Optical Resolution and Determination of Absolute Configuration of Nipradilol

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It was confirmed that the title compound, a new antihypertensive drug, consists of four optical isomers: two diastereomers and their enantiomers. Separation of the diastereomers was effected by recrystallization. Optical resolution of the enantiomers was carried out by repeated recrystallization of their diastereomeric salts with (+)- or (−)-2-[1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetoxy-2-phenylacetate acid or by high performance liquid chromatography of the 1-methoxy-acycl derivatives. The absolute configurations of the separated isomers were determined on the basis of the circular dichroism spectra and proton nuclear magnetic resonance spectra.

Keywords—nipradilol; antihypertensive drug; optical resolution; absolute configuration; CD spectra; 1H-NMR spectra

Nipradilol,1) 3,4-dihydro-8-(2′-hydroxy-3′-isopropylamino)propoxy-3-nitroxy-2H-1-benzopyran, is a newly synthesized antihypertensive drug,2) in which the presence of four possible optical isomers is expected in view of the existence of two asymmetric centers. It is well known that optical isomers may have extremely different biological activity. For example, such a difference is observed in the case of β-blockers such as propranolol, labetalol and so on.3) Therefore we wished to determine the absolute configuration of each isomer. In this paper, we describe the separation and structure determination of the four optical isomers.

Results and Discussion

To establish the ratios of optical isomers in nipradilol (I), we tried to separate them by high performance liquid chromatography (HPLC) as diastereomeric derivatives. Compound 1 was converted into the N,O-bis-1-methoxyacetyl derivative, which showed four peaks on HPLC, the areas of which were all nearly equal (Fig. 1). This result showed that nipradilol is a mixture of four optical isomers.

Separation of two diastereomers (1A and 1B) was effected by repeated recrystallization from ethyl acetate.4) The N,O-bis-1-methoxyacetyl derivatives of 1A showed two peaks (peak 1 and 2) of longer retention time, and those of 1B, two peaks (peak 3 and 4) of shorter retention time (Fig. 1).

To resolve 1A as well as 1B, the formation of the salts with an optically active acid was necessary. We then searched for a suitable acid for this purpose and were able to obtain salts of 1 with acemetacin5) (4, R′ = H in Chart 1), though it lacks an asymmetric center. We therefore synthesized optically active phenyl derivatives ((+)-4 and (−)-4) of acemetacin from indomethacin6) (2). Compound 2 was converted into the corresponding acid chloride (3) by reaction with thionyl chloride. The reaction of 3 with (+)-mandelic acid gave (+)-4 and that with (−)-mandelic acid, (−)-4 (Chart 1).
Resolution of 1A was effected through the formation of diastereomeric salts with (+)-4 and (-)-4 (Chart 2). Recrystallization of the salts of 1A and (+)-4 four times provided the enantiomerically pure salt of 1A1 and (+)-4. The purity was checked by HPLC as the N,O-bis-l-menthoxycetyl derivative of 1A1 (Fig. 1). The salt of 1A2 and (-)-4 was similarly obtained from the salts of 1A and (-)-4, and the purity was also checked by HPLC. A similar procedure was carried out for the resolution of 1B using (+)-4. However, we have not yet isolated pure enantiomer but only a mixture which is rich in 1B1, because it took more than several months for a single recrystallization. We had planned to determine the absolute configurations of the isomers in 1 on the basis of the dibenzoate chirality rule. We therefore
Fig. 1. Chromatograms of \(N, O\)-Bis-\(\beta\)-menthoxyacetyl Derivatives of (a) Nipradilol (1), (b) 1A, (c) 1B, (d) 1A1 and (e) 1A2

Column: Partisil-10 (10 \(\mu\)m) (Whatman). 4 \(\times\) 200 mm. Eluent: hexane-ethyl acetate = 5:1 at 1.5 ml/min. Detection: UV 275 nm.

Fig. 2. CD Spectra of (a) 7A1, 7A2, 7B1 and 7B2 and (b) 10A1 and 10A2

tried to separate 1B into its components by HPLC of diastereomeric derivatives which could be converted into \(N, O\)-bis-\(p\)-chlorobenzoyl derivatives for measurements of circular dichroism (CD) spectra after the separation. Thus, 1B was converted into \(N\)-\(p\)-chlorobenzoyl derivatives (5B) and then into \(N\)-\(p\)-chlorobenzoyl-\(O\)-\(\beta\)-menthoxyacetyl derivatives (6B). The resulting 6B could be separated into two components by HPLC. The first component 6B2 was the derivative of the enantiomer 1B2 and the second component, 6B1, that of the enantiomer 1B1 (Chart 2).

For the assignment of the absolute configuration at C2' in the \(\beta\)-side chain, two enantiomers (1A1 and 1A2) were directly converted into \(N, O\)-bis-\(p\)-chlorobenzoyl derivatives (7A1 and 7A2), and 6B1 and 6B2 were converted into 5B1 and 5B2 by partial hydrolysis and then into \(N, O\)-bis-\(p\)-chlorobenzoyl derivatives (7B1 and 7B2) (Chart 3). On the other hand, for the assignment of the absolute configuration at C3 in the benzopyran ring, 1A1 and 1A2 were converted into 8-hydroxy-3-nitrobenzopyrans (8A1 and 8A2) by pyrolysis and then into 3,8-dihydroxybenzopyrans (9A1 and 9A2) by hydrolysis. Further, the resulting 9A1 and 9A2 were converted into 3,8-bis-\(p\)-chlorobenzoyloxybenzopyrans (10A1 and 10A2) (Chart 3). CD spectra of 7A1, 7A2, 7B1 and 7B2 are shown in Fig. 2a and those of 10A1 and 10A2, in Fig. 2b.

The dibenzoate chirality rule is now widely accepted for the determination of absolute configurations. It can be applied not only to the benzoate system but also to the benzamide system. Three staggered conformers are possible for \(2'R\) configuration in the \(\beta\)-side chain (Fig. 3). It was predicted that conformer i, which would be positive at the longer-wavelength
band and negative at the shorter-wavelength band (positive Cotton effect), would be more stable than conformer iii because of the difference between their steric hindrances, and conformer ii should give little or no Cotton effect because of the symmetric arrangement of the two benzoyl groups. As can be seen in the CD spectra in Fig. 2a, 7A1 and 7B1 showed positive Cotton effects and 7A2 and 7B2, negative. The configurations at C2' in 7A1 and 7B1 are therefore R and those in 7A2 and 7B2, S. On the other hand, it was predicted that 3S configuration in the benzopyran ring would show positive Cotton effect and conversely 3R, negative. Since 10A1 showed a negative Cotton effect and 10A2, positive (Fig. 2b), the configuration at C3 in 10A1 is R and that in 10A2, S. Thus, 1A1 and 1A2 were assigned the 2'R,3R and 2'S,3S configurations, respectively, and 1A is therefore the racemate of 2'R,3R and 2'S,3S. From these results, 1B is clearly the racemate of 2'R,3S and 2'S,3R. Since the configuration at C2' in 7B1 is R and that in 7B2 is S, 1B1 and 1B2 were assigned as 2'R,3S and 2'S,3R, respectively.

In order to confirm the above assignments, proton nuclear magnetic resonance (1H-NMR) studies were carried out. There was no appreciable difference between the 1H-NMR spectra of the two diastereomers (1A and 1B). Compounds 1A and 1B were therefore converted into dihydroxy compounds (11A and 11B) and then N-acetyl derivatives (12A and
Chart 4. Synthesis of Cyclic Diesters for Measurements of $^1$H-NMR Spectra

![Chart showing the synthesis of cyclic diesters]

Fig. 4. Partial $^1$H-NMR Spectra (199.5 MHz, CCl$_4$) of Cyclic Diesters
I, 13A; II, 13B. i) Assignment of proton. ii) Coupling constant.

![NMR spectra graphs]

Fig. 5. Stereomodels of Cyclic Diesters Having 3S Configuration in the Benzopyran Ring
I, 2'S, 3S configuration; II, 2'R, 3S configuration. ●, carbon; ○, hydrogen; ○, oxygen.
Further, the resulting 12A and 12B were converted into cyclic diesters (13A and 13B) by reaction with succinyl chloride (Chart 4).

The 1H-NMR spectra of 13A and 13B are shown in Fig. 4. It was observed that the H1'a, H1'b and H2' signals of 13A, in comparison to those of 13B, were 0.13 ppm downfield, at nearly the same position, and 0.30 ppm upfield, respectively. We estimated the influence of the circular current in the benzene ring on the chemical shifts of H1'a, H1'b and H2' in 2'S,3'S configuration as well as in 2'R,3'S configuration on the basis of molecular models of the cyclic diesters, and could predict that the H2' signal in 2'S,3'S would appear at higher field than in 2'R,3'S, in spite of various available conformers of the 14-membered ring in the diester. This analysis suggested that 2'S,3'S is a component of 13A and 2'R,3'S is a component of 13B. As regards the split patterns, H1'a and H1'b in 13A were a doublet ($J_{gem}=13.1$ Hz, $J_{cis}=7.6$), respectively, and in 13B, a doublet ($J_{gem}=13.5$, $J_{cis}=7.6$) and doublet ($J_{gem}=13.5$, $J_{cis}=7.6$), respectively. The approximative dihedral angles between the C1'--H1'a and C2'--H2' bonds and between the C1'--H1'b and C2'--H2' bonds in 13A were estimated to be 90 and 30°, respectively, and those in 13B, 150 and 90°, respectively. The molecular models I (2'S,3'S) and II (2'R,3'S) having the above-mentioned torsion angles (Fig. 5) could be easily constructed without severe steric hindrance assuming that 2'S,3'S is a component of 13A and 2'R,3'S is a component of 13B. Further, the above-mentioned differences between the chemical shifts of protons in 13A and in 13B could be explained on the basis of models I and II. Thus, the results of 1H-NMR studies supported the results of CD spectroscopic studies. Figure 1 shows the assignment of each peak on HPLC.

We can now assign the isomers in nipadiol (1). The biological behavior of the diastereomers (1A and 1B) and the optical pure compounds (1A1, 1A2, 1B1 and 1B2) are being investigated at present, and the results will be reported elsewhere.

**Experimental**

HPLC was performed with a JASCO TRI ROTAR-II equipped with a UVIDEC-100II detector. Analytical and preparative thin-layer chromatographies (TLC) were performed on E. Merck silica gel 60F254 plates (20 x 20 cm; thickness, 0.25 or 2 mm). 1H-NMR spectra were recorded on a JEOL JNM-FX200 spectrometer (199.5 MHz). Chemical shifts are reported in ppm (δ) from internal trimethylsilylamine. In the case of measurement in CCl4, CDCl3 was used to provide an external lock signal. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded on JEOL JMS-D300 and JMS-DX300 mass spectrometers. CD spectra were recorded on a JASCO J-500A spectrophotometer. Optical rotations were recorded on a JASCO DIP-4 polarimeter.

**Preparation of Diacyl Compounds** — General Procedure: An acid chloride (β-menthyoxacetyl chloride or ω-chlorobenzoyl chloride) (50 µl) was added to a solution of the precursor (1, 5B, 1A1, 1A2, 6B1, 6B2, 9A1 or 9A2) (5—10 mg) of a diacyl compound in dry pyridine (0.5 ml) at room temperature. After 30 min, water (50 µl) was added to the solution and the solvent was removed in vacuo. The residue was dissolved in chloroform (5 ml) and washed with 1 N HCl (3 ml x 2), saturated NaHCO3 solution (3 ml) and then water (3 ml). After being dried (Na2SO4), the solution was evaporated in vacuo and the residue was purified by preparative TLC with hexane–ethyl acetate (1:1) as the developing solvent.

3,4-Dihydro-8-[3'-(N-isopropyl-1-menthyoxacyl)amino-2'-1-menthoxacetyl]propoxy-3-nitroxy-2H-1-benzopyran (N,O-Bis-1-menthoxacetyl Derivative) — Reaction of 1 (5 mg) with 1-menthoxacetyl chloride according to the general procedure gave the N,O-bis-1-menthoxacetyl derivatives (oil, 7 mg), which were analyzed by HPLC under the conditions described in Fig. 1. LRMS (FAB) m/z: 719 (MH+), 674, 508, 478, 460. HRMS (EI): Calc'd for C45H42N2O10: 719.4479. Found: 719.4469.

2-[1-(ω-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetooxy-2-phenylacetic Acid (+)-4 and (−)-4 — A mixture of 2 (2 g), dry dioxane (1 ml) and thionyl chloride (0.28 ml) was refluxed. After 30 min, (+)-mandelic acid (0.8 g) and dry dioxane (10 ml) were added to the solution, and the mixture was further refluxed for 30 min then concentrated in vacuo. The residue was dissolved in ethyl acetate (40 ml) and isopropylamine (3 ml) was added to the solution. The salts that separated were collected by suction and then shaken in 0.5 N HCl (40 ml) and ethyl acetate (20 ml). The organic layer was washed with water, treated with charcoal and dried (Na2SO4). Isopropylamine (0.5 ml) was added to the solution and the salts that separated were treated once more as above. The organic layer was then...
concentrated to dryness in vacuo to give (+)-4 (yellow solid, 1.2 g). Compound (−)-4 was prepared in the same manner using (−)-mandelic acid instead of (+)-mandelic acid. [α]D20 = 0.1, CHCl3); (−)-4, 66.2°; (−)-4, −65.9°. Anal. Calcd for C22H22Cl2N2O6: C, 61.65; H, 5.42; N, 5.14. Found: (−)-4, C, 61.41; H, 5.48; N, 5.07. Optical Resolution of Racemate 1A—A solution of (+)-4 (300 mg) and 1A (200 mg) in hot ethyl acetate (15 ml) was mixed with hot hexane (15 ml), and allowed to stand overnight at room temperature. After removal of the mother liquid by decantation, the salts were dissolved in hot ethyl acetate (17 ml). The solution was mixed with hot hexane (15 ml) and left overnight at room temperature. This recrystallization procedure was repeated four times. The salts which were optically resolved were dissolved in chloroform (5 ml) and shaken with 1 N HCl (5 ml). The aqueous layer was transferred to another container, made alkaline with NH3–NH4Cl buffer solution (5 ml, pH 10) and extracted with chloroform (10 ml). The organic layer was dried (Na2SO4) and concentrated to dryness in vacuo. The residue was recrystallized from ethyl acetate to give enantiomer 1A1 (white crystals, 40 mg). Enantiomer 1A2 was obtained in the same manner using (−)-4 instead of (+)-4. The purity of each enantiomer was checked by HPLC as the N-O-bis-l-menthyl acetal derivative under the conditions described in Fig. 1. [α]D20 = 0.1, CHCl3); 1A1, 14.4°; 1A2, −14.2°. Anal. Calcd for C15H15NO3C: C, 55.21; H, 6.79; N, 8.58. Found: 1A1, C, 55.08; H, 6.68; N, 8.47. 1A2, C, 55.30; H, 6.66; N, 8.51. NMR (CDCl3): δ = 1.08 (d, 6H, −CH(CH3)2), 2.7–2.9 (m, 3H, −CH2−−CH−CH3), 3.03 and 3.28 (br, dd, 2H, 4-CH2), 3.9–4.1 (m, 3H, 1′-CH2, 2′-CH2), 4.28 and 4.42 (br, dq, 2H, 2-CH2), 5.48 (m, 1H, 3-CH2), 6.7–7.0 (m, 3H, Ar-H). LRM8 (E1) m/z: 465 (M+)4; 446, 254, 139 (base). HRMS (EI): Calcd for C22H22Cl2N2O6: 465.1425. Found: 465.1415.

3.4-Dihydro-8-[3′-(N-p-chlorobenzylo-N-isopropylamino-2’-hydroxy)propoxy-3-nitroxy-2H-1-benzopyran (SB)—Triethylamine (0.1 ml) and a solution of p-chlorobenzoic chloride (25 mg) in benzene (10 ml) were added to a solution of 1B (50 mg) in benzene (15 ml) at room temperature. After standing for 30 min, the solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC with hexane–AcOEt (1:1) as the developing solvent to give 5B (oil, 60 mg). 1H-NMR (CDCl3): δ = 1.20 (q, 6H, −CH(CH3)2), 3.03 and 3.31 (br, dd, 2H, 4-CH2), 3.71 (brs, 2H, 3′-CH2), 3.8–4.5 (m, 6H, 2-CH2, 1′-CH2, 2′-CH2, −CH2−CH3), 5.48 (m, 1H, 3-CH2), 6.7–7.0 (m, 3H, Ar-H). LRM8 (E1) m/z: 466 (M+)4; 616, 465, 450, 420.

Partial Hydrolysis of 6B1 and 6B2—Compounds 6B1 (10 mg) was dissolved in isopropylamine (2 ml). After 24 h at room temperature, the solvent was removed in vacuo. The residue was purified by preparative TLC with hexane–AcOEt (1:1) as the developing solvent to give 5B1 (oil, 5 mg). The same treatment of 6B2 gave 5B2. Spectral data of 5B1 and 5B2 were identical with those of 5B.

3.4-Dihydro-8-[2′-p-chlorobenzoxo-3′-(N-p-chlorobenzylo-N-isopropylamino)-2’-hydroxy-3-nitroxy-2H-1-benzopyran (7A1, 7A2, 7B1 and 7B2)—Reaction of 1A1, 1A2, 6B1 or 6B2 (5 mg) with p-chlorobenzoic chloride according to the general procedure gave 7A1, 7A2, 7B1 or 7B2 (colorless crystals, 5–7 mg), respectively. 1H-NMR (acetone-d6): δ = 1.19 and 1.20 (d, 6H, −CH(CH3)2), 3.09 and 3.30 (br, dd, 2H, 4-CH2), 3.8–4.1 (m, 3H, 3′-CH2, −CH2−CH3), 4.2–4.6 (m, 4H, 2-CH2, 1′-CH2), 5.68 (m, 1H, 3-CH2), 5.89 (m, 1H, 2′-CH2), 6.8–7.0 (m, 3H, Ar-H), 7.3–8.1 (m, 8H, benzoyl-H). LRM8 (E1) m/z: 602 (M+)4; 539, 446, 393, 139 (base). HRMS (EI): Calcd for C28H30Cl2NO8: 602.2200. Found: 7A1, 602.1200; 7A2, 602.1180; 7B1, 602.1187; 7B2, 602.1241.

3.4-Dihydro-8-hydroxy-3-nitroxy-2H-1-benzopyran (8A1 and 8A2)—Compounds 1A1 (300 mg) was heated at 145°C for 30 min. The resulting mixture was separated by preparative TLC with chloroform–acetone–isopropylamine (10:5:1) as the developing solvent to give 8A1 (colorless crystals, 20 mg, Rf: about 0.7). Similar treatment of 1A2 gave 8A2. 1H-NMR (CDCl3): δ = 3.04 and 3.28 (br, dd, 2H, 4-CH2), 4.29 and 4.45 (br, dq, 2H, 2-CH2), 5.47 (m, 1H, 3-CH2), 6.6–6.9 (m, 3H, Ar-H). LRM8 (E1) m/z: 211 (M + base), 147, 135, 122, 107, 91, 77.

3.4-Dihydro-3,8-dihydroxy-2H-1-benzopyran (9A1 and 9A2)—A solution of 8A1 (10 mg) in 2 N HCl (2 ml) was heated at 105°C for 3 h. After cooling, the solution was neutralized and extracted with ethyl acetate (5 ml). The organic layer was dried (Na2SO4) and concentrated in vacuo. The residue was purified by preparative TLC with chloroform–isopropyl ether–methanol–triethylamine (12:3:3:2) as the developing solvent to give 9A1 (colorless crystals, 7 mg). Similar treatment of 8A2 gave 9A2. 1H-NMR (CDCl3): δ = 2.83 and 3.10 (br, dd, 2H, 4-CH2), 4.2 (m, 2H, 2-CH2), 5.30 (m, 1H, 3-CH2), 6.6–6.9 (m, 3H, Ar-H). LRM8 (E1) m/z: 166 (M + base), 147, 135, 122, 107, 91, 77.

3.4-Dihydro-3,8-bis(p-chlorobenzoxoxy)-2H-1-benzopyran (10A1 and 10A2)—Reaction of 9A1 (5 mg) and p-chlorobenzoxoxy chloride according to the general procedure gave 10A1 (colorless crystals, 5 mg). Similar treatment of 9A2 gave 10A2. 1H-NMR (acetone-d6): δ = 3.14 and 3.41 (br, dd, 2H, 4-CH2), 4.33 and 4.41 (br, dq, 2H, 2-CH2), 5.59 (m, 1H, 3-CH2), 6.7–7.2 (m, 3H, Ar-H), 7.5–8.3 (m, 8H, benzoyl-H). LRM8 (E1) m/z: 442 (M + base), 286, 139 (base),
111. HRMS (EI): Caled for C_{23}H_{16}ClO_{5}: 442.0374. Found: 10A1, 442.0397; 10A2, 442.0374.

3,4-Dihydro-3-hydroxy-8-(2′-hydroxy-3′-isopropylamino)propoxy-2H-1-benzopyran (11A and 11B) —— Compound 1A (500 mg) in 0.3 N H_{2}SO_{4} (80 ml) was refluxed for 24 h. After cooling, the solution was washed with chloroform (40 ml × 2), made alkaline with 5 N NaOH and then extracted with chloroform (50 ml × 2). The combined extracts were washed with a small amount of water, dried (Na_{2}SO_{4}) and concentrated in vacuo to give 11A (colorless solid, 350 mg). Similar treatment of 1B gave 11B. ^{1}H-NMR (CDCl_{3}) \( \delta \): 1.07 (d, 6H, -CH(CH_{3})_{2}), 2.6–2.9 (m, 3H, 3′-Cl_{2}, -CH(CH_{3})_{2}), 2.8 and 3.05 (br d, dd, 2H, 4-CH_{2}), 3.4–3.7 (m, 3H, 1′-CH_{3}, 3′-CH_{2}), 3.9 (m, 2H, 2′-CH_{2}), 4.14 (m, 2H, 2′-CH_{2}), 4.23 (m, 2H, 3′-CH_{2}), 6.6–6.9 (m, 3H, Ar-H). LRMS (EI) m/z: 281 (M^+), 237, 166, 91, 77, 72.

3,4-Dihydro-8-[3′-(N-acetyl-N-isopropylamino)-2′-hydroxy]propoxy-3-hydroxy-2H-1-benzopyran (12A and 12B) —— Acetic anhydride (0.2 ml) was added to a solution of 11A (200 mg) in dry pyridine (20 ml) at room temperature. The mixture was allowed to stand for 1 h, then water (0.5 ml) was added and the solvent was removed in vacuo. The residue was dissolved in chloroform (20 ml) and the solution was washed with 1 N HCl (10 ml × 2), saturated NaHCO_{3} solution (10 ml) and then water (10 ml). After being dried (Na_{2}SO_{4}), the organic layer was concentrated in vacuo to give 12A (oil, 190 mg). Similar treatment of 11B gave 12B. ^{1}H-NMR (CDCl_{3}) \( \delta \): 1.21 and 1.28 (d, d, 6H, -CH(CH_{3})_{2}), 2.19 (s, 3H, -COCH_{3}), 2.82 and 3.09 (dd, dd, 2H, 4-CH_{2}), 3.56 (m, 2H, 3′-CH_{2}), 3.83 (t, 1H, one of 1′-CH_{2}), 4.05 (m, 1H, -CH(CH_{3})_{2}), 4.1–4.2 (m, 4H, one of 1′-CH_{2}, 2′-CH, 2-CH_{2}), 4.25 (m, 1H, 3-CH), 6.6–7.0 (m, 3H, Ar-H). LRMS (EI) m/z: 323 (M^+), 308, 305, 200, 158 (base).

2′,3-Succinylxoxy-3,4-dihydro-8-[3′-(N-acetyl-N-isopropylamino)propoxy-2H-1-benzopyran (13A and 13B) —— Succinyl chloride (50 μl) was added to a solution of 12A (100 mg) in ethanol-free dry chloroform (10 ml) in a sealed tube, and the solution was heated at 80 °C for 4 h, then cooled. Methanol (0.5 ml) was added and the solution was concentrated in vacuo. The residue was purified by preparative TLC with hexane-AcOEt (2:1) as the developing solvent to give 13A (colorless crystals, 40 mg; R_f: about 0.25). Similar treatment of 12B gave 13B. ^{1}H-NMR (CDCl_{3}) \( \delta \): 13A, 1.16 (m, 6H, -CH(CH_{3})_{2}), 2.30 (s, 3H, -COCH_{3}), 2.2–2.7 (m, 4H, -COCH_{2}CH_{2}CO-), 2.82 (br d, dd, 2H, one of 4-CH_{2}), 3.0–3.2 (m, 2H, one of 4-CH_{2}, one of 3′-CH_{2}), 3.50 (dd, 1H, one of 3′-CH_{2}), 3.88 and 4.56 (br d, br d, 2H, 2′-CH_{2}, 2-CH_{2}), 4.16 and 4.41 (br d, dd, 2H, 1′-CH_{2}), 4.85 (m, 2H, 2′-CH), 5.11 (m, 1H, 2′-CH), 6.6–6.8 (m, 3H, Ar-H). 13B, 1.22 and 1.32 (dd, dd, 6H, -CH(CH_{3})_{2}), 2.06 (s, 3H, -COCH_{3}), 2.0–2.8 (m, 4H, -COCH_{2}CH_{2}CO-), 2.75 and 3.05 (br d, dd, 2H, 4-CH_{2}), 2.90 and 3.56 (dd, dd, 2H, 3′-CH_{2}), 3.85–4.1 (m, 3H, one of 4-CH_{2}, one of 4-CH_{2}, -CH(CH_{3})_{2}), 4.3 (br d, d, 1H, one of 2′-CH_{2}), 4.45 (br d, 1H, one of 1′-CH_{2}), 5.15 (m, 1H, 2′-CH_{2}), 5.24 (m, 1H, 3-CH), 6.5–6.9 (m, 3H, Ar-H). LRMS (EI) m/z: 405 (M^+, base), 362, 320, 258, 216, 148, 140.

HRMS (EI): Caled for C_{22}H_{27}NO_{7}: 405.1785. Found: 13A, 405.1753; 13B, 405.1785.

References and Notes

4) Acmetacin, [1-(p-chlorobenzyloxy)-5-methoxy-2-methylindol-3-yl]acetoxycetic acid; indomethacin, [1-(p-chlorobenzyloxy)-5-methoxy-2-methylindol-3-yl]acetic acid. These compounds have been used as antiinflammatory drugs.