to yield enone **6** (11.0 g): mp 128–130 °C (recrystallized from CH_3OH); ν_{max} 1740 and 1250 (OAc), 1720 (CO_2CH_3), and 1660 and 1630 cm^{-1} (C=CC=O); ^1H NMR δ 5.69 (peak, 1p, C-7), 5.26 (peak, 1p, 12β-H), 4.69 (hump, 1p, 3β-H), 3.66 (s, 3p, OCH_3), 2.8 (m, 4p, C-9, C-14, C-23), 2.17 and 2.00 (2S, 6p, 3α-OAc and 12α-OAc), 0.93 (S, 3p, C-19), and 0.71 (s, 3p, C-18); λ_{max} 243 (log ϵ_{max} 4.28); *m/e* (%) 502 (9, M^+), 442 (62, M − HOAc), 382 (100, M − 2HOAc), 327 (36, M − HOAc − $C_6H_{11}O_2$), and 267 (98, M − 2HOAc − $C_6H_{11}O_2$).

Anal. Calcd for $C_{29}H_{42}O_7$: C, 69.30; H, 8.42; O, 22.28. Found: C, 69.01; H, 8.42; O, 22.47.

Acknowledgment

The technical assistance of M. Rahman is acknowledged, and thanks is given to Dr. G. B. Staal, Director of Biological Research at Zoecon, Corp., for performing the insect moulting hormone bioassays.

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Received for review December 17, 1976. Accepted April 25, 1977. This investigation was supported by Grant No. 5-R01-CA15824, awarded by the National Cancer Institute, Department of Health, Education and Welfare.

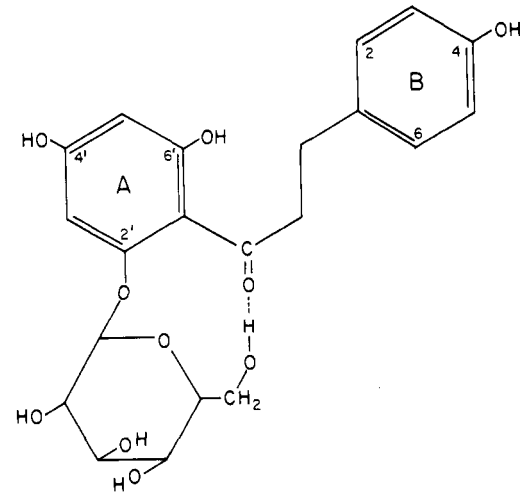
Preparation and Physical Properties of Some Desoxybenzoins and Isoflavones

Donald F. Diedrich*
Department of Pharmacology, University of Kentucky, Lexington, Kentucky 40506

Terrance A. Scahill and S. L. Smith
Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Simple esters of 2′,4′,6′-trihydroxyphenyl 4-nitrobenzyl ketone cannot be obtained when this desoxybenzoin is reacted with acetic anhydride or benzoyl chloride under mild conditions normally employed to acylate phenols. Instead, C_2-methyl or C_2-phenyl substituted isoflavones and their respective acetate and benzoate derivatives are formed. The IR and NMR spectral data as well as other physical properties of this series of flavonoids are reported.

The dihydrochalcone glucoside, phlorizin (I), is a valuable pharmacological tool for investigators studying membrane transport phenomena. It is a potent competitive inhibitor of the presumed receptor protein which facilitates the movement of glucose across cell membranes. A series of phlorizin analogues was prepared (*6*) in order to determine the structural features essential for I to interact with this membrane receptor in an in vitro intestinal (*7*) and an in situ renal (*13*) test system. The results of these studies suggested that the drug–receptor interaction depends, in part, on the formation of a strong hydrogen bond through the *p*-hydroxyl group on the B ring of phlorizin. In order to further investigate this interaction, some additional phlorizin derivatives were required especially one in which the critical nature and intramolecular spacing of this phenolic group could be tested. An appropriately substituted phenyl benzyl ketone (desoxybenzoin; II) was considered to be one of several aglycones that would be a suitable starting material to prepare 4-nitro- and 4-amino-substituted phlorizin-like test compounds. In order to form 2′-β-glycosides of II, the more acidic *p*-hydroxyl group had to be transiently protected and it was at this juncture, during routine attempts to acylate II in the 4′-position, that the



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exceptional reactivity of the methylene group in this compound was realized. When we used conditions comparable with those employed to partially acetylate or benzoylate the analogous phenyl methyl ketone, phloracetophenone (*5*), no simple 4′-ester of II could be isolated; instead acylation first occurs at the α-position to form III which spontaneously undergoes a Baker-Venkataraman type rearrangement (*1, 12*) to form the C_2-substituted isoflavone, IV. Although IV, as the free phenol, is the first

Table I. Experimental and Spectral Data for Some Desoxybenzoins and Isoflavones

Compd	Mp, °C	R_f	IR,[a] Wavenumber, cm^{-1}	MS, *m/e* [fragment]
IIa	250–252	0.33	3350 b (OH) 1650, 1610 (C═CC═O) 1575, 1520, 1350, 860 (C—NO_2) 1160, 1080, 1020, 805, 735	
IIb	240–242	0.15	3510, 3375, 3295, 3050 b (Ar—NH_2, OH) 1650, 1610 (C═CC═O) 1460, 1235, 1075, 1020, 985, 900, 825	
IVa	266–268	0.46	3150 b (OH) 1650, 1615 (C═CC═O) 1600, 1510, 1340, 860 (C—NO_2) 1235, 1075 (═COC) 1160, 750	313 $[M]^+$; 294 $[M - H_2O]^+$; 266 $[M - NO_2]^+$
IVb	198–200	0.93	1765, 1205 (-COOC═C-) 1660, 1620 (C═CC═O) 1590, 1515, 1345, 860 (C—NO_2) 1120, 815	355 $[M]^+$; 339 $[M - O]^+$; 313 $[M - CH_2CO]^+$; 309 $[M - NO_2]^+$; 276 [metastable peak; 355 → 313]
IVc	158–160	0.86	3390, 3350 (Ar—NH_2) 1770 (-COOC═C-) 1650, 1615 (C═CC═O) 1585, 1485, 1440, 1300, 1245, 1185, 840, 830	
IVd	195–197[b]	0.84	1790, 1770 d, 1205 (-COOC═C-) 1650, 1625 (C═CC═O) 1600, 1520, 1340, 860 (C—NO_2) 1175, 1125	397 $[M]^+$; 381 $[M - O]^+$; 355 $[M - CH_2CO]^+$; 313 $[M - 2(CH_2CO)]^+$; 266 $[M - NO_2 - 2(CH_2CO)]^+$; 311 [metastable peak; 397 → 351]
IVe	295–298	0.51	3200 b (OH) 1650, 1615 (C═CC═O) 1575, 1520, 1350, 860 (C—NO_2) 1250 (═COC) 1170, 1040, 750, 710	
IVf	225–227	0.98	1750 (-COOC═C-) 1650, 1615 (C═CC═O) 1580, 1520, 1350, 860 (C—NO_2) 1250 (═COC) 1135, 1060, 705	

[a] Most of the absorption bands having greatest intensity are reported. Key: b = broad, d = doublet. [b] Dutta and Bose (*8*) reported mp 190 °C.

Table II. NMR Spectral Data of Some Isoflavones

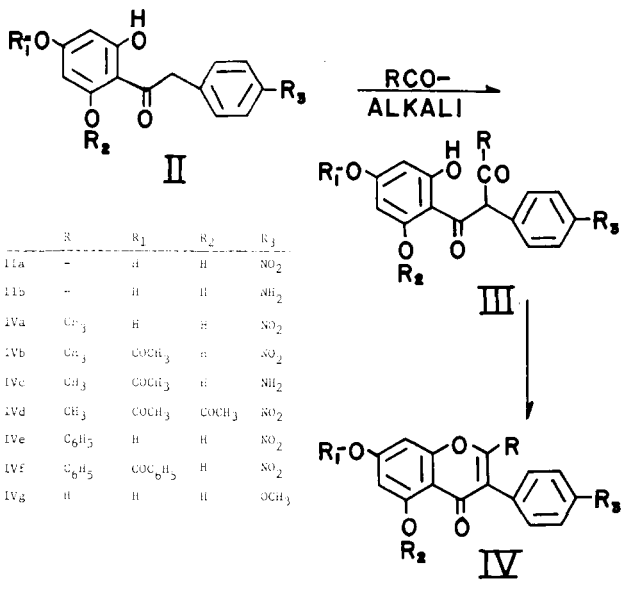
	Proton site							
Compd	6	8	2′,6′	3′,5′	5-OH	7-OH	2-CH_3	CH_3CO
IVg[a]	6.23	6.42	7.50	6.97	13.00	10.92		
IVa	6.22	6.40	7.63	8.30	12.65	10.87	2.27	
IVb	6.58	6.73	7.48	8.33	12.48		2.33	2.33
IVd	6.85	7.25	7.45	8.29			2.28	2.36
IVf	6.80	7.07	7.52	8.23				

[a] See ref 2.

product detectable by thin-layer chromatography (TLC), the 7-alkoxyl derivative is rapidly generated. Under suitable conditions, the chelated 5-hydroxyl group is also esterified. Both mono- and diesters are easily saponified and the free phenolic form of C_2-methyl and C_2-phenyl isoflavone can be isolated in good yield. Physical constants and IR spectral data for these compounds and two amine derivatives are shown in Table I.

Structures of the isoflavone derivatives were confirmed by NMR analysis. Chemical shift values are listed in Table II. Lines due to the methyl group in the 2 position are at very high field and are comparable with spectra of the same type molecule (*3*). Protons at C_6 and C_8 were assigned by their AB pattern, by their characteristic meta coupling and by comparison with similar compounds (*4*). Both exhibit chemical shifts to lower field with successive substitution of neighboring acetoxy groups. This observation is consistent with the diamagnetic anisotropic effect of acetoxy groups which deshield the protons at C_6 and C_8. Protons in the nitro benzyl group show an AA′BB′ pattern with those at $C_{2'}$ and $C_{6'}$ having absorptions at higher field than those at $C_{3'}$ and $C_{5'}$.

Both phenolic protons are reactive; their NMR signal is lost



upon exchange in D_2O. Since the C_5 phenolic proton is known to be chelated with the carbonyl oxygen (*10*), it was assigned the most remote peak downfield from Me_4Si.

While our synthetic work was in progress, Szabó et al. (*11*) reported that the reaction we inadvertantly discovered was indeed a practical method for the preparation of isoflavones variously substituted at C_2, and they discussed the mechanism of the reaction. We present here the melting point and R_f values as well as the mass spectral and IR, and NMR spectral data for all the compounds we isolated including three reported but uncharacterized elsewhere (*8, 11*).

Experimental Section

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. TLC was performed on silica gel GF precoated plates using the solvent system benzene, 95% ethanol, acetic acid (90, 10, 1). Mass spectra (MS) were measured at standard 70 eV and low voltage scans using a Hitachi Perkin-Elmer RMV-7 double focusing mass spectrometer. IR spectra were taken in KBr pellets on a Beckman IR-8 spectrometer. NMR spectra were obtained with a Varian T-60 spectrometer from 500-Hz scans at 25 °C. Samples were not degassed and 10% concentrations were prepared in Me_2SO-d_6 (compound IVa) and $CDCl_3$ (compounds IVc and IVd). Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.; where analyses are indicated only by symbols of the elements, the analytical results for those elements were within 0.2% of the theoretical values. *p*-nitrophenylacetonitrile was obtained from Aldrich Chemical Co., Milwaukee, Wis.

2′,4′,6′-Trihydroxy-4-nitrodesoxybenzoin (IIa). A solution of 30 g (0.184 mol) of *p*-nitrophenylacetonitrile in 150 mL of chloroform was added to 2.5 L of anhydrous diethyl ether containing 23.2 g (0.184 mol) of dried phloroglucinol. This solution was cooled in an ice bath and 6.0 g of zinc chloride was added just prior to the introduction of dry hydrogen chloride gas. Otherwise, the directions given by Gulati et al. (*9*) for the comparable Hoesch synthesis of phloracetophenone were followed except that crude product was generated directly from the intermediate ketimine hydrochloride with boiling water in which the desoxybenzoin is insoluble. Yellow needles (35.1 g; 66%) were obtained from methanol. Anal. ($C_{14}H_{11}O_6N$) C, H, N.

Acetylation: 2-Methyl-5,7-dihydroxy-4′-nitroisoflavone and Acetate Derivatives (IVa, IVb, and IVd). Method A. To a solution of 0.005 mol (1.45 g) of desoxybenzoin IIa in 50 mL of ethyl acetate was added 0.01 mol of acetic anhydride and the mixture was allowed to stand at room temperature for 15 min. Small but significant amounts of product having an R_f equal to IVa could be detected by TLC analysis of a sample taken at this time; a trace of IVb was also detectable. To the above mixture was added 20 mL of 0.5 M sodium methoxide (in methanol) dropwise over 20 min with vigorous stirring. After 2 h, the reaction mixture was cooled to 0 °C and the first crop of the monoacetate IVb (0.3 g) was harvested as a white solid. The solvents were evaporated to give a residue from which a second crop of IVb (0.05 g; 20% total yield) was gained by crystallization in methanol. TLC analysis of the methanolic mother liquor demonstrated the presence of small amounts of unreacted IIa and free IVa with traces of three unidentifiable compounds. The analytical sample of IVb was obtained from ethanol–ethyl acetate (3:1) as white needles. Anal. ($C_{18}H_{13}O_7N$) C, H, N.

Method B. To 0.008 mol (2.3 g) of IIa in 30 mL of pyridine was added 0.012 mol of acetic anhydride and after 1 h at room temperature, the mixture was poured into crushed ice. The sticky white mass which formed overnight was first crystallized in 95% ethanol and then ethanol–ethyl acetate to give 0.6 g (21%) of IVb.

Method C. IIa (0.01 mol) and 0.8 g of sodium acetate in 20 mL (0.2 mol) of acetic anhydride were refluxed for 1 h. The mixture was cooled and poured into crushed ice and the resulting white tacky mass was treated with 25 mL of hot methanol.The alcohol insoluble white solid was almost pure diacetate IVd (1.45 g, 36.5%); smaller amounts of IVa and IVb could be isolated from the methanol extract. The analytical sample of IVd was obtained by recrystallization in ethyl acetate. Anal. ($C_{20}H_{15}O_8N$) C, H, N.

Saponification of the Acetates. IVb or IVd (0.007 mol) was suspended in 8 mL of methanol containing either 0.006 or 0.012 equiv of sodium methoxide, respectively, and the mixture was heated at 60 °C for 2–3 min. The solution was cooled and neutralized with 0.1 N methanolic HCl and then water was added slowly to give free isoflavone as a yellow solid in about 60% yield. The analytical sample of IVa was obtained from ethyl acetate as shiny, yellow plates. Anal. ($C_{16}H_{11}O_6N$). H, N; C: calcd, 61.33; found, 60.82.

Benzoylation: 2-Phenyl-5,7-dihydroxy-4′-nitroisoflavone and the Monobenzoate (IVe and IVf). Method A. IIa (0.5 g, 0.0017 mol) was dissolved in 125 mL of ice cold 0.04 N KOH and 1 mL (0.009 mol) of benzoyl chloride was added dropwise with vigorous stirring. Mixing was continued for 15 min after which an oil formed. Solid sodium bicarbonate was added to saturation and this stirred mixture was allowed to stand overnight. The tan solid that formed was filtered, washed exhaustively with water, and dried. TLC analysis indicated that this crude material consisted of seven compounds. Two were identified by their R_f values as IVe and IVf; a small amount of unreacted starting material was also present. The solid was dissolved in diethyl ether. This solution was extracted three times with 25-mL volumes of ice cold 3.5% sodium carbonate and then washed repeatedly with water. The ether solution was dried and evaporated to yield a semisolid which was dissolved in the minimum of methanol. Pale yellow, chalky crystals of the monobenzoate, IVf, were isolated (0.08 g, 9.8%) and recrystallized from ethyl acetate. Anal. ($C_{28}H_{17}O_7N$) C, H, N.

Method B. Benzoyl chloride (1.0 mL) was added to a solution of IIa (2.3 g; 0.008 mol) in 50 mL of pyridine. The mixture was allowed to stand at room temperature for 2 h and then poured into ice slush. The resulting solid was washed with 0.05 N hydrochloric acid to remove pyridine, dried, dissolved in ether, and otherwise treated as described in method A. IVf was collected and crystallized from methanol as a white chalk (0.4 g; 10.4%).

Saponification of the Benzoate. When IVf was treated in a manner identical with that described above for the dealkylation of the acetate esters, shiny, yellow plates of IVe were gained from methanol. Anal. ($C_{21}H_{13}O_6N$) N; C: calcd, 67.19; found, 67.54; H: calcd, 3.75; found, 3.19.

Nitro Group Reduction: Formation of the Amines, IIb and IVc. Methanol and acetone were used to dissolve 0.001 mol quantities of either IIa or IVb. Hydrogenation was performed at atmospheric pressure in the presence of 10% Pd/C (0.2 g); both compounds took up theoretical amounts of hydrogen with first-order kinetics within 20 min. Filtration and concentration of the solvents gave the free amines. IIb was recrystallized from methanol–water to form pale yellow prisms. Anal. ($C_{14}H_{13}O_4N$) C, H, N.

The analytical sample of IVc was obtained by recrystallization from methanol as pale yellow needles. Anal. ($C_{18}H_{15}O_5N$) Calcd: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.81; H, 4.94; N, 3.99.

Acknowledgment

Terence L. Gutgsell, as a medical student summer fellow, made important contributions in the synthesis of some of these compounds. We are thankful to Dr. Edward Magarian for some helpful discussions.

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Received for review February 14, 1977. Accepted May 30, 1977. Part of this work was supported by Public Health Service Grant AM 06878.

Synthesis and Characterization of 3-Alkylbenzothiazolium Salts

P. J. Nigrey* and A. F. Garito
Department of Physics and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Six 3-alkyl substituted benzothiazolium iodides were synthesized by quaternization of benzothiazol with alkyl iodides. The above iodides were converted to corresponding perchlorate salts using silver perchlorate. UV, IR, and NMR spectral data are reported.

Although a few 3-alkylbenzothiazolium iodides have been known for some time, these were restricted to methyl- and ethyl-substituted (*3, 5*) ones, with the characterization of these having been poor and for many others unavailable. Recently, interest in cyanine dye studies (*4*), nucleophilic carbenes (*6*), catalysis (*1*), and charge-transfer complexes (*2*) has made the synthesis and systematic study of these types of compounds a worthwhile endeavor particularly since most studies to date have been restricted to methyl- and ethyl-substituted types. We report here a simple technique for the systematic synthesis of 3-alkylbenzothiazolium iodides and a novel scheme for the preparation of the corresponding perchlorates to give analytically pure samples in good yields.

Experimental Section

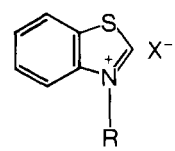
All melting points were taken on a Mettler FP5 melting point apparatus using a Mettler FP 52 microscope hot stage attachment and are uncorrected. Elemental chemical analysis were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ultraviolet (UV) absorption spectra were recorded on a Cary 14 recording spectrophotometer in 10^{-5} M solutions in acetonitrile. Infrared (IR) spectra were recorded on a Perkin-Elmer 225 grating spectrophotometer in KBr pellets. Nuclear magnetic resonance (NMR) spectra were obtained at 60 MHz on a Varian A-60 spectrometer in deuterated dimethyl sulfoxide solutions with tetramethylsilane (Me_4Si) as the internal standard. All values for chemical shifts (δ) were reported downfield from Me_4Si in parts per million.

Materials. All reagents used in these studies were used as commercially available without further purification. Silver perchlorate (Alfa inorganics, anhydrous) was stored over desiccant prior to usage.

Preparation of 3-Alkylbenzothiazolium Salts. In the following representative methods for the synthesis of **1a, 5a,** and **5b** yields were not optimized.

Method I. A 25-mm medium-wall Pyrex tube was filled with benzothiazol (8.68 g, 64.3 mmol) and methyl iodide (11.4 g, 80.3 mmol). The contents of the tube were solidified in liquid nitrogen (−196 °C), sealed off, allowed to warm to room temperature, and then placed in an oven at 140 °C for 15 min. After cooling to room temperature, the tube was again cooled to −196 °C and

Table I. Physical Properties of 3-Alkylbenzothiazolium Salts[a]



	R	X^-	Method of prep	Reaction time, h	Mp, °C	Yield, %	Solvent of recryst
1a	CH_3	I	I	0.25	216.3–217.1	71	A/E
1b	CH_3	ClO_4	III		144.6–145.5	85	A/EA
2a	C_2H_5	I	I	1	140.4–141.0	75	A/E
2b	C_2H_5	ClO_4	III		91.4–92.1	95	A/EA
3a	*n*-C_3H_7	I	II	1	158.1–158.5	70	A/EA
3b	*n*-C_3H_7	ClO_4	III		88.4–88.7	78	A/EA
4a	*i*-C_3H_7	I	I	4	131.3–132.2	74	A/EA
4b	*i*-C_3H_7	ClO_4	III		108.1–109.1	72	AC/EA
5a	*n*-C_4H_9	I	I	0.50	114.6–115.2	67	A/EA
5b	*n*-C_4H_9	ClO_4	III		97.7–98.0	60	A/EA
6a	*n*-C_5H_{11}	I	I	0.50	119.0–120.0	70	A/EA
6b	*n*-C_5H_{11}	ClO_4	III		99.4–99.9	90	A/EA

[a] Elemental analyses (C,H,N,Cl,I,O,S) were in agreement with theoretical values and submitted for review. [b] Key: A = acetonitrile, E = ethanol, EA = ethyl acetate, AC = acetone.