pound or 0.5% Tween 80 vehicle by gastric gavage at 60 min prior to the intraperitoneal injection of PBQ (0.15 mL of a 0.02% solution/10 g body weight). The number of writhes made by each group of mice was determined for 15 min after the PBQ injection. The percent inhibition of writhing was calculated relative to the vehicle control group, and the ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

2. Randall–Selitto Paw Pressure Assay. Analgesic activity was measured in the inflamed rat hindpaw by a modification of the method of Randall and Selitto.[13] Groups of 10 male Sprague–Dawley rats (180–200 g) received an intraplanar injection of 0.1 mL of Freund's Complete Adjuvant (5 mg dead and dried *Mycobacterium butyricum* in 1 mL of mineral oil) into the left hindpaw. Test compound or vehicle was administered 24 h thereafter by gastric gavage, and the pain threshold was determined 1 h later with a paw pressure apparatus (Ugo Basile, Comeria, Italy). Animals were defined as having an analgesic effect if their pain threshold was at least 50% greater than the mean of the vehicle-treated group. The ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

3. Carrageenan Paw Edema. Acute antiinflammatory activity was determined according to the method of Winter et al.[14] Test compounds were administered by gastric gavage at 1 h prior to the intraplanar injection of 2% carrageenan in 0.9% saline into the left hindpaw. The acute edema volume was determined as the difference in hindpaw volume measured at the time of carrageenan injection and 3 h after carrageenan. The percent inhibition of edema formation was determined relative to the vehicle-treated controls, and the ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

4. Ulcerogenesis Assay. Male Sprague–Dawley rats (180–200 g), fasted for 8 h, were administered a single dose of test compound by gastric gavage. Food was withheld, but the animals were allowed free access to water. Stomachs were assessed for the presence or absence of a lesion on a quantal basis at 18 h after test compound administration. The UD_{50} (dose of drug causing lesions in 50% of the animals) and its 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[12]

Registry No. **1**, 91-56-5; **2**, 103-25-3; (±)-**3** (isomer 1), 113996-90-0; (±)-**4**, 113975-69-2; **5**, 1912-33-0; (±)-**6**, 113975-70-5; **7**, 87-51-4; (±)-**8**, 113975-71-6; **11**, 104065-67-0; (±)-**12a**, 113975-73-8; (±)-**12b**, 113975-83-0; (±)-**13**, 103024-44-8; **13a**, 114030-44-3; **13a** ((−)-borneol ester), 114030-43-2; **13b**, 114030-45-4; (±)-**14**, 113975-74-9; **15**, 18372-22-0; **16**, 113975-75-0; (±)-**17**, 113975-76-1; (±)-**18**, 113975-77-2; (±)-**19**, 113975-78-3; (±)-**20**, 113975-79-4; (±)-*cis*-**21**, 113975-80-7; (±)-*trans*-**21**, 113975-84-1; (±)-*cis*-**22**, 113975-81-8; (±)-*trans*-**22**, 113975-85-2; (±)-*cis*-**23**, 113975-82-9; (±)-*trans*-**23**l, 113975-86-3; $EtCOCH_2CO_2Me$, 3044-53-9; tryptophol, 526-55-6.

Supplementary Material Available: Listings of bond lengths, bond angles, atomic coordinates, and thermal parameters for (±)-pemedolac and (+)-pemedolac (*S*)-(−)-borneol ester (16 pages); tables of observed and calculated structure factors for (±)-pemedolac and (+)-pemedolac (*S*)-(−)-borneol ester (20 pages). Ordering information is given on any current masthead page.

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(15) Computer generated by using the SYBYL software package, version 3.4, Tripos Associates, St. Louis, MO.

An Intensely Sweet Dihydroflavonol Derivative Based on a Natural Product Lead Compound[1]

N. P. Dhammika Nanayakkara, Raouf A. Hussain, John M. Pezzuto, D. Doel Soejarto, and A. Douglas Kinghorn*

Program for Collaborative Research in the Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612. *Received December 29, 1987*

The dihydroflavonol dihydroquercetin 3-acetate (1) was isolated as a sweet constituent of the young shoots of *Tessaria dodoneifolia* (Hook. & Arn.) Cabrera (Compositae). Compound 1 and dihydroquercetin 3-acetate 4′-(methyl ether) (2), a novel synthetic analogue of this natural product lead compound, were rated by a taste panel as being 80 and 400 times sweeter than a 2% w/v sucrose solution, respectively. Synthetic dihydroquercetin 4′-(methyl ether) (3) showed a reduced sweetness intensity when compared to 2, while (+)-dihydroquercetin (4) was devoid of sweetness. Dihydroflavonol derivatives 1–3 represent a new class of potentially noncaloric and noncariogenic intense sweeteners.

As part of our continuing search for intensely sweet compounds of plant origin, we have investigated *Tessaria dodoneifolia* (Hook. & Arn.) Cabrera (family Compositae). This herb was obtained in a medicinal plants market in Asunción, Paraguay, where it was sold as a native remedy under the name "kaá hê-ê" (sweet herb). The young shoots of this plant were collected from a cultivated stand of *T. dodoneifolia*, and the sweetness was traced to an ethyl acetate soluble constituent, dihydroquercetin 3-acetate (1). Compound 1 was isolated initially from this plant source[2] and subsequently from two other plant species,[3] although its sweet taste had not been recognized previously. However, preliminary stability studies showed that this compound underwent slow spontaneous oxidation in neutral and basic media. This poor stability profile would render this compound unacceptable for use as a sweetener in foods, beverages, or medicines.

The structural similarity of 1 to intense sweeteners in the dihydrochalcone[4] and dihydroisocoumarin[5] classes

(1) Part 13 in the series Potential Sweetening Agents of Plant Origin. For part 12, see: Compadre, C. M.; Hussain, R. A.; Nanayakkara, N. P. D.; Pezzuto, J. M.; Kinghorn, A. D. *Biomed. Environ. Mass Spectrom.*, **1988**, *15*, 211.
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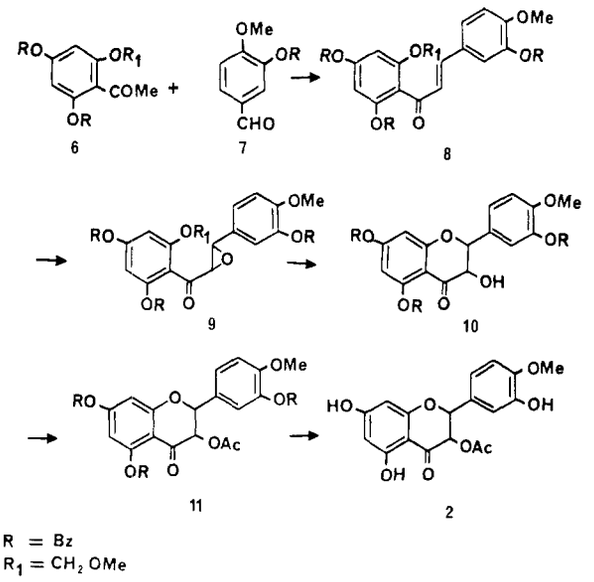
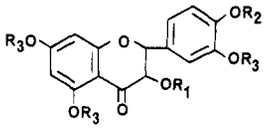
Scheme I. Synthetic Route to Dihydroquercetin 3-Acetate 4′-(Methyl ether) (**2**)



R = Bz
R_1 = CH_2OMe

suggested that the sweetness potency of isolated **1** could be enhanced by the introduction of a 4′-methoxy group in ring B to produce dihydroquercetin 3-acetate 4′-(methyl ether) (**2**). Furthermore, compound **2** would be expected to be more stable than compound **1** at neutral and high pH values, since free-radical formation at the 4′-position would be inhibited.[6]



1 R_1 = Ac, R_2 = R_3 = H (2*R*,3*R*)
2 R_1 = Ac, R_2 = Me, R_3 = H
3 R_1 = H, R_2 = Me, R_3 = H
4 R_1 = R_2 = R_3 = H (2*R*,3*R*)
5 R_1 = R_2 = R_3 = Ac (2*R*,3*R*)

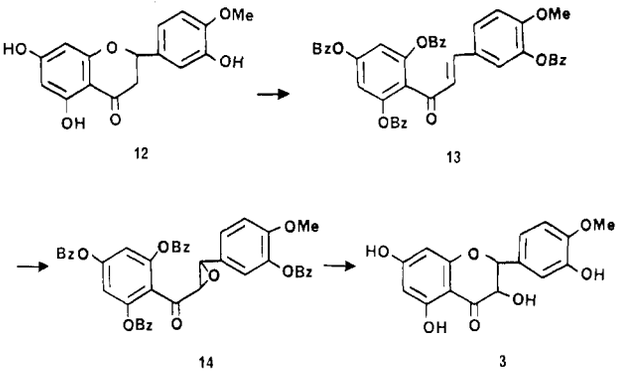
In the present paper, we present a comparison of the sweetness intensities of the naturally occurring **1** with synthetic **2** and dihydroquercetin 4′-(methyl ether) (**3**) and a commercial sample of (+)-dihydroquercetin (**4**). In this manner, a preliminary notion has been obtained of the functionalities necessary for the exhibition of sweetness within this new class of sweeteners.

Chemistry

The absolute stereochemistry of **1** at C-2 and C-3, which was not confirmed at the time of its first isolation from *T. dodoneifolia*,[2] was determined as 2*R*,3*R* by comparing the optical activity of its peracetylated derivative (**5**) with that of the identical (+)-dihydroquercetin 3,5,7,3′,4′-pentaacetate (**5**), obtained by the acetylation of a commercial sample of (+)-dihydroquercetin, a compound of known absolute stereochemistry (2*R*,3*R*).[7]

(±)-Dihydroquercetin-3-acetate 4′-(methyl ether) (**2**), mp 182–184 °C, was synthesized from 2,4-bis(benzyloxy)-6-(methoxymethoxy)acetophenone[8] (**6**) and 3-(benzyloxy)-4-methoxybenzaldehyde[9] (**7**), through the intermediates **8**–**11**, as shown in Scheme I. This reaction sequence is based on a known method for producing dihydroflavonols,[10] and compound **2** was obtained in 7% overall yield.

Scheme II. Synthetic Route to Dihydroquercetin 4′-(Methyl ether) (**3**)



(±)-Dihydroquercetin 4′-(methyl ether) (**3**), mp 190–192 °C, was synthesized from hesperetin (**12**), in 64% yield, according to Scheme II. Treatment of **12** with benzyl chloride in the presence of anhydrous potassium carbonate in dry dimethylformamide at 120 °C yielded the chalcone **13**. Oxidation of **13** with hydrogen peroxide in basic medium afforded the corresponding chalcone epoxide **14**, which was treated with hydrogen gas in the presence of palladium–carbon and acid. Under these conditions, (±)-dihydroquercetin 4′-(methyl ether) (**3**) was obtained as the major product.

Sensory Evaluation and Discussion

A small panel of three experienced tasters determined the sweetness intensities of compounds **1**–**3** in 3% ethanol–water solution. Compounds **1**–**3** were rated as being equivalent in sweetness intensity to sucrose at 20 000 ppm (in 3% ethanol–water solution) at 250 (80×), 50 (400×), and 500 ppm (40×), respectively. Compound **4** was devoid of sweetness and was not tested by the taste panel.

Compound **2** is therefore a novel dihydroflavonol derivative possessing intense sweetness, a property that has not hitherto been associated with this class of compounds. The rationale for the production of **2** was suggested after the initial isolation of the prototype sweet molecule, **1**, combined with a knowledge of existing structure–activity relationships of sweeteners in the dihydrochalcone[4] and dihydroisocoumarin (phyllodulcin)[5] classes. Our preliminary data suggest that at least two functionalities in the molecular structure of **2** are important for the conferment of its sweet properties, since substitution of the 4′-methoxy group or the 3-acetoxy functionality by a phenolic hydroxy group as in **1** and **3**, respectively, led to decreased sweetness intensities. Furthermore, replacement of both the 3- and 4′-substituents in this manner to give **4** led to a compound that was not sweet at all. Given the bittersweet nature of natural dihydrochalcones such as glycyphyllin, compound **1** is the first intensely sweet naturally occurring flavonoid to have been detected, with the vast majority of such

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compounds being either bitter- or neutral-tasting.[5b,11] 3-Acetylated dihydroflavonol derivatives such as 1 are very rare in the plant kingdom.[12]

Experimental Section

General Methods. Melting points were determined with a Kofler hot-stage instrument and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The UV and IR spectra were obtained, respectively, on a Beckman DB-6 spectrometer and a Nicolet MX-1 FR-IR-interferometer. ^{1}H NMR spectra were recorded in $CDCl_3$, with tetramethylsilane as internal standard, employing either a Nicolet NT-360 (360 MHz) or a Varian XL-300 (300 MHz) instrument. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Nicolet NT-360 instrument (90.8 MHz), with tetramethylsilane as internal standard. Low-resolution and certain high-resolution EI-MS determinations were performed on a Varian MAT 112S instrument, operating at 70 eV. The remaining high-resolution MS determinations were made with a Kratos MS-50 instrument. The elemental compositions of the new compounds obtained were established by high-resolution MS, and, in all cases, experimentally obtained data of this type were within 40 ppm of calculated values. Synthetic intermediates 8–11 (Scheme I) and 13 and 14 (Scheme II) gave IR, ^{1}H NMR, and MS spectral data consitent with their proposed structures.

(+)-Dihydroquercetin [4, (+)-taxifolin, (2*R*,3*R*)-3,5,7,3′,4′-pentahydroxyflavanone] was purchased from Atomergic Chemetals Corp., and 2,4,6-trihydroxyacetophenone, isovanillin, and hesperidin were obtained from Aldrich Chemical Co.

Isolation and Characterization of Dihydroquercetin 3-Acetate (1). The identity of a sweet-tasting medicinal plant purchased in a market place in April 1981, was established as *T. dodoneifolia* (Hook. & Arn.) Cabrera by one of us (D.D.S.). A voucher specimen representing this collection (No. FM-1973054) has been deposited at the Herbarium of the Field Museum of Natural History, Chicago. Subsequently, a larger quantity of plant material for isolation studies was obtained by cultivation at the University of Illinois Pharmacognosy Field Station.

The dried, young growing tips of *T. dodoneifolia* (600 g) were extracted with MeOH–H_2O (4:1, 3 × 2 L) by percolation. The combined extracts were evaporated to dryness at 50 °C to afford a gum (240 g), which was suspended in H_2O (4 L) and extracted with EtOAc (6 × 1.5 L), into which the sweetness of the initial MeOH–H_2O extract was preferentially concentrated. The organic layer was washed with H_2O (2 × 500 mL) and evaporated to dryness to afford 116 g of a residue. A portion of the EtOAc extract (100 g) was chromatographed (SiO_2, 2.5% MeOH in $CHCl_3$) to yield a sweet fraction (6.8 g), from which a major constituent, dihydroquercetin 3-acetate (1; 0.9 g, 0.15% w/w yield), was recrystallized from $CHCl_3$–MeOH as pale yellow needles, mp 133–135 °C; $[\alpha]^{21}_D$ +40.7° (*c* 4.87, $CHCl_3$), which exhibited closely comparable UV, IR, ^{1}H NMR, and MS data to literature values[2-4] for this isolate. On acetylation of 1 with acetic anhydride and pyridine, the known (2*R*,3*R*)-dihydroquercetin 3,5,7,3′,4′-pentaacetate[4] (5) was produced, mp 126–128 °C, $[\alpha]^{21}_D$ +65.3 (*c* 1.1, $CHCl_3$), which exhibited the same physical and spectral (^{1}H NMR, MS) data as a sample of 5 produced by the acetylation of commercial (+)-dihydroquercetin (4), when treated in a similar manner to 1.

3,4′,6′-Tris(benzyloxy)-2′-(methoxymethoxy)-4-methoxychalcone (8). 2,4-Bis(benzyloxy)-6-(methoxymethoxy)acetophenone (6) was prepared from commercial 2,4,6-trihydroxyacetophenone according to literature procedures.[8] The other starting material, 3-(benzyloxy)-4-methoxybenzaldehyde (7), was prepared from isovanillin by a previous method.[9] A solution of 6 (3.92 g, 10 mmol), 7 (2.42 g, 10 mmol), and NaOH (14 g) in EtOH (100 mL) was stirred at room temperature for 3 days. Solvent was removed in vacuo, and the residue was triturated with water and filtered. The precipitate was then recrystallized from MeOH to afford 8 (4.8 g, 78%), mp 126–128 °C and measured mass 616.2450 ($C_{39}H_{36}O_7$ requires 616.2461).

α,β-Epoxy-3,4′,6′-tris(benzyloxy)-2′-(methoxymethoxy)-4-methoxychalcone (9). A solution of 8 (4.3 g, 7.0 mmol) in acetone (80 mL) was shaken with a mixture of 30% H_2O_2 (10 mL), 2 N NaOH (10 mL) in MeOH (30 mL) for 2 h and occasionally brought to boiling temperature. Solvent was removed in vacuo, and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with aqueous KI (10% w/v, 200 mL), aqueous $Na_2S_2O_3$ (10% w/v, 200 mL), and H_2O and then evaporated to dryness. The residue was recrystallized from MeOH to afford 9 (3.4 g, 77%), mp 125–127 °C and measured mass 632.2428 ($C_{39}H_{36}O_8$ requires 632.2410).

5,7,3′-Tris(benzyloxy)dihydroflavonol 4′-(Methyl ether) (10). A mixture of 9 (3.2 g, 5.1 mmol), concentrated HCl (10 mL), MeOH (100 mL), and THF (10 mL) was refluxed for 1 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was recrystallized from MeOH to afford 10 (0.6 g, 20%), mp 196–198 °C and measured mass 588.2162 ($C_{37}H_{32}O_7$ requires 588.2148).

5,7,3′-Tris(benzyloxy)dihydroflavonol 3-Acetate 4′-(Methyl ether) (11). Compound 10 (0.55 g, 0.94 mmol) was heated on a steambath with acetic anhydride (2 mL) and pyridine (1 mL) for 30 min. After the usual workup, the reaction product was recrystallized from MeOH to afford 11 (0.5 g, 85%), mp 130–131 °C and measured mass 630.2286 ($C_{39}H_{34}O_8$ requires 630.2254).

5,7,3′-Trihydroxydihydroquercetin 3-Acetate 4′-(Methyl ether) (2). The benzyl protecting groups of 11 (0.4 g, 0.63 mmol in DMF, 40 mL) were removed by stirring with Pd–C (10%, 0.25 g) and concentrated HCl (15 drops) in an H_2 atmosphere for 2 h. The catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residue was chromatographed (SiO_2, $CHCl_3$) to afford pure 2 (0.17 g, 74%): mp 182–184 °C; $[\alpha]^{21}_D$ 0°; UV λ_{max} (MeOH) 230 (log ϵ 4.34), 289 (4.30), 331 (sh) nm (3.79); IR ν_{max} (KBr) 3513, 3236, 1733, 1641, 1585, 1517, 1465, 1273, 1166, 1086, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (3 H, s, OAc), 3.91 (3 H, s, OMe), 5.25 (1 H, d, J = 12 Hz, H-2), 5.77 (1 H, d, J = 12 Hz, H-3), 5.98, 6.03 (1 H each, d, J = 2 Hz, H-6, H-8), 6.87 (1 H, d, J = 8 Hz, H-5′), 6.96 (1 H, dd, J = 8, 2 Hz, H-6′), 7.03 (1 H, d, J = 2 Hz, H-2′); ^{13}C NMR ($CDCl_3$, 90.8 MHz) δ 20.3 ($OCOCH_3$), 55.7 (OCH_3), 72.3 (C-3), 80.7 (C-2), 95.9 (C-6), 97.2 (C-8), 101.3 (C-10), 110.5 (C-5′), 113.5 (C-2′), 119.3 (C-6′), 127.8 (C-1′), 145.2 (C-3′), 147.3 (C-4′), 162.3 (C-9), 163.7 (C-5), 166.1 (C-7), 170.1 ($OCOCH_3$), 191.5 (C-4); MS (relative intensity), *m/z* 360 (M^+, 12), 318 (5), 300 (85), 166 (100), 164 (67), 153 (88), 137 (25); measured mass 360.0845 ($C_{18}H_{16}O_8$ requires 360.0853).

3,2′,4′,6′-Tetrakis(benzyloxy)-4-methoxychalcone (13). The aglycone, hesperetin (12), was prepared by hydrolysis of its commercially available glycoside, hesperidin, by a published procedure.[13] A mixture of 12 (30 g, 100 mmol), anhydrous K_2CO_3 (150 g), and benzyl chloride (75 mL), in anhydrous DMF (500 mL), was heated at 120 °C for 5 h. The reaction mixture was filtered, and the solvent was evaporated in vacuo to give a yellow oil, which was poured into H_2O and extracted with $CHCl_3$. On drying, the $CHCl_3$-soluble residue was recrystallized from EtOAc to afford 13 (54 g, 82%), mp 158–160 °C and measured mass 662.2647 ($C_{44}H_{38}O_8$ requires 662.2668).

α,β-Epoxy-3,2′,4′,6′-tetrakis(benzyloxy)-4-methoxychalcone (14). A mixture of 13 (21 g, 31.7 mmol), 7.1 N NaOH (30 mL), H_2O_2 (30%, 20 mL), $CHCl_3$ (525 mL), and MeOH (300 mL) was stirred at room temperature for 18 h. The solvents were evaporated in vacuo, and the reaction product was partitioned into $CHCl_3$. This organic phase was washed with aqueous KI (10% w/v, 10 mL), aqueous $Na_2S_2O_3$ (10% w/v, 200 mL), and H_2O and evaporated to dryness. The residue was recrystallized from $CHCl_3$–MeOH to afford 14 (19.2 g, 89.3%), mp 124–126 °C and measured mass 678.2650 ($C_{44}H_{38}O_7$ requires 678.2618).

Dihydroquercetin 4′-(Methyl ether) (3). A mixture of 14 (15 g, 22.1 mmol), Pd–C (10%, 6 g), and concentrated HCl (4.5 mL) in DMF (600 mL) was stirred under an H_2 atmosphere for 4 h. The reaction mixture was filtered, poured into H_2O, and extracted with EtOAc. The residue from this organic layer was chromatographed [SiO_2, petroleum ether (bp 60–80 °C)–acetone,

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17:3] to afford **3** (6.2 g, 88%): mp 190–192 °C; $[\alpha]^{21}_D$ 0°; UV λ_{max} (MeOH) 229 (log ϵ 4.42), 289 (4.35), 329 (sh) nm (3.85); IR ν_{max} (KBr) 3412, 1637, 1590, 1519, 1474, 1270, 1155, 1131, 1083 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 3.79 (s, OMe), 4.83 (1 H, d, J = 11 Hz, H-3), 5.04 (1 H, d, J = 11 Hz, H-2), 5.89, 5.95 (1 H each, d, J = 2 Hz, H-6, H-8), 6.91 (1 H, d, J = 8 Hz, H-6′), 6.94 (1 H, br s, H-2), 6.96 (1 H, d, J = 8 Hz, H-5′); ^{13}C NMR (DMSO-d_6, 90.8 MHz) δ 55.7 (OCH_3), 71.6 (C-3), 82.9 (C-2), 95.1 (C-6), 96.1 (C-8), 100.5 (C-10), 111.7 (C-5′), 115.1 (C-2′), 119.3 (C-6′), 129.7 (C-1′), 146.2 (C-3′), 148.0 (C-4′), 162.5 (C-9), 163.5 (C-5), 166.8 (C-7), 197.7 (C-4); measured mass 318.0739 ($C_{16}H_{14}O_7$ requires 318.0733).

Sensory Evaluation of Compounds 1–3. Prior to being evaluated by a human taste panel consisting of three persons, compounds **1–3** were shown to be pure in several TLC systems. Also, these substances were found to be not acutely toxic for mice, when administered by oral intubation at a dose of 1 g/kg body weight, according to a previously described protocol.[14] Compounds **1–3** were not mutagenic for *Salmonella typhimurium* strain TM677, both in the presence and absence of a metabolic activating system, at various concentrations ranging up to 1.38 μg/mL, when tested as described previously.[15]

Compounds **1–3** were dissolved in 3% EtOH–H_2O and were found to match the sweetness intensity of 20 000 ppm sucrose (in 3% EtOH–H_2O) at 250, 50, and 500 ppm, respectively. No bitterness was ascribed to the taste sensation exhibited by the most intensely sweet of these derivatives, compound **2**.

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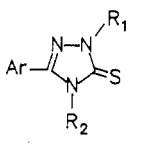
2,4-Dihydro-3*H*-1,2,4-triazole-3-thiones as Potential Antidepressant Agents

John M. Kane,* Mark W. Dudley, Stephen M. Sorensen, and Francis P. Miller

Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215. *Received November 9, 1987*

A series of 5-aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones was prepared and evaluated for potential antidepressant activity. Members of this series were generally prepared by the alkaline ring closures of the corresponding 1-aroylthiosemicarbazides. Several members of this series were potent antagonists of both RO 4-1284-induced hypothermia and reserpine-induced ptosis in mice. In general the more active members of this series were substituted by haloaryl groups at the 5-position of the triazole nucleus and by methyl groups at the 2- and 4-positions. Exchange of the thiocarbonyl group at the 3-position for a carbonyl group resulted in the complete loss of activity. Biochemical evaluation of the more active members of this series indicated that the aforementioned activities were not a consequence of either norepinephrine (NE) uptake or monoamine oxidase inhibition. In an attempt to determine a mechanism of action, one member of this series, compound **22**, was selected for further evaluation in an electrophysiological model where it was found to reduce norepinephrine function in the cerebellum as measured by the NE augmentation of GABA inhibition of Purkinje neurons.

Drug intervention in the treatment of depression has traditionally been accomplished by the use of either monoamine oxidase inhibitors or biogenic amine reuptake inhibitors.[1] Unfortunately both therapies are associated with a number of undesirable side effects[2–6] and neither has shown a rapid onset of action.[7,8] More recently, a structurally diverse array of compounds has been described as potential second-generation antidepressants.[9–11] The mechanisms of action of these compounds appear to differ from those of their predecessors, which has spawned the hope that more efficacious therapies might be close at hand. We have recently described an unusual cleavage reaction of a diaryl ketone which afforded 2,4-dihydro-2,4-dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (**1**).[12] Biological evaluation of **1** demonstrated potent effects in



Ar=C_6H_5, R_1=R_2=CH_3

1

several test systems designed to detect potential antidepressant activity. In order to more systematically inves-

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