INTRODUCING AMINO GROUP ON 1(2H)-PHTHALAZINONE DERIVATIVES

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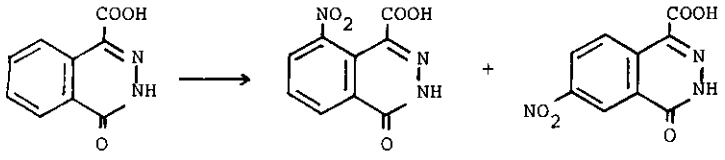
Abstract --- Nitration of 4-ethoxycarbonyl-1(2H)-phthalazinone (4) with KNO_3 and conc sulfuric acid at room temperature afforded the corresponding 5-nitro derivative (5) in about 50% yield. The latter compound was converted to 5-acetylamino-4-hydroxymethyl-1(2H)-phthalazinone (9). The preparation of 4-amino-7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone (13) through the Curtius reaction of the hydrazide (10) was also described.

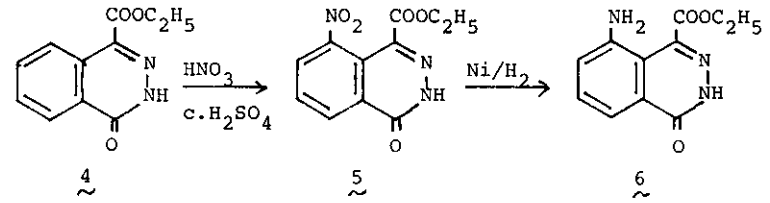
In the course of the studies on antiatherosclerotic agent, our attention was directed to 4-hydroxymethyl-1(2H)-phthalazinone derivative carrying a nitro or amino derivative. It appeared preferable to introduce a nitro substituent by nitration on an appropriate phthalazinone derivative rather than the ring closure of a nitro compound to a phthalazinone derivative. Concerning the nitration of 1(2H)-phthalazinone, there are several reports by Kanahara[1] dealing with the nitration of 1(2H)-phthalazinone, 4-methyl-1(2H)-phthalazinone, and 4-carboxy-1(2H)-phthalazinone (1), using a mixture of KNO_3 and conc. sulfuric acid as a nitrating agent. By allowing the nitration mixture to stand for one week at room temperature, according to his report, the latter compound (1) afforded the nitration products 2 and 3 in about 50 and 5% yield, respectively.

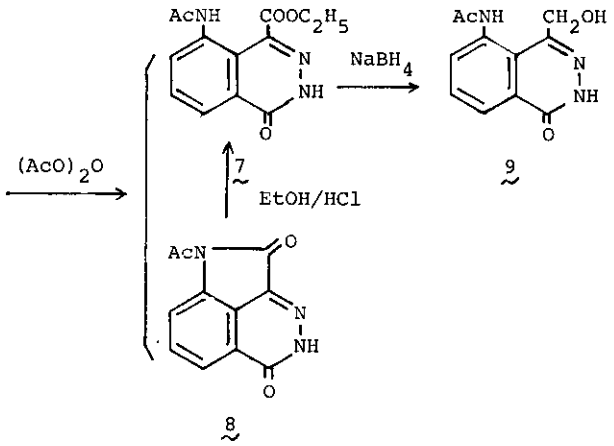


1 2 3

Keeping the precedent in mind we carried out the nitration on the 4-ethoxycarbonyl-1(2H)-phthalazinone (4) in a similar manner with Kanahara's method, and obtained a nitration product of mp 198-200°, $C_{11}H_9O_5N_3$ (5) in 50% yield.

The NMR spectrum of 5 displays signals at 8.10 ppm (1H, triplet, J=8Hz) and 8.60 ppm (2H, multiplet). Based on spectral data which suggest existence of C_7-proton on the benzene ring, the compound (5) was assumed to be 7-ethoxycarbonyl-5-nitro-1(2H)-phthalazinone. The structure of 5 was further supported by the following experiment. Reduction of 5 under an atmosphere of hydrogen over Raney nickel afforded the corresponding amino compound of mp 140-141° (6). Upon acetylation of 6 in boiling acetic anhydride, a crystalline product of mp 240-242°, $C_{13}H_{13}O_4N_3$ (7) and a product (8) which did not melt at 280°, $C_{11}H_7O_3N_3$ were obtained in 80 and 13% yield, respectively. The structure of the former product (7) was considered to be a simply acetylated product of the amino compound (6) and the latter (8) was assumed to have a structure formed by losing EtOH from 7, since by boiling in EtOH in the presence of HCl 8 was converted into 7 in good yield. On the basis of spectral data, the structure of 8 which showed an absorption band due to carbonyl group of 5-membered N-acetyllactam at 1765 cm^{-1} in the IR spectrum, was determined to be the lactam compound shown in the following chart.



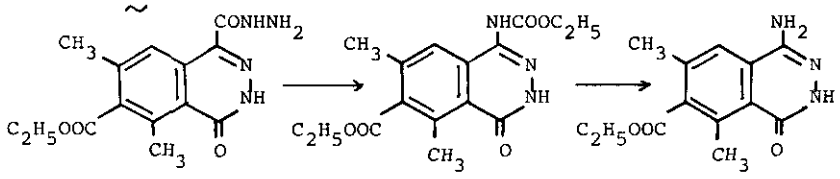


Whereas the nitro compound (5) did not afford the corresponding 4-hydroxymethyl derivative by reduction with $NaBH_4$, 7 was reduced smoothly with $NaBH_4$ to 5-acetyl-

amino-4-hydroxymethyl-1(2H)-phthalazinone of mp 206-207°, $C_{11}H_{11}O_3N_3$ (9).

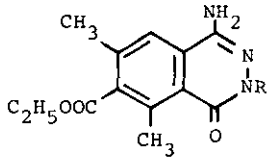
Against our expectation, the above compounds (5-9) did not reveal any attractive biological activity. We next planned introduction of an amino substituent at the position 4 or 7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone by means of the Curtius reaction of the corresponding 4-hydrazinocarbonyl derivative.

The hydrazid, 7-ethoxycarbonyl-4-hydrazinocarbonyl-6,8-dimethyl-1(2H)-phthalazinone of mp 249-252°, $C_{14}H_{16}O_4N_4$ (10) prepared from 4,7-bis (ethoxycarbonyl)-6,8-dimethyl-1(2H)-phthalazinone was treated with $NaNO_2$ and conc.HCl under an ice-salt cooling with vigorous stirring to give an acylazide compound (11). On refluxing in EtOH, 11 was converted into colorless needles of mp 127-129° (49%), $C_{16}H_{19}O_5N_3$, NMR(DMSO-d_6)δ: 1.20(3H, t, J=7Hz), 1.30(3H, t, J=7Hz), 2.30(3H, s), 2.70 (3H, s), 4.02(2H, q, J=7Hz), 4.32(2H, q, J=7Hz), 7.35(1H, s), 9.25(1H, s), 12.00 (1H, s), whose structure was determined by analytical and spectral data as the corresponding urethane, 7-ethoxycarbonyl-4-ethoxycarbonylamino-6,8-dimethyl-1(2H)-phthalazinone (12).



10 12 13

Hydrolysis of 12 with alcoholic KOH gave 4-amino-7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone (13) of mp 218-220°, $C_{13}H_{15}O_3N_3$, NMR(DMSO-d_6)δ: 1.30(3H, t, J=7Hz), 2.40(3H, s), 2.75(3H, s), 4.36(2H, q, J=7Hz), 4.50(2H, broad), 7.65(1H, s), 11.00(1H, s). The related 4-amino derivatives are shown below.



14 R: CH_3 mp 131-132°, $C_{14}H_{17}O_3N_3$, NMR($CDCl_3$)δ: 1.40(3H, t, J=7Hz), 2.39 (3H, s), 2.88(3H, s), 3.67(3H, s), 3.65-4.20(2H, broad), 4.88(2H, q, J=7Hz), 7.32(1H, s).

15 R: C_6H_5 mp 173-174°, $C_{19}H_{19}O_3N_3$, NMR($CDCl_3$)δ: 1.45(3H, t, J=7Hz), 2.48 (3H, s), 2.90(3H, s), 4.32(2H, s), 4.50(2H, q, J=7Hz), 7.40(1H,), 7.50(5H, m).

These amino compounds (13-15), particularly 13, were found to show potent vasodilating and hypotensive activities in spontaneously hypertensive rats by oral administration. The test for the relaxing effect of blood vessel was carried out by a conventional procedure as follows and the result is shown in Table I.

The thoracic aorta excised from albino rabbits were cut into strips, which were suspended in an organ bath filled with Krebs-Henseleit solution. After 2 hr equilibration, each strips was constricted by addition of KCl in a final concentration of 20 mM. When the constriction induced by KCl reached a maximum, a solution of test compound in DMSO was added to the bath in a concentration of 3×10^{-5}M, and the resulting relaxation was recorded. The concentration of the DMSO did not exceed 0.3%. At the end of each series of experiments, papaverine was added to the bath in a concentration of 3×10^{-4}M, and relaxation induced by papaverine was taken as 100%. The relaxing effects of test compounds shown in Table I were expressed as percentages against the maximum relaxation induced by papaverine (3×10^{-4}M), and the relaxation effect is a mean value obtained from the experiments indicated in Table I.

Table I.

Test compound	Concentration	Relaxing effect of blood vessel (% ± standard error)	Number of experiments
papaverine	3×10^{-5}M	52 ± 3.7	20
compound 13	3×10^{-5}M	53 ± 4.6	5

As shown in Table I, the compound (13) exhibited equipotent blood vessel relaxing activity with papaverine, and the pharmacological results on the compound (13) will be reported in detail in the near future.

Acknowledgement We thank Miss Masako Nakajima in our institute for carrying out the biological test.

References

1) S. Kanahara, J. Pharm. Soc. Japan, 1965, 84, 483.

2) M. Ishikawa, Y. Eguchi, and A. Sugimoto, Chem. Pharm. Bull. (Tokyo), 1980, 28, 2764.

Received, 2nd September, 1980