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Synthesis of 2,2′-Biflavanones from Flavone via Electrolytic Reductive Coupling

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Flavone (**1**) was easily reduced by using the electrochemical method to give two hydrodimers of 2,2′-biflavanone(racemate) (**5a**) and 2,2′-biflavanone(meso) (**5b**) and one reductive product of flavanone (**6**). Their yields were dependent on the nature of electrodes, the kinds of supporting electrolytes and the reaction temperature. They were found to afford higher yields of 2,2′-biflavanone(racemate) (**5a**) and 2,2′-biflavanone (meso) (**5b**) (32.4% and 24.8%, 35.8% and 13.4%, respectively,) in the reaction conditions of Pb(-)/C(+)-H_2SO_4-7F/mol and C(-)/C(+)-H_2SO_4-5F/mol.

INTRODUCTION

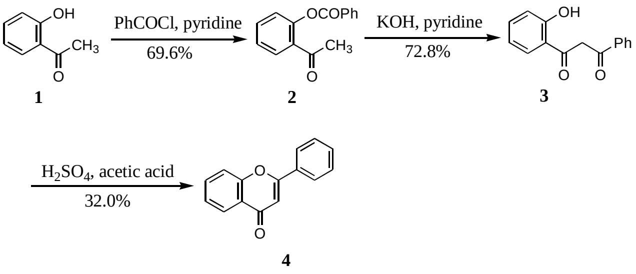
Biflavonoids are widely distributed in natural plants.[1] Early on, they were found to have strong biological activities including spasmolysis,[2a] peripheral vasodilatation, anti-bradykinin activity and antispasmogenic action against prostaglandin $PGE_{1,}$[2b] inhibition of cyclic GMP and cyclic AMP phosphodiesterase[2c~d] and inhibition of hepatoma cells.[2e] Recently, some biflavonoids were demonstrated to enhance suppression of lymphocyte preliferation,[3a] inhibition of phospholipase$C_{r1,}$[3b] anti-inflammatory activity,[3c] anti-HIV activity,[3d~e] anticomplementatory activity,[3f] antiviral activity[3g] and chemoprevention of hepatotoxicity.[3h]

Many synthetic attempts including Ullmann coupling,[4] Baker-Venkataraman rearrangement and cyclization,[5] cyclization from bichalcone,[6] oxidative coupling[7] and reductive coupling[8] were developed for preparations of some biflavonoids. Recently, Pd-cathode reduction[9] and photoinduced electron transfer reaction[10] were carried out for transformation of flavones to biflavanones. In our continuous study for synthetic application of biflavonoids, we report herein synthesis of 2,2′-biflavanones from flavones via electrolytic reductive coupling.

RESULTS AND DISCUSSION

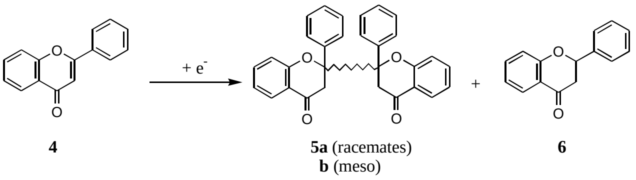
o-Hydroxyacetophenone (**1**) underwent an esterification with benzoyl chloride in the presence of pyridine to give o-benzoyloxyacetophenone (**2**) with a yield of 69.6%. o-Benzoyloxyacetophenone (**2**) followed a base-catalyzed Fries rearrangement to convert into o-hydroxydibenzoylmethane (**3**) with a yield of 72.8%. Finally, flavone (**4**) was obtained from cyclization of o-hydroxydibenzoylmethane (**3**) in the presence of acid with a yield of 32.0%, as shown in Scheme I.[11]

Scheme I



The electrochemical reduction of flavone (**4**) was carried out by using the H-type cell with a glass-filter diaphragm equipped with a series of electrodes and methanol with sulfuric acid or p-toulenesulfonic acid used as supporting electrolytes. Flavone (**4**) was found to be easily reduced to yield two dimers of 2,2′-biflavanone(racemate) (**5a**) and 2,2′-biflavanone(meso) (**5b**) and one reductive product of flavanone (**6**), as shown in Scheme II.

Scheme II



As shown in Table 1 and Table 2, yields were largely affected by the nature of electrodes, the kinds of supporting

Table 1. The Yields of Products for the Electrochemical Reduction of Flavone (**4**) at 0 °C

Entries	Reaction Conditions*[1]	Conversion (%)	Yields of Products (%)*[2] **5a**	**5b**	**6**	Current Efficiency (%)
1	Zn(-)/C(+), 0.1M H_2SO_4, 10F/mol	59.6	10.1	30.2		4.0
2	Al(-)/C(+), 0.1M H_2SO_4, 17F/mol	70.0	15.8	19.5	24.1	3.5
3	Pb(-)/C(+), 0.1M H_2SO_4, 7F/mol	68.3	32.4	24.8	2.0	8.5
4	C(-)/C(+), 0.1M H_2SO_4, 5F/mol	79.6	35.8	13.4		9.8
5	Cu(-)/C(+), 0.1M H_2SO_4, 10F/mol	100.0	4.1	2.0	62.1	6.8
6	Pt(-)/C(+), 0.1M H_2SO_4, 10F/mol	93.9	2.1	2.1	31.7	3.6
7	Ni(-)/C(+), 0.1M H_2SO_4, 15F/mol	50.3	1.1	0.8	5.6	0.4
8	Zn(-)/C(+), 0.1M PTSA, 5F/mol	62.8	24.8	8.5		6.6
9	Al(-)/C(+), 0.1M PTSA, 8F/mol	77.5	14.7	4.9		2.4
10	Pb(-)/C(+), 0.1M PTSA, 4F/mol	87.9	21.5	7.3		7.2
11	C(-)/C(+), 0.1M PTSA, 4F/mol	83.7	23.3	12.4		8.9
12	Cu(-)/C(+), 0.1M PTSA, 6F/mol	72.3	2.8	2.2	53.7	9.7
13	Pt(-)/C(+), 0.1M PTSA, 6F/mol	69.6	1.3	1.1	18.2	3.4
14	Ni(-)/C(+), 0.1M PTSA, 6F/mol	83.7	11.4	6.2		2.9

*[1] PTSA: p-toulenesulfonic acid.

*[2] Yield based on consumed flavone (**4**).

Table 2. The Temperature Effects of the Product Yields for the Electrochemical Reduction of Flavone (**4**)

Entries	Reaction Temperature at a Specified Condition*[3]	Yields of Products (%)*[4] **5a**	**5b**	**6**	Current Efficiency (%)
1	-10 °C at A Condition	28.2	9.9		7.6
2	0 °C at A Condition	35.8	13.4		9.8
3	+10 °C at A Condition	16.8	11.1	2.7	6.1
4	-10 °C at B Condition	9.8	5.1		2.9
5	0 °C at B Condition	23.3	12.4		8.9
6	+10 °C at B Condition	13.0	8.9	12.8	6.8
7	-10 °C at C Condition	17.8	12.1	1.9	4.5
8	0 °C at C Condition	32.4	24.8	2.0	8.5
9	+10 °C at C Condition	5.1	6.1	30.4	5.9
10	-10 °C at D Condition	15.5	9.6		6.3
11	0 °C at D Condition	21.5	7.3		7.2
12	+10 °C at D Condition	16.0	9.9	17.5	10.8

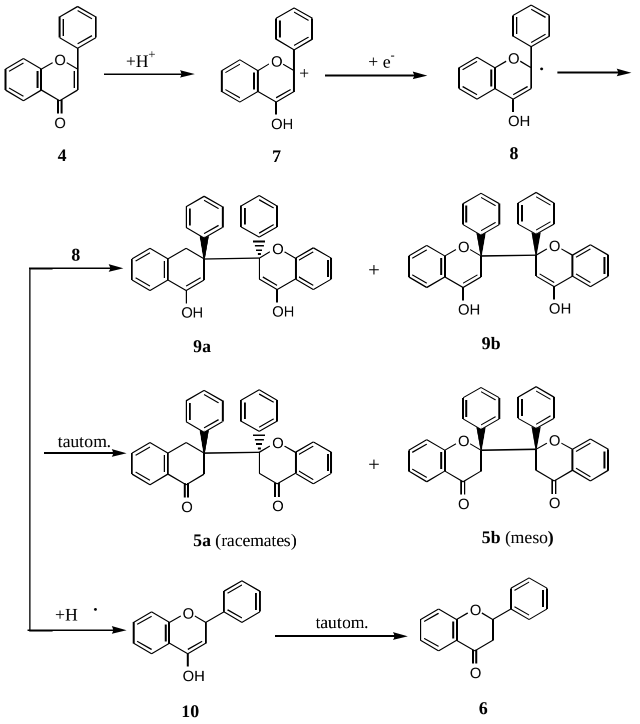
*[3] A Condition: C(-)/C(+), 0.1M H_2SO_4, 5F/mol; B Condition: C(-)/C(+), 0.1M PTSA, 4F/mol; C Condition: Pb(-)/C(+), 0.1M H_2SO_4, 7F/mol; D Condition: Pb(-)/C(+), 0.1M PTSA, 4F/mol.

*[4] Yield based on consumed flavone (**4**).

electrolytes and the reaction temperature. The reaction conditions of Pb(-)/C(+)-H_2SO_4-7F/mol (Entry 3 in Table 1) and C(-)/C(+)-H_2SO_4-5F/mol (Entry 4 in Table 1) were found to afford higher yields of 2,2′-biflavanone(racemate) (**2a**) and 2,2′-biflavanone(meso) (**2b**) (32.4% and 24.8%, 35.8% and 13.4%, respectively). However, there was a higher yield of flavanone (**6**) (62.1%) in the reaction condition of Cu(-)/C(+)-H_2SO_4-10F/mol (Entry 5 in Table 1).

Electrolytic coupling of α,β-unsaturated carbonyl compounds may have two main ways of dimerization; one is coupled at the β-carbon, the other is at the α-carbon.[12] Often a β,β-coupled compound is given as a major product. Although flavone (**4**) has a phenyl substitutent at the 2-position, the coupling at the 2-position was still achieved. Therefore the mechanism of the electrochemical reduction of flavone (**4**) is proposed as showed in Scheme III. Flavone (**4**) was first protonated to yield a cation (**7**)[9] and then followed to accept one electron to give a radical (**8**). The radical (**8**) could undergo either to couple with a radical (**8**) and then to follow tautomerism to afford 2,2′-biflavanone (**5a**) and 2,2′-biflavanone

Scheme III



(**5b**) or to accept a proton to afford enol (**10**) and then to follow tautomerism to form flavanone (**6**).

CONCLUSION

Flavone (**4**) was easily coupled by using the electrochemical method to give two dimers of 2,2′-biflavanone (racemate) (**5a**) and 2,2′-biflavanone(meso) (**5b**) and one reductive product of flavanone (**6**). Their yields were dependent on the nature of electrodes, the kinds of supporting electrolytes and the reaction temperature. Therefore 2,2′-biflavanoves were easily synthesized from flavones via an electrolytic reductive coupling.

EXPERIMENTAL SECTION

General

The melting points were measured without correction on a Yanagimoto Micromelting Point Apparatus. ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured on a Varian INOVA-500 spectrometer. Mass spectral were determined on a VG Quattro GC/MS/MS DS spectrometer. High resolution mass spectra were determined on a VG 70-250S GC/MS spectrometer. Elemental analyses were measured on a Heraeus CHN-O-Rapid Analyzer.

Synthesis of Flavone (4)

(a) o-Benzoyloxyacetophenone (2)

A solution of o-hydroxyacetophenone (**1**) (10.04 g, 73.74 mmol) and pyridine (14.50 g, 103.15 mmol) in a flask was stirred in a water bath at 40 °C and to which was added benzoyl chloride (14.50 g, 103.15 mmol). The reaction solution was stirred for 30 minutes at 40 °C and was poured into a solution of 1 M HCl (120 mL). The precipitate was filtered and was washed with water. The product was recrystallized from methanol to give a white crystal of 12.32 g of o-benzoyloxyacetophenone (**2**) with a yield of 69.6%, m.p. 87-8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.55 (s, 3H), 7.23-7.26 (m, 1H), 7.35-7.40 (m, 1H) 7.51-7.66 (m, 4H), 7.86-7.89 (m, 1H), 8.20-8.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 29.78, 123.90, 126.16, 128.69, 129.21, 130.26, 130.29, 131.26, 133.40, 133.81, 149.35, 165.14, 197.55; MS (FAB, *m/z*, %): 105 (100), 136 (55.2), 154 (64.5), 241 (14.2, M), 242 (4.3, M+1); Anal.: Found: C: 74.32%, H: 5.03%; Calcd. for $C_{15}H_{12}O_3$: C: 74.99%, H: 5.03%.

(b) o-Hydroxydibenzoylmethane (3)

o-Benzoyloxyacetophenone (**2**) (3.01 g, 12.54 mmol) was dissolved in 5 mL of dry pyridine. The solution was heated to 50 °C in a water bath and to which was added 1.06 g of dry potassium hydroxide (18.89 mmol). The reaction solution was stirred for 30 minutes at 50 °C. The solution was acidified by adding 10% acetic acid (30 mL) and the precipitate was collected by suction filtration. The precipitate was recrystallized to afford a yellow crystal of 2.19 g of o-hydroxydibenzoylmethane (**3**) with a yield of 72.8%, m.p. 120-1 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.85 (s, 1H), 6.90-7.03 (m, 2H), 7.45-7.57 (m, 4H), 7.78-7.81 (m, 1H), 7.93-7.97 (m, 2H), 12.10 (s, 1H), 15.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 92.26, 118.80, 118.94, 119.08, 126.80, 128.49, 128.78, 128.88, 132.42, 135.84, 162.45, 177.48, 195.67; MS (EI, *m/z*, %): 105 (100), 121 (13.0), 240 (m, 8.6), 241 (M+1, 1.2); MS (FAB, *m/z*, %): 154 (100), 240 (19.8), 241 (M+1, 46.5); Anal.: Found: C: 74.90%, H: 5.10%; Calcd. for $C_{15}H_{12}O_3$: C:74.99%, H: 5.03%.

(c) Flavone (4)

A solution of o-hydroxydibenzoylmethane (**3**) (7.74 g, 32.25 mmol) dissolved in 55 mL of glacial acetic acid was heated in a boiling water bath and to which was added 5 mL of concentrated sulfuric acid. The reaction solution was stirred for 1 hour in a boiling water bath and was poured into 200 mL of water. The precipitate was filtered and was recrystallized from n-hexane to produce a white crystal of 2.29 g of flavone (**4**) with a yield of 32.0%, m.p. 98-9 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.84 (s, 1H), 7.41-7.43 (m, 1H), 7.53-7.60 (m, 4H), 7.69-7.71 (m, 1H), 7.93-7.96 (m, 1H), 8.23-8.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 107.62, 118.09, 123.97, 125.24, 125.72, 126.31, 129.05, 131.61, 131.80, 133.78, 156.27, 163.42, 178.49; MS (EI, *m/z*, %): 92 (75.7), 120 (96.8), 165 (13.0), 194 (45.3), 222 (M, 100); MS (FAB, *m/z*, %): 136 (89.4), 154 (100), 233 (M+1, 40.3); Anal.: Found: C:81.06%, H: 4.63%; Calcd. for $C_{15}H_{10}O_2$: C: 81.07%, H: 4.54%.

Typical Anodic Dimerization of Flavone (4)

Cathodic dimerization of flavone (**4**) was carried out in a 40 mL H-type cell with a glass-filter diaphragm equipped with a Pb-plat (2 × 2 cm) as a cathode and a graphite rod (diameter: 0.7 cm) as an anode. The cathode compartment contained a solution of flavone (**4**) (100.0 mg, 0.35 mmol) in 2 mL of methanol with sulfuric acid (0.1 mL, 0.1 M) used as supporting electrolytes. The anode compartment contained a solution of 20 mL of methanol with sulfuric acid (0.1 mL, 0.1 M) used as supporting electrolytes. After 7 F/mol of electricity was passed with constant current of 10 mA under the condition of external cooling (0 °C), the cathode solution was evaporated to remove the solvent under a reduced pressure. The residue was dissolved in ethyl ether and was washed with saturated aqueous sodium bicarbonate and saturated brine. The organic layer was dried over sodium sulfate and evaporated to remove the solvent. The residue was chromatographed on silica gel and was eluted with benzene to give three white crystals: 2,2′-biflavanone(recemate) (**5a**) (32.5 mg, 0.07 mmol, 32.4%, m.p. 212-5 °C), 2,2′-biflavanone (meso) (**5b**) (24.9 mg, 0.06 mmol, 24.8%, m.p. 288-290 °C) and flavone (**6**) (2.3 mg, 2.0%, m.p. 77-80 °C); 2,2′-biflavanone(recemate) (**5a**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.35 (d, 2H, J = 16.5 Hz), 3.96 (d, 2H, J = 16.5 Hz), 6.91-6.94 (m, 4H), 7.08-7.18 (m, 10H), 7.50-7.47 (m, 2H), 7.67-7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 41.02, 87.96, 118.23, 121.40, 121.47, 126.48, 127.74, 128.61, 128.84, 135.00, 136.18, 159.27, 191.24; MS (EI, *m/z*, %): 92 (16.1), 103 (14.9), 121 (54.6), 223 (M/2, 100), 224 (M/2+1, 14.2); HRMS: 446.1515 (M^+), calcd. 446.1518; 2,2′-biflavanone (meso) (**5b**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.12 (d, 2H, J = 16.0 Hz), 3.65 (d, 2H, J = 16.0 Hz), 6.88-6.91 (m, 2H). 7.12 (d, 2H, J = 8.0 Hz), 7.22-7.39 (m, 8H), 7.39 (d, 2H, J = 6.5 Hz), 7.46-7.49 (m, 2H), 7.58-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 42.42, 87.11, 117.94, 121.34, 121.50, 126.50, 128.10, 128.48, 129.09, 135.91, 126.22, 158.76, 190.50; MS (EI, *m/z*, %): 121 (14.2), 223 (M/2, 100), 224 (M/2+1, 14.2); HRMS: 446.1517 (M^+), calcd. 446.1518; flavanone (**6**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.86-2.90 (m, 1H), 3.05-3.11 (m, 1H), 5.46-5.49 (m, 1H), 7.03-7.06 (m, 2H), 7.37-7.50 (m, 6H), 7.9-7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 30.91, 44.66, 79.59, 118.12, 121.61, 126.13, 127.03, 128.77, 128.84, 136.20, 207.01; MS (EI, *m/z*, %): 92 (85.0), 104 (44.7), 120 (100), 121 (22.9), 147 (45.3), 223 (21.7), 224 (M, 24.8), 225 (M+1, 3.1); HRMS: 224.0834 (M^+), calcd. 224.0837.

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Key Words

Flavone; Flavanone; Biflavanones; Electrolytic reductive coupling; Hydrodimerization.

REFERENCES

1. (a) Harborne, J. B.; Mabry, T. J. *The Flavonoids: Advances in Reseach*; Chapman and Hall: New York, 1982; pp 505-533. (b) Ferreira, D.; Steynberg, J. P.; Roux, D. G.; Brandt, E. V. *Tetrahedron* **1992**, *48*, 1743.
2. (a) Horhammer, L.; Wagner, H.; Reinharht, H. *Z. Naturforsch* **1967**, *22B*, 768. (b) Natarajan, S.; Murti, V. V. S.; Seshadri, T. R.; Ramaswami, A. S. *Curr. Sci.* **1970**, *39*, 533. (c) Ruckstuhl, M.; Beretz, W. B.; Anton, R.; Landry, Y. *Biochem. Pharmacol.* **1979**, *28*, 535. (d) Beretz, A.; Joly, N.; Stochet, J. C.; Anton, R. *Planta. Med.* **1979**, *36*, 193. (e) Joly, M.; Beck, J. P.; Haag-Berrcuier, M.; Anton, R. *Planta. Med.* **1980**, *39*, 230.
3. (a) Lee, S. L.; Choi, J. H.; Son, K. H.; Chang, H. W.; Kong, S. S.; Kim, H. p. *Life Sci.* **1995**, *57*, 551. (b) Lee, H. S.; Ko, H. R.; Ryu, S. Y.; Oh, W. K.; Kim, B. Y.; Ahn, S. C.; Mheen, T. I.; Ahn, J. S. *Planta Med.* **1997**, *63*, 266. (c) Gil, B.; Sanz, M. J.; Terencio, M. C.; Gunasegaran, R.; Paya, M.; Alcaraz, M. J. *Biochem. Pharmacol.* **1997**, *53*, 733. (d) Lin, Y. M.; Anderson, H.; Flavin, M. T.; Pai, Y. H. *J. Nat. Prod.* **1997**, *60*, 884. (e) Vlietinck, A. J.; Breuyne, T. D.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97. (f) Cimanga, K.; Bruyne, T. D.; Aper, S.; Pireters, L.; Totte, J.; Kambu, K.; Tona, L.; Bakana, P.; Ufford, L. Q.; Beukelman, C.; Labadie, R.; Vlietinok, A. J. *Planta Med.* **1999**, *65*, 213. (g) Lin, Y. M.; Flavin, M. T.; Schure, R.; Chen, F. C.; Sidwell, R.; Barnard, D. L. *Planta*

Med. **1999**, *65*, 120. (h) Farombi, E. O.; Tahnteng, J. G.; Agboola, A. O. *Food Chem. Toxicol*. **2000**, *38*, 1535.

4. Mitsuhashi, H.; Shimizu, Y. *Chem. Pharm. Bull. Jpn*. **1959**, *7*, 748.
5. (a) Moriyama, S.; Okigawa, M.; Kawano, N. *Tetrahedron Lett*. **1972**, 2105. (b) Zhu, J.; Wang, Q.; Li, Y. *J. Chem. Soc. Chem. Commun*. **1988**, 1549.
6. (a) Ahmad, S.; Razaq, S. *Tetrahedron* **1976**, *32*, 503. (b) Ahmad, S.; Razaq, S. *Tetrahedron Lett*. **1971**, 4633.
7. (a) Berge, D. D.; Kale, A. V.; Sharma, T. C. *Chem. Ind.(London)* **1979**, 282. (b) Molyneux, R. J.; Waiss, A. C.; Haddon, W. F. *Tetrahedron* **1970**, *26*, 1409.
8. (a) Kirrsretter, R. G. H.; Vagt, U. *Chem. Ber.* **1981**, *114*, 630. (b) Li, Y. L.; Zhang, F. J.; Wang, Q. G. *Chin. J. Chem*. **1992**, *10*, 359.
9. Lu, K. K.; Tan, Z.; Li, Y. L.; Wang, X. *Chin. Chem. Lett.* **1995**, *6*, 143.
10. (a) Yokoe, I.; Taguchi, H.; Shirataki, Y.; Komatsu, M. *J. Chem. Soc. Chem. Commun*. **1979**, 333. (b) Chen, C. F.; Zha, Y.; Liu, Y. C.; Xu, J. H. *Tetrahedron Lett*. **1995**, *36*, 2835.
11. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman Scientific & Technical: New York, 1989; pp 1193-1195.
12. (a) Lund, H.; Baizer, M. M. *Organic Electrochemistry*; Marcel Dekker, Inc.: New York, 1991; pp 433-464. (b) Jaeger, D. A.; Bolikal, D.; Nath, B. *J. Org. Chem*. **1987**, *52*, 276.