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SYNTHESIS OF CALEBERTIN AND CALEPRUNIN A

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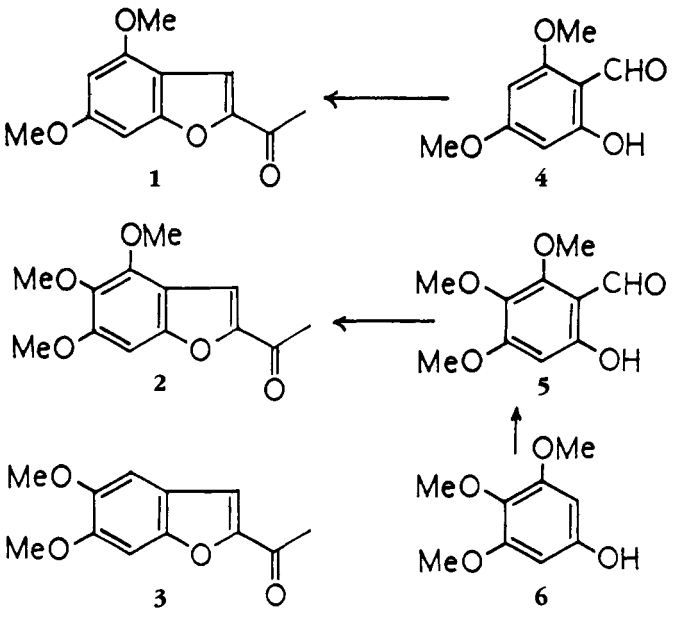
In their biochemical investigations of the genus *Calea*, Fischer and co-workers (1) have recently described the isolation of calebertin (**1**), a benzofuran obtained from the aerial parts of *Calea berteriana* DC collected in Venezuela, and two additional benzofurans, designated as caleprunin A (**2**) and caleprunin B (**3**), from plant material of *Calea prunifolia* Kunth collected in Costa Rica. The structures were based on spectral considerations and, in the case of calebertin, confirmed by single crystal X-ray diffraction. As part of our continuing studies on the synthesis of natural benzofurans, we report here simple syntheses of calebertin and caleprunin A and comment on earlier work regarding caleprunin B. Utilizing the commercially readily available 4,6-dimethoxysalicylaldehyde (**4**) as starting material, treatment with chloroacetone and K_2CO_3 in DMF solution at room temperature readily afforded 2-acetyl-4,6-dimethoxybenzofuran (**1**) with melting point and spectrometric data in excellent agreement with that reported for calebertin. The aldehyde required to prepare caleprunin A by a similar procedure is 6-hydroxy-2,3,4-trimethoxybenzaldehyde (**5**) and this was obtained by a Gattermann formylation of 3,4,5-trimethoxyphenol (**6**), which is itself the natural phenol, antiarol, isolated from the latex of *Antiaris toxicaria* (2). Reaction of the trimethoxysalicylaldehyde (**5**) with chloroacetone afforded a simple synthesis of caleprunin A (**2**).

Two syntheses have previously been described (3,4) for 2-acetyl-5,6-dimethoxybenzofuran (**3**), the structure proposed for caleprunin B, and the same compound, named eupatarone, has been isolated from the aerial parts of *Eupatorium sternbergianum* DC (**5**).

EXPERIMENTAL

2-ACETYL-4,6-DIMETHOXYBENZOFURAN



(CALEBERTIN) (**1**).—Anhydrous K_2CO_3 (3.81 g) was added to a solution of 4,6-dimethoxysalicylaldehyde (1.79 g) and chloroacetone (0.80 ml) in DMF (10 ml) and the mixture suspension stirred at room temperature overnight. Aqueous NaOH solution (8%, 40 ml) was then added and the product extracted with Et_2O. Evaporation of the washed and dried ($MgSO_4$) neutral extract gave a crystalline residue (1.50 g), mp 112-113°, which was recrystallized from CH_2Cl_2-light petroleum to yield calebertin (**1**) as yellow elongated prisms, mp 118-120° [lit. (1), mp 118.5-119°]; ^{1}H nmr δ ($CDCl_3$) 2.53 (s, $COCH_3$), 3.85 (s, OMe), 3.90 (s, OMe) 6.30 (d, *J* 2 Hz, H-5), 6.62 (dd, *J* 2,1 Hz, H-7), 7.52 (d, *J* 1 Hz, H-3); ^{13}C nmr δ ($CDCl_3$), 187.2, 162.5, 157.9, 155.1, 150.9, 112.1, 111.9, 95.1, 87.8, 55.7, 55.6, and 25.9.[1]

6-HYDROXY-2,3,4-TRIMETHOXYBENZALDEHYDE (**5**).—HCl was bubbled through a suspension of zinc cyanide (2.60 g) and 3,4,5-trimethoxyphenol (1.86 g) in Et_2O (100 ml) at room temperature for 2 h. The solvent was then decanted, H_2O (30 ml) added to the residual solid, and the mixture heated on the steam bath for 15 min. On cooling, the orange-red solid which precipitated was dissolved in Et_2O and the dried solution evaporated to give the crude aldehyde (1.46 g). It was purified by elution of a CH_2Cl_2 solution through a short column of silica gel giving (**5**) as a pale yellow solid, mp 61-62° [lit. (6) 65°]; ^{1}H nmr δ ($CDCl_3$) 3.79 (s, OMe), 3.90 (s, OMe), 4.05 (s, OMe), 6.19 (s, ArH), 10.05 (s, OH), and 12.11 (s, CHO).

2-ACETYL-4,5,6-TRIMETHOXYBENZOFURAN (CALEPRUNIN A) (**2**).—Anhydrous K_2CO_3 (415 mg) was added to a solution of the aldehyde (**5**) (231 mg) and chloroacetone (0.1 ml) and DMF (1.2 ml). The reaction was conducted and worked up as for calebertin (above) to give caleprunin A as a yellow gum; ^{1}H nmr δ ($CDCl_3$) 2.55 (s, $COCH_3$), 3.86 (s, OMe), 3.93 (s, OMe), 4.14 (s, OMe), 6.79 (s, H-7), and 7.59 (s, H-3); ^{13}C nmr δ ($CDCl_3$) 187.3, 155.7, 152.9, 151.2, 146.9, 137.2, 113.0, 112.1, 89.9, 61.2, 60.5, and 25.9.[1]

LITERATURE CITED

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[1]These data for calebertin are in excellent agreement for the values previously reported (1) except that the methoxyl signals (55.7, 55.6) were resolved and a C-9 signal was at 111.9 (instead of 94.2). The data for caleprunin A was also in excellent agreement except for the C-9 at 113.0 (instead of the reported 100.0). From correspondence and exchange of spectra with Professor Fischer, it is likely that the weak signals previously observed and attributed to C-9 have an impurity origin.