instrument. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer. Evaporations were done under reduced pressure with a bath temperature below 40°. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter.

5-*S*-Acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I).—Compound I was prepared according to published directions.[5]

5-*S*-Acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II).—Compound I (30 g) was dissolved in 750 ml of glacial acetic acid at 25° and to this solution 750 ml of water was added with stirring. The stirred mixture was heated at 70° under nitrogen for 36 hr. The reaction mixture was concentrated on a rotatory evaporator to a solid mass which was taken in 750 ml of chloroform. The chloroform solution was washed sequentially with 10% aqueous sodium chloride, dilute aqueous sodium bicarbonate, and water until the washings were neutral. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness, whereupon the residue solidified. The solid was recrystallized by dissolving it in 100 ml of ether. To this was added 300 ml of hexane and the solution was set aside at 25° to obtain compound II as flocculent needles: yield 20 g; mp 104–105°; $[\alpha]^{25}D$ −40° (*c* 1.2, $CHCl_3$). The supernatant from the recrystallization, on being examined by tlc in solvent A, showed the presence of some more of compound II (R_f 0.34) and compound III (major component having R_f 0.24); and hence was concentrated and chromatographed over a silica gel column using solvent A as eluent, to give an additional 1.25 g of compound II. Total yield of compound II was 21.25 g (78%): ir λ_{max} (Nujol) 3450 (OH) and 1685 (S-acetyl); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic) and 7.76 (s, 3, *S*-acetyl). The nmr spectrum of compound II in $CDCl_3$ integrated for 26 protons with assignable resonances at τ 2.71 (10 H, aromatic) and 7.76 (3 H, S-acetyl), and none for the isopropylidene protons in the region of 8.5–8.7.

Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.65. Found: C, 62.95; H, 6.42; S, 7.45.

The fractions having R_f 0.24 were combined and concentrated to give 4 g (16.2%) of pure compound III. An analytical sample prepared by recrystallization from ether–hexane, had mp 102–103°; $[\alpha]^{25}D$ +97.5° (*c* 1, $CHCl_3$); ir λ_{max} (Nujol) 3500 (OH); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic), 5.26 and 5.56 (2 s, 4, CH_2 of benzyl).

Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.8; H, 6.4; S, 8.52. Found: C, 64.0; H, 6.30; S, 8.41.

1,2-Di-*O*-acetyl-5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (IX).—Compound II (1.046 g) was acetylated using pyridine and acetic anhydride and the reaction mixture was worked up in the usual manner. Compound IX was recrystallized from ether–hexane as needles: mp 85–86°; $[\alpha]^{25}D$ +1.2° (*c* 1.07, $CHCl_3$); ir λ_{max} (Nujol) 1740 (O-acetyl) and 1685 (S-acetyl).

Anal. Calcd for $C_{26}H_{30}O_8S$: C, 62.13; H, 6.02; S, 6.38. Found: C, 61.96; H, 6.16; S, 6.54.

Methyl 2,5-Di-*O*-benzyl-4-thio-α- and -β-D-arabinofuranoside (V and VI).—To a stirred solution of compound II (24.4 g, 0.058 mol) in 300 ml of ethanol was added a solution of neutral sodium metaperiodate (13.65 g, 0.0638 mol) in 300 ml of water. The mixture was stirred below 30° for 30–40 min, then filtered, using a little ethanol to wash the precipitate. The filtrate was concentrated under diminished pressure at a bath temperature below 30° to remove ethanol and water. The oily residue was then taken in 500 ml of chloroform and washed twice with water to remove the inorganic salts. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give an almost quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydro*-D-arabinose (IV) (22 g) which crystallized on standing. Compound IV exhibited λ_{max} (Nujol) 1730 (aldehyde) and 1685 (*S*-acetyl).

Compound IV thus obtained, was dissolved in 400 ml of 0.5% solution of hydrogen chloride in methanol. The solution was refluxed for 3 hr, after which time it was cooled in ice water and neutralized with silver carbonate. The mixture was filtered and the filtrate was concentrated. The syrupy mixture of the anomeric glycosides were readily separated by column chromatography over silica gel using solvent C as eluent. The pure components were crystallized from ether–hexane to give 9.5 g (40.7%) of methyl 2,5-di-*O*-benzyl-4-thio-α-D-arabinofuranoside (V): mp 43–45°, $[\alpha]^{25}D$ +112° (*c* 1.4, $CHCl_3$), and 11 g (52.2%) of methyl 2,5-di-*O*-benzyl-4-thio-β-D-arabinofuranoside (VI), mp 74–75°, $[\alpha]^{25}D$ −139° (*c* 1.26, $CHCl_3$). In subsequent preparations, it was possible to achieve fractional crystallization of VI by seeding a solution of the mixture in ether–hexane. The nmr ($CDCl_3$) of compound V was suggestive of α configuration: τ 2.69 (s, 10, aromatic), 5.36 and 5.50 (2 s, 4, CH_2 of benzyl), 6.72 (s, 3, CH_3O–), and 4.93 (broad s, 1, H-1).

Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.90. Found: C, 66.38; H, 7.00; S, 8.84.

The nmr ($CDCl_3$) for compound VI showed τ 2.7 (s, 10 H, aromatic), 5.35 and 5.48 (2 s, H, CH_2 of benzyl), and 6.76 (s, 3, CH_3O–).

Anal. Found: C, 66.83; H, 6.86; S, 9.12.

Methyl 4-Thio-α-D-arabinofuranoside (VII).—To a stirred solution of compound V (21.6 g, 0.06 mol) in liquid ammonia (500 ml) contained in a 1-l.. three-necked flask, fitted with mechanical stirrer and Dry Ice–acetone condenser, was added 100 ml of dry 1,2-dimethoxyethane to assist the solubility of V during reduction. Freshly cut sodium was added in small pieces (about 200-mg size), one at a time, until the blue color of the solution persisted for 15 min or more. The reaction mixture was then carefully decomposed with excess solid ammonium chloride and ammonia was allowed to evaporate overnight in a current of nitrogen. Chloroform (500 ml) was added and the solution warmed to 40° to drive off the trace of dissolved ammonia, with a current of nitrogen bubbling through the solution. The reaction mixture was filtered to separate the inorganic salts and the filtrate concentrated under reduced pressure to a yellowish syrup which was chromatographically homogeneous in solvent D but contained some bibenzyl, which was removed by silica gel chromatography using solvent D as eluent. The product (10.6 g, ~100%) crystallized spontaneously upon removal of the solvent and was recrystallized from either chloroform or ethyl acetate as small needles: mp 71–72°; $[\alpha]^{25}D$ +299° (*c* 1, CH_3OH). The nmr spectrum of VII in D_2O showed the complete absence of the benzyl groups and showed the anomeric proton as a doublet centered at τ 5.01 ($J_{1,2}$ = 4.5 Hz); the methoxyl resonance occurred at τ 6.80.

Anal. Calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 39.73; H, 6.88; S, 17.65.

Methyl 4-Thio-β-D-arabinofuranoside (VIII).—In a similar manner described above for the α anomer, compound VI (21.6 g, 0.06 mol) was debenzylated. The resultant syrup was chromatographed using solvent E as eluent. Pure compound VIII (10.5 g, ~100%) so obtained was recrystallized from hotc hloroform as long needles: mp 98°; $[\alpha]^{25}D$ −156° (*c* 1.25, CH_3OH). Again, the nmr spectrum of compound VIII in D_2O showed the absence of benzyl groups. Assignable resonance signals for the anomeric proton occurred at τ 5.3 ($J_{1,2}$ = 3.8 Hz), and for the methoxyl protons at τ 6.38.

Anal. Found: S, 17.53.

Registry No.—II, 22538-35-8; III, 22538-36-9; V, 22377-93-1; VI, 22377-94-2; VII, 22377-95-3; VIII, 22377-96-4; IX, 22554-94-5.

The Structure and Conformation of the *cis* and *trans* Isomers of 1-(*p*-Chlorobenzylidene)-2-methyl-5-methoxyindenylacetic Acid

KARST HOOGSTEEN AND NELSON R. TRENNER

Department of Biophysics and Pharmacology, Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065

Received March 20, 1969

During the course of a research program on anti-inflammatory agents, 1-(*p*-chlorobenzylidene)-2-methyl-5-methoxyindenylacetic acid was synthesized in a study of indomethacin analogs.[1] The presence of

(1) T. Y. Shen, R. L. Ellis, B. E. Witzel, and A. R. Matzuk, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. P003.

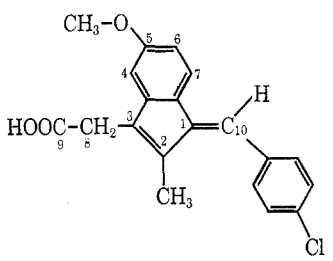
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR COMPOUNDS I AND II[a]

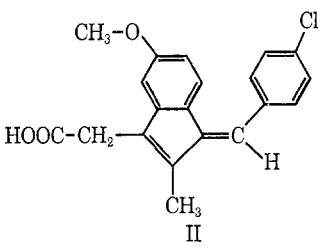
	Solvent	Protons of *p*-chlorophenyl ring	H-10	H-7, *ortho* only, J_{ortho}	H-4, *meta* only, J_{meta}	H-6, *ortho–meta*, $J_{ortho-meta}$	CH_3O	CH_2COOH	CH_3
I	$CDCl_3$	2.68	2.59	2.49 (s) 2.63 (s)	3.25 (d)	3.29 (d) 3.43 (d)	6.16	6.45	8.19
		UF[b]	DF[b]	DF	DF	DF	DF	UF	UF
	Acetone-d_6	2.58	2.53[c]	2.40[c] (s) 2.48 (s)	3.13	3.31 (d) 3.43 (d)	6.21	6.44	8.17
II	$CDCl_3$	2.60	3.00	2.71 (s) 2.87 (s)	3.27 (d)	3.55 (d) 3.68 (d)	6.22	6.42	7.85
	Acetone-d_6	2.52	2.93	2.78 (s) 2.90 (s)	3.20 (d)	3.56 (d) 3.70 (d)	6.26	6.43	7.83
Δ, chemical-shift differences, I − II	$CDCl_3$	+0.08	−0.41	0.22	−0.02	−0.26	−0.06	+0.03	+0.34
	Acetone-d_6	+0.06	−0.40	−0.38	−0.07	−0.25	−0.05	+0.01	+0.34

[a] J_{ortho} = 0.10 = 6 cps; J_{meta} = 2.4 cps. [b] UF, upfield; DF, downfield. [c] H-7 and =CH proton resonances overlapped.

a double bond between the atoms C-1 and C-10 gives rise to two isomers, one with the C-2 atom *cis* (I) and one with the C-2 atom *trans* (II) with respect to the *p*-chlorophenyl substituent.



I



II

Fractional crystallization of the final crude product synthesized according to Shen, *et al.*,[1] from a benzene solution gives crystalline material with the following physical properties: mp 168–169°; uv λ_{max} 339 mμ (ε 14,300), 288 (14,900), and 238 (21,900). On examination of the nuclear magnetic resonance spectrum of imcompletely purified material, a number of small satellite bands near the main resonances were observed, suggesting the presence of an isomeric compound. This isomer was isolated with the procedure mentioned in the Experimental Section and possessed the following physical properties: mp 186–188°; uv λ_{max} 343 mμ (ε 15,000) and 286 (25,200). The results, discussed below, obtained by nuclear magnetic resonance spectroscopy and single-crystal X-ray structure determination, show that the lower melting compound (mp 168–169°) can be identified as the *trans* isomer (II) and that the *cis* isomer (I) is the compound with the higher melting point (186–188°). The biological activity is associated with compound II, whereas compound I only shows marginal anti-inflammatory activity.

Results

The nuclear magnetic resonance data in the two solvents chloroform and acetone are presented in Table I. The assignment of the spectrum could be made on the basis of the observed chemical shifts, the relative integrated band areas, and the typical *ortho*, *ortho–meta*, and *meta* aromatic coupling patterns given by the protons at C-4, C-6, and C-7 of the indenyl substituent, while those of the *p*-chlorophenyl substituent occur as a singlet band. Compound I has protons identical in type with II and is isomerically related to it. This is supported by its elemental composition (see Experimental Section).

The magnetic anisotropy caused by the electrons in the benzene ring makes it possible to describe the relative proximity and orientation of the planes of the aromatic rings in the two isomers I and II. Protons situated in the plane of an aromatic ring are subject to paramagnetic or downfield frequency shifts, whereas protons located over the aromatic ring plane are subject to diamagnetic or upfield frequency shifts.

With these anisotropy rules in mind, it will be observed that the chemical-shift differences Δ presented in Table I are consistent with the structural and conformational assignments made in this paper for isomers I and II. Protons on the C-6, C-7, and C-10 atoms and the C-2 methyl are especially dominant in these considerations. Isomer I thus must have the *cis* configuration with its C-2 methyl over the plane of the aromatic ring of the indene system.

Since I and II are geometrical isomers, it was thought to be of interest to see if thermal and photochemical isomerization could be induced here as, for example, in the case of maleic and fumaric acids. Heating the isomer I in a *p*-dioxane solution containing some concentrated hydrochloric acid at 100° showed, on examination by uv spectroscopy at 238 and 288 mμ, that an equilibrium of *ca.* 96% II and 4% I is established in *ca.* 3–4 hr. Under these conditions, compound II reaches the same equilibrium. In methanol solution to which a small amount of iodine has been added, both I and II are isomerized to a similar equilibrium when exposed for 24 hr in quartz vessels to a quartz GE-AH5 high-pressure mercury arc lamp. Thus, II is thermodynamically the more stable isomer, and this accounts for the

fact that only a few per cent of I is formed during the synthesis of II.

An independent confirmation of the structural assignment, based on nuclear magnetic resonance data, was obtained with a single-crystal structure determination. The methyl ester of the biologically active, low-melting isomer II could be crystallized and the structure was determined with the isomorphous replacement method. Crystal data and other details are summarized in the Experimental Section.

Figure 1 shows the electron-density map representing the projection of the crystal structure along the *c* axis. All atoms are resolved and it is clear that the C-2 atoms occupy the *trans* configuration with respect to the *p*-chlorophenyl ring. Also, the molecular conformation in the crystalline state, as viewed along the axis of projection, is consistent with the nmr results in solution; the plane of the *p*-chlorophenyl ring appears approximately normal to the plane of the indene ring.

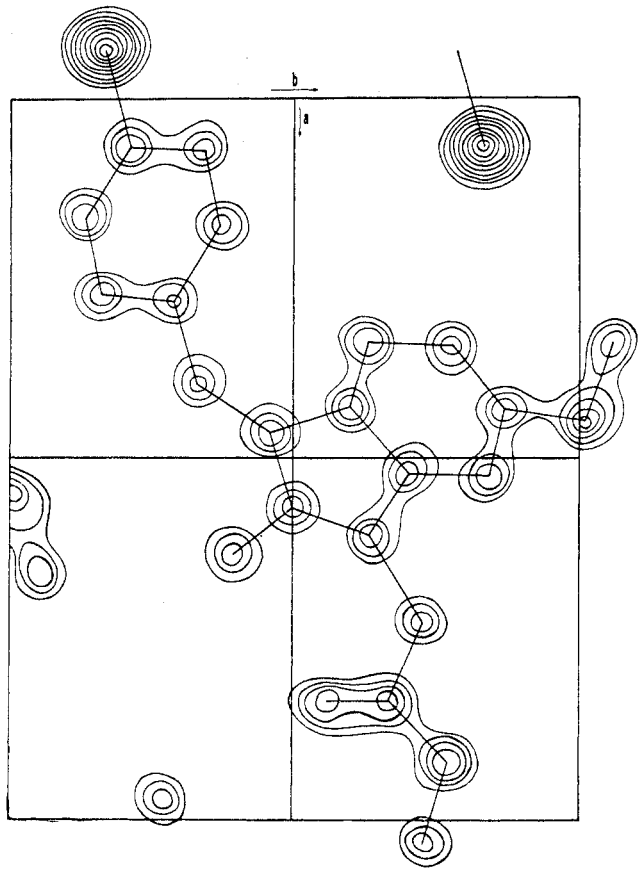


Figure 1.—Fourier synthesis of the electron-density projection along the direction of the *c* axis.

Experimental Section

All nmr data reported here were obtained with a Varian Associates Model 4300B high-resolution spectrometer equipped with a superstabilizer and a phase detector and operating at 60 Mcps. All spectra were obtained with 5–10% (w/v) solutions in deuteriochloroform or deuterioacetone placed in a spinning Wilmad precision-bore tube. The resonance positions were determined relative to benzene as an external reference and scaled by the use of side bands[2] generated by a frequency counter calibrated Hewlett–Packard audio oscillator, Model 2000 CD. The chemical shifts were calculated with the equation $t = \Delta\nu/\nu^\circ + 3.50$,[3] where $\Delta\nu$ is the observed resonance displacement from benzene in cycles per second and ν° is the spectrometer frequency in megacycles. All data in Table I are converted to internal TMS as a reference.

Isolation of I from the original mother liquor solids of II was carried out as follows. Ten grams of the total mother liquor was dissolved in 100 ml of boiling absolute ethanol, and 50 ml of hot water was added until a slight turbidity occurred. When the solution was cooled slowly to 60–70°, 320 mg of crystals were separated by hot filtration. These crystals were recrystallized in 5 ml of boiling absolute ethanol, and 2 ml of hot water was added. When the solution was cooled slowly to *ca.* 50°, 190 mg of pure I was obtained. The purity of this material was determined by uv and nmr spectroscopy and by solubility analysis, which demonstrated it to be better than 99% pure.

Anal. Calcd for $C_{20}H_{17}O_3Cl$ (mol wt 340.81): C, 70.6; H, 5.0; Cl, 10.4. Found: C, 70.72; H, 5.11; Cl, 9.93.

Initial separation of the isomers I and II from a slightly impure (*ca.* 5%) sample of II was obtained by reverse-phase partition column chromatography. The column consisted of dichlorodimethylsilane (GE Dri-Film) treated silicic acid powder as carrier containing a 1:1 chloroform–isooctane stationary phase, through which flowed a mobile phase consisting of 65:35 methanol–water. The ratio of carrier to stationary phase was 0.5 ml/g. The column bed was 25 ml in diameter and *ca.* 0.5 m long. The sample was charged by dissolving 0.06 g in 2 ml of the stationary phase and letting this flow into the top of the column bed. Isomer I occurs first behind the liquid front followed by II. The effluent is easily monitored by uv spectroscopy and observation of the ratio of the 286- to 238-mμ absorptions. Although the chromatographic bands of I and II from the above column are not widely separated, fractionation of I and II is good enough for subsequent purification of the eluted material by simple crystallization from chloroform–petroleum ether. This method is slow and tedious but seems to be the only one which works with samples of II containing only small amounts (<10%) of I.

Single crystals of the methyl ester of low-melting form II, grown from methanol, are orthorhombic, with $a = 22.12$ Å, $b = 17.36$ Å, $c = 4.71$ Å; $d_{obsd} = 1.26$ g/cm^3, $d_{calcd} = 1.30$ g/cm^3; space group $P_{2_12_12_1}$ (from systematic absences), four molecules of $C_{21}H_{19}O_3Cl$ per unit cell. The structure is isomorphous with the corresponding bromo derivatives. The intensities of the hko reflections, necessary for the *c*-axis projection, were determined from Weissenberg photographs by visual estimation.

After the positions of the heavy atoms were determined with Patterson syntheses, the structure was solved in the usual way and refined by difference Fourier syntheses. The final Fourier synthesis is shown in Figure 1, and the final *R* factor is 0.145. A list of coordinates and structure factors is available from the authors on request.

Registry No.—I, 22287-03-2; II, 20754-69-2.

(2) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).
(3) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

A New Synthetic Route to Dibenzo[*b*,*h*]biphenylene and Its 5,6,11,12-Tetramethyl and -Tetraphenyl Derivatives

NICOLAAS PETRUS DU PREEZ, PETRUS JANSE VAN VUUREN, AND JOHANNES DEKKER

Organic Section, Department of Chemistry, Potchefstroom University for C.H.E., Potchefstroom, South Africa

Received May 19, 1969

Since the first[1] successful synthesis of I (R = H) was achieved, several alternative routes[2-4] to I (R = H) and

(1) R. F. Curtiss and G. Viswanath, *Chem. Ind.* (London), 1174 (1954); *J. Chem. Soc.*, 1670 (1959).
(2) E. R. Ward and B. D. Pearson, *ibid.*, 1676 (1959).
(3) E. R. Ward and B. D. Pearson, *ibid.*, 515 (1961).
(4) J. W. Barton and S. A. Jones, *ibid.*, 1276 (1967).