*Synthesis of 1, 2, 5-Trisubstituted Naphthalene Derivatives**

By Takeshi MATSUMOTO and Akira SUZUKI

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Since the elucidation of the structures of Garrya alkaloids by K. Wiesner[1], a number of alkaloids have been shown to be related to the tricyclic diterpenoid[2]. Lycoctonine[3] as well as luciclusculine[4], both of which have been studied in this laboratory under the leadership of Professor H. Suginome for the past several years, are supposed to belong also to this class. Mainly in this connection, the authors became interested in constructing model compounds with the 2-aza-perhydro-1, 4a-(propano)-phenanthrene ring system (I). In the present paper the authors describe the preparation of 2-methoxy-5-hydroxy-1-naphthylacetic acid (II) and of other suitably substituted 1, 2, 5-naphthalene derivatives, which appeared to be potentially useful building blocks for the synthesis of the above skeleton (I). At first, the synthesis of 1-hydroxymethyl-2-methoxy-5-hydroxynaphthalene (III), which would form the B, C ring of the hydrophenanthrene, was attempted.

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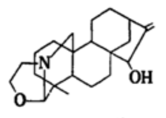
* Approaches to the Synthesis of Diterpenoid Alkaloid Models. I. Part II: T. Matsumoto and A. Suzuki, This Bulletin, **32**, 1283 (1959).

[1] K. Wiesner, *Experientia*, **11**, 255 (1955).

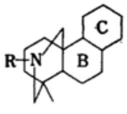
[2] For reviews, see E. S. Stern in "The Alkaloids", Vol. 4, Academic Press, New York (1954), p. 275; A. R. Pinder, "Annual Reports on the Progress of Chemistry", Vol. 52, The Chemical Society, London (1956), p. 253; G. F. Smith, ibid., Vol. 53, (1957), p. 248; idem., ibid., Vol. 54, (1958), p. 260.

[3] H. Suginome, S. Imato, Yamada and N. Katsui, This Bulletin, **32**, 819 (1959).

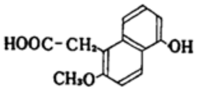
[4] T. Amiya, ibid., **30**, 667 (1957); H. Suginome, T. Amiya and T. Shima, ibid., **32**, 824 (1959)



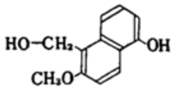
Garryine[1]



(I)

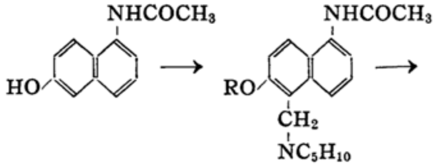


(II)

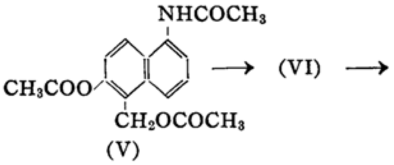


(III)

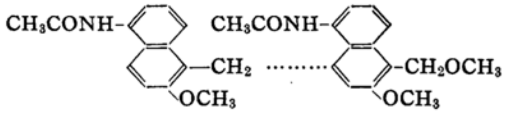
The starting material for this purpose was 1-acetoxymethyl-2-acetoxy-5-acetamidonaphthalene (V), which was prepared from 1-piperidino-methyl-5-acetamido-2-naphthol (IVa) by a slight modification of Cornforth and Robinson's method[5] from 5-acetamido-2-naphthol.



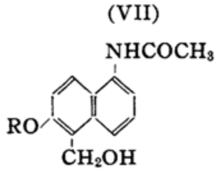
(IV) a, R=H
b, R=CH_3



(V)

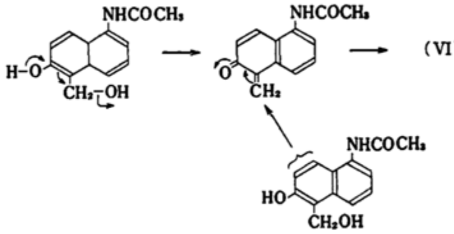


(VII)



(VIII) a, R=H
b, R=CH_3

Attempts to hydrolyze the triacetyl compound V with aqueous alkali however resulted in the formation of an amorphous product VI which could not be caused to crystallize by any means. After methylation with dimethyl sulfate a crystalline methyl derivative was obtained. The derivative was not, however, the expected compound VIIIb. The elemental analysis, determination of the methoxyl group, and measurement of molecular weight of the methyl derivative indicated that its formula corresponds to $C_{26}H_{21}N_2O_2(OMe)_3$. In addition, the compound exhibited infrared absorption in nujol at 3280 (N-H), 1645 (amide I), 1510 (amide II), 1275 (aryl ether), 1100 (alkyl ether), 800 (three adjacent H), 805 cm^{-1} (three adjacent H)[6]. On these grounds formula VII is proposed as a likely structure for this compound, the point of attachment (dotted line) of disubstituted naphthylmethyl moiety however being uncertain. Fromation of this coupled product may be interpreted as follows:



Reaction behaviors of certain phenolic Mannich bases have already been explained in a similar manner[7]. According to the above view, the formation of the coupled product should be controlled through replacement of the phenolic hydroxyl by a methoxyl group. 1-Piperidinomethyl-5-acetamido-2-naphthol methyl ether (IVb), which would form a methoxyl derivative (VIIIb) through acetolysis and hydrolysis, however could not be obtained by treatment of IVa with diazomethane, probably because compound IVa exists almost completely as a zwitter ion. The

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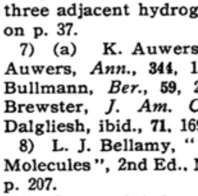
[5] J. W. Cornforth, O. Kauder, J. E. Pike and R. Robinson, *J. Chem. Soc.*, **1955**, 3348.

[6] The absorption bands at 800 and 805 cm^{-1} suggest the presence of two naphthalene rings which contain three adjacent hydrogen atoms, respectively. See *Note* on p. 37.

[7] (a) K. Auwers, *Ber.*, **36**, 1878 (1903). (b) K. Auwers, *Ann.*, **344**, 131 (1906). (c) K. Auwers and P. Bullmann, *Ber.*, **59**, 2719 (1926); H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948); C. E. Dalgliesh, ibid., **71**, 1697 (1949).

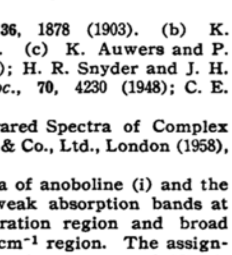
[8] L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed., Methuen & Co., Ltd., London (1958), p. 207.

[9] Reported infrared spectra of anoboline (i) and the compound (ii) exhibit very weak absorption bands at N-H and O-H stretching vibration region and broad absorption band at 2260∼2800 cm^{-1} region. The assignment of 3440 and 3400 cm^{-1} bands of compoud IVa is however not conclusive. One of them might be responsible for the hydroxyl group.



(i)

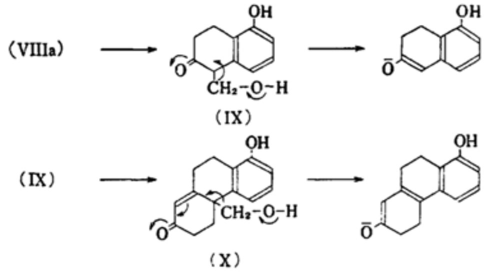
R. A. Heacock and Léo Marion, *Can. J. Chem.*, **34**, 1782 (1956).



(ii)

H. Pflieninger and H. Kasiwagi, *Ber.*, **88**, 550 (1955).

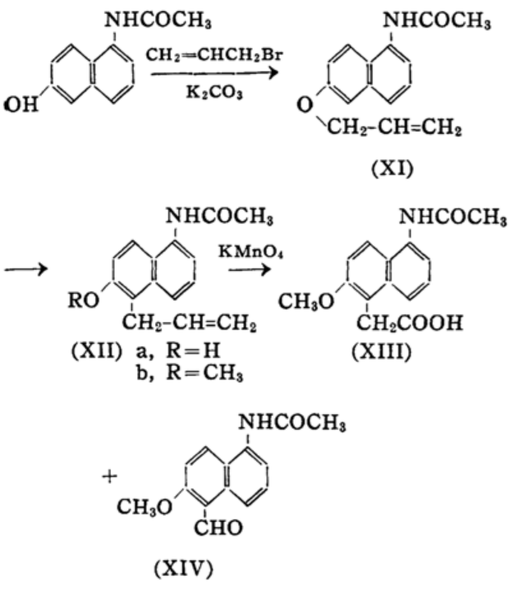
dipolar character seems to be reflected by the infrared absorption of IVa.

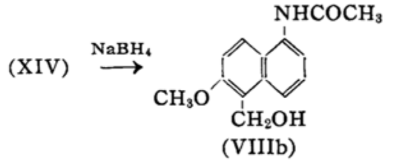


The compound in chloroform exhibited twin secondary amide N-H absorption bands[8] at 3400 and 3440 cm^{-1}, a broad weak band extending from 2260 to 2800 cm^{-1}, and no absorption band characteristic of the hydroxyl group[9].

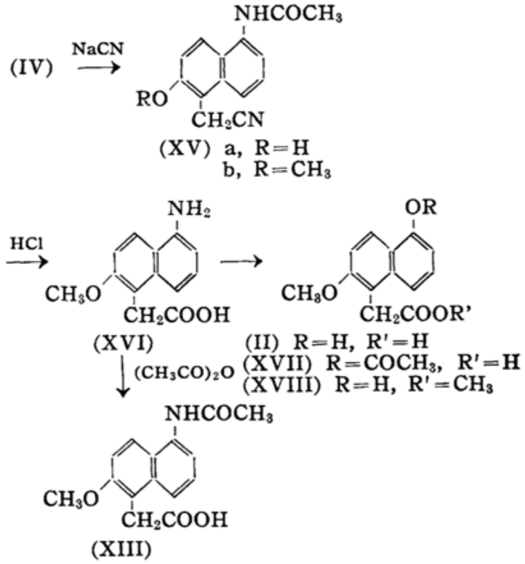
Since the first attempt to synthesize 1-hydroxymethyl-2-methoxy-5-naphthol was thus unsuccessful, and moreover, since it was felt that hydronaphthalene (IX) or hydrophenanthrene (X) derived from the naphthol might be likely to undergo carbon-carbon bond cleavage at a certain later stage as illustrated above, the present authors abandoned attempts to find conditions to effect conversion V→VIIIa and turned attention to the preparation of 2-methoxy-5-hydroxy-1-naphthylacetic acid (II) which contains two, rather than one, side chain carbon atoms. Introduction of the carboxymethyl group to naphthalene nucleus has been achieved by two methods. Steps involved are summarized as follows:

Method A





Method B



Of these, method B gave an excellent result.

The reaction of 5-acetamido-2-naphthol with allyl bromide in boiling acetone afforded the allyl ether (XI) in quantitative yield. The latter compound, on being heated in an atmosphere of nitrogen for an hour at 185~195°C, was converted into 1-allyl-5-acetamido-2-naphthol (XIIa) in a yield of 99.5%. The methylation of XIIa with dimethyl sulfate in the presence of alkali proceeded without difficulty (yield, 81.7%). For the formation of naphthylacetic acid, the methyl ether (XIIb) was then treated with potassium permanganate. Oxidation at room temperature resulted in the formation of a difficultly separable mixture, but at below −10°C in ethanol, even though in a yield of 13%, the desired acid (XIII) was obtained along with a non-acidic product (20%). The latter compound was characterized as 2-methoxy-5-acetamido-1-naphthaldehyde (XIV) on the basis of elemental and infrared spectral analyses. The aldehyde was smoothly reduced in a good yield (94%) to the corresponding alcohol (VIIIb) by the use of sodium borohydride. Two promising intermediates, XIII and VIIIb, have thus been obtained. However, for the present purpose, the yield of the oxidation stage

TABLE I

Substituents	1650~1500 cm^{-1}	900~700 cm^{-1}
1-NHAc 5-Allyl 6-OH (XIIa)	a) 1630 (s) 1617 (s) c) 1602 (m) 1580 (m) b) 1533 (s) 1512 (s)	905 (s) 890 (w) 830 (m) 802 (s) 773 (s) 750 (s)
1-NHAc 5-Allyl 6-OMe (XIIb)	a) 1645 (s) 1620 (s) 1598 (m) c) 1585 (w) b) 1540 (s) 1505 (s)	895 (w) 874 (w) 840 (w) 798 (s) 755 (m) 735 (s)
1-NHAc 5-CH_2CO_2H 6-OMe (XIII)	a) 1642 (s) 1620 (m) 1598 (w) c) 1580 (w) b) 1545 (s) 1507 (s)	890 (w) 875 (w) 840 (w) 795 (s) 760 (m) 725 (m)
1-NHAc 5-CHO 6-OMe (XIV)	a) 1650 (s) 1620 (m) 1600 (w) c) 1570 (w) b) 1540 (m) 1510 (m)	890 (w) 845 (w) 820 (m) 800 (s) 755 (s) 720 (s)
1-NHAc 5-CH_2OH 6-OMe (VIIIb)	a) 1645 (s) 1620 (m) 1597 (w) 1590 (w) b) 1545 (m) 1507 (s)	875 (m) 845 (w) 810 (w) 792 (s) 753 (s) 720 (s)
1-NHAc 5-Pr^n 6-OMe	a) 1640 (s) 1620 (m) 1595 (w) 1580 (w) b) 1532 (m) 1508 (s)	890 (w) 880 (w) 850 (w) 837 (w) 812 (w) 795 (s) 750 (m) 720 (m)
1-NHAc 5-$CH_2\underset{Br}{\underset{\mid}{CH}}\underset{Br}{\underset{\mid}{CH_2}}$ 6-OMe	a) 1640 (s) 1620 (m) 1595 (w) 1580 (w) b) 1540 (m) 1510 (s)	890 (w) 870 (w) 842 (w) 825 (m) 815 (m) 796 (s) 755 (s) 720 (m)
1-NHAc 5-CH_2OAc 6-OAc (V)	a) 1648 (s) 1624 (m) 1602 (w) 1590 (w) b) 1565 (s) 1510 (m)	900 (m) 890 (w) 873 (w) 855 (w) 844 (w) 820 (w) 800 (s) 765 (s) 725 (s)
1-NHAc 5-CH_3 6-OH	c) 1635 (m) 1620 (s) c) 1610 (m) 1584 (w) c) 1545 (s) b) 1535 (s) 1510 (s)	900 (w) 865 (w) 850 (w) 820 (m) 800 (s) 755 (m) 720 (m)
1-NHAc 5-$CH_2NC_5H_{10}$ 6-OH (IVa)	a) 1640 (s) 1617 (s) c) 1600 (w) 1582 (w) b) 1545 (s) 1512 (s)	895 (w) 879 (w) 870 (w) 858 (w) 843 (w) 818 (s) 796 (s) 783 (s) 745 (s) 720 (w) 707 (w)
1-$N(CH_3)Ac$ 5-CH_2CN 6-OMe	a) 1647 (s) 1617 (s) 1595 (m) 1580 (m) 1510 (m)	900 (w) 862 (m) 830 (m) 805 (s) 790 (m) 757 (m) 723 (w)
1-NHAc 5-CH_2CN 6-OH (XVa)	a) 1650 (s) 1620 (s) 1600 (m) 1587 (m) b) 1530 (m) 1508 (s)	910 (m) 890 (m) 860 (w) 855 (w) 830 (m) 805 (s) 755 (s) 725 (m)
1-NHAc 5-CH_2CN 6-OMe (XVb)	a) 1645 (s) 1623 (m) 1600 (w) 1580 (w) b) 1545 (m) 1510 (s)	910 (m) 890 (m) 860 (w) 835 (m) 815 (m) 800 (s) 755 (s) 725 (m)

1-OH 5-CH_2CO_2H 6-OMe (II)	1625 1600 1582 1520 (m) (m) (m) (m)	875 837 825 805 755 735 723 (w) (m) (m) (s) (m) (m) (m)
1-OAc 5-CH_2CO_2H 6-OMe (XVII)	1625 1600 1580 1515 (m) (m) (w) (m)	900 870 835 818 805 760 735 720 (m) (m) (w) (m) (s) (m) (m) (m)
1-OH 5-CH_2CO_2Me 6-OMe (XVIII)	1625 1595 1580 1520 (m) (m) (m) (m)	876 865 837 820 800 760 725 (w) (w) (m) (w) (s) (m) (m)

TABLE II

Substituents	1650~1500 cm^{-1}	900~700 cm^{-1}
1-OH	1630 1597 1580 1515 (m) (s) (s) (m)	876 862 790 765 (m) (m) (s) (s)
2-OH	1629 1600 1586 1521 (s) (s) (m) (s)	903 875 843 813 765 740 (m) (m) (s) (s) (w) (s)
1-OH 6-OH	1630 1605 1585 1515 (m) (m) (s) (m)	872 855 848 832 818 780 747 (m) (s) (s) (m) (m) (s) (s)
1-NHAc 6-OH	a) 1625 1600 c) 1590 b) 1540 1510 (s) (m) (w) (s) (s)	862 852 822 790 770 750 (s) (s) (m) (m) (s) (s)
1-NHAc 6-O-Allyl (XI)	a) 1645 c) 1630 1602 c) 1590 b) 1550 1507 (s) (s) (w) (w) (s) (m)	890 860 835 826 790 767 750 725 (w) (m) (m) (s) (w) (m) (m) (m)

a) amide I b) amide II c) shoulder

was too low. Therefore, plans were again changed and exploration was made of an alternative route, method B.

On treatment of IV with sodium cyanide in aqueous ethanol for 12 hr. under reflux, 1-cyanomethyl-5-acetamido-2-naphthol was obtained in almost quantitative yield[10].

Methylation of XVa to XVb (yield, 93%) by dimethyl sulfate in sodium hydroxide solution, followed by hydrolysis with hydrochloric acid in aqueous ethanol afforded the amino acid hydrochloride (XVI·HCl). In this case, when an excess of dimethyl sulfate and of alkali was used, 1-cyanomethyl-2-methoxy-5-(*N*-methyl)-acetamidonaphthalene was formed as a by-product. The reaction of the amino acid (XVI) with acetic anhydride gave 2-methoxy-5-acetamido-1-naphthylacetic acid, which should be identical with compound XIII obtained by method A. The identity of these products was proved by melting and mixed melting point determinations. Finally, the amino acid hydrochloride (XVI·HCl) was treated under Bucherer conditions. The expected product, 2-methoxy-5-hydroxy-1-naphthylacetic acid (II) was obtained in a 91% yield.

A Note on the Infrared Spectra of 1, 2, 5-Trisubstituted Naphthalenes

In the course of the above work, infrared spectra of all the prepared 1,2,5-trisubstituted naphthalenes have been measured. Data on absorption bands at 1650~1500 cm^{-1} (skeletal vibration) and at 900~700 cm^{-1} (C–H out-of-plane vibration) are presented in Table I.

It can be seen that all the 1,2,5-trisubstituted naphthalenes so far examined show a fairly strong band within a narrow frequency range of 800±8 cm^{-1}. This band may be attributed to the presence of three

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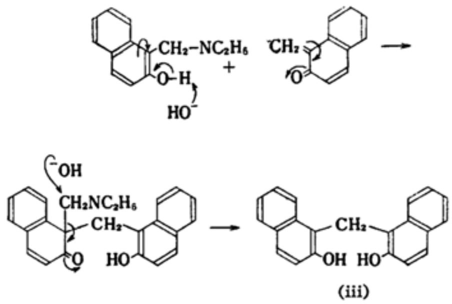
[10] In the reaction of 1-dimethylaminomethyl-2-naphthol with sodium cyanide the diarylmethane (iii) is formed at least in 20% yield [J. Brewster, "Organic Reactions", Vol. VII, John Wiley & Sons, Inc., New York (1953), p. 109] clearly through the process outlined below. It is interesting that in the present case, no dinaphthylmethane was produced, although its formation was expected.



aromatic vicinal hydrogen atoms in these compounds. It is to be expected that these compounds exhibit also a band at 860～800 cm^{-1} (two vicinal hydrogen atoms), but this latter band is obscured owing to the complexity at this region.

In the range of 1650～1500 cm^{-1} the naphthalene derivatives listed above show in common *four* bands. It has been stated[11] that aromatic compounds, in general, exhibit *three* absorption bands in this range[12]. The results given in Table I indicate that the examined naphthalene derivatives present two strong bands at ca. 1620 and ca. 1510 cm^{-1} and two subsidary absorption bands between these wave numbers. Scope and limitation of this generalization are not yet clear. However, it may be mentioned at this point that a number of, of course if not all, naphthalene derivatives except these with electronegative nitro and halogen substituents, exhibit the characteristic four absorption bands between 1650～1500 cm^{-1}. Naphthalene itself[13], 1-naphthol[14], 2-naphthol[14], 1,6-dihydroxynaphtalene[14], 1-acetamido-6-hydroxynaphthalene[14] and 1-acetamido-6-allyloxy naphthalene[14] present the above feature. The following naphthalenes, spectra of which appear in the API[15] and DMS[16] cards, fall also in this category (kind and position of substituents, and serial number[17] are given):

1-methyl (762), 2-methyl (763) (1530cm^{-1}: weak), 1-ethyl (764), 2-ethyl*,[18] (765), 1,3-dimethyl* (767), 1,5-dimethyl* (769), 1,6-dimethyl* (770), 2,3-dimethyl* (773), 2,7-dimethyl* (775), 2-*n*-propyl* (777), 1-*n*-buthyl (778), 2-*n*-buthyl* (779), 1-*n*-amyl (780), 2-*n*-amyl* (781), 2-methoxy (*1766*), di-1-naphthylmethane (*2777*), 1-cyanoethyl-2-hydroxy (*2640*), di-1-naphthylketone (*2527*) (1621 cm^{-1}: sh), 1-benzyl (*2287*) (an extra band at the 1500 cm^{-1} region; attributable to phenyl vibration?), 2-benzyl* (*2288*) (an extra band like 1-isomer), di-2-naphthylketone (*2528*) (1515 cm^{-1}: weak).

In the following compounds the subsidary absorption band- or bands- are obscure:

1,4-dimethyl (768), 1,7-dimethyl* (771), 1,8-dimethyl (772), 2,6-dimethyl* (774), 1-*n*-propyl (776), 2,4-dimethyl* (1209).

Experimental[19]

1-Piperidinomethyl-5-acetamido-2-naphthol (IVa).—The procedure of Cornforth and Robinson[5] was slightly modified as follows: Formaldehyde (16.5 ml., 37% solution) was added to a mixture of piperidine (22.5 ml.) 5-acetamido-2-naphthol (37.5 g.) and ethanol (350 ml.). After being kept at room temperature for three days, the crude product, which separated, was collected, washed with a small amount of ethanol and dried. A yield of 88% (49 g.) of piperidino-base was obtained. Recrystallization from isoamyl alcohol gave colorless plates, m. p. 198～199°C. *o-Methylation* of the piperidino-base was attempted by the addition of ethereal solution of excess diazomethane to the base dissolved in chloroform. No generation of nitrogen was observed. On removal of volatile substances after 24 hr., the piperidino-base was recovered in an almost quantitative yield.

1-Acetoxymethyl-2-acetoxy-5-acetamidonaphthalene (V).—A mixture of the piperidino-base (IVa) (20 g.) and acetic anhydride (160 cc.) was heated on a steam bath for 3 hr. After addition of water during warming until the solution became clear, the solution was extracted three times with chloroform. The extract was then washed successively with 5% sodium bicarbonate and water, dried and the chloroform removed. The residue was crystallized on being triturated with ether. Recrystallization from ethanol-water gave colorless clustered prisms, m. p. 170～171°C (5.2 g., 24.6%).

Hydrolysis of V.—A suspension of 2 g. of V in 20 ml. of 5% aqueous potassium hydroxide was heated at 100°C for several minutes, and then a homogeneous solution was obtained. The solution was then cooled to 0°C and acidified to pH 2 with 6 N hydrochloric acid; an amorphous solid (1.4 g.), which separated, was collected. Methylation was effected as follows: A mixture of the above amorphous solid, sodium hydroxide (0.3 g.) and water (4.2 ml.) was shaken with dimethyl sulfate (0.66 cc.) for half an hour. Additional amount of sodium hydroxide and dimethyl sulfate was then added and shaking continued for a further half hour. The excess of dimethyl sulfate was

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[11] L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen & Co., Ltd., London (1958), p. 69—79.

[12] Since the measurement presented in the table was taken by the nujol mull method, the fourth aromatic skeletal absorption at ca. 1450 cm^{-1} was not taken into account.

[13] R. N. Jones and C. Sandorfy, "Chemical Applications of Spectroscopy", Interscience Publishers, Inc., New York (1956), p. 401.

[14] See Table II.

[15] American Petroleum Institute Research Project 44, Infrared Spectral Data (1943—1958), Carnegie Institue of Technology, Pittsburgh 13, Pa., U. S. A.

[16] Documentation of Molecular Spectroscopy, Butterworths Scientific Publications, London (1956—1958).

[17] Serial numbers of the DMS cards are given in italics.

[18] In the compounds marked with an asterisk, absorption band at the highest frequency (ca. 1620 cm^{-1}) splits into two bands of comparable intensity. It may be noted that most of these compounds possess a 2-alkyl group.

[19] All melting points are uncorrected. Infrared spectra were taken on a Koken model DS-301 infrared spectrophotometer. The authors wish to thank Mr. O. Yonemitsu of the Pharmaceutical Institute of Hokkaido University for the spectral data and Miss N. Fujino for the microanalyses.

destroyed by gentle heating on a steam bath. Crude methoxyl compound, which separated, amounted to 1.34 g. The product was then dissolved in tetrahydrofuran and chromatographed on alumina (ca. 30 g.). A portion eluted with ethanol was crystallized. For analysis a sample was recrystallized from ethanol; m. p. 285°C (decomp.), colorless small needles.

Anal. Found: C, 71.01; H, 6.33; OCH_3, 19.07; mol. wt. (Rast), 443.5. Calcd. for $C_{26}H_{21}O_2N_2(OCH_3)_3$: C, 71.58; H, 6.22; OCH_3, 19.13%; mol. wt., 486.6.

5-Acetamido-2-naphthyl Allyl Ether XI. — 5-Acetamido-2-naphthol was converted into allyl ether by heating a mixture of the material (20g.) with allyl bromide (14.4 g.), finely powdered potassium carbonate (28 g.) and purified acetone (600 ml.) for 12 hr. on a steam bath with mechanical stirring. After evaporation of the solvent, the residue was diluted with water and the precipitated allyl ether (24 g., 100%) was collected; m. p. 130~132°C. A portion, recrystallized from aqueous ethanol, gave a pure specimen of XI as colorless needles, m. p. 136°C.

Anal. Found: C, 74.96; H, 6.31. Calcd. for $C_{15}H_{16}O_2N$: C, 74.66; H, 6.27%.

1-Allyl-5-acetamido-2-naphthol (XIIa).—The crude ether (XI) (18 g.) was heated in an atmosphere of nitrogen for 1 hr. in an oil bath maintained at 185~195°C. The reaction product was then completely dissolved in 10% sodium hydroxide (360 cc.), and the solution was acidified with 6 N hydrochloric acid, the product (17.5 g., 99.5%) being precipitated. Recrystallization from aqueous ethanol gave the naphthol (XIIa) as colorless needles, m. p. 176~177°C.

Anal. Found: C, 74.53; H, 6.35. Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27%.

1-Allyl-2-methoxy-5-acetamidonaphthalene(XIIb). —A mixture of XIIa (4.4 g.), dimethyl sulfate (4 g.) and aqueous 10% sodium hydroxide (14.5 ml.) was shaken for 0.5 hr., and the precipitated product was filtered, washed with water and dried; yield, 3.8 g. (81.7%). The crude methyl ether was recrystallized from aqueous ethanol as colorless needles, m. p. 147~147.5°C.

Anal. Found: C, 75.09; H, 6.85. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71%.

1-(2,3-Dibromopropyl)-2-methoxy-5-acetamidonaphthalene.—To a solution of the methyl ether (XIIb) (0.5 g) in 6 ml. of chloroform, 0.31 g. of bromine dissolved in 4 ml. of chloroform was added drop by drop with shaking. After standing for 1 hr. at room temperature, the solvent was evaporated. The thick sirupy residue solidified upon scratching and was purified by recrystallization from aqueous ethanol; colorless needles, m. p. 168.5~170°C.

Anal. Found: C, 45.87; H, 4.41. Calcd. for $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13%.

Dihydro Derivative of XIIb.—Another portion of XIIb (0.8 g.) in ethyl acetate (35 ml.) was hydrogenated over 10% palladized charcoal (0.2 g.). Uptake of hydrogen was completed after about 3 hr. The solution was filtered from the catalyst which was washed with ethyl acetate. The solvent was removed from the combined filtrate and washings under reduced pressure. *1-Propyl-2-methoxy-5-acetamidonaphthalene* was obtained from aqueous ethanol as colorless needles, m. p. 151.5~152.5°C.

Anal. Found: C, 74.20; H, 7.71. Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44%.

Oxidation of XIIb with Potassium Permanganate.—The methyl ether (XIIb) (5 g.) dissolved in 300 ml. of 95% ethanol and potassium carbonate (1.25 g.) in 12.5 ml. of water were placed in a flask surrounded with an ice-salt bath. A solution of potassium permanganate (10 g.) in 240 ml. of water was then run into the flask at such a rate that the temperature did not rise above −10°C with constant stirring. After the completion of the oxidation, manganese dioxide was filtered off and washed with hot ethanol. The filtrate and washings are combined, the whole was concentrated to about 130 ml., and the residue was extracted three times with chloroform. The combined chloroform extracts were then washed with water, dried and evaporated. A neutral product, *2-methoxy-5-acetamido-1-naphthaldehyde (XIV)* was obtained; yield, 1 g. (20%). A pure sample was obtained on recrystallization from ethanol as pale yellow needles and had an m. p. 232~233°C, $\nu_{\max}^{\text{nujol}}$ 3265 (N–H), 1668 (CHO) and 1655 cm^{-1} (NHCO).

Anal. Found: C, 69.18; H, 5.63. Calcd. for $C_{14}H_{14}O_3N$: C, 69.12; H, 5.39%.

To the above aqueous alkaline solution, separated from the chloroform layer, concentrated hydrochloric acid was added in excess to precipitate acidic products; the crude acid was collected (0.5 g.). The filtrate was extracted three times with chloroform, the extracts were combined, dried and evaporated. An additional amount (0.2 g.) of the above acid was obtained. Recrystallization from ethanol gave *2-methoxy-5-acetamido-1-naphthylacetic acid (XIII)* as colorless needles, m. p. 245°C.

Anal. Found: C, 65.80; H, 5.84. Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53%.

1-Hydroxymethyl-2-methoxy-5-acetamidonaphthalene (VIIIb).—The aldehyde (XIV) (190 mg.) was dissolved in 5 ml. of methanol containing a small amount of sodium methoxide and the solution was cooled to produce a fine suspension. On addition of sodium borohydride, the aldehyde dissolved, crystallization of the reduction product began after several minutes, and was completed after 12 hr. The product was collected, washed with water and dried. Removal of the solvent from the filtrate gave further a small quantity of the hydroxymethyl compound. The product weighed 172 mg. (94%) and was purified by recrystallization from ethanol, m. p. 214~215°C.

Anal. Found: C, 68.41; H, 6.37. Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16%.

1-Cyanomethyl-5-acetamido-2-naphthol (XVa).—A mixture of the piperidino-bass (IV) (9 g.), sodium cyanide (15 g.), ethanol (220 ml.) and water (30 ml.) was refluxed for 12 hr. Water was then added to the reaction mixture, and the solution was concentrated under reduced pressure to expel ethanol, and acidified with concentrated hydrochloric acid. The solid (7.2 g., 99.5%) which separated was filtered. For analysis a sample was recrystallized from ethanol; m. p. 239°C (decomp.), $\nu_{\max}^{\text{nujol}}$ 3350 (OH), 3210 (N—H), 2240 (C≡N), and 1660 cm^{-1} (NHCO).

Anal. Found: C, 69.54; H, 5.17; N, 11.57. Calcd. for $C_{14}H_{12}O_2N_2$: C, 69.95; H, 5.03; N, 11.66%.

1-Cyanomethyl-2-methoxy-5-acetamidonaphthalene (XVb).—The above naphthol (XVa) (6 g.) in aqueous 10% sodium hydroxide (12.5 ml.) was shaken with dimethyl sulfate (3 ml.) for 1 hr., and the reaction mixture was allowed to stand overnight. The methyl ether, which separated, was collected; yield, 5.9 g. (93%); m. p. 211~215°C. Upon recrystallization from ethanol, it formed colorless small needles, m. p. 226~227°C, $\nu_{\max}^{\text{nujol}}$ 3270 (NH), 2240 (C≡N), and 1660 cm^{-1} (NHCO).

Anal. Found: C, 70.70; H, 5.73. Calcd, for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.55%.

When a large excess of dimethyl sulfate and of alkali was used, *1-cyanomethyl-2-methoxy-5-(N-methyl)-acetamidonaphthalene* was obtained. Recrystallization from ethanol gave colorless prisms, m. p. 172~173.5°C, $\nu_{\max}^{\text{nujol}}$ 2240 (C≡N) and 1660 cm^{-1} (NHCO); no appreciable band in the N-H stretching vibration region.

Anal. Found: C, 71.58; H, 6.32; N, 10.32. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44%.

Hydrolysis of XVb to 2-Methoxy-5-amino-1-naphthylacetic Acid (XVI).—A mixture consisting of XVb (1.5 g.), ethanol (7.5 ml.), water (5 ml.) and concentrated hydrochloric acid (20 ml.) was refluxed on a steam bath for 5 hr. and was then cooled well with ice. The precipitates were filtered and dried. A yield of 1.52 g. of the amino acid (XVI)·HCl with m. p. 253°C (decomp.) was obtained. The acetate of compound XVI was prepared through the addition of 10% sodium hydroxide solution and acetic anhydride to the aqueous solution of XVI · HCl. The pure sample of the acetate formed colorless needles, m. p. 245°C. No depression in the melting point was observed on admixture of XIII.

2-Methoxy-5-hydroxy-1-naphthylacetic Acid (II).—A mixture of the amino acid (XVI) hydrochloride (1.5 g.) and 40% sodium bisulfite solution (85 ml.) in a three-necked flask provided with a reflux condenser and mechanical stirrer, was heated at 95~100°C for 20 hr. At the end of this time 60% aqueous sodium hydroxide (30ml.) was slowly added to the boiling solution with vigorous stirring and the mixture was heated under slightly reduced pressure until the evolution of ammonia had ceased (ca. 3 hr.). After cooling, concentrated hydrochloric acid (85 ml.) was added drop by drop to expel sulfur dioxide and the mixture was heated on a steam bath for 1 hr. The solution was allowed to stand overnight. The crude naphthol (II) (1.23 g., 91%), which separated, was recrystallized from glacial acetic acid as small colorless prisms, m. p. 229~230°C (decomp.), $\nu_{\max}^{\text{nujol}}$ 3200~3400 (OH), 1710 (CO_2H) and 1687 cm^{-1} (CO_2H)[20].

Anal. Found: C, 67.04; H, 5.32. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

The methyl ester (XVIII) was prepared as follows: Fifty milligrams of II was dissolved in 2.5 ml. of 5% methanolic hydrogen chloride. The solution was kept at room temperature. After 48 hr., water and ethyl acetate were added. The ethyl acetate layer was washed with sodium bicarbonate solution, dried and evaporated. The crystalline residue (50 mg., 94.4%), m. p. 150~153°C, was recrystallized from benzene to give a pure sample, m. p. 155.5~156.5°C, $\nu_{\max}^{\text{nujol}}$ 3400 (OH) and 1720 cm^{-1} (ester).

Anal. Found: C, 68.15; H, 5.95. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

2-Methoxy-5-acetoxy-1-naphthylacetic Acid (XVII).—The above hydroxy acid (II) (920 mg.) was dissolved in a mixture of anhydrous pyridine (10 ml.) and acetic anhydride (4.5 ml.). After being kept at room temperature overnight, the reaction mixture was concentrated to dryness in vacuo, and the residue was washed with water and dried. Crude acetate (1.02 g., 94%) with m. p. 180~183°C was obtained. The sample for analysis was prepared by recrysallization from benzene; it had m. p. 185.5~186.5°C, $\nu_{\max}^{\text{nujol}}$ 1755 (phenolic acetate CO), 1200 (phenolic acetate), 1716[20] (carboxyl group) and 1685 cm^{-1} (carboxyl group).

Anal. Found: C, 65.31; H, 5.25. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15%.

Summary

A synthesis of 2-methoxy-5-hydroxy-1-naphthylacetic acid has been described.

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[20] It is interesting to note that both acids, II and XVII, exhibit in nujol two carbonyl bands of comparable strength. Two examples of the similar splitting of carboxyl carbonyl band have been reported in the literature (M. St. C. Flett, *J. Chem. Soc.*, **1951**, 962). This abnormal absorption is probably due to the hydrogen bond of the carboxyl group in the solid state, since i) both the acids exhibit a single absorption in dioxane solution at 1715 cm^{-1} and ii) the abnormal absorption band disappears in the methyl ester (XVIII) of II.