[Chem. Pharm. Bull. 12 (4) 495 ~ 497]

UDC 547.657

Zen-ichi Horii, Masanori Sakamoto, Takefumi Momose, and Yasumitsu Tamura : 2-Acetyl-1-naphthoic and 2-Acetyl-3,4-dihydro-1-naphthoic Acid.

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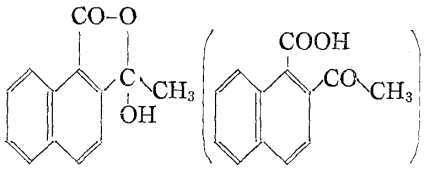
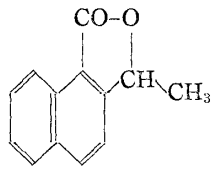
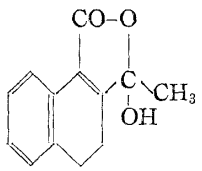
Synthesis of 2-acetyl-1-naphthoic acid (I) from 1,2-naphthalenedicarboxylic acid through the half ester, the ester-chloride and the naphthoylmalonate has already been described by Ried and Bönnighausen.[1] However, the over-all yield for this four-steps synthesis is very poor, and, further, conclusive evidence for the assigned orientation of the acetyl group is unavailable, since the structural assignment of the half ester is uncertain and rearrangement might occur at any subsequent stage of the reactions.[2] We found that Doebner reaction[3] of 1,2-naphthalenedicarboxylic anhydride[4,5] with malonic acid in pyridine afforded I[*2] in over-all yield of 27%. The method is superior to the former method from the point of view of yield and convenience.



I



II



III

In order to remove any doubt concerning the structure of I, I was reduced with sodium borohydride or hydriodic acid to 2-(1-hydroxyethyl)-1-naphthoic acid γ-lactone (II), which was compared with an authentic sample prepared by the following unequivocal procedure. Aldol condensation[6] of ethyl 2-ethoxalyl-4-phenylbutyrate[5] with acetaldehyde followed by cyclization with concentrated sulfuric acid and dehydrogenation over palladium on carbon gave II, which was found to be identical with the compound obtained by the reduction of I.

3,4-Dihydro-1,2-naphthalenedicarboxylic anhydride[5] was also found to yield similarly 2-acetyl-3,4-dihydro-1-naphthoic acid on the Doebner reaction. The structure of the product was determined by dehydrogenation with sulfur to I, which was identical with the authentic sample of I described above.

Reduction of I by Huang-Minlon procedure did not give 2-ethyl-1-naphthoic acid, but 4-methylbenzo[*h*]phthalazin-1(2*H*)-one. Other reduction such as with zinc powder in alkaline medium, by Schwenk-Papa procedure or by Clemmensen procedure gave no single product.

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*2 2-Acetyl-1-naphthoic acid and 2-acetyl-3,4-dihydro-1-naphthoic acid are assumed to have the hydroxylactone structures, I and III, from the infrared spectra, respectively.

1) W. Ried, K. H. Bönnighausen : Ann., **639**, 56 (1961).
2) B. H. Chase, D. H. Hey : J. Chem. Soc., **1952**, 553.
3) H. L. Yale : J. Am. Chem. Soc., **69**, 1547 (1947).
4) E. F. Bradbrook, R. P. Linstead : J. Chem. Soc., **1936**, 1739.
5) L. F. Fieser, E. B. Hershberg : J. Am. Chem. Soc., **57**, 1851 (1953); Org. Syntheses, Coll. Vol. II, 194 (1948).
6) H. Schinz, M. Hinder : Helv. Chim. Acta, **30**, 1349 (1947).

Experimental*3

2-Acetyl-3,4-dihydro-1-naphthoic Acid (III)——A mixture of 2.5 g. of 3,4-dihydro-1,2-naphthalenedicarboxylic anhydride[5] and 1.4 g. of malonic acid (dried in an oven at 100° for 2 hr.) in 1.6 ml. of anhyd. pyridine was heated on a water bath at 100° for 3 hr. until evolution of CO_2 ceased. The reaction mixture was diluted with 20 ml. of H_2O, acidified with conc. HCl, and the deposited crystalline product was washed with H_2O and dried. Recrystallization from benzene gave 0.68 g. of III, m.p. 157~158°. The mother liquor of recrystallization was chromatographed on silica gel using $CHCl_3$ as eluent to give 0.08 g. of the second crops. Total yield was 0.76 g. (28%). *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.68; H, 5.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3455, 3350 (OH), 1752 (C=O).

2-Acetyl-1-naphthoic Acid (I)——a) From 1,2-naphthalenedicarboxylic anhydride: A mixture of 2.5 g. of 1,2-naphthalenedicarboxylic anhydride[5] and 1.9 g. of malonic acid in 1.6 ml. of anhyd. pyridine was treated according to the same procedure as described for III, giving 0.72 g. (27%) of I, m.p. 199~200° (lit.,[1] m.p. 198.5~199.5°). *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.76; H, 4.86. IR $\nu_{max}^{(CHCl_2)_2}$ cm^{-1}: 3509 (OH), 1751 (C=O).

b) From III: A mixture of 0.42 g. of III and 0.07 g. of S was heated in an oil bath at 240~250° for 1.5 hr., during which time vigorous evolution of H_2S was observed. After cooling, the reaction mixture was extracted with benzene, the benzene extract was reextracted with 10% KOH, and the alkaline solution was acidified with dil. H_2SO_4. The deposited product was washed with H_2O, dried and recrystallized from benzene, giving 0.17 g. of I, m.p. 199~200°, which was identified with a sample prepared in (a) by mixed melting point determination and comparison of IR spectrum.

2-(1-Hydroxyethyl)-1-naphthoic Acid γ-Lactone (II)——a) By reduction of I with $NaBH_4$: To a solution of 1.6 g. of $NaBH_4$ in 80 ml. of EtOH was added a solution of 3 g. of I in 100 ml. of EtOH, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with 700 ml. of H_2O, acidified with HCl and extracted with Et_2O. The Et_2O extract was washed with $NaHCO_3$ solution and H_2O, dried over anhyd. Na_2SO_4 and evaporated. Recrystallization of the residue from EtOH-H_2O gave 1.2 g. (58%) of II, m.p. 104~105°. *Anal.* Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.92; H, 5.07. IR: $\nu_{max}^{CHCl_3}$ 1742 cm^{-1} (C=O).

b) By reduction of I with HI: A solution of 0.5 g. of I, 16 ml. of AcOH and 6 ml. of 52% HI was refluxed for 3 hr. The reaction mixture was diluted with 100 ml. of H_2O and extracted with AcOEt. The AcOEt extract was washed successively with H_2O, satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was distilled under reduced pressure, giving 0.4 g. (87%) of II, $b.p_{0.08}$ 170° (bath), which solidified on standing. Recrystallization from EtOH-H_2O gave colorless needles, m.p. 104~105°, which was identical with a sample of II prepared in (a).

c) From ethyl 2-ethoxalyl-4-phenylbutyrate: To a cooled suspension of the crude ethyl 2-ethoxalyl-4-phenylbutyrate (prepared from 12.5 g. of ethyl 4-phenylbutyrate according to the method of Fieser and Hershberg[5]) in 20 ml. of H_2O was added 15 g. of 80% acetaldehyde and then 4.8 g. of K_2CO_3 under vigorous stirring below 15°, and stirring was continued at room temperature for 2 hr. After adding 7 ml. of conc. HCl, the reaction mixture was heated at 50° for further 15 min., cooled and extracted with Et_2O (20 ml. × 5). The Et_2O extract was washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. $MgSO_4$. Evaporation of the solvent left 9.5 g. of an orange-red oily material[6] (IR: $\nu_{max}^{CHCl_3}$ 1790 cm^{-1}), which was not purified further.

The crude oil (4.6 g.) obtained above was added to 20 ml. of conc. H_2SO_4 under ice-cooling and stirring, and stirring was continued at 50° for 2 hr. The dark red reaction mixture was poured onto 120 g. of cracked ice and extracted with AcOEt (15 ml. × 3). The AcOEt extract was washed with satd. $NaHCO_3$ and satd. NaCl solution, and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 0.2 g. of an oily material, which was not also purified further.

The crude oil (0.1 g.) obtained above was heated with 0.1 g. of 10% Pd-C at 260° for 2.5 hr. The reaction mixture was extracted with 10 ml. of Et_2O, the Et_2O extract was washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a pasty material, which was extracted with 5 ml. of hot petr. ether. On cooling for several hours, the petr. ether solution separated 5 mg. of colorless needles, m.p. 104~105°, whose IR spectrum was accorded with that of II prepared in (a) throughout the range.

Huang-Minlon Reduction of I——A mixture of 0.2 g. of I, 0.3 g. of KOH, 1.4 ml. of 70% hydrazine hydrate and 14 ml. of diethylene glycol was refluxed for 2 hr. Further 4 ml. of 70% hydrazine hydrate was added and refluxing was continued for an additional 4.5 hr. The reaction mixture was concentrated under reduced pressure to a volume of 2 ml., and 20 ml. of ice H_2O was added. The white precipitates were recrystallized from EtOH to give 0.2 g. (95%) of 4-methylbenzo[*h*]phthalazin-1(2*H*)-one, as colorless needles, m.p. 257~258°. *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.27; H, 4.79; N, 13.08. Found: C, 74.06; H, 4.72, N, 13.34. IR ν_{max}^{Nujol} cm^{-1}: 3140 (NH), 1637 (C=O).

*3 All melting points are uncorrected.

The authors express their thanks to Mr. I. Iijima for his technical assistance.

Summary

Doebner reaction of naphthalene- or 3,4-dihydro-1,2-naphthalenedicarboxylic anhydride with malonic acid in pyridine provided a convenient method for 2-acetyl-1-naphthoic- or 2-acetyl-3,4-dihydro-1-naphthoic acid. The structures of the products were also established.

(Received November 28, 1963)

[Chem. Pharm. Bull. 12 (4) 497 ~ 499]

UDC 547.495.9 : 547.491

Takeo Ueda, Kiyoshi Takahashi, and Sachiko Kobayashi : Reaction of 1,1-(2,2'-Oxydiethyl)biguanide with Dicyanodiamide.

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Melander[1] reported that 1,1-(2,2'-oxydiethyl)biguanide hydrochloride (ABOB) showed a protective *in vivo* effect on mouse-adapted influenza A (PR 8) and B (Lee 1). However, the re-examination[2] with this reagent have proved that ABOB did not show any antiviral activity on influenza viruses in both experimental and clinical investigations. These conflicting results suggested that the effect of ABOB might be due to by-products and admixtures, which were formed in the course of reactions for synthesis of ABOB. Namely, on the supposition that when either dicyanodiamide or morpholine hydrochloride was in excess, either of those reactants possibly further reacted with the product (ABOB), afforded by the reaction of dicyanodiamide with morpholine hydrochloride, the reactions of ABOB with dicyanodiamide and ABOB with morpholine hydrochloride were investigated.

This paper is concerned with the reaction of ABOB with dicyanodiamide and that of ABOB with morpholine hydrochloride.

Reaction of 1,1-(2,2'-Oxydiethyl)biguanide with Dicyanodiamide

Under the same conditions as the synthetic procedure of ABOB from dicyanodiamide and morpholine hydrochloride,[3] a mixture of equimolar amounts of ABOB and dicyanodiamide was heated for 6 hr. at 160~180° in an oil bath. The reaction mixture, once melted to fluid, gradually solidified as a viscous mass, evolving ammonia gas. After reacting, the fusion mixture was divided into two parts, alcohol-soluble and alcohol-insoluble, in approximately equal quantities. From the former, ABOB and dicyanodiamide were obtained, while from the latter, a compound shaped in colorless needles, m.p. 242~244.5° (I).

The elementary analysis of the compound (I) gave an empirical formula, $C_7H_{12}ON_6$.

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1) B. Melander : Toxicology and Applied Pharmacology, **2**, 474 (1960); B. Melander : Antibiotics and Chemotherapy, **10**, 34 (1960).
2) G. G. Jackson, R. L. Muldon, L. W. Akers, O. Liu, G. C. Jhonson, C. Engel : "Antimicrobial Agents and Chemotherapy", 883 (1961).
3) S. L. Shapiro, V. A. Parrino, L. Freedman : J. Am. Chem. Soc., **81**, 3728 (1959).