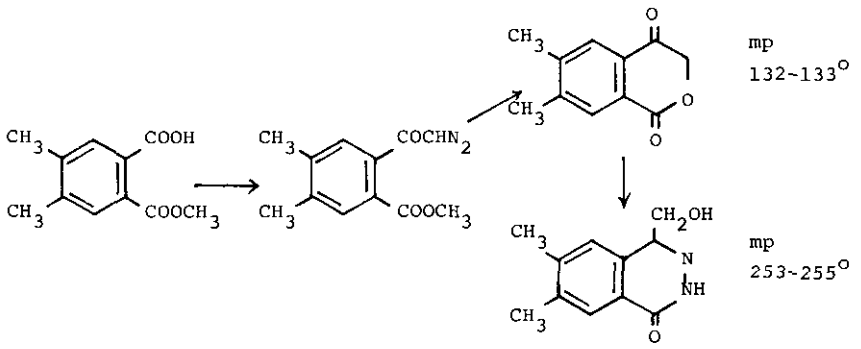
Seki et al.[6] investigated extensively the $NaBH_4$ reduction of ester groups in protic solvents to find out that the ester group attached to an electron deffi-cent carbon atom is more susceptible to the reduction. Clearly, the successful reduction of 9 and 10 will be due to the electron withdrawing effect of the 1(2H)-phthalazinone ring on the 4-ethoxycarbonyl group.

By this way 4-hydroxymethyl-1(2H)-phthalazinone having substituents, such as, ethoxycarbonyl, halogen, methoxyl,.. on the benzene ring could be prepared in good yield. For example, 2,4-dimethylacetophenone obtained by the Friedel-Crafts acylation from m-xylene was oxidized with $KMnO_4$, followed by treatment of the aqueous filtrate with hydrazine hydrate, and then esterified by a conventional procedure to afford 4,7-bis (ethoxycarbonyl)-1(2H)-phthalazinone (11) in 72% yield. When the reduction with $NaBH_4$ was carried out in EtOH at low temperature between -10° and 5° in the presence of $CaCl_2$, 7-ethoxycarbonyl-4-hydroxymethyl-1(2H)-phthalazinone was obtained in 78% yield, mp 206-207°, $C_{12}H_{12}O_4N_2$, NMR(DMSO-d_6)δ: 1.32 (3H, t, J=7Hz), 4.29(2H, q, J=7Hz), 4.55(2H, s), 5.43(1H, broad), 8.10(1H, q, J=8Hz, J=2Hz), 8.30(1H, d, J=8Hz), 8.80(1H, d, J=2Hz), 12.40(1H, s).(12).
In order to determine unambiguously the structure of 12, the compound was prepared in an alternative way from 7-bromo-4-hydroxymethyl-1(2H)-phthalazinone of mp 222-223°, $C_9H_7O_2N_2Br$ (13), which was synthesized starting from m-bromotoluene by the same reaction sequences. Heating at 160° with a equimolar cuprous cyanide in DMF for 15 hr, converted 13 into 7-cyano-4-hydroxymethyl-1(2H)-phthalazinone (14) of mp 226-227°, $C_{10}H_7O_2N_3$ in 60% yield, which showed a typical absorption band due to C≡N at 2220 cm^{-1} in the IR spectrum. By the treatment with 20%-KOH solution at 70°, 14 was hydrolyzed to 7-carboxy-4-hydroxymethyl-1(2H)-phthalazinone of mp 298-300°, which was then esterified with EtOH in the presence of conc. H_2SO_4 to afford 12 of mp 204-206°. The spectroscopic data were identical with those of a sample



obtained by the foregoing procedure.

The synthesis of phthalazinone derivatives having alkyl group on the benzene ring as 15 was preferably carried out by the method using diazomethane, starting from 4,5-dimethylphthalic anhydride.[7]



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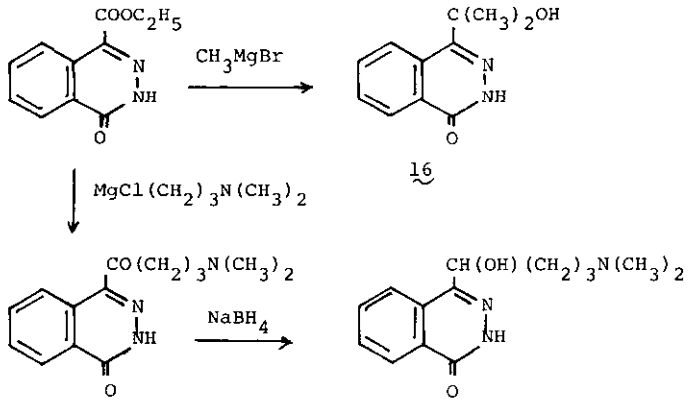
In order to modify the hydroxymethyl group at the position 4, the ester (9) was subjected to the Grignard reaction to give 4-(1-hydroxy-1-methylethyl)-1(2H)-phthalazinone melted at 212-213°, $C_{11}H_{12}O_2N_2$ (16). In the case of the Grignard reaction of N,N-dimethylaminopropylmagnesium chloride on 9, contrary to our expectation, 4-(N,N-dimethylaminopropylcarbonyl)-1(2H)-phthalazinone of mp 159-160°, $C_{14}H_{17}O_2N_3$ (17) was formed as the main product in 43% yield. Poor nucleophilicity of this reagent and steric hindrance around 4-position presumably made the second attack of the Grignard reagent to the carbonyl intermediate difficult.



16 17 18

When 17 was allowed to react with $NaBH_4$ in EtOH at room temperature, the corresponding secondary alcohol 4-(4-N,N-dimethylamino-1-hydroxybutyl)-1(2H)-phthalazinone of mp 100-102°, $C_{14}H_{19}O_2N_3$ (18) was obtained.

The 4-hydroxymethyl-1(2H)-phthalazinone derivatives thus prepared played an important role for the clarification of the structure-activity relationship and the results will be reported separately.

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