

Synthesis of 2',3',4,4',6'-Pentahydroxychalcone, an Aglycone of Carthamin, and Its Isomerization into 4',5,6,7- and 4',5,7,8-Tetrahydroxyflavanone, Carthamidin and Isocarthamidin¹⁾

Heitaro OBARA,* Jun-ichi ONODERA, Yuji KURIHARA, and Fumitada YAMAMOTO

Department of Applied Chemistry, Faculty of Engineering, Yamagata University, Yonezawa 992

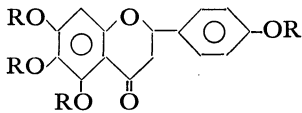
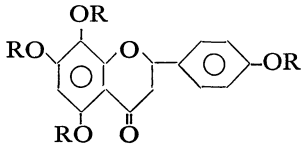
(Received June 10, 1978)

2',3',4,4',6'-Pentahydroxychalcone (**4**), an aglycone of carthamin, was synthesized by the demethoxymethylation of 2',3',4,4',6'-pentakis(methoxymethoxy)chalcone prepared by the condensation of 2,3,4,6-tetrakis(methoxymethoxy)acetophenone with *p*-methoxymethoxybenzaldehyde. **4** was converted into 4',5,6,7- and 4',5,7,8-tetrahydroxyflavanone (**5** and **6**) by boiling with methanolic hydrochloric acid. On the basis of the comparisons of the properties of **5** and **6** with those of carthamidin (**A**) and isocarthamidin (**B**) derived from natural product, the structures originally assigned for **A** and **B** should be reversed.

In 1930, Kuroda²⁾ obtained two flavanones, carthamidin (**A**) and isocarthamidin (**B**), by the hydrolysis of carthamin, the red coloring matter of the flowers of Safflower (*Carthamus tinctorius* L.) and proposed the structures of 4',5,7,8- and 4',5,6,7-tetrahydroxy-

flavanone (**6** and **5**) for **A** and **B**, respectively. However, the identification of **A** and **B** has not yet been accomplished synthetically. In 1949, Seshadri *et al.*³⁾ reported the synthesis of **5** and **6** by the demethylation of the corresponding tetramethoxyflavanones in the presence

TABLE 1. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS OF 4',5,6,7- AND 4',5,7,8-TETRAHYDROXYFLAVANONE (**5** AND **6**), 4',5,6,7- AND 4',5,7,8-TETRAACETOXYFLAVANONE (**7** AND **8**), AND 4',5,6,7- AND 4',5,7,8-TETRAMETHOXYFLAVANONE (**9** AND **10**)

 5 R=H, 7 R=Ac, 9 R=Me		 6 R=H, 8 R=Ac, 10 R=Me	
5^{a)}		6^{a)}	
C ₃ -H	2.72 (1H, q, <i>J</i> =16.9 and 3.3 Hz) 3.21 (1H, q, <i>J</i> =16.9 and 11.9 Hz)	2.64 (1H, q, <i>J</i> =17.2 and 3.3 Hz) 3.13 (1H, q, <i>J</i> =17.2 and 12.3 Hz)	
C ₂ -H	5.43 (1H, q, <i>J</i> =11.9 and 3.3 Hz)	5.38 (1H, q, <i>J</i> =12.3 and 3.3 Hz)	
C ₆ -H		5.84 (1H, s)	
C ₈ -H	5.94 (1H, s)		
C _{3',5'} -H	6.80 (2H, d, <i>J</i> =8.5 Hz)	6.68 (2H, d, <i>J</i> =8.5 Hz)	
C _{2',6'} -H	7.36 (2H, d, <i>J</i> =8.5 Hz)	7.25 (2H, d, <i>J</i> =8.5 Hz)	
OH	8.01, 9.52, 10.36, and 11.72 (4H, s)	7.88, 9.46, 10.82, and 11.62 (4H, s)	
7^{b)}		8^{b)}	
OAc	2.21, 2.23, 2.24, and 2.34 (12H, s)	2.21, 2.27, 2.28, and 2.34 (12H, s)	
C ₃ -H	2.74 (1H, q, <i>J</i> =17.0 and 2.7 Hz) 2.99 (1H, q, <i>J</i> =17.0 and 13.7 Hz)	2.78 (1H, q, <i>J</i> =16.9 and 2.8 Hz) 3.01 (1H, q, <i>J</i> =16.9 and 13.4 Hz)	
C ₂ -H	5.46 (1H, q, <i>J</i> =13.7 and 2.7 Hz)	5.49 (1H, q, <i>J</i> =13.4 and 2.8 Hz)	
C ₆ -H		6.22 (1H, s)	
C ₈ -H	6.87 (1H, s)		
C _{3',5'} -H	7.10 (2H, d, <i>J</i> =8.5 Hz)	7.10 (2H, d, <i>J</i> =8.5 Hz)	
C _{2',6'} -H	7.40 (2H, d, <i>J</i> =8.5 Hz)	7.40 (2H, d, <i>J</i> =8.5 Hz)	
9^{b)}		10^{b)}	
OMe	3.82, 3.86, and 3.97 (12H, s)	3.78, 3.81, 3.91, and 3.93 (12H, s)	
C ₃ -H	2.75 (1H, q, <i>J</i> =16.8 and 2.2 Hz) 3.01 (1H, q, <i>J</i> =16.8 and 14.0 Hz)	2.83 (1H, q, <i>J</i> =16.7 and 3.7 Hz) 3.00 (1H, q, <i>J</i> =16.7 and 11.5 Hz)	
C ₂ -H	5.36 (1H, q, <i>J</i> =14.0 and 2.2 Hz)	5.41 (1H, q, <i>J</i> =11.5 and 3.7 Hz)	
C ₆ -H		6.10 (1H, s)	
C ₈ -H	6.35 (1H, s)		
C _{3',5'} -H	6.95 (2H, d, <i>J</i> =8.5 Hz)	6.90 (2H, d, <i>J</i> =8.5 Hz)	
C _{2',6'} -H	7.50 (2H, d, <i>J</i> =8.5 Hz)	7.50 (2H, d, <i>J</i> =8.5 Hz)	

a) In DMSO-*d*₆. b) In CDCl₃.

of anhydrous aluminium chloride in benzene solution, but the direct comparisons with the natural products were not undertaken.

In this paper, we wish to report the synthesis of 2',3',4,4',6'-pentahydroxychalcone (**4**) and its isomerization into 4',5,6,7- and 4',5,7,8-tetrahydroxyflavanone

(**5** and **6**) and, furthermore, the new fact that the structures originally assigned for **A** and **B** should be reversed from the comparisons of the properties of **5** and **6** with those of **A** and **B** derived from the natural product.

The alkaline condensation of 2,3,4,6-tetrakis(methoxymethoxy)acetophenone (**2**) prepared by the methoxymethylation of 2,3,4,6-tetrahydroxyacetophenone (**1**) with *p*-methoxymethoxybenzaldehyde afforded 2',3',4,4',6'-pentakis(methoxymethoxy)chalcone (**3**) as a pale yellow viscous oil. The subsequent demethoxymethylation of **3** with dilute hydrochloric acid in methanol gave 2',3',4,4',6'-pentahydroxychalcone (**4**). The structure of this chalcone was identified by its conversion into 2',3',4,4',6'-pentamethoxychalcone, which was identified by a comparison of the melting point, UV, and IR spectrum with those of an authentic sample.²⁾

A mixture of 4',5,6,7- and 4',5,7,8-tetrahydroxyflavanone (**5** and **6**) was obtained by boiling **4** with dilute hydrochloric acid in methanol; it was chromatographed on a column of silica gel to give **5** and **6**, both in 25% yields. 4',5,6,7- and 4',5,7,8-Tetraacetoxyflavanone (**7** and **8**) were obtained by acetylation of **5** and **6** with acetic anhydride-sulfuric acid and both **7** and **8** afforded 2',3',4,4',6'-pentaacetoxychalcone (**11**) by heating with a mixture of acetic anhydride and sodium acetate.

The structure of **5** and **6** were confirmed by the elemental analyses, by the studies of their UV, IR, and PMR spectra, and by the comparison of their tetramethyl ethers with the authentic samples of 4',5,6,7-⁴⁾ and 4',5,7,8-tetramethoxyflavanone⁵⁾ (**9** and **10**), prepared in a manner similar to that in the literature. The PMR spectral data of **5**, **6**, **7**, **8**, **9**, and **10** are shown in Table 1.

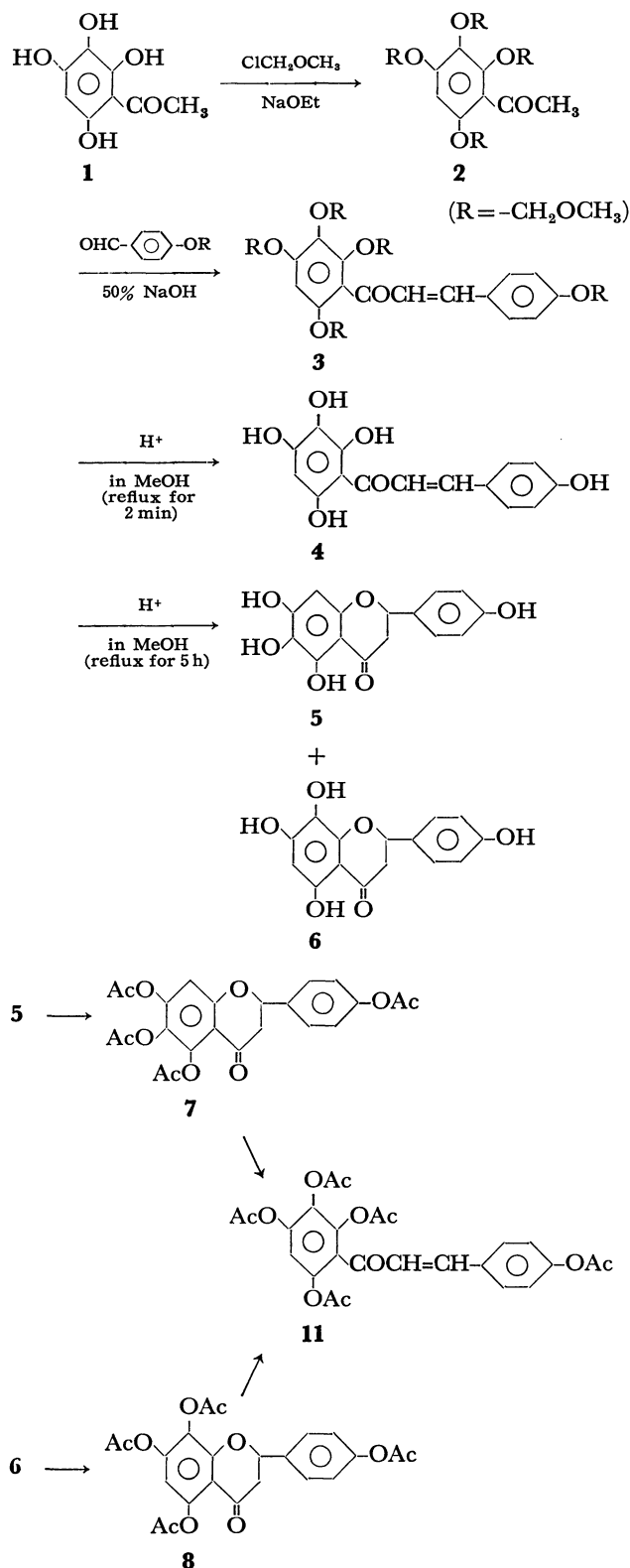
While Kuroda²⁾ proposed the structures **6** and **5** for carthamidin (**A**), mp 220 °C, and isocarthamidin (**B**), mp 240 °C, on the basis of the color phenomena of their hydroxyl groups, the IR spectra of **A** and **B** obtained from carthamin according to Kuroda's method²⁾ were identical with those of the synthetic **5** and **6**, respectively. Accordingly, it was proved that the old structures assigned for carthamidin (**A**) and isocarthamidin (**B**) should be reversed, as mentioned above. Finally, the comparison of the melting points of the synthetic **5**, **6**, **7**, **8**, and **11** with those of the derivatives of carthamin reported by Kuroda²⁾ are shown in Table 2.

TABLE 2. THE MELTING POINTS OF THE SYNTHETIC AND REPORTED **5**, **6**, **7**, **8**, AND **11**

Compound	Synthesized (°C)	Reported (°C)
4',5,6,7-Tetrahydroxyflavanone (5)	218	240
4',5,7,8-Tetrahydroxyflavanone (6)	248	220
4',5,6,7-Tetraacetoxyflavanone (7)	160	180
4',5,7,8-Tetraacetoxyflavanone (8)	178	158
2',3',4,4',6'-Pentaacetoxychalcone (11)	142	142

Experimental

All the melting points were uncorrected. The UV and IR spectra were recorded with a Hitachi 135 spectrophotom-



Scheme 1.

eter and Hitachi EPI-S2 spectrophotometer, respectively. The PMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz), using tetramethylsilane as an internal standard. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer.

2,3,4,6-Tetrahydroxyacetophenone (1). Into a mixture of 20 g of 1,2,3,5-benzenetetrol,⁶⁾ 10 g of acetonitrile, and 7 g of anhydrous zinc chloride in 200 ml of dry ether, dry hydrogen chloride gas was passed for 3 h under cooling with ice water, and the reaction mixture was left to stand overnight at 0 °C. After the solvent was removed by decantation, the residue was refluxed with 600 ml of water for 3 h. The reaction mixture was decolored with charcoal and filtered. After cooling, **1** was obtained from the filtrate as light yellow needles (16.8 g, 65%), mp 236–238 °C (lit.⁷⁾ 206–208 °C); MS *m/e* 184 (*M*⁺); IR (KBr) 1630 cm⁻¹ (C=O); PMR (DMSO-*d*₆) δ 2.60 (3H, s, -OAc), 6.02 (1H, s, C₅-H), 9.98, 11.18, and 12.18 (4H, -OH). Found: C, 52.39; H, 4.63%. Calcd for C₆H₈O₅: C, 52.18; H, 4.38%. Tetramethyl ether, mp 55–56 °C (lit.⁸⁾ 54 °C). Found: C, 60.33; H, 6.95%. Calcd for C₁₂H₁₆O₈: C, 59.99; H, 6.71%. Tetraacetate, mp 110–111 °C. Found: C, 54.61; H, 4.70%. Calcd for C₁₆H₁₆O₉: C, 54.55; H, 4.58%.

2,3,4,6-Tetrakis(methoxymethoxy)acetophenone (2). Into a solution of **1** (5 g) in 100 ml of absolute ethanol was added one fifth volume of a solution of sodium (8.8 g) in 140 ml of absolute ethanol with stirring at 15–20 °C. After 30 s, one fifth volume of chloromethyl ether (31 g) was added to the above solution over a 5 min interval with stirring at 15–20 °C, this operation was repeated four times under the same conditions. After the addition was completed, the reaction mixture was stirred for 10 min at 40 °C. The solvent was removed *in vacuo* and 100 ml of water was added to the residue and extracted with ether. The ether was evaporated to give an oily residue, which was chromatographed over silica gel. Elution with benzene-ethyl acetate (4:1) afforded **2** as a light yellow oil (2.9 g, 30%). IR (CHCl₃) 1963 cm⁻¹ (C=O); PMR (CDCl₃) δ 2.53 (3H, s, -OAc), 3.49, 3.51, 3.53, and 3.62 (8H, s, -CH₂-×4), 5.12, 5.16, 5.17, and 5.24 (12H, s, -CH₃×4), 6.86 (1H, s, C₅-H). Found: C, 52.99; H, 6.61%. Calcd for C₁₆H₂₄O₉: C, 53.33; H, 6.71%.

2',3',4,4',6'-Pentakis(methoxymethoxy)chalcone (3). To a mixed solution of **2** (600 mg) and *p*-methoxymethoxybenzaldehyde (510 mg) in 12 ml of methanol was added 6 ml of 50% aqueous sodium hydroxide solution with stirring at room temperature. After standing overnight, the reaction mixture was poured into cold water and extracted with ether. The evaporation of the solvent gave an oily residue, which was chromatographed over silica gel. Elution with benzene-ethyl acetate (4:1) afforded **3** as a viscous light yellow oil (830 mg, 98%). IR (CHCl₃) 1640 cm⁻¹ (C=O); PMR (CDCl₃) δ 3.34, 3.36, 3.42, 3.49, and 3.57 (15H, s, -CH₃×5), 5.05, 5.07, and 5.18 (6H, s, -CH₂-×3), 5.13 (4H, s, -CH₂-×2), 6.78 (1H, s, C₅-H), 6.99 (2H, d, *J*=8.5 Hz, C_{3,5}-H), 7.43 (2H, d, *J*=8.5 Hz, C_{2,6}-H), 6.85 (1H, d, *J*=16.0 Hz, C_α-H), 7.32 (1H, d, *J*=16.0 Hz, C_β-H). Found: C, 59.44; H, 6.65%. Calcd for C₂₅H₃₂O₁₁: C, 59.05; H, 6.34%.

2',3',4,4',6'-Pentahydroxychalcone (4). A mixture of **3** (400 mg) and 6 M hydrochloric acid (6 ml) in 16 ml of methanol was refluxed for 2 min. After cooling, the reaction mixture was poured into 30 ml of cold brine and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated to about 10 ml *in vacuo*. A small quantity of petroleum ether was added to the concentrated solution to give **4** as yellow crystals (170 mg, 74%), mp 181 °C. UV (EtOH) max: 375 nm (log ε=4.47); IR (KBr) 1625 cm⁻¹ (C=O); PMR (acetone-*d*₆) δ 6.07 (1H, s, C₅-H),

6.96 (2H, d, *J*=8.5 Hz, C_{3,5}-H), 6.73 (2H, d, *J*=8.5 Hz, C_{2,6}-H), 7.83 (1H, d, *J*=16.0 Hz, C_α-H), 8.24 (1H, d, *J*=16.0 Hz, C_β-H), 8.95, 11.36, and 11.54 (4H, s, OH). Found: C, 62.15; H, 4.54%. Calcd for C₁₅H₁₂O₆: C, 62.50; H, 4.20%.

Methylation of 4. A mixture of **4** (100 mg), potassium carbonate (2 g), and dimethyl sulfate (0.3 ml) in 20 ml of acetone was refluxed for 8 h. The reaction mixture was worked up in the usual manner and the crude product was chromatographed on a column of silica gel with benzene-ethyl acetate (4:1) to give the methyl ether of **4** (50 mg, 40%), mp 92–93 °C. UV (EtOH) max: 326 nm (log ε=4.47); IR (KBr) 1640 cm⁻¹ (C=O); PMR (acetone-*d*₆) δ 3.70 (6H, s, -OMe×2), 3.74, 3.77, and 3.87 (9H, s, -OMe×3), 6.52 (1H, s, C₅-H), 6.77 (1H, d, *J*=16.0 Hz, C_α-H), 7.22 (1H, d, *J*=16.0 Hz, C_β-H), 6.90 (2H, d, *J*=8.5 Hz, C_{3,5}-H), 7.53 (2H, d, *J*=8.5 Hz, C_{2,6}-H). Found: C, 66.82; H, 6.31%. Calcd for C₂₀H₂₂O₆: C, 67.01; H, 6.19%. The UV, IR, and PMR spectra of this methyl ether were completely identical with those of 2',3',4,4',6'-pentamethoxychalcone, mp 92–93 °C (lit.⁹⁾ 112 °C), which was prepared by the condensation of 2,3,4,6-tetramethoxyacetophenone with *p*-anisaldehyde.

Isomerization of 4 into 4',5,6,7- and 4',5,7,8-Tetrahydroxyflavanone (5 and 6).

A mixture of **4** (500 mg) and 6 M hydrochloric acid (5 ml) in 40 ml of methanol was refluxed for 5 h. The reaction mixture was evaporated *in vacuo* and the resulting residue was extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous sodium sulfate, the solvent was removed *in vacuo*, and the residue was chromatographed on a column of silica gel. Elution with ether-petroleum ether-formic acid (24:16:1) afforded a mixture of **5** and **6**. The subsequent silica gel column chromatography with carbon tetrachloride-ether-acetic acid (8:1:1) afforded **5** (100 mg, 20%) and **6** (100 mg, 20%), respectively.

4',5,6,7-Tetrahydroxyflavanone (5): Mp 218 °C (from chloroform); UV (EtOH) max: 300 nm (log ε=4.13) and 368 nm (log ε=3.18); IR (KBr) 1643 cm⁻¹ (C=O). Found: C, 62.31; H, 4.40%. Calcd for C₁₅H₁₂O₆: C, 62.50; H, 4.20%.

Tetraacetate (7): Mp 158 °C; UV (EtOH) max: 313 nm (log ε=4.04) and 327 nm (log ε=3.63); IR (KBr) 1685 and 1775 cm⁻¹ (C=O). Found: C, 60.22; H, 4.36%. Calcd for C₂₅H₂₀O₁₀: C, 60.52; H, 4.42%.

4',5,7,8-Tetrahydroxyflavanone (6): Mp 248 °C; UV (EtOH) max: 299 nm (log ε=4.17) and 370 nm (log ε=3.52); IR (KBr) 1642 cm⁻¹ (C=O). Found: C, 62.22; H, 4.68%. Calcd for C₁₅H₁₂O₆: C, 62.50; H, 4.20%.

Tetraacetate (8): Mp 178 °C; UV (EtOH) max: 264 nm (log ε=4.03) and 322 nm (log ε=3.52); IR (KBr) 1684 and 1770 cm⁻¹ (C=O). Found: C, 60.22; H, 4.35%. Calcd for C₂₅H₂₀O₁₀: C, 60.52; H, 4.42%.

Methylation of 5. A mixture of **5** (50 mg), potassium carbonate (3 g), and dimethyl sulfate (2 ml) in 15 ml of dry acetone was refluxed for 1 h. The reaction mixture was worked up in the usual manner and the crude product was chromatographed on a column of silica gel with ether-petroleum ether (3:1) to afford light yellow crystals. Recrystallization from methanol gave tetramethyl ether of **5** (27 mg, 46%), mp 120–121 °C; UV (EtOH) max: 280 nm (log ε=4.22) and 330 nm (log ε=3.68); IR (KBr) 1670 cm⁻¹ (C=O). Found: C, 66.27; H, 5.85%. Calcd for C₁₉H₂₀O₆: C, 66.27; H, 5.85%. The IR spectrum of this compound was completely identical with that of the authentic sample of 4',5,6,7-tetramethoxyflavanone (**9**) (mp 121 °C, lit.⁴⁾ 119.5–120.6 °C) prepared by the literature method.⁴⁾

Methylation of 6. Tetramethyl ether of **6**, mp 114–116 °C (37%), was obtained in a similar manner to that

described above. UV (EtOH) max: 286 nm ($\log \epsilon=4.23$) and 332 nm ($\log \epsilon=3.66$); IR (KBr) 1673 cm^{-1} (C=O). Found: C, 66.09; H, 5.93%. Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_6$: C, 66.27; H, 5.85%.

The IR spectrum of this compound was completely identical with that of the authentic sample of 4',5,7,8-tetramethoxyflavanone (**10**) (mp $114\text{--}115^\circ\text{C}$, lit.⁵) $138\text{--}140^\circ\text{C}$) prepared by the literature method.⁵⁾

2',3',4,4',6'-Pentaacetoxychalcone (11). This pentaacetate, mp 142°C (lit.²) mp 142°C), was obtained by acetylation of **7** and **8** in a manner similar to that described by Kuroda.²⁾ UV (EtOH) max: 313 nm ($\log \epsilon=4.47$); IR (KBr) 1640 and 1770 cm^{-1} (C=O); PMR (CDCl_3) δ 2.09, 2.11, and 2.27 (9H, s, $-\text{OAc} \times 3$), 2.22 (6H, s, $-\text{OAc} \times 2$), 7.12 (1H, s, $\text{C}_5\text{-H}$), 6.83 (1H, d, $J=16.0\text{ Hz}$, $\text{C}_6\text{-H}$), 7.43 (1H, d, $J=16.0\text{ Hz}$, $\text{C}_8\text{-H}$), 7.11 (2H, d, $J=8.5\text{ Hz}$, $\text{C}_{3,5}\text{-H}$), 7.54 (2H, d, $J=8.5\text{ Hz}$, $\text{C}_{2,6}\text{-H}$).

Carthamidin (A) and Isocarthamidin (B). Both **A**, mp 218°C (lit.²) 220°C), and **B**, mp 248°C (lit.²) mp 240°C), were obtained by hydrolysis of carthamin according to Kuroda's method.²⁾ The IR spectra of **A** and **B** were identi-

cal with those of **5** and **6**, respectively.

The present work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

- 1) Preliminary communications: H. Obara, J. Onodera, and Y. Kurihara, *Bull. Chem. Soc. Jpn.*, **44**, 289 (1971); H. Obara, J. Onodera, and F. Yamamoto, *Chem. Lett.*, **1973**, 915.
- 2) C. Kuroda, *Nippon Kagaku Zasshi*, **51**, 237 (1930).
- 3) N. Narasimhachari, V. D. Nageswara, and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A*, **29**, 404 (1949).
- 4) M. G. Stout, H. Reich, and M. N. Huffman, *J. Pharmaceutical Sciences*, **53**, 192 (1964).
- 5) G. Bargellini and S. M. Zoras, *Gazz. Chim. Ital.*, **64**, 202 (1934); *Chem. Abstr.*, **28**, 5054 (1934).
- 6) J. Onodera and H. Obara, *Nippon Kagaku Zasshi*, **1973**, 1808.
- 7) M. Nierenstein, *J. Chem. Soc.*, **1917**, 6.