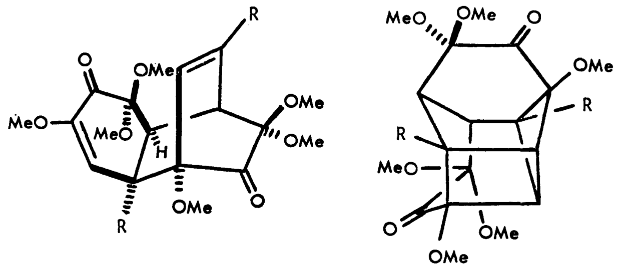
Acid-catalyzed Rearrangements of Tetrahydroasatone and Tetrahydroisoasatone

Shosuke YAMAMURA and Yukimasa TERADA
Faculty of Pharmacy, Meijo University, Showa-ku, Nagoya 468
(Received March 2, 1976)

Tetrahydroasatone (**3**) and tetrahydroisoasatone (**4**) both are pretty unstable to various kinds of acid. Action of 6M·HCl–AcOH on the former converted it to the naphthalene-type compound (**5**) in high yield, whose structure was determined on the basis of its spectral data. In the case of tetrahydroisoasatone, twofold Wagner-Meerwein rearrangements take place, leading to the formation of the isomer-A (**9**), further rearrangements of which give rise to the bisnordiadamantane-type isomer-B (**10a**).

In the previous paper.[1] We reported the isolation and structures of two novel neolignans, asatone (**1**) and isoasatone (**2**). From a structural point of view, the former has a bicyclo[2.2.2]oct-5-en-2-one system as a part of the structure (**1**). In the case of isoasatone (**2**), it has a highly strained bicyclo[2.2.0]hexane system. Both of them are pretty unstable to various kinds of acid. In this paper, we wish to describe some interesting acid-catalyzed rearrangements of tetrahydroasatone (**3**) and tetrahydroisoasatone (**4**), both of which have been already produced on catalytic hydrogenation from **1** and **2**, respectively. Particularly, the structures of the reaction products are discussed in detail.



1 R=$CH_2CH{=}CH_2$　　**2** R=$CH_2CH{=}CH_2$
3 R=*n*-Pr　　**4** R=*n*-Pr

Fig. 1.

As described above, asatone (**1**) and tetrahydroasatone (**3**) both are unstable in acidic solution, and many spots are found on an analytical TLC plate. However, when treated with 6 M·HCl–AcOH under vigorous conditions (100 °C, 1.5 h), tetrahydroasatone was converted in high yield (*ca.* 85%) into the yellow substance with a molecular formula (mp 181—182 °C; $C_{20}H_{22}O_5$), the structure (**5**) of which was elucidated on the basis of its spectral data (see Table 1), as follows.

The IR and UV spectra of this compound (**5**) suggest that it has a highly substituted naphthalene chromophore [ν_{max} 1605, 1570, and 1525 cm^{-1}: λ_{max} 415, 329, 289, and 226 nm]. This is also confirmed by the ^{13}C NMR spectral data of **5** [δ 99.42 (d) and 113.70 (s)—150.71 (s) ppm].[2]

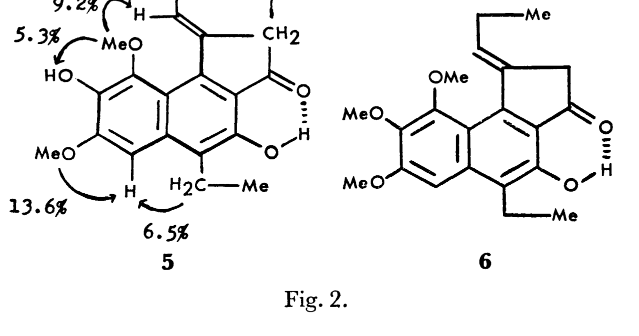
This yellow substance (**5**) has two MeO groups (δ 3.60 and 4.00 ppm) in addition to two OH groups [ν_{max} 3400 br.cm^{-1}: δ 5.93 and 9.53 ppm], one of which has been readily converted into a MeO group on treatment of **5** with diazomethane in ether leading to the formation of the corresponding monomethyl ether (**6**), mp 138—139 °C; $C_{21}H_{24}O_5$; ν_{max} 3200 cm^{-1}; δ 3.72 (3H, s), 4.02 (3H, s) and 4.03 (3H, s) ppm. Of five oxygen atoms in **5**, the remaining one should be included in the CO group ν_{max} 1640 (s)cm^{-1}; δ 206.55 ppm], the IR absorption band of which is shifted to 1665 cm^{-1} in the case of **6**. Furthermore, it is noted that **5** is proved to have two partial structures [A and B] on the basis of its ^{1}H and ^{13}C NMR spectral data [A: δ 1.20, 2.96, 13.87, and 24.51 ppm; B: δ 1.09, 2.24, 3.30, 6.76, 13.55, 17.85, 40.17, 134.68, and 113.70—150.71 ppm[2]].

CH_3CH_2-C=　　CH_3CH_2CH=C-CH_2-C-
[A]　　[B]

Finally, in the light of the structure of **3** consisting of two C_6-C_3 units, the structure of the yellow substance

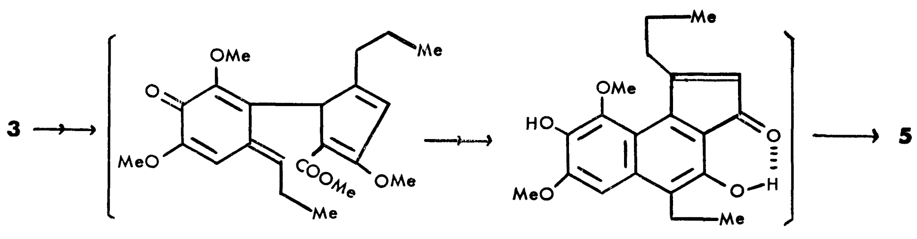
Table 1. The spectral data of the yellow substance

ν_{max}(Nujol)	3400br., 1640, 1605, 1570, and 1525 cm^{-1}
λ_{max}(MeOH)	415, 329, 289, and 226 nm (ε 5000, 11000, 28000, and 20000, respectively)
^{13}C NMR ($CDCl_3$)	13.55(q), 13.87(q), 17.85(t), 24.51(t), 40.17(t), 55.91(q), 61.11(q), 99.42(d), 113.70(s), 122.63(s), 122.88(s), 129.93 (s), 134.16(s), 134.68(d), 137.16(s), 142.19(s), 146.17(s), 148.85(s), 150.71 (s) and 206.55(s) ppm
^{1}H NMR ($CDCl_3$)	1.09(3H, t, J=7.0 Hz), 1.20(3H, t, J=7.8 Hz), 2.24(2H, quintet, J=7.0 Hz), 2.96 (2H, q, J=7.8 Hz), 3.30 (2H, d, J=1.7 Hz), 3.60(3H, s), 4.00(3H, s), 5.93(1H, s, OH), 6.76(1H, br.t, J=7.0 Hz), 6.95(1H, s) and 9.53(1H, s, OH) ppm



5　　**6**

Fig. 2.



7 8

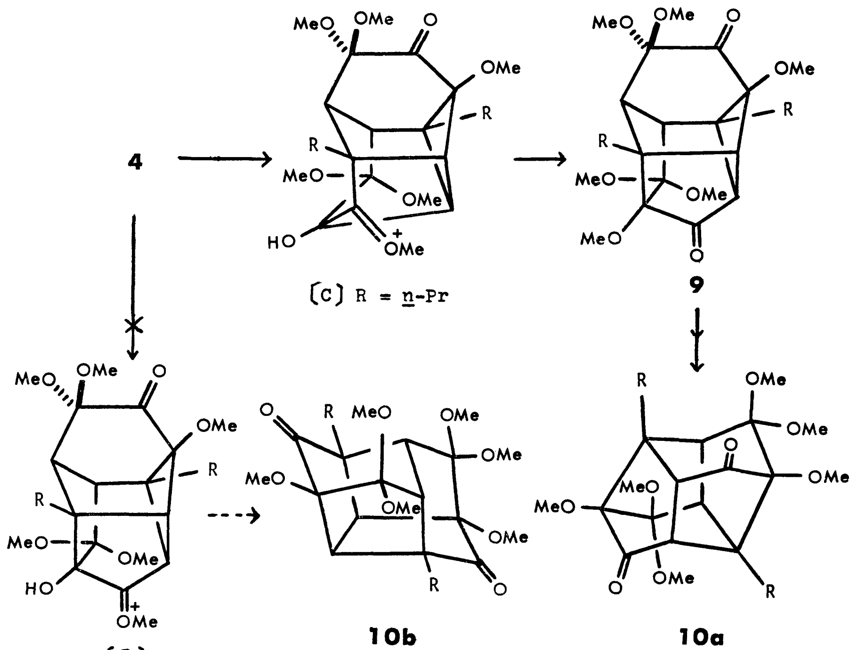
Scheme 1. A plausible reaction path-way from **3** to **5**.

(**5**) was determined by measurements of intramolecular nuclear Overhauser effects, and the final result was shown in Fig. 2.

Probably, the yellow substance (**5**) is produced from a plausible intermediate (**7**) *via* an α,β-unsaturated ketone (**8**) (see Scheme 1), although the formation process of **5** is not clear. In Scheme 1, it is quite reasonable that the conjugated ketone (**8**) is readily converted into the more stable ketone (**5**), for the former has an unstable cyclopentadienone system.

Isoasatone (**2**) and tetrahydroisoasatone (**4**) both are also unstable in acidic solution, and many spots are detected on an analytical TLC plate. However, when treated with dry ether saturated with HCl gas (room temp., 8 h),[3] tetrahydroisoasatone (**4**) with a symmetric structure was readily converted into an isomer-A (**9**) in 87.5% yield (mp 135.5—136.5 °C; $C_{24}H_{36}O_8$; ν_{max} 1755 and 1738 cm^{-1}). The NMR spectrum of **9** indicates that six MeO groups and four methine protons are all in different environment to one another. The IR absorption band at 1755 cm^{-1} indicates the presence of a five-membered ring CO group, which has been newly formed from one of the two six-membered ring CO groups (ν_{max} 1735 cm^{-1}) in **4**. On further treatment with zinc powder in MeOH containing one drop of concd HCl (room temp., 8 h), the isomer-A (**9**) afforded a mixture containing several compounds, from which another symmetrical isomer-B (**10a**) was obtained in *ca.* 10% yield (mp 152—153 °C; $C_{24}H_{36}O_8$; ν_{max} 1760 cm^{-1}). In the NMR spectrum of the isomer-B, only half of the total protons are observed as follows: δ 0.98 (6H, t, J=7.0 Hz), 1.2—2.3 (8H, complex), 2.52 (2H, dd, J=2.1 and 1.4 Hz), 2.89 (2H, dd, J=2.1 and 1.4 Hz), 3.23 (6H, s), 3.38 (6H, s) and 3.46 (6H, s) ppm. From the IR and NMR spectra of the isomer-B, two possible structures (**10a** and **10b**) are considered (see Scheme 2). As suggested by Yonemitsu and Witkop,[4] however, the cationic intermediate [C] at the initial step is unambiguously more favorable than another intermediate [D]. Therefore, the structures of two isomers A and B should be represented by **9** and **10a**, respectively.

In the course of the reaction (**4**—**10a**), twofold Wagner-Meerwein rearrangements take place after protonation of one of the two CO groups in **4**, leading to the formation of the isomer-A (**9**) which is a less strained cage-compound as compared with **4**. Further Wagner-Meerwein rearrangements released the strain energy due to the remaining cyclobutane ring in **9** to give the bisnordiadamantane-type isomer-B (**10a**). In the present study, the cage-compound (**9**) was first isolated as an intermediate between **4** and **10a**.



[D] **10b** **10a**

Scheme 2. Twofold Wagner-Meerwein rearrangements of **4**.

Experimental

All mps were uncorrected. The IR and UV spectra were obtained on a JASCO Model IR-S and on a Perkin-Elmer 202 spectrophotometer, respectively. The NMR spectra were taken on a JEOL JNM-PS 100 (100 MHz) using $CDCl_3$ as solvent. Chemical shifts are given in ppm from TMS as an internal standard. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy (70 eV).

*Formation of the Yellow Substance (**5**).* A solution of tetrahydroasatone (200 mg) in 6 M·HCl (8 ml) and AcOH (1.5 ml) was heated at 100 °C for 1.5 h, and then poured into large amounts of water to give yellow crystals which were collected by filtration. Recrystallization from acetone–hexane afforded yellow plates of **5** (128 mg), mp 181—182 °C; *m/e* 342 (M^+) and 327 (Found: C, 70.23; H, 6.51%. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%).

*Formation of the Methyl Ether (**6**).* To a solution of excess diazomethane in ether (50 ml) was added the compound (**5**) (15 mg) with stirring. The resulting solution was stirred at room temp. overnight, and then concentrated under reduced press. to give a crystalline solid (15 mg). Recrystallization from acetone–hexane afforded pale yellow crystals of **6**, mp 138—139 °C; ν_{max} (Nujol) 3200, 1665, 1605, 1565, and 1510 cm^{-1}; λ_{max} (MeOH) 416, 331, 291, and 225 nm (ε, 4600, 9000, 30000, and 19700, respectively); δ 1.15 (3H, t, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz), 2.31 (2H, quintet, J=7.5 Hz), 3.20 (2H, q, J=7.5 Hz), 3.39 (2H, d, J=2 Hz), 3.72 (3H, s), 4.02 (3H, s), 4.03 (3H, s), 6.92 (1H, br.t, J=7.5 Hz), 7.10 (1H, s), and 9.82 (1H, s, OH) ppm: *m/e* 356 (M^+) and 341 (Found: *m/e* 356.16336. Calcd for $C_{21}H_{24}O_5$: *m/e* 356.16236).

*Conversion of Tetrahydroisoasatone (**4**) to the Isomer-A (**9**).* A solution of **4** (20 mg) in anhydrous ether (5 ml) saturated with HCl gas was allowed to stand at room temp. for 8 h, and then carefully concentrated under reduced press. to give a colorless viscous liquid which was subjected to preparative TLC [Kieselgel PF_{254}; hexane–EtOAc (3:1)]. From the most nonpolar fraction, a colorless viscous liquid was obtained and dissolved in small amounts of hexane to give white crystals of **9** (17.5 mg), mp 135.5—136.5 °C (from hexane); ν_{max} (Nujol) 1755 and 1738 cm^{-1} (no OH band); δ 0.90 (6H, t, J=6.5 Hz), 1.1—2.0 (8H, complex), 2.56 (1H, dd, J=2.2, and 1.6 Hz), 2.73 (1H, dd, J=6.8, and 1.6 Hz), 2.99 (1H, t, J=2.2 Hz), 3.13 (1H, dd, J=6.8, and 2.2 Hz), 3.24 (3H, s), 3.25 (3H, s), 3.32 (3H, s), 3.33 (3H, s), 3.34 (3H, s), and 3.48 (3H, s) ppm; *m/e* 452 (M^+), 437, 424, 420, 409, 405, and 392 (Found: *m/e* 452.24543. Calcd for $C_{24}H_{36}O_8$: *m/e* 452.24100).

*Further Rearrangement of **9** to the Isomer-B (**10a**).* The isomer-A (50 mg) was dissolved, with stirring, in a solution of MeOH (3 ml) containing one drop of concd HCl at −5 °C. To this solution was added activated zinc powder (500 mg) with vigorous stirring. The reaction mixture was allowed to stand at room temp. for 8 h with continuous stirring, and then poured into large amounts of water and extracted with ether. The ethereal extracts were washed with sat. NaCl aq. solution, and then dried over Na_2SO_4. Removal of the solvent afforded a pale brown oil, which was subjected to preparative TLC [Kieselgel PF_{254}; hexane–EtOAc (5:1)]. From the most nonpolar fraction, a crystalline solid was obtained by elution with ether. Recrystallization from hexane afforded white crystals of the isomer-B (6 mg), mp 152—153 °C; ν_{max} (Nujol) 1760 cm^{-1} (no OH band); *m/e* 452 (M^+), 421, 406, and 390 (Found: *m/e* 452.24479. Calcd for $C_{24}H_{36}O_8$: *m/e* 452.24100).

The authors wish to thank Drs. M. Kurono and M. Toda (Ono Pharmaceutical Co., Ltd.) for measurements of high resolution mass spectra. They are also indebted to Prof. Y. Okumura and Dr. H. Irikawa (Shizuoka University) for measurements of ^{13}C NMR spectra.

References

1) K. Sasaki, Y. Hirata, S. Yamamura, Y. Chen, M. Hong, and H. Hsu, *Tetrahedron Lett.*, **1973**, 4881; S. Yamamura, Y. Terada, Y. Chen, H. Hsu, and Y. Hirata, *ibid.*, **1975**, 1903.

2) One of ten singlets (δ 113.70—150.71 ppm) is due to the quanternary carbon atom of a tri-substituted double bond in the partial structure [B].

3) This reaction should be carried out under completely anhydrous condition.

4) K. Hirao, M. Taniguchi, T. Iwakuma, O. Yonemitsu, J. L. Flippen, I. Karle, and B. Witokop, *J. Am. Chem. Soc.*, **97**, 3249 (1975), and references cited therein.