The earlier reported synthesis[2] of **1** had used acetyl groups for protection of the hydroxyl groups during formation of the N-methylurea and during formation of the N-nitroso urea, but their removal was accompanied by severe degradation. To avoid this, we investigated the direct reaction of **2** and N-methyl isocyanate (MIC).

It was found that if MIC was added to a cold aqueous solution of **2** (free base), a high yield of **3** resulted. Infrared and mass spectra showed that the expected by-product **4** was not present and that **5** was present in only trace amounts. The infrared spectrum of the product revealed a strong band at 1645 cm^{-1}; we assigned this to the open-chain urea.[3] Supporting evidence for this was a strong amide II band[4a] at 1580 cm^{-1}. The infrared spectrum of authentic bicyclic urea **5**[5] has a carbonyl peak at 1660 cm^{-1} and no amide II band[4a] in the region 1500–1600 cm^{-1}. The product could not be a urethan compound such as **4** because the carbonyl absorption of a urethan occurs at *ca.* 1710–1740 cm^{-1}.[4b]

Vapor phase chromatography (vpc) of the trimethylsilyl (TMS) derivative[6,7] of **3** showed two major peaks. Vpc–mass spectrometry[8a] of the TMS derivative gave identical spectra for each major peak, confirming that they were anomeric. A weak *m/e* 524 peak was assigned to the molecular ion; a *m/e* 509 peak [(M − 15)$^+$], a *m/e* 450 peak [(M − 74)$^+$], and an intense *m/e* 188 peak were present. The mass spectrum of the TMS derivative of **2**[6,7] showed an intense *m/e* 131 peak which is due to the C_1–C_2 fragment **6**. We assigned the *m/e* 188 peak of the TMS derivative of **3** to **7**. A high-resolution mass determination[8b] of the *m/e* 450 peak gave a mass of 450.2144 corresponding to $C_{15}H_{42}O_5Si_4$ (calculated, 450.2105). Presumably this is the sugar fragment after a McLafferty rearrangement type cleavage of the urea moiety. These data confirm the presence of the urea moiety in **3**. The nmr spectrum of the trimethylsilyl derivative of **3** gave an N-methyl peak at τ 7.25 and integrated for four trimethylsilyl groups.

When the temperature of the reaction was kept between −2 and 2°, 90–95% of the desired urea **3** resulted. However, if the temperature went above 12° during the addition of MIC to the reaction, the yield of **3** was reduced to *ca.* 40% and unidentified products of higher molecular weight (as shown by mass spectrometry) were formed.

The crude product **3** was treated with nitrous acid generated from commercial nitrogen trioxide[9] to give **1** in 77–80% overall yield from **2**. The synthetic and natural products were shown to be identical by uv and ir spectroscopy, bioassay,[10] and tlc. In addition, synthetic **1** was shown to be diabetogenic in male rats,[11] and anti-leukemic in mice.[12] These physiological properties of synthetic **1** correspond in every way to **1** obtained by fermentation.

(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 223.

(4) (a) Reference 3, pp 219–220; (b) p 222.

(5) Kindly provided by A. D. Argoudelis, who prepared it from natural streptozotocin (see ref 2).

(6) The conditions referred to are: 10-mg sample, 1.0 ml of dry pyridine, 0.2 ml of hexamethyldisilazane, and 0.1 ml of trimethylsilyl chloride shaken for 1 hr at room temperature; *cf.* C. C. Sweeley, R. Beltley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(7) The TMS derivative was isolated by the method reported by B. T. Golding, R. W. Richards, and M. Berber, *Tetrahedron Lett.*, 2615 (1964).

(8) (a) An LKB-9000 mass spectrometer was used under the direction of Dr. P. Bowman, The Upjohn Co.; (b) a CEC-21-110 mass spectrometer was used under the direction of R. Wnuk, The Upjohn Co.

(9) Nitrogen trioxide was purchased from the Matheson Co.

(10) Bioassay was performed as a paper disc agar diffusion with the test organism *Proteus vulgaris*.

Experimental Section

D-Glucosamine free base (**2**) was prepared from the hydrochloride salt as described by Breuer.[13]

D-Glucosamine N-Methylurea (**3**).—A solution of **2** (179.0 g, 1.0 mol) in water (800 ml) was cooled to −2°. Freshly distilled MIC (65.0 ml, 63.0 g, 1.10 mol) was added slowly over a period of 30 min, so that the temperature of the stirred solution did not exceed 2°. After the solution was stirred for 1 hr at 0°, an aliquot (50 μl) was removed, and converted to the TMS derivative[6] for vpc. This showed the presence of the anomeric urea mixture **3**. The urea could be isolated by lyophilization. The vpc conditions are: 3% OV-1 on gas Chromosorb Q, 100/120 mesh, 6 ft × 0.25 in. column, 190°; on a Hewlett–Packard Model 402, with a flame ionization detector.

Streptozotocin (**1**).—The urea **3** was converted to **1** without isolation. Liquid nitrogen trioxide (27 ml, 39.0 g, 0.51 mol) was added to the urea solution over a period of 5 min with stirring at 0°. After the solution was stirred further for 15 min, an aliquot was removed for tlc (50 μl solution diluted to 1 ml with 1:1 methanol–water). The diluted solution was spotted on a microslide and developed in 1:3:1 ethanol–ethyl acetate–cyclohexane. Visualization of the components was accomplished in an iodine chamber. A low-R_f component (R_f *ca.* 0.1) corresponding to **3** and a high-R_f component (R_f *ca.* 0.6) corresponding to **1** were present. More liquid nitrogen trioxide (*ca.* 42 g) was added until the tlc assay indicated that **3** had completely reacted. Cold 1-butanol (4 l.) was added, and at a bath temperature of 35° the mixture was concentrated under reduced pressure to remove the water. During the concentration **1** crystallized. The concentrate (*ca.* 2 l.) was stored at −10° for 3 hr. Compound **1** was collected by filtration; it was washed with 1:1 butanol–ether and ether, and dried to yield 213 g (80% from **2**) of pale yellow crystals, mp 115–115.5° dec. Elemental analysis was acceptable.

Registry No.—**1**, 18883-66-4.

Acknowledgment.—Valuable discussions with Professor C. Sweeley, Dr. M. Grostic, and Dr. P. Bowman regarding mass spectral data were appreciated. Technical assistance was provided by J. E. Wiersma.

(11) W. E. Dulin, private communication.

(12) B. K. Bhuyan, private communication.

(13) R. Breuer, *Chem. Ber.*, **31**, 2193 (1898).

Rotenoids. XXII. Total Synthesis of Isomillettone[1]

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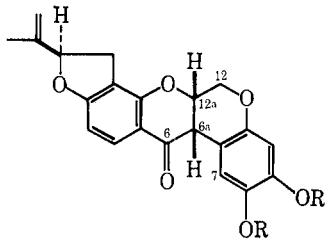
A number of 3,4-methylenedioxyphenyl compounds are known[2] to be excellent synergists for pyrethroids, the insecticidal principles of pyrethrum flowers. Enhanced mitocidal activity of a 3,4-methylenedioxyphenyl compound when applied in conjunction with

(1) Part XXI: M. Miyano, *J. Amer. Chem. Soc.*, **87**, 3962 (1965).

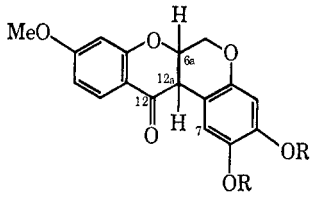
(2) For example, see (a) M. Ohno, M. Hamada, and H. Takahara, *Bull. Inst. Chem. Res. Kyoto Univ.*, **38**, 34 (1960); *Chem. Abstr.*, **55**, 22275 (1961); (b) M. Beroza, *Anal. Chem.*, **28**, 1550 (1956); (c) R. Nash, *Ann. Appl. Biol.*, **41**, 652 (1954); *Chem. Abstr.*, **49**, 4221 (1955); (d) O. F. Hedenburg, U. S. Patent 2,485,600 (1949); *Chem. Abstr.*, **44**, 5522 (1950).

rotenone, an insecticidal principle of derris root, was also shown.[3]

The purpose of this research was to synthesize the methylenedioxy analogs (**1b** and **2b**) of rotenone (**1a**),[4] the most active and one of the most complicated rotenoids, and munduserone (**2a**),[5] the simplest rotenoid, for biological evaluation. These analogs (**1b**, **2b**), possessing a synergistic grouping and insecticidal properties in the same molecule, might exhibit enhanced insecticidal activity.



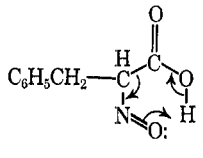
1a, R = CH_3
b, 2R = $>CH_2$

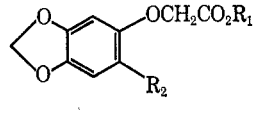


2a, R = CH_3
b, 2R = $>CH_2$

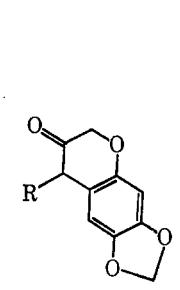
The existence of **1b** in the root of Jamaican Dogwood was recently suggested[6] and the name isomillettone was proposed, although the substance was obtained only as a mixture with millettone and hence neither chemical nor biological properties have been rigorously established. Unfortunately, an incorrect structure was shown in the text,[6] and these authors must have intended compound **1b** as isomillettone.

4,5-Methylenedioxysalicylaldehyde was smoothly converted into 2-carboxymethyloxy-4,5-methylenedioxyphenylpyruvic acid (**5**) through **3** and **4** as in the corresponding 4,5-dimethoxy series.[7] Treatment of **5** with alkaline hydroxylamine gave the aldoxime **6**, which must have been formed by spontaneous decarboxylation of the ketoxime carboxylic acid, presumably by a cyclic mechanism. In the corresponding dimethoxy compound, no such decarboxylation was reported under the same reaction conditions.[8] The diester **8**, prepared by oxidative decarboxylation of **5** followed by esterification, underwent a Dieckmann condensation to afford a β-keto ester **9**, as in the preparation of the corresponding 6,7-dimethoxy compound.[9] Decarboxylation of **9** by boiling with aqueous sulfuric acid gave a poor yield of 3,4-dihydro-6,7-methylenedioxy-2H-1-benzopyran-3-one (**10**), whereas the corresponding 6,7-dimethoxy compound had been obtained in excellent yield.[10] The major product of the decarboethoxylation was a poorly soluble and high-melting crystalline material having a broad melting point. This product is probably a mixture of a few isomeric dimers represented as **11**. One isomer was obtained pure by chromatography followed by recrystallization. It was found later that both **10** and **11** could be converted into the same monomeric enamine (**12**).[11]

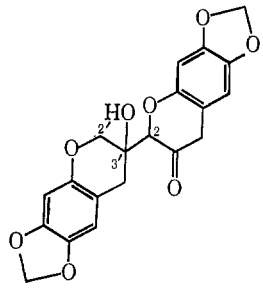




3, $R_1 = C_2H_5$; $R_2 = CHO$
4, $R_1 = C_2H_5$; $R_2 = CH{=}C{-}C{=}O$ (N, O, C_6H_5)
5, $R_1 = H$, $R_2 = CH_2COCO_2H$
6, $R_1 = H$, $R_2 = CH_2CH{=}NOH$
7, $R_1 = H$, $R_2 = CH_2CO_2H$
8, $R_1 = C_2H_5$, $R_2 = CH_2CO_2C_2H_5$

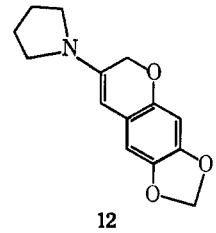


9, R = $CO_2C_2H_5$
10, R = H



11

The pyrrolidine enamine **12** underwent condensation with 1-tubaic acid chloride (**13a**)[10] to give **14a**, which was reduced with borohydride to **15a** and finally reoxidized to **1b** by Oppenauer reaction. The *cis* configuration of C-6a and C-12a of the crystalline product (**1b**) was demonstrated by the nmr spectrum. The appearance of the C-6a proton signal at τ 6.23 (d, J = 3.5 Hz, H_d in **16**) suggested that H_d and H_c



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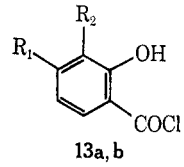
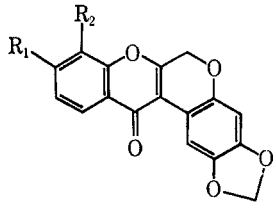
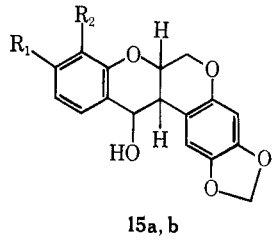


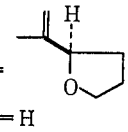
13a, b



14a, b



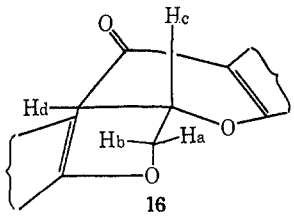
15a, b



a, R_1 with R_2 =
b, $R_1 = OCH_3$; $R_2 = H$

(3) Cooper, McDougall & Robertson Ltd., British Patent 999,960 (1965); *Chem. Abstr.*, **63**, 10603 (1965).
(4) For the total synthesis, see ref 10. For stereochemistry, see ref 14.
(5) For the review and total synthesis, see J. R. Herbert, W. D. Ollis, and R. C. Russell, *Proc. Chem. Soc.*, 177 (1960).
(6) C. P. Falshaw, W. D. Ollis, J. A. Moore, and K. Magnus, *Tetrahedron, Suppl.*, **7**, 344 (1966).
(7) A. Robertson, *J. Chem. Soc.*, 1380 (1932).
(8) A. Robertson, *ibid.*, 1163 (1933).
(9) A. Robertson, and G. L. Rusby, *ibid.*, 212 (1936).
(10) M. Miyano, *J. Amer. Chem. Soc.*, **87**, 3958 (1965).
(11) See Experimental Section.

may be *cis* as shown in **16**, but not *trans* as in **17**. The position of H_c was not clear because of overlapping



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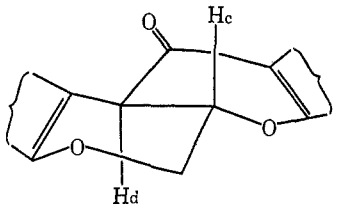

17

with other resonances. Signals of H_a (or H_b) at τ 5.88 (d, J = 11.5 Hz) and H_b (or H_a) at τ 5.41 (d of d, J_{ab} = 11.5 Hz, J_{bc} = 3 Hz) were consistent with **16**. Nmr spectra of rotenoids were first discussed by Crombie and Lown.[12] They concluded that the stereochemistry of the juncture of the two oxygen-containing rings could be determined by the chemical shift of the C-7 proton on the aromatic ring. The appearance of the aromatic proton of **1b** at τ 3.26 was consistent with the *cis* structure. The optical rotation of $[\alpha]^{24}D$ −87.5° (*c* 2.10, benzene) of the synthetic substance **1b** clearly indicates that this is a 1:1 molecular complex of 6aβ,12aβ-*cis* compound (**1b**) and 6aα,12aα-*cis* compound. In other words, the synthetic material is the methylenedioxy analog of mutarotenone,[13] which is a 1:1 molecular complex of l-rotenone and *d*-epirotenone.

Condensation of the enamine **12** and 4-methoxysalicyl chloride (**13b**) gave **14b**, which was reduced with borohydride, followed by Oppenauer oxidation to afford **2b**. Since this compound was not sufficiently soluble in any solvent tried so far, an nmr spectrum could not be taken. However the *cis* stereochemistry was deduced from the fact that this material (**2b**) was obtained in at least 49% overall yield from **14b**. Therefore, **2b** is very probably the more thermodynamically stable isomer; that is, the 6a and 12a hydrogens are *cis* to each other.[14]

Experimental Section

Following a procedure similar to that for the preparation of the corresponding 4,5-dimethoxy compounds,[7,9] 4,5-methylenedioxysalicylaldehyde was converted into **3**, **4**, **5**, **7**, **8**, and **9**.

Ethyl 2-Formyl-4,5-methylenedioxyphenoxyacetate (3).—This compound had mp 102.5–104° (recrystallized from ethanol); ir ($CHCl_3$) 5.67 (C=O), 5.94 (C=O), and 10.65 μ (methylenedioxy).

Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.03; H, 4.66.

Azlactone (4).—This compound was recrystallized from ethyl acetate; mp 230.5–231.5°.

Anal. Calcd for $C_{21}H_{17}O_7N$: C, 63.79; H, 4.33; N, 3.54. Found: C, 64.03; H, 4.33; N, 3.49.

2-Carboxymethoxy-4,5-methylenedioxyphenylpyruvic Acid (5).—The analytical sample was recrystallized from aqueous methanol: mp 235–237°; ir (KBr) 5.71–5.97 (complicated carbonyl absorptions) and 10.71 μ (methylenedioxy).

Anal. Calcd for $C_{12}H_{10}O_8$: C, 51.07; H, 3.57. Found: C, 50.94; H, 3.78.

2-Carboxymethoxy-4,5-methylenedioxyphenylacetaldoxime (6).—A solution of 11 g of crude keto acid **5**, 14 g of hydroxylamine hydrochloride, and 10 g of sodium hydroxide in 100 ml of water was warmed to 50–70° for 30 min, set aside for 24 hr, acidified with 35 ml of concentrated hydrochloric acid, cooled in the refrigerator for 1 hr, filtered with suction, and washed with a small amount of cold water. The dried material (11.8 g) melted at 155.5° with vigorous decomposition. A portion of the product was recrystallized from hot water: mp 165° dec; ir (KBr) 5.73 and 10.73 μ.

Anal. Calcd for $C_{11}H_{11}O_6N$: C, 52.17; H, 4.38; N, 5.53. Found: C, 52.07; H, 4.28; N, 5.38.

2-Carboxymethyl-4,5-methylenedioxyphenoxyacetic Acid (7).—The analytical sample was prepared by repeated recrystallization from water: mp 170–172°; ir (KBr) 5.7–5.85 (complicated carbonyl absorption) and 10.79 μ (methylenedioxy).

Anal. Calcd for $C_{11}H_{10}O_7$: C, 51.97; H, 3.97. Found: C, 52.33; H, 4.10.

Diethyl 2-Carboxymethyl-4,5-methylenedioxyphenoxyacetate (8).—This compound was recrystallized from Skelly C: mp 74.5–75.5°; ir ($CHCl_3$) 3.58 (methylenedioxy), 5.65 (C=O), 5.73 (C=O), and 10.70 μ (methylenedioxy); nmr ($CDCl_3$) τ 4.08 (s, methylenedioxy), 5.45 (s, OCH_2CO), and 6.37 (s, $PhCH_2CO$).

Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 58.33; H, 5.67.

3,4-Dihydro-3-keto-4-carboethoxy-6,7-methylenedioxy-2H-1-benzopyran (9).—Recrystallization from ethanol afforded the analytical sample: mp 88–89°; ir ($CHCl_3$) 3.60 (methylenedioxy), 6.03 (C=O), 6.23 (enolic C=C), and 10.67 μ (methylenedioxy); uv (ethanol) 246.5 (ϵ 13,740) and 315.5 mμ (ϵ 7980); nmr ($CDCl_3$) τ −2.80 (s, 1, enolic OH), 4.09 (s, 2, methylenedioxy), and 5.44 (s, 2, OCH_2C=).

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.12; H, 4.69.

3,4-Dihydro-6,7-methylenedioxy-2H-1-benzopyran-3-one (10) and the Dimeric Form (11).—A suspension of 19.0 g of β-keto ester **9** in 200 ml of 10% (w/v) sulfuric acid was refluxed for 2 hr. The cooled reaction mixture was extracted with chloroform. The organic extracts were washed with water, twice with 1% sodium hydroxide solution, and again with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue (10.6 g) was recrystallized from 100 ml of ethanol, giving 3.6 g of crystalline product melting at *ca.* 146° (crystal A). The mother liquor was concentrated and treated with 40 ml of ethanol–chloroform (5:2) to afford 2.7 g of crystals melting at 161–163° (crystal B). These crystalline products are mixtures of stereoisomeric dimers like **11**, which also contain a small amount of monomer **10**, and it was found later that they were suitable for conversion into the monomeric pyrrolidine enamine **12** without further purification. One isomer was obtained in pure state by chromatography of 6 g of the crude dimer (A and B) dissolved in 1.5 l. of warm benzene on 400 g of Woelm neutral alumina (activity I). The column was eluted with ether and fractions containing 1.3 l. of eluate were collected. The fourth fraction (1.95 g) gave 0.65 g of colorless fine needles of **11** melting at 208–210° on recrystallization from ether–benzene: ir (KBr) 2.93 (OH), 3.59 (methylenedioxy), 5.80 (C=O), and 10.67 and/or 10.95 (methylenedioxys); uv (methanol) identical with **10** (see below); nmr (CD_3SOCD_3) τ 4.05 (s, 2, methylenedioxy), 4.12 (s, 2, methylenedioxy), and 5.86 (s, 1, C-2 H).

Anal. Calcd for $C_{20}H_{16}O_8$: C, 62.50; H, 4.20. Found: C, 62.66; H, 4.40.

The second and third ether fractions gave 0.7 g of big, transparent plates of **10** melting at 84.5–85.5° after recrystallization from ethanol containing benzene: ir ($CHCl_3$) 3.56 (methylenedioxy), 5.70 (C=O), and 10.61 μ (methylenedioxy); uv (methanol) 300.0 mμ (ϵ 5300); nmr ($CDCl_3$) τ 4.06 (s, 2, methylenedioxy), 5.66 (s, 2, OCH_2CO), and 6.50 (s, 2, $OCCH_2Ph$).

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.65; H, 4.47.

Pyrrolidine Enamine of 10 (12).—This compound was prepared in the usual manner[10] and recrystallized from benzene, giving large, colorless, transparent plates: mp 135.5–136.5°; ir ($CHCl_3$) 6.08, 6.22, 6.72, 8.53, 9.60, and 10.62. μ

Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.42; H, 6.18; N, 5.40.

Identical material was obtained by the same procedure from the dimeric ketone **11**.

1,2-Dihydro-2-isopropenyl-8,9-methylenedioxy[2H-1]benzopyrano[3,4-*b*]furo[2,3-*h*][1]benzopyran-6-one (14a).—The procedure was similar to that used for the corresponding dimethoxy compound.[10] The compound was recrystallized from chloroform–ethanol (14.6% overall yield from **10**): mp 218.5–219.5°; ir ($CHCl_3$) 3.60 (methylenedioxy), 6.08 (C=O), 10.64 (methylenedioxy), and 10.97 μ (isopropenyl).

(12) L. Crombie and J. W. Lown, *J. Chem. Soc.*, 775 (1962).

(13) R. S. Cahn, R. F. Phipers, and J. J. Boam, *ibid.*, 513 (1938).

(14) The fact that the *cis* configuration of rotenoids is the more stable one was first disclosed by G. Büchi, L. Crombie, P. J. Godin, J. S. Kaltenbronn, K. S. Siddalingaiah, and D. A. Whiting, *ibid.*, 2843 (1961).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29. Found: C, 70.03; H, 4.50.

2,3-Methylenedioxy-9-methoxy[2H-1]benzopyrano[3,4-*b*][1]-benzopyran-12-one (14b).—The sample for analysis was recrystallized from chloroform–benzene: mp 225° dec; ir ($CHCl_3$) 3.56 (methylenedioxy), 6.05 (C=O), and 10.55 μ (methylenedioxy).

Anal. Calcd for $C_{18}H_{12}O_6$: C, 66.67; H, 3.73. Found: C, 66.83; H, 3.86.

1,2,12,12a-Tetrahydro-2-isopropenyl-8,9-methylenedioxy[1]-benzopyrano[3,4-*b*]furo[2,3-*h*][1]benzopyran-6(6aH)-one (Isomillettone, 1b) and 1,2,12,12a-Tetrahydro-2-isopropenyl-8,9-methylenedioxy[1]benzopyrano[3,4-*b*]furo[2,3h][1]benzopyran (18).—The preparation was similar to a general method published previously[15] and the crude product was chromatographed on neutral alumina. Compound **18** was recrystallized from benzene–cyclohexane: mp 180°; ir ($CHCl_3$) 3.60 (methylenedioxy), 6.13 (C=C), 6.18 (C=C), 10.64 (methylenedioxy), and 11.00 μ (isopropenyl).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01. Found: C, 72.74; H, 4.99.

Isomillettone (**1b**) was recrystallized from ethanol: mp 166–167.5°; ir ($CHCl_3$) 3.61 (methylenedioxy), 5.97 (C=O), 6.21 (the strongest band), 10.64 (methylenedioxy), and 11.04 μ (isopropeneyl); uv (EtOH) 237.5 (ϵ 10,800) and 297.5 mμ (ϵ 15,000); nmr ($CDCl_3$) see text; $[\alpha]^{24}D$ −87.5° (*c* 2.10, benzene).

Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.83; H, 4.80. Found: C, 69.76; H, 5.08.

Methylenedioxy Analog of Munduserone. 2,3-Methylenedioxy-9-methoxy-6,6a-dihydro[1]benzopyrano[3,4-*b*][1]benzopyran-12(12H)-one (2b).—Eight hundred milligrams of **14b** was converted into **2b** in the usual manner.[15] Without the use of chromatography, the product crystallized from 20 ml of benzene to give rise to 245 mg of colorless, long needles, mp 210–211.5°. From the mother liquor a second crop of 151 mg, mp 202°, was obtained. The final mother liquor deposited more crystalline product on standing for a few days. Total yield was at least 396 mg (49.2%). The first crop was used for analysis: ir ($CHCl_3$) 3.59 (methylenedioxy), 5.94 (C=O), 6.19 (the strongest band), and 10.65 μ (methylenedioxy); uv (MeOH) 231.5 (ϵ 14,880), 275.5 (ϵ 15,760), and 305 mμ (ϵ 11,750).

Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32. Found: C, 66.07; H, 4.43.

Registry No.—**1b**, 22256-05-9; **2b**, 22256-06-0; **3**, 13668-86-5; **4**, 22297-78-5; **5**, 22252-99-9; **6**, 22253-00-5; **7**, 22253-01-6; **8**, 22253-02-7; **9**, 22253-03-8; **10**, 22253-04-9; **11**, 22253-05-0; **12**, 22253-06-1; **14a**, 22256-07-1; **14b**, 22297-79-6; **18**, 22256-08-2.

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Studies on Reactions of Isoprenoids. VII.[1] Acid-Catalyzed Hydrolysis of 5,5-Dimethylbicyclo[2.1.1]hexane-1-epoxyethane

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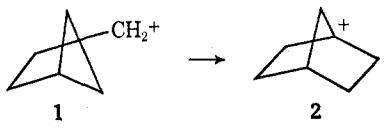
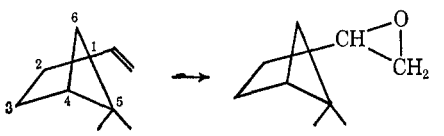
Although facile ring expansion of the bicyclo[2.1.1]-hexane-1-carbinyl cation (**1**) to the 1-norbornyl cation (**2**) (eq 1) is documented as one of the general carbocyclic ring expansion reactions of Wagner–Meerwein type rearrangements,[2] the initial cationic species seems to be restricted mostly to the primary cation.[3] In this paper we wish to describe the somewhat difficult ring expansion of a bicyclo[2.1.1]hexane-1-carbinyl to a 1-norbornyl system as the result of acidic hydrolysis of the title epoxide, in which the ring-enlargement aptitude is diminished by the intervention of a secondary cationic species and also by a possible cyclobutane ring fission facilitated by the presence of a *gem*-dimethyl group at C-5.



1 2 (1)

The title epoxide **4** was readily prepared by oxidation of 5,5-dimethyl-1-vinylbicyclo[2.1.1]hexane (**3**)[4] with perbenzoic acid (eq 2). The epoxide **4**, however



3 4 (2)

was shown to be an inseparable mixture (55:45) of two stereoisomers by vpc analysis[5] and by the nmr spectrum (100 MHz), in which partly overlapping sets of multiplets in the typical ABX pattern were observed at τ 7.00–7.67 for three protons assignable to protons of the HC(–O–)–O–CH_2 moiety and also two singlet signals at τ 8.73 and 8.77 for three protons assignable to one of the methyl protons at C-5 were observed in a ratio of *ca.* 4:6. The formation of two isomeric epoxides is reasonable, because a new asymmetric carbon is produced on the epoxidation of **3**, though their separation was not successful.

Hydrolysis of **4** was carried out by refluxing an ether solution containing 5% sulfuric acid, and the reaction was followed on vpc (PG-6000). After 11 days, the conversion was 83%; then the products were purified by chromatography on a silica gel column to give 14% of recovered **4**, 7.5% of oily vinyl ketone **5**, and 72.5% of a semicrystalline glycol mixture. The recovered **4** had a different isomer ratio from the starting material (32:68 as compared with the original 55:45),[5] indicating that one of the isomers reacted faster than the other.[6]

The structure of **5** was established as 3-(1,1-dimethyl-2-propenyl)cyclopentanone on the basis of the analytical data and the following spectral evidence: ir (neat) 1740 (cyclopentanone), 1643, 980, and 920 cm^{-1} (vinyl); nmr (CCl_4) τ 3.60–5.10 (m of a typical ABX

(1) Part VI of this series: T. Sasaki, S. Eguchi, M. Ohno, and T. Oyobe, *Bull. Chem. Soc. Jap.*, in press.

(2) K. B. Wiberg and B. R. Lowry, *J. Amer. Chem. Soc.*, **85**, 3188 (1963).

(3) For a review about bicyclo[*n*.1.1]alkanes, see J. Meinwald and Y. C. Meinwald, "Advances in Alicyclic Chemistry," Vol. I, Academic Press, New York, N. Y., 1966, pp 2–51.

(4) R. H. Liu and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 4936 (1967).

(5) The major isomer had a slightly longer retention time than that of the minor one on vpc (PG-6000).

(6) We could not obtain further detailed information on the stereoselectivity in the reaction of such conformationally mobile epoxide without pure isomers. For similar reactions which have been more extensively explored, see C. J. Cheer and C. R. Johnson, *J. Amer. Chem. Soc.*, **90**, 178 (1968).