SYNTHESES OF 2-HYDROXYMETHYL-4(3H)-QUINAZOLINONE AND ITS ANALOGS

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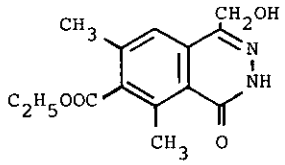
Abstract --- The syntheses of 6-ethoxycarbonyl-2-hydroxymethyl-5,7-dimethyl-4(3H)-quinazolinone, 7-(or 6-)-ethoxycarbonyl-2,6,8-(or 2,5,7-)-trimethyl-3-phenyl-4(3H)-quinazolinone were described. The 3-phenyl-4(3H)-quinazolinone compounds were further converted to the corresponding 2-hydroxymethyl derivative. The starting compounds, 2-amino-4-ethoxycarbonyl-3,5-dimethylbenzoic acid and 2-amino-5-ethoxycarbonyl-4,6-dimethylbenzoic acid were prepared by the Hofmann reaction of the corresponding phthalimide.

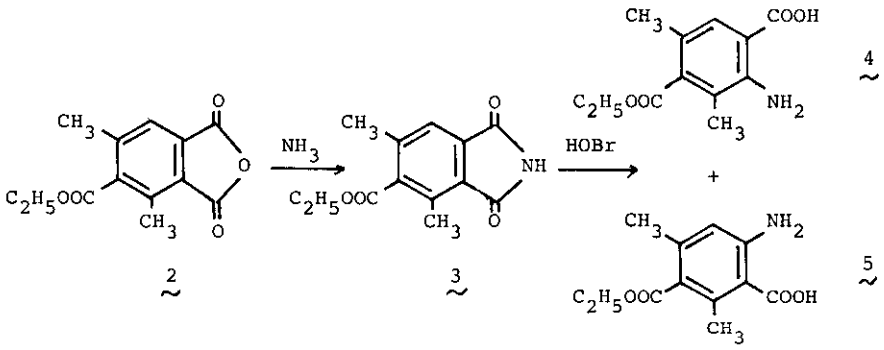
In quest for effective antiathereosclerotic agents, we have synthesized many derivatives of substituted 1(2H)-phthalazinone and found 7-ethoxycarbonyl-4-hydroxymethyl-6,8-dimethyl-1(2H)-phthalazinone (1) to have potent biological activities. In the present paper we describe synthetic studies of 4(3H)-quinazolinone derivatives which are closely related to 1.



1

4-ethoxycarbonyl-3,5-dimethylphthalic anhydride[1] (2) was heated with conc. ammonia solution to dryness to afford the 4-ethoxycarbonyl-3,5-dimethylphthalimide of mp 132-133°, $C_{13}H_{13}O_4N$ (3). The nucleophilic attack of ammonia against the 4-ethoxycarbonyl group of 2 was completely blocked by the two methyl groups at both sides of the ester group. When 3 was treated with bromine in dil. KOH solution at room temperature, an oily product was obtained. Purification of the product by partial crystallization from MeOH gave 2-amino-4-ethoxycarbonyl-3,5-dimethylbenzoic

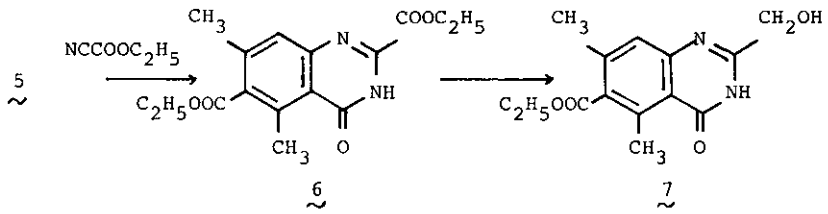
acid (4) of mp 161-162° (24%), $C_{12}H_{15}O_4N$, NMR($CDCl_3$)δ: 1.40(3H, t, J=7Hz), 2.15 (3H, s), 2.20(3H, s), 4.45(2H, q, J=7Hz), 7.50(2H, s), 7.75(1H, s). The mother liquor of 4 was purified by column chromatography on silica gel eluting with ether to give pale yellow needles of 2-amino-5-ethoxycarbonyl-4,6-dimethylbenzoic acid (5) of mp 113-115° (14%), $C_{12}H_{15}O_4N$, NMR($CDCl_3$)δ: 1.35(3H, t, J=7Hz), 2.25(3H, s), 2.45(3H, s), 4.40(2H, q, J=7Hz), 6.40(1H, s), 7.45(2H, s).



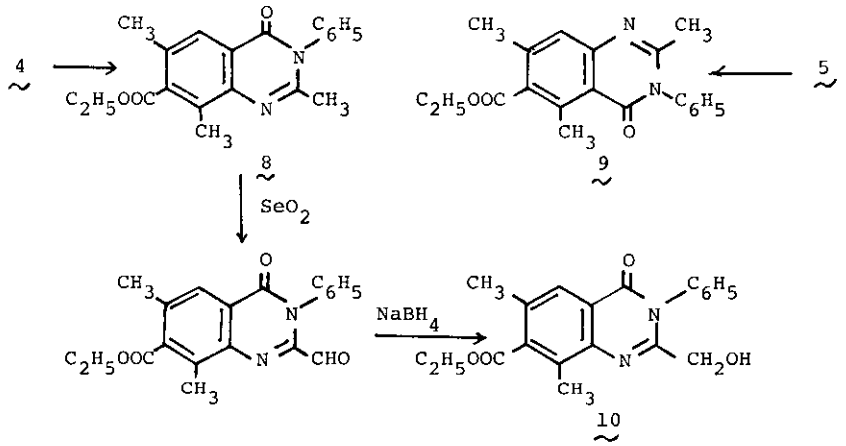
2 3 4 5

Each structure of 4 and 5 was determined by comparison of their NMR spectra, in which the ring proton of 4 appeared at 7.75 ppm, while that of 5 at 6.40 ppm. The former signal demonstrates that the existence of a carbonyl group on adjacent side of the proton. On the other hand, from the latter signal, an amino group was expected at the ortho position of the proton. In addition, the methyl protons at 3-position of 4 appeared at 2.15 ppm, a higher field under the influence of the adjacent amino group, while the methyl protons at 6-position of 5 appeared at 2.45 ppm, shifting to a lower field by the effect of the neighbouring carbonyl group. From these observations, each structure of the isomeric products from the Hofmann reaction[2] of 3 is reasonably concluded.

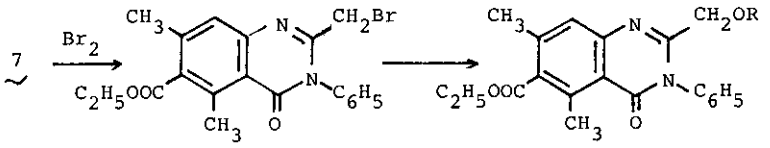
Starting from the anthranilic acid (5) thus prepared, 6-ethoxycarbonyl-2-hydroxymethyl-5,7-dimethyl-4(3H)-quinazolinone (7), which corresponds to the phthalazinone derivative (1), was prepared by the route depicted below in analogous way to the method of Sugiyama et al.[3] Condensation of hydrochloride of 5 with ethyl cyanoformate in AcOH containing 1.86% hydrogen chloride at 120° for 3 hr afforded the expected 2-ethoxycarbonyl-4(3H)-quinazolinone derivative (6) of mp 154-156°, $C_{16}H_{18}O_5N_2$, recrystallized from EtOH. (51%). Reduction of 6 with $NaBH_4$ in EtOH in the presence of $CaCl_2$ was smoothly carried out to afford the desired 7 of mp 208-210°, $C_{14}H_{16}O_4N_2$, NMR(DMSO-d_6)δ: 1.32(3H, t, J=7Hz), 2.32(3H, s), 2.70(3H, s), 4.39(2H, q, J=7Hz), 4.38(2H, s), 7.38(1H, s), 11.70(1H, broad).



By conventional method[4] for the preparation of 3-phenyl substituted 4(3H)-quinazolinone derivative, anthranilic acid 4 and 5 was converted into 7-ethoxycarbonyl-2,6,8-trimethyl-3-phenyl-4(3H)-quinazolinone of mp 140-141°, $C_{20}H_{20}O_3N_2$ (8) and 6-ethoxycarbonyl-2,5,7-trimethyl-3-phenyl-4(3H)-quinazolinone of mp 102-104°, $C_{20}H_{20}O_3N_2$ (9), respectively. Oxidation with SeO_2 in dioxane and following $NaBH_4$ reduction converted 8 to 7-ethoxycarbonyl-2-hydroxymethyl-6,8-dimethyl-3-phenyl-4(3H)-quinazolinone of mp 179-180°, $C_{20}H_{20}O_4N_2$ (10). On the other hand, the same oxidation carried out on 9 gave an oily mixture, from which no crystalline product was isolated.



As an alternative synthetic route, 9 was treated with an equimolar amount of bromine in boiling glacial acetic acid for 5 hr to give a brown oil, which was purified by column chromatography on silica gel to afford 2-bromomethyl-6-ethoxycarbonyl-5,7-dimethyl-3-phenyl-4(3H)-quinazolinone of mp 129-130° (58%), $C_{20}H_{19}O_3N_2Br$ (11). Refluxing of 11 for 2 hr with CH_3COONa in EtOH gave the corresponding acetoxy compound of mp 98-99° (63%), $C_{22}H_{22}O_5N_2$ (12). Subsequent treatment of 12 with CH_3ONa in dry MeOH afforded 6-ethoxycarbonyl-2-hydroxymethyl-5,7-dimethyl-3-phenyl-4(3H)-quinazolinone (13) in a yield of only 37%, mp 107-108°, $C_{20}H_{20}O_4N_2$.



11

12 R: $COCH_3$

13 : H

The biological activities of these quinazolinone derivatives were assayed by our screening methods. To our disappointment the quinazolinone compound (7) did not show the biological activities which were displayed by the phthalazinone compound (1). But, interestingly, it was found that the 3-phenyl-4(3H)-quinazolinone derivative (13) exhibited potent blood vessel relaxing and hypotensive effects on animals. The pharmacological results on these compounds will be reported elsewhere in the near future.

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