

FURAN *o*-AMINONITRILES AS PRECURSORS TO FLAVONE ANALOGUES¹

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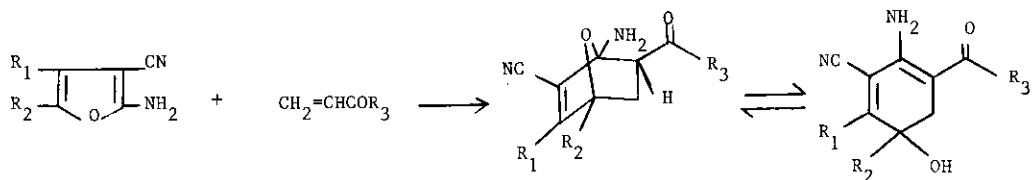
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Abstract - A procedure utilizing furan *o*-aminonitriles as precursors in the synthesis of substituted flavone analogues is reported. The key intermediates, *o*-hydroxyacetophenones, are obtained by a Diels-Alder reaction between the furans and methyl vinyl ketone.

We have previously demonstrated² that the Diels-Alder reaction between furan *o*-aminonitriles (1, Scheme 1)³ and various dienophiles (2) such as methyl vinyl ketone or methyl acrylate could be exploited for the synthesis of uniquely substituted anthranilic acid analogues (2-aminobenzo-nitriles) (4), which in turn serve as starting materials for the synthesis of novel substituted heterocyclic systems; *viz.*, benzodiazepines⁴ and quinazolones.⁵ This Diels-Alder reaction between the furan *o*-aminonitrile and monoactivated dienophiles occurs under mild conditions (*i.e.*, refluxing acetone or dioxane). This is in sharp contrast to the drastic conditions generally employed in Diels-Alder reactions with 2,5-disubstituted furans.⁶ Work-up of the Diels-Alder adduct (3) with concentrated sulfuric acid and glacial acetic acid leads to the formation of anthranilic acid analogues (4, R₃ = OCH₃, CH₃) through dehydration of the adduct. On the other hand, work-up of the adduct with aqueous hydrochloric acid leads directly to *o*-hydroxyacetophenones (5, R₃ = CH₃) as the only isolable product (Scheme 1). In this latter case, the enamine form (3) of the adduct is hydrolyzed prior to dehydration.

We wish to report now the utilization of several *o*-hydroxyacetophenones derived by this procedure as precursors for the synthesis of previously inaccessible substituted flavone analogues (Scheme 2).⁷⁻¹³ The esterification of the readily obtained *o*-hydroxyacetophenones (5) with an appropriate benzoyl chloride proceeded without difficulty to yield the benzoates (7), according to the classical Schotten-Baumann reaction. The Baker-Venkataraman rearrangement was utilized for the synthesis of the α -benzoyl-2-hydroxyacetophenones (8). Treatment of the benzoates (7) with potassium hydroxide and pyridine⁷⁻¹⁰ gave the diketones (8) in good yields. The flavones were obtained without difficulty by refluxing the diketones (8) in glacial acetic

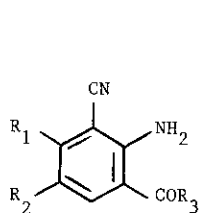
Scheme 1



1a, $R_1 = R_2 = CH_3$

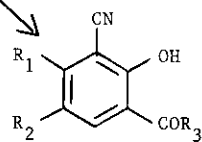
1b, $R_1/R_2 = -(CH_2)_4-$

2



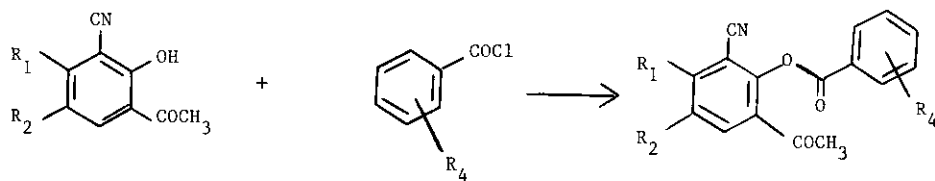
4

3



5

Scheme 2

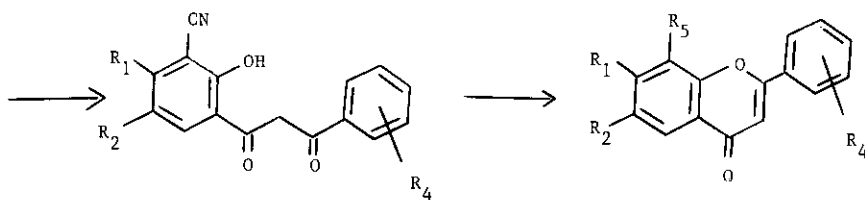


5a, $R_1 = R_2 = CH_3$

5b, $R_1/R_2 = -(CH_2)_4-$

6

7



8

9, $R_5 = CN$

10, $R_5 = CONH_2$

11, $R_5 = COOH$

acid and sodium acetate.⁷⁻¹⁰ Structural assignments were based on ir and ¹H-nmr spectra, as well as elemental analyses.

Hydrolysis of ortho disubstituted aromatic nitriles to aromatic acids is known to proceed with difficulty.¹⁴⁻¹⁶ Acid hydrolysis (80% sulfuric or syrupy phosphoric acid) will yield the amide (10) which is subject to marked steric inhibition by ortho substituents. Such sterically hindered amides may be converted to the carboxylic acids¹⁷ by treatment with nitrous acid.¹⁴⁻¹⁶

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Melting points in excess of 300°C were determined on a Mel-Temp capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Satisfactory ir (Perkin-Elmer 684 grating spectrophotometer, KBr) and ¹H-nmr (90 MHz JEOL FX90Q spectrometer, Me₄Si as internal reference) spectra were obtained for all new compounds. Low-resolution mass spectra were determined on a Finnigan 4023 chromatograph-mass spectrometer by a direct probe and are expressed in m/z units.

3-Cyano-4,5-dimethyl-2-hydroxyacetophenone (5a). 2-Amino-3-cyano-4,5-dimethylfuran³ (1a, 72g, 0.53 mol) was dissolved in 400 ml of acetone, treated with 37.1 g (0.53 mol) of methyl vinyl ketone and refluxed with continuous stirring. After about 7 h a small amount of precipitate formed. Water (40 ml) was added to dissolve the precipitate and the reflux was continued. After 18 h, the mixture was poured into 1 l of water containing 100 ml of concentrated HCl. This mixture was heated at 80±5°C for 2 h. An off-white solid appeared as voluminous needles. The mixture was cooled and the solid was collected, washed with water, and air dried. The product was recrystallized from ethyl acetate-petroleum ether (bp 30-60°C) to yield 80.5 g (81%) of 5: mp 131-133°C (lit.⁴ mp 133-134°C): ir (KBr) 3000 (br), 2220, 1630 cm⁻¹; ¹H-nmr (Me₂SO-d₆) δ 2.26 (s, 3H, 5-CH₃), 2.42 (s, 3H, 4-CH₃), 2.65 (s, 3H, COCH₃), 8.02 (s, 1H, 6-CH), 12.80 (s, 1H, OH).

3-Cyano-2-hydroxy-4,5-tetramethyleneacetophenone (5b). This compound was prepared from 2-amino-3-cyano-4,5-tetramethylenefuran³ and methyl vinyl ketone after the procedure described for 5a. The product was recrystallized from ethyl acetate (54% yield): mp 150-152°C; ir (KBr) 2220, 1640 (br) cm⁻¹; ¹H-nmr (CDCl₃) δ 1.70 (m, 4H, -(CH₂)₂-), 2.50 (s, 3H, COCH₃), 2.70 (m, 4H, -(CH₂)₂-), 7.45 (s, 1H, 6-CH), 12.55 (s, 1H, OH). Anal. Calcd for C₁₃H₁₃N₂O₂: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.60; H, 6.11; N, 6.54.

3-Cyano-4,5-dimethyl-2-benzoyloxyacetophenone (7a) The 2-hydroxyacetophenone (5, 30 g, 0.159 mol) and benzoyl chloride (22.5 g, 0.159 mol) were dissolved in 400 ml of dioxane. To this solution, triethylamine (32.2 g, 0.318 mol) was added dropwise over a period of 30 min. The

mixture was allowed to stir overnight at room temperature. During this time, a white precipitate (triethylamine hydrochloride) appeared. The precipitate was removed by filtration and the golden supernate was concentrated in vacuo. The concentrate was dissolved in ethyl acetate and treated with charcoal. After removing the charcoal, petroleum ether (bp 30-60°C) was added to the hot ethyl acetate solution until the mixture was turbid. This mixture was allowed to stand at room temperature to complete precipitation of pure (ethyl acetate-petroleum ether) **7a** (37 g, 79%): mp 122-124°C; ir (KBr) 2225, 1745, 1690 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 2.40 (s, 3H, 5- CH_3), 2.51 (s, 3H, 4- CH_3), 2.53 (s, 3H, COCH_3), 7.50-8.20 (m, 6H, ArH). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.61; H, 5.17; N, 4.73.

Some substituted analogues of **7a** prepared in a similar manner are included in Table I and Table III (**7c** - **7k**).

3-Cyano-4,5-tetramethylene-2-benzoyloxyacetophenone (7b). This compound was prepared from **5b** and benzoyl chloride after the procedure described for **7b**. The product was recrystallized from ethyl acetate (80.7%): mp 148-151°C; ir (KBr) 2225, 1745, 1680 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 1.75 (m, 4H, $-(\text{CH}_2)_2-$), 2.49 (s, 3H, COCH_3), 2.90 (m, 4H, $-(\text{CH}_2)_2-$), 7.50-8.30 (m, 6H, ArH).

α -Benzoyl-2-hydroxy-3-cyano-4,5-dimethylacetophenone (8a). Compound **7a** (5g, 0.017 mol) and powdered potassium hydroxide (1.8g, 0.032 mol) were refluxed with stirring for 2 h in 80 ml of pyridine under a nitrogen atmosphere. After refluxing for 2 h, an additional 30 ml of pyridine was added to the mixture. The yellow slurry was allowed to stir overnight at room temperature. The yellow slurry was poured into 100 ml of cold water containing 20 ml of concentrated HCl. The pH was then adjusted, if necessary, to Congo Red before the yellow precipitate was collected, washed with water, and air dried. The product was recrystallized from ethanol to give 3.8 g (76%): mp 216-218°C; ir (KBr) 3120, 2210, 1610 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 2.30 (s, 3H, 5- CH_3), 2.50 (s, 3H, 4- CH_3), 6.75 (s, 1H, vinylic proton), 7.48 (m, 6H, ArH), 12.75 (s, 1H, phenolic OH), 15.35 (s, 1H, enolic OH). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3$: C, 73.72, H, 5.12; N, 4.78. Found: C, 73.77; H, 5.17; N, 4.75.

Some substituted analogues of **8a** prepared in a similar manner are included in Table I and Table III (**8c-8k**).

α -Benzoyl-2-hydroxy-3-cyano-4,5-tetramethyleneacetophenone (8b). This compound was prepared from **7b** after the procedure described for **8a**. The product was recrystallized from ethanol (79.5%): mp 179-181°C; ir (KBr) 2225, 1610 cm^{-1} .

8-Cyano-6,7-dimethylflavone (9a). Compound **8a** (2 g, 0.007 mol) was suspended in 35 ml of glacial acetic acid. To this mixture was added 9.3 g (0.07 mol) of sodium acetate. This mixture was heated at reflux (oil bath temperature was 140 $\pm$ 2°C) for 4 h with stirring. The yellow suspension became a dark clear solution. The reaction mixture was allowed to cool to

room temperature, and then it was poured into 100 ml of ice cold water. The pale yellow precipitate was collected, washed with water, and allowed to air dry. The material was recrystallized from methanol, with sufficient dimethylformamide for dissolution, to give 1.7 g (91%) of **9**: mp 245-247°C; ir (KBr) 3070, 2220, 1640, 1625, 1605, 1570 cm^{-1} ; $^1\text{H-nmr}$ ($\text{Me}_2\text{SO-d}_6$) δ 2.40 (s, 3H, 6- CH_3), 2.61 (s, 3H, 7- CH_3), 6.79 (s, 1H, 3-CH), 7.48-8.08 (m, 6H, ArH). Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 78.55; H, 4.73; N, 5.09. Found: C, 78.65; H, 4.75; N, 5.05.

Some substituted analogues of **9a** prepared in a similar manner are included in Table I and Table III (**9c-9k**).

8-Cyano-6,7-tetramethyleneflavone (9b). This compound was prepared from **8b** after the procedure described for **9a**. The product was recrystallized from methanol, with sufficient dimethylformamide for dissolution (89.3%): mp 230.5-232.5°C; ir (KBr) 2260, 1660 cm^{-1} ; $^1\text{H-nmr}$ ($\text{Me}_2\text{SO-d}_6$) δ 1.90 (m, 4H, $-(\text{CH}_2)_2-$), 3.00 (m, 4H, $-(\text{CH}_2)_2-$), 6.80 (s, 1H, 3-CH), 7.50-8.00 (m, 6H, ArH). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_2$: C, 79.72; N, 5.02; H, 4.65. Found: C, 79.55; N, 5.05; H, 4.67.

8-Carboxamido-6,7-dimethylflavone (10a). Compound **9a** (3 g, 0.01 mol), 15 ml of water, and 35 ml of sulfuric acid were heated in an oil bath at temperatures of $170\pm 5^\circ\text{C}$ for 3 h. The dark solution was cooled to room temperature and poured into 200 ml of ice-water. The off-white solid was filtered and recrystallized from dioxane to give 1.6 g (55%) of slightly tan crystals: mp 346-347°C; ir (KBr) 3330, 3060, 1675, 1595 cm^{-1} ; $^1\text{H-nmr}$ ($\text{Me}_2\text{SO-d}_6$) δ 2.37 (s, 3H, 6- CH_3), 2.50 (s, 3H, 7- CH_3), 7.05 (s, 1H, 3-CH), 7.61 (m, 6H, ArH). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.68; H, 5.20; N, 4.74.

4'-Methoxy-8-carboxamido-6,7-dimethylflavone (10c). Compound **9c** (2 g, 0.0066 mol) was suspended in 100 ml of 85% H_3PO_4 and stirred at $170\pm 5^\circ\text{C}$ in an oil bath for 2 h. The dark mixture was cooled and poured into 800 ml of ice water. The beige solid was collected and recrystallized from dioxane, with sufficient dimethylformamide for dissolution, to give 2 g (94%) of **10c**: mp 354-355°C; ir (KBr) 3310, 3280, 1680, 1630, 1610 cm^{-1} ; $^1\text{H-nmr}$ (CF_3COOD) δ 2.62 (s, 3H, 6- CH_3), 2.70 (s, 3H, 7- CH_3), 4.05 (s, 3H, 4'- CH_3O), 7.29-8.31 (m, 6H, ArH). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.65; H, 5.35; N, 4.31.

6,7-Dimethylflavone-8-carboxylic Acid (11a). 8-Cyano-6,7-dimethylflavone (**9a**, 5 g, 0.02 mol) was suspended in 50 ml of 80% sulfuric acid. This mixture was heated with stirring at $170\pm 5^\circ\text{C}$ in an oil bath for 3 h. In general, the resulting amides (**10a**) were typically not isolated. Thus, the dark reddish clear solution was cooled to room temperature and transferred to a 1 l beaker. The mixture was cooled to 5°C with an ice-salt bath and treated with 3 g of sodium nitrite (0.4 mol) dissolved in a minimal amount of water. For best results, the aqueous sodium nitrite must be added below the acidic layer. The addition of sodium nitrite solution generally

required about 30 min with much foaming occurring. The mixture was stirred for 1 h at 5°C once the addition of sodium nitrite was complete. Urea (3 g) was then added to the mixture and the temperature was slowly raised to 80°C and kept there for 2 h. The mixture was cooled and diluted with 100 ml of water. The resulting precipitate was collected, air dried, and recrystallized from ethanol and benzene to yield 4.8 g (81%) of 11a: mp 244-246°C; ir (KBr) 3340 (br), 3060, 1705, 1610 cm^{-1} ; $^1\text{H-nmr}$ ($\text{Me}_2\text{SO-d}_6$) δ 2.38 (s, 6H, 6,7- CH_3), 7.03 (s, 1H, 3-CH), 7.98-8.06 (m, 7H, ArH); ms, m/z: 294. Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{O}_4$: C, 73.48; H, 4.79. Found: C, 73.51; H, 4.84.

Some substituted analogues of 11a prepared in a similar manner are included in Table II and Table III (11c-11k).

6,7-Tetramethylene-flavone-8-carboxylic Acid (11b). 8-Cyano-6,7-tetramethylene-flavone (9b, 2 g, 0.00664 mol) was suspended in 75 ml of 85% H_3PO_4 and stirred in an oil bath at 175°C for 3 h. The mixture was cooled slightly and poured onto ice-water. A beige product (amide) was collected and air dried. Into a 1 l beaker containing 50 g of crushed ice was charged 100 ml of concentrated sulfuric acid. When the internal temperature reached 20°C, the amide was added with stirring. The mixture was cooled to 0-5°C and cautiously treated with 6 g of solid sodium nitrite (excess) maintaining the temperature of the stirred mixture below 10°C. After stirring at 0°C for 2 h, the mixture was allowed to warm to room temperature. After stirring overnight at room temperature, the mixture was cooled and treated with 6 g of urea dissolved in a minimum amount of water. The chilled mixture was diluted to 800 ml with water and filtered. The pale yellow solid was collected and air dried. After recrystallization from ethanol, 2.1 g (98%) of 11b was obtained: mp 258-260°C; ir (KBr) 1710, 1610 cm^{-1} ; $^1\text{H-nmr}$ ($\text{Me}_2\text{SO-d}_6$) δ 1.78 (s, 4H, $-(\text{CH}_2)_2-$), 2.88 (s, 4H, $-(\text{CH}_2)_2-$), 7.02 (s, 1H, 3-CH), 7.60 (m, 3H, ArH), 7.80 (s, 1H, 5-CH), 8.00 (m, 2H, ArH); ms, m/z: 320. Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{O}_4$: C, 74.99; H, 5.04. Found: C, 75.12; H, 5.06.

Table I. Benzoyloxyacetophenones (7), α -Benzoyl-2-hydroxyacetophenones (8), 8-Cyanoflavones (9), and 8-Carboxamidoflavones (10)

Compd	R ₄	mp, °C	yield, %	formula
7a	H	122-124	79 ^a	C ₁₈ H ₁₅ NO ₃
7c	4'-CH ₃ O	131-133	83 ^a	C ₁₉ H ₁₇ NO ₄
7d	3'-CH ₃ O	155-156	77 ^a	C ₁₉ H ₁₇ NO ₄
7e	4'-CH ₃	127-129	93 ^a	C ₁₉ H ₁₇ NO ₃
7f	4'-F	107-109	76 ^a	C ₁₈ H ₁₄ FNO ₃
7g	2'-Cl	118-121	85 ^a	C ₁₈ H ₁₄ ClNO ₃
7h	4'-Cl	117-119	78 ^a	C ₁₈ H ₁₄ ClNO ₃
7i	2',4'-diCl	145-147	81 ^a	C ₁₈ H ₁₃ Cl ₂ NO ₃
7j	2'-CH ₃	123-124	85 ^a	C ₁₉ H ₁₇ NO ₃
7k	3'-CH ₃	116-117	94 ^a	C ₁₉ H ₁₇ NO ₃
8a	H	216-218	76 ^b	C ₁₈ H ₁₅ NO ₃
8c	4'-CH ₃ O	185-187	65 ^a	C ₁₉ H ₁₇ NO ₄
8d	3'-CH ₃ O	192-193	74 ^b	C ₁₉ H ₁₇ NO ₄
8e	4'-CH ₃	203-205	73 ^a	C ₁₉ H ₁₇ NO ₃
8f	4'-F	140-142	80 ^b	C ₁₈ H ₁₄ FNO ₃
8g	2'-Cl	171-173	87 ^c	C ₁₈ H ₁₄ ClNO ₃
8h	4'-Cl	194-196	74 ^b	C ₁₈ H ₁₄ ClNO ₃
8i	2',4'-diCl	202-204	65 ^b	C ₁₈ H ₁₃ Cl ₂ NO ₃
8j	2'-CH ₃	177-178	68 ^c	C ₁₉ H ₁₇ NO ₃
8k	3'-CH ₃	195-197	73 ^c	C ₁₉ H ₁₇ NO ₃
9a	H	245-247	91 ^d	C ₁₈ H ₁₃ NO ₂
9c	4'-CH ₃ O	248-250	79 ^e	C ₁₉ H ₁₅ NO ₃
9d	3'-CH ₃ O	222-223	88 ^d	C ₁₉ H ₁₅ NO ₃
9e	4'-CH ₃	189-190	90 ^b	C ₁₉ H ₁₅ NO ₂
9f	4'-F	206-208	98 ^d	C ₁₈ H ₁₂ FNO ₂
9g	2'-Cl	171-173	79 ^e	C ₁₈ H ₁₂ ClNO ₂
9h	4'-Cl	234-236	83 ^d	C ₁₈ H ₁₂ ClNO ₂
9i	2',4'-diCl	228-230	78 ^d	C ₁₈ H ₁₁ Cl ₂ NO ₂
9j	2'-CH ₃	186-187	56 ^d	C ₁₉ H ₁₅ NO ₂
9k	3'-CH ₃	202-203	83 ^d	C ₁₉ H ₁₅ NO ₂
10a	H	346-347	55 ^g	C ₁₈ H ₁₅ NO ₃
10b	4'-CH ₃ O	354-355	95 ^h	C ₁₉ H ₁₇ NO ₄

^aEtOAc-Petroleum Ether (bp 30-60°C). ^bEtOH. ^cBenzene-Hexane.^dMeOH-DMF. ^eMeOH. ^fMeOH-Chloroform. ^gDioxane. ^hDioxane-DMF

Table II. Flavone-8-carboxylic Acids (2)

Compd	R ₄	mp, °C	yield, %	formula
11a	H	244-246	81 ^a	C ₁₈ H ₁₄ O ₄
11c	4'-CH ₃ O	290-292	71 ^b	C ₁₉ H ₁₆ O ₅ ·0.25H ₂ O ^c
11d	3'-CH ₃ O	304-305	67 ^b	C ₁₉ H ₁₆ O ₅
11e	4'-CH ₃	308-310	64 ^b	C ₁₉ H ₁₆ O ₄ ·0.25H ₂ O ^d
11f	4'-F	289-300	73 ^a	C ₁₉ H ₁₃ FO ₄
11g	2'-Cl	248-249	75 ^a	C ₁₈ H ₁₃ ClO ₄
11h	4'-Cl	302-304	72 ^e	C ₁₈ H ₁₃ ClO ₄
11i	2',4',diCl	288-290	72 ^e	C ₁₈ H ₁₂ Cl ₂ O ₄
11j	2'-CH ₃	218-219	85 ^a	C ₁₉ H ₁₆ O ₄
11k	3'-CH ₃	286-287	56 ^f	C ₁₉ H ₁₆ O ₄

^aEtOH-Benzene. ^bEtOH-DMF. ^cMS, m/z 324. ^dMS, m/z 308. ^eHOAc.^fEtOH-EtOAc.

Table III. Microanalyses (%)

Compd	Calcd.				Found			
	C	H	N	Cl	C	H	N	Cl
7a	73.72	5.12	4.78		73.61	5.17	4.73	
7g	66.06	4.28	4.28		66.03	4.30	4.22	
7h	66.06	4.28	4.28		65.94	4.33	4.20	
8a	73.72	5.12	4.78		73.77	5.17	4.75	
8d	70.57	5.30	4.33		70.42	5.35	4.30	
9a	78.55	4.73	5.09		78.65	4.75	5.04	
9c	74.75	4.92	4.59		74.90	4.98	4.54	
9e	78.89	5.19	4.84		79.03	5.23	4.79	
9f	73.71	4.13	4.77		73.64	4.17	4.77	
9g	69.90	3.88	4.53	11.33	69.77	3.94	4.49	11.39
9h	69.90	3.88	4.53	11.33	69.85	3.93	4.50	11.30
9i	62.81	3.22	4.07	20.60	62.79	3.26	4.06	20.66
10a	73.72	5.12	4.78		73.68	5.20	4.74	
10c	70.58	5.30	4.33		70.65	5.35	4.31	
11a	73.40	4.79			73.51	4.84		
11c	69.39	5.06			69.68	5.01		
11c	70.36	4.97			70.29	5.02		

Table III - (continued)

Compd	Calcd.				Found			
	C	H	N	Cl	C	H	N	Cl
11e	72.95	5.16			73.05	5.36		
11f	69.22	4.37			69.18	4.37		
11g	65.76	3.99		10.78	65.85	4.02		10.68
11h	65.76	3.99		10.78	65.63	4.06		10.72
11i	59.52	3.34		19.52	59.42	3.36		19.60
11j	74.01	5.23			73.93	5.26		
11k	74.01	5.23			74.08	5.27		

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17. The carboxylic acid analogues are of particular interest since flavone-8-acetic acid (FAA, NSC-347512, LM-975) is a new antitumor agent in clinical trials in the United States and Europe.¹⁸⁻²³ FAA has a broad spectrum of activity against murine transplantable tumors including the pancreatic adenocarcinoma (No. 2) which is unresponsive to all chemotherapeutic agents currently available.^{20,24} Also, FAA possess a high level of activity against the colon 38 tumors,¹⁹ which is often relatively resistant to cytotoxic agents. FAA is more effective on slow growing solid tumors than on rapidly proliferating leukemias such as L1210 and P388.^{8,20,24} Furthermore, FAA possesses none of the usual properties of cytotoxic agents such as nausea, vomiting and myelosuppression.^{21,25,26} Although the activity reported in mice is exciting, this range of activity has not been duplicated in humans.²⁵ Nevertheless, the unusual spectrum of activity which FAA possesses and the ability of FAA to systemically augment natural killer (NK) cell activity in normal and tumor bearing mice and in human patients ²⁰ suggest a lead for further chemical studies to develop a potential chemotherapeutic drug which may also function as a biological response modifier (BRM). The 8-carboxylic acid analogues (11) are presently being evaluated against a variety of tumor models and the results will be published elsewhere. (As an example, while FAA¹⁸ exhibited an ILS (increase in lifespan) of 17% at 100 mg/kg in the P388 leukemia screen,^{27,28} our 6,7-dimethylflavone-8-carboxylic acid (11a) exhibited an ILS of 48% and 61% at 120 and 240 mg/kg.)
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Received, 8th January, 1990