**Reduction of α-Methyl-α-((1-*tert*-butoxy-2-methyl-2,3-epoxypropyl)oxy)-β-propiolactone (3a).** Lithium aluminium hydride (0.5 g) in 10 mL of absolute ether was put into a flask containing a magnetic stirring bar and fitted with a septum and protected by a calcium chloride tube. A solution of 2 mL (9 mmol) of **3a** in 5 mL of absolute ether was added, with continous stirring, over a period of 30 min. The mixture was then stirred for a further 4 h. The excess $LiAlH_4$ was destroyed by careful addition of ice–water, until hydrogen was no longer evolved, and 5 mL of 10% sulphuric acid was added to dissolve the precipitated aluminium hydroxide. The layers were separated, the aqueous layer extracted with ether three times, and the combined organic phases were then washed with sodium chloride, dried over magnesium sulfate, filtered, and concentrated by evaporation of the ether. The components of the mixture thus obtained were separated using PGC, and the following substances were collected.

**2-Methyl-2,3-epoxy-1-propanol (6):** yield, 362 mg (47.3%); IR (capillary cell) $\nu_{max}$ 3420, 2980, 2940, 2870, 1450, 1380, 1200, 1090 $cm^{-1}$; MS *m/e* 88 ($M^+ - 1$) (34), 75 (23), 74 (25), 59 (31), 58 (11), 57 (100), 43 (22), 41 (29), 39 (7), 31 (5), 29 (20); $^1H$ NMR ($CCl_4$) $\nu$ 1.3 (s, 3, $CH_3$), 2.53, 2.79 (AB q, 2, $J$ = 5 Hz, $CH_2OCCH_3$), 3.56, (s, 2, $CH_2OH$), 3.97 (s, 1, $CH_2OH$). Anal. Calcd for $C_4H_8O_2$: C, 54.53; H, 9.15. Found: C, 54.42; H, 9.22.

**2-Methyl-2-*tert*-butoxypropane-1,3-diol (7):** yield, 1.092 g (74.9%); IR (capillary cell) $\nu_{max}$ 3450, 2970, 2870, 1370, 1250, 1100 $cm^{-1}$; MS, *m/e* (molecular ion was not detected) 105 (45), 75 (73), 59 (22), 58 (16), 57 (100), 56 (5), 43 (14), 41 (21), 31 (7), 29 (15); $^1H$ NMR ($CCL_4$) δ 1.05 (s, 3, $CH_3$–C), 1.16 [s, 9, $C(CH_3)_3$], 3.25 (s, 2, $CCH_2OH$), 3.32, 3.46 (AB q, 2, $J$ = 12 Hz, $CCH_2OH$), 3.81 (s, 2, $CH_2OH$). Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.35; H, 11.20.

Diol **7** reacted with acetic anhydride forming a diacetate with a PMR spectrum that confirmed the structure of **7**: $^1H$ NMR ($CDCl_3$) δ 1.09 (s, 3, $CCH_3$), 1.12 [s, 9, $C(CH_3)_3$], 2.04 [s, 6, $C(O)CH_3$], 3.95 (s, 4, $CH_2O$).

The reduction of **3a** with excess $LiAlH_4$ (mol ratio 1:3) leads in addition to compounds **6** and **7** to the formation of 2-methylpropane-1,3-diol (**8**): IR (capillary cell) $\nu_{max}$ 3380, 2980, 2940, 2880, 1480, 1390, 1370, 1230, 1170, 1065, 990 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 1.11 [s, 6, $C(CH_3)_3$], 3.30 (s, 2, $CH_2OH$), 3.43 (s, 2, OH). Anal. Calcd for $C_4H_{10}O_2$: C, 53.29; H, 11.20. Found: C, 53.15; H, 11.24.

**Registry No.** **1**, 52788-68-8; **3a**, 67872-66-6; **5a**, 89346-43-0; **5b**, 89346-44-1; **5b** (urethane derivative), 89346-45-2; **6**, 872-30-0; **7**, 89346-46-3; **7** (diacetate), 89346-47-4; **8**, 2163-42-0.

# Synthesis of 3-Hydroxy-3-(hydroxymethyl)-5-methylcyclohexane-1,2-dione Dibenzoate, a Reported Hydrolytic Degradation Product of Leucogenenol

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2-Hydroxy-2-(hydroxymethyl)cyclohexanone (**3a**), 2-hydroxy-2-(hydroxymethyl)-4-methylcyclohexanone (**3b**), and 2-hydroxy-2-(hydroxymethyl)-5-methylcyclohexanone (**6**) were converted with $MoO_5$·pyridine·HMPA (MoOPH) into the respective 6-hydroxy analogues, which were oxidized with trifluoroacetic anhydride–$Me_2SO$–$Et_3N$ to the corresponding α-diones **1a**, **1b**, and **9**. The title compound **1b** was not identical with a compound reported to have the same structure obtained by Rice through the degradation of leucogenenol.

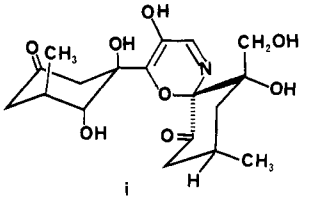
For a projected (but now abandoned, at least temporarily) study of the biosynthesis of leucogenenol, a so-called thymothyroid hormone[1] of unknown structure[2-4] isolated from *Penicillium gilmanii*[3] and from various animal (including human) tissues,[5,6] we required the leucogenenol degradation product **1b**. Although a synthesis of this dione has previously been reported,[7] the method used was rather lengthy (eight steps from 5-methyl-1,3-cyclohexanedione). We therefore developed, and now report, the alternative synthetic route, shown in Scheme I, to **1b** (only one diastereomer of **1b** being obtained). The method developed is a useful route to cyclohexane-1,2-diones and was also used for the synthesis of diones **1a** and **9**.

Because of the commercial avaiability of **2a**, the route leading to **1a** was first attempted. Treatment of **2a** with trioxymethylene and alkali by a modification of a published method[8] gave **3a**, which was converted by treatment with excess benzoyl chloride in pyridine at 70 °C into the dibenzoate **4a**.[9] Treatment of **4a** with $MoO_5$·pyridine·HMPA (MoOPH)[10] gave a good yield of the α-hydroxy analogue **5a**, apparently a single stereoisomer (of unknown stereochemistry) as suggested by the NMR spectrum that showed a clean AB pattern for the $CH_2O$ protons. Finally, oxidation of **5a** by treatment with trifluoroacetic anhydride–$Me_2SO$–$Et_3N$[11] gave the desired **1a** in fair yield. As expected, the compound was essentially completely enolized, showing a vinylic proton signal at δ 6.23.

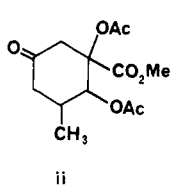
† Worcester Foundation for Experimental Biology.
‡ Cornell University.

(1) Rice, F. A. H.; McCurdy, J. D.; Oresajo, C. *Am. J. Physiol.* **1980**, *238*, E540–E542.

(2) The structure i for leucogenenol was proposed by Rice,[3] largely on the basis of degradative chemistry. However, this structure was recently




i




ii

shown to be untenable by Salomon et al.,[4] who synthesized all possible diastereomers of one of the degradation products having a proposed structure ii. None of the synthetic compounds was identical with the degradation product reported by Rice.[3]

(3) Rice, F. A. H. *J. Chem. Soc. C* **1971**, 2599–2606.

(4) Salomon, R. G.; Salomon, M. F.; Zagorski, M. G.; Reuter, J. M.; Coughlin, D. G. *J. Am. Chem. Soc.* **1982**, *104*, 1008–1013.

(5) (a) Rice, F. A. H.; Shaikh, B. *Biochem. J.* **1970**, *116*, 709–711. (b) Rice, F. A. H.; Shaikh, B.; Chen, C. G. *Johns Hopkins Med. J.* **1974**, *35*, 336–343.

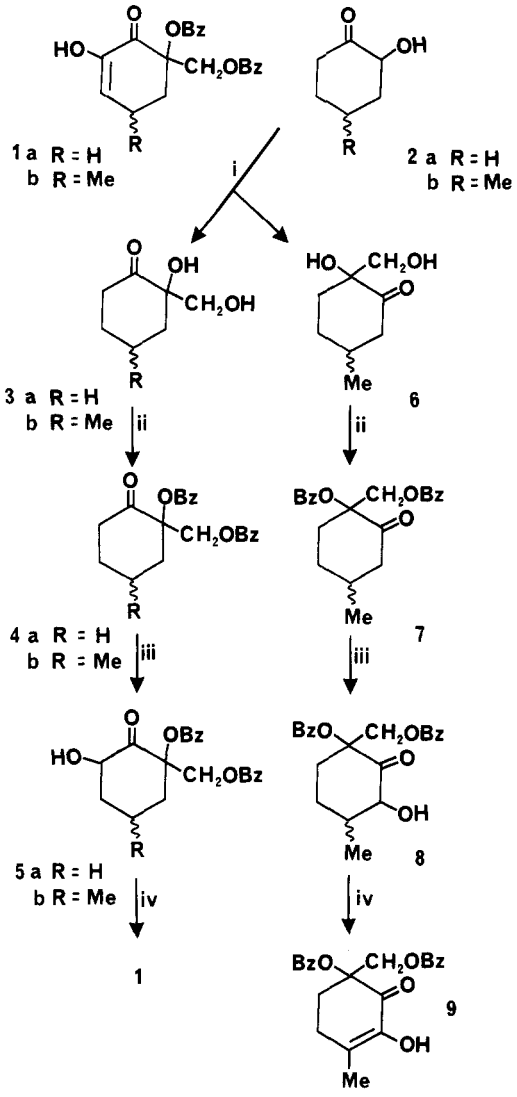
(6) For recent papers on the biological effects of leucogenenol, see: (a) Rice, F. A. H.; McCurdy, J. D. *J. Immunol.* **1982**, *128*, 1769–1771. (b) Rice, F. A. H.; Oresajo, C.; Heath, J. R.; Breyere, E. J.; McCurdy, J. D. *Cancer Res.* **1981**, *41*, 4976–4980. (c) Rice, F. A. H.; Koo, M.-J. *J. Immunol.* **1981**, *128*, 1601–1603. (d) Rice, F. A. H.; Aziz, K. *Life Sci.* **1983**, *33*, 2235–2240.

(7) Rice, F. A. H. *Carbohydr. Res.* **1972**, *21*, 65–71.

(8) Colonge, J.; Vaginay, Y. *Bull. Soc. Chim. Fr.* **1965**, 3140–3143.

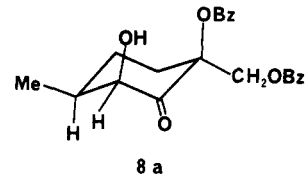
0022-3263/84/1949-2429$01.50/0 

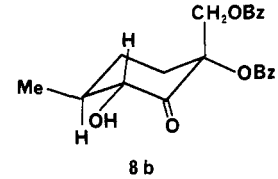
Scheme I. Synthesis of α-Diones 1a, 1b, and 9

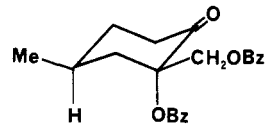


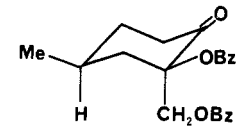

[a] Reagents: i, trioxymethylene, NaOH; ii, BzCl/pyridine; iii, $MoO_5$·pyridine·HMPA/LiN(*i*-Pr)$_2$; iv, $(CF_3CO)_2O/Me_2SO/Et_3N$.

Similarly, **2b**[12,13] (mixture of stereoisomers) was treated with trioxymethylene and alkali, leading to an inseparable mixture of diols **3b** + **6**, which was benzoylated to give a mixture consisting mainly of **4b** + **7**. After a combination of crystallizations and chromatographic steps, the entire mixture was resolved into three dibenzoates designated, for the purposes of discussion, as **dibenzoate** 1 (DB1), **dibenzoate 2** (DB2), and **dibenzoate 3** (DB3). No evidence could be secured for the presence of an expected fourth dibenzoate in the product mixture, although a small amount of an unidentified enol benzoate was also isolated. The structures of DB1, DB2, and DB3 could not be conveniently deduced at this stage, and therefore each was carried through the oxidative sequence used with **2a**. Thus, oxidation of DB1 and DB2 with MoOPH gave α-hydroxy ketones, each showing in the $^1$H NMR spectrum, for the proton on the hydroxylated carbon, a clean doublet (δ 4.66 ($J$ = 6 Hz) from DB1, δ 4.04 ($J$ = 10 Hz) from DB2), consistent with their formulation as **8**. The chemical shifts and couplings of these protons suggest relative configurations as shown in **8a** (product from DB1) and **8b** (product from DB2). In contrast, DB3, upon treatment


8a


8b


12a

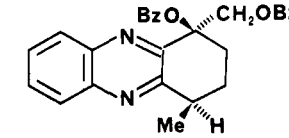

12b

with MoOPH, gave an α-hydroxy ketone showing, for the proton on the hydroxylated carbon, a clean doublet of doublets, δ 4.73 ($J_1$ = $J_2$ = 7 Hz). Thus, this product is formulated as a diastereomer of **5b** and its precursor, DB3, as **4b**. Each hydroxy ketone was then oxidized, as before, to the corresponding α-dione. The $^1$H NMR spectra of these products indicated that they were essentially unenolized diketones. However, if a trace of $Et_3N$ was added to the $CDCl_3$ solution, the spectra rapidly changed to those expected of fully enolized products. Also, if the reaction mixture was allowed to warm to room temperature before workup, the enolized products were obtained directly. The single enolic product **9** obtained from both isomers of **8** showed no vinylic proton signal, but the methyl group signal underwent a substantial downfield shift from its position in the spectra of **8**, to that expected of a vinylic methyl. In contrast **1b** (enolized form) obtained from **5b** showed a vinylic proton signal at δ 6.05 consistent with expectations.

Although neither **1b** nor **9** could be crystallized, each gave satisfactory FAB mass spectra.[14] Also, each product was further characterized as the crystalline quinoxaline derivative **10** (from **1b**) and **11** (from **9**). The NMR spectra of these products were fully consistent with the assigned structures. In particular, the $^1$H NMR of **10** showed a one-proton multiplet at δ 2.36, which was shown by double irradiation to be coupled to all other aliphatic protons except to the $CH_2O$ group protons. In addition, the $^{13}$C NMR of **10** supported the assigned structure. The off-resonance-decoupled spectrum showed a carbon bearing a single hydrogen at δ 27.57, consistent with structure **10** but not **11**. In contrast, the $^1$H NMR of **11** showed a one-proton multiplet at δ 3.45, which was the sole signal sharpened (or in any way affected) by irradiation of the methyl signal.

Unfortunately, the relative configurations of products **10** or **11** (or their precursors) could not be deduced with a high degree of confidence from their spectral parameters.


10


11

(9) At room temperature, only the primary monobenzoate of **3a**, mp 76–78 °C was formed.

(10) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

(11) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3331.

(12) Colonge, J.; Brison, P. *Bull. Soc. Chim. Fr.* **1962**, 98–101. Compound **2b**, prepared by treatment of 4-methylcyclohexanone with $Pb(OAc)_4$,[13] followed by saponification, may in fact be a mixture of 2-hydroxy-2-(hydroxymethyl)-4-methylcyclohexanone plus 2-hydroxy-2-(hydroxymethyl)-5-methylcyclohexanone.

(13) Cavill, G. W. K.; Solomon, D. H. *J. Chem. Soc.* **1955**, 4426–4429.

(14) In addition to the M + 1 peak, these spectra (taken in a MeOH-containing matrix) showed peaks for M + MeOH and M + MeOH − $H_2O$.

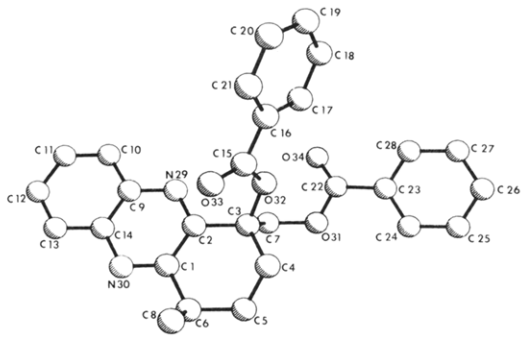


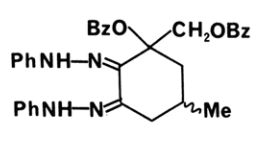

**Figure 1.** Computer-generated perspective drawing of the final X-ray model of quinoxaline (**11**).

Of the various crystalline products obtained in this work, only one diastereomer of **7** (DB1) and the quinoxaline derivative **11** gave well-formed crystals suitable for crystallography. An X-ray investigation of the quinoxaline derivative revealed the configuration shown in **11** and in Figure 1.

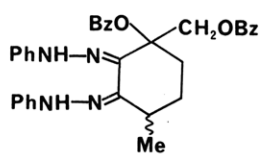
Since DB3 (**4b**) was apparently formed essentially as a single diastereomer whereas the regioisomer **7** was formed as an approximately equal mixture of two diastereomers (DB1 and DB2), we tentatively propose **12a** as the most probable configuration of this product.

Since our initial objective was to prepare the $\alpha$-dione obtained by Rice from leucogenenol, the NMR parameters of our synthetic product **1b** were compared with the NMR data reported by Rice[3,7] for **1b**. In fact, the data show that these compounds are not identical. The most prominent differences are the signals in Rice's compound extending to $\delta$ 3.9 for the ring methylene and methine protons and the *doublet* at $\delta$ 5.4 ($J$ = 3 Hz) for the $CH_2O$ group. Although it is conceivable that Rice's compound might be the other diastereomer of **1b** not obtained in our work, i.e., **12b**, we regard this as quite unlikely. In the total of 15 compounds possessing the $CH_2OBz$ group prepared in our work, the $CH_2O$ group protons appeared in a rather narrow spectral range, $\delta$ 4.70–5.17 ($J$ = 12 Hz), substantially to high field of the reported $\delta$ 5.4 ($J$ = 3 Hz).[15]

Since Rice reported the preparation of a bis(phenylhydrazone) derivative of **1b**, we also prepared this derivative, **13** and **14**, from our synthetic products **1b** and **9**,




**13**




**14**

respectively. Only the bis(phenylhydrazone) **13** obtained from the diketone **1b** was obtained in crystalline form. Its melting point, 157–159 °C, was fairly close to that reported (164 °C) for this derivative by Rice.[3] However, Rice reported[3] for this compound a UV spectrum having $\lambda_{max}$ (EtOH) 239 ($\epsilon$ 6.5 × $10^4$) and 274 ($\epsilon$ 4.4 × $10^4$). In contrast, our derivative **13** showed a long wavelength maximum of $\lambda_{max}$ 385 ($\epsilon$ 1.8 × $10^4$), very similar to that of 1,2-cyclohexanedione bis(phenylhydrazone)[16] having $\lambda_{max}$ 390 ($\epsilon$ 1.6 × $10^4$). It therefore seems highly unlikely that the derivative prepared by Rice was a bis(phenylhydrazone) of a 1,2-cyclohexanedione.

Unfortunately, it has not been possible to compare our synthetic diketones or the bis(phenylhydrazone) derivative with the synthetic or degradative products obtained by Rice, since none of his compounds remain available and their spectra could not be located. Although we wished to directly examine leucogenenol and its degradation products ourselves, this has so far been impossible. Rice refused to provide us with a culture of the *P. gilmanii* from which, apparently,[3] large quantities of leucogenenol can be isolated. To date, we have failed to isolate any leucogenenol from bovine liver (reported to contain ca. 5 mg/kg, dry weight).[17]

Thus, in summary, we have developed a useful route to the preparation of cyclohexane-1,2-diones such as **1a**, **1b**, or **9** structurally related to the reported degradation product of leucogenenol. Although it is not possible to state unequivocally that Rice's degradation product does not have structure **1b**, *since only one diastereomer of* **1b**, *probably having structure* **12a**, *was obtained* in *our work*, Rice's compound certainly is not identical with the diastereomer of **1b** obtained in our work.

## Experimental Section

**General Data.** NMR spectra were taken on a Varian EM-360 or EM-390 instrument or on a Bruker WM-250 instrument. Mass spectra were run on a CEC-110 (EI spectra) or on a Varian MAT-731 (FAB spectra) instrument at MIT. HPLC was performed on a Waters Associates instrument having an M-6000A pump, a U6K injector, and a Model 450 variable-wavelength detector. UV spectra were run on a Perkin-Elmer Model 202 instrument. Melting points were taken on a hot stage apparatus and are uncorected. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Some of the mass spectra were run by Shrader Analytical and Consulting Laboratories, Detroit, MI.

**2-Hydroxy-2-(hydroxymethyl)cyclohexanone[8] (3a), 2-Hydroxy-2-(hydroxymethyl)-4-methylcyclohexanone (3b), and 2-Hydroxy-2-(hydroxymethyl)-5-methylcyclohexanone (6).** 2-Hydroxycyclohexanone (**2a**) (dimer, Aldrich, 11.4 g, 50 mmol) was heated in an open flask in an oil bath at 150–160 °C for 10 min. Then EtOH (60 mL) was added to the hot melt, and the solution was cooled to 25 °C. Trioxymethylene (3.0 g) and 2 N KOH/MeOH (4 mL) were added, and the mixture was stirred under $N_2$ at 25 °C for 1 h. The solution was acidified with dilute HCl, and the solvent was evaporated under reduced pressure. The residue was diluted with saturated NaCl (50 mL) and extracted with 3 × 150 mL of $CH_2Cl_2$. The extract was dried ($Na_2SO_4$) and evaporated under reduced pressure to a viscous oil (9.1 g). This was chromatographed on a column of silica gel (100–200 mesh, 300 g), eluting with 50% EtOAc–hexane followed by 75% EtOAc–hexane. Fractions containing essentially pure (by TLC, solvent 75% EtOAc–hexane) **3a** were pooled and evaporated, yielding **3a**: viscous oil; 6.76 g (47%); NMR ($CDCl_3$) $\delta$ 1.4–2.4 (6 H, m), 2.6–2.8 (2 H, m), 3.68 and 4.03 (2 H, AB, $J_{AB}$ = 12 Hz).

In a similar manner, 2-hydroxy-4-methylcyclohexanone dimer[12] (mixture of stereoisomers) (20.5 g, 0.16 mmol) was converted to a mixture of **3b** + **6** (44%), a viscous oil which became semicrystalline on standing at room temperature: NMR ($CDCl_3$) $\delta$ 1.0 ($^3/_2$ H, d, $J$ = 6 Hz), 1.07 ($^3/_2$ H, d, $J$ = 6 Hz), 1.2–2.8 (7 H, m), 3.2–4.2 (2 H, m), 4.50 (2 H, br s, $W_{1/2}$ = 10 Hz, $D_2O$ exchangeable).

**2-Hydroxy-2-(hydroxymethyl)cyclohexanone Dibenzoate (4a), 2-Hydroxy-2-(hydroxymethyl)-4-methylcyclohexanone Dibenzoate (4b), and 2-Hydroxy-2-(hydroxymethyl)-5-methylcyclohexanone Dibenzoate (7).** 2-Hydroxy-2-(hydroxymethyl)cyclohexanone (**3a**) (4.24 g, 29.4 mmol) in dry pridine (35 mL) at 0 °C was treated with benzoyl chloride (10 mL, 86 mmol), and the mixture was then stirred at 70 °C for 21 h. Additional benzoyl chloride (3 mL, 26 mmol) was added, and stirring was continued for 24 h. The mixture was then cooled,

(15) Presumably Rice interpreted the central lines of an AB pattern as a doublet. Even so, with $J$ = 12 Hz, at 60 MHz, the chemical shifts would be $\delta$ 5.27 and 5.53.

(16) Bloink, G. J.; Pausacker, K. H. *J. Chem. Soc.* **1950**, 1328–1331.

(17) We strongly agree with Salomon et al.[4] that leucogenenol must be reisolated and its structure reexamined by modern spectroscopic methods.

diluted with $H_2O$, and extracted with ether. The extract was washed (dilute HCl, dilute $K_2CO_3$, saturated NaCl), and the solvent was evaporated under reduced pressure to give an oil (10 g) that gave prisms from MeOH. After several recrystallizations **4a** (7.48 g, 72%) was obtained: mp 105–107 °C; NMR ($CDCl_3$) $\delta$ 1.5–2.2 (4 H, m), 2.3–2.8 (2 H, m), 4.76 and 5.09 (2 H, AB, $J_{AB}$ = 12 Hz), 7.2–7.6 (6 H, m), 7.8–8.2 (4 H, m). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.80; H, 5.84.

Similarly the above mixture of diols **3b + 6** (5.0 g, 31.6 mmol) was converted to the corresponding mixture of dibenzoates **4b + 7**, which showed two main spots (equal intensity) on TLC (solvent 10% EtOAc–hexane, $R_f$ 0.39 (mixture of DB1 and DB2) and 0.45 (DB3 only)). A minor spot of $R_f$ 0.35 was also visible. The main products were also readily separable by HPLC (3.9 mm × 30 cm, 10 $\mu$m particle size $\mu$-Porasil column, solvent 0.2% 2-propanol–isooctane, 2 mL/min, retention times 10.5 and 14.6 min). Crystallization of the mixture from MeOH first at 25 °C, then at −10 to −20 °C gave, after recrystallization from MeOH, pure **dibenzoate 1**: 4.2 g; prisms; mp 78–80 °C; NMR ($CDCl_3$) $\delta$ 1.06 (3 H, d, $J$ = 6.6 Hz), 1.4–2.9 (7 H, m), 4.79 and 4.89 (2 H, AB, $J_{AB}$ = 12.2 Hz), 7.2–7.6 (6 H, m), 7.8–8.1 (4 H, m).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 72.38; H, 6.17.

The mother liquors from the above first crystallization were concentrated to a ca. 30% solution and were left for several days at −20 °C, yielding, after recrystallization from ether–hexane, the slower running product **dibenzoate 3**: 3.7 g; prisms; mp 86–87 °C; NMR ($CDCl_3$) $\delta$ 1.09 (3 H, d, $J$ = 6.3 Hz), 1.4–2.9 (7 H, m), 4.78 (2 H, s), 7.2–7.6 (6 H, m), 7.8–8.1 (4 H, m).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 72.02; H, 6.20.

After as much **dibenzoate 1** as possible was crystallized from the above crude product, a portion was separated by preparative TLC. The zone of $R_f$ 0.35 was extracted to yield a product tentatively identified as an enol benzoate by its NMR: $\delta$ ($CDCl_3$) 1.09 (3 H, d, $J$ = 5.6 Hz), 2.1–2.5 (5 H, m), 4.80 and 4.91 (2 H, AB, $J_{AB}$ = 11.7 Hz), 5.99 (1 H, d, $J$ = 4.3 Hz), 7.2–8.1 (15 H, m). Also the zone of $R_f$ 0.39 was recovered to give nearly pure **dibenzoate 2**, which was crystallized from ether–hexane: needles; mp 65–67 °C; NMR ($CDCl_3$) $\delta$ 1.03 (3 H, d, $J$ = 6.4 Hz), 1.7–2.8 (7 H, m), 4.74 and 5.09 (2 H, AB, $J_{AB}$ = 12.7 Hz), 7.3–8.1 (10 H, m).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11, H, 6.05. Found: C, 72.23; H, 6.16.

**2-(Benzoyloxy)-2-((benzoyloxy)methyl)-6-hydroxycyclohexanone (5a), 2-(Benzoyloxy)-2-((benzoyloxy)methyl)-6-hydroxy-4-methylcyclohexanone (5b), and 2-(Benzoyloxy)-2-((benzoyloxy)methyl)-6-hydroxy-5-methylcyclohexanone (8).** A solution of lithium diisopropylamide was prepared by treatment of diisopropylamine (1 mL) in dry THF (5.6 mL) with *n*-BuLi–hexane (1.7 M, 4 mL) at −70 °C for 10 min and then allowing it to warm to room temperature. The solution was cooled to −70 °C, and then **4a** (2.24 g, 6.35 mmol) was added in dry THF (65 mL). After the mixture was stirred for 30 min at −70 °C, MoOPH[10] (4.0 g, 9.2 mmol) was added all at once, and the temperature was allowed to warm to −30 °C. The green solution was stirred at −30 °C for 90 min, was then allowed to warm to 0 °C, and was treated with saturated $Na_2SO_3$, warmed to 25 °C, and extracted with ether. The extract was washed with dilute HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated under reduced pressure to a residue that was chromatographed on a column of silica gel (100–200 mesh, 60 g). Elution with 30% EtOAc–hexane gave **5a**: 1.5 g (64%); blades from ethyl acetate–hexane; mp 101–102 °C; NMR ($CDCl_3$) $\delta$ 1.3–2.9 (6 H, m), 3.25 (1 H, br s, $W_{1/2}$ = 12 Hz, $D_2O$ exchangeable), 4.38 (1 H, dd, $J_1 = J_2$ = 5 Hz), 4.72 and 5.10 (2 H, AB, $J_{AB}$ = 12 Hz), 7.2–7.6 (6 H, m), 7.7–8.1 (4 H, m); mass spectrum, $m/z$ 368 ($M^+$).

Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.26; H, 5.53.

In a similar manner, **dibenzoate 1** (7) was converted into 8: needles from ether–hexane; mp 84–85 °C; NMR ($CDCl_3$) $\delta$ 0.84 (3 H, d, $J$ = 6 Hz), 1.5–2.8 (5 H, m), 3.40 (1 H, br s, $W_{1/2}$ = 8 Hz, $D_2O$ exchangeable), 4.66 (1 H, d, $J$ = 6 Hz), 4.80 and 5.10 (2 H, AB, $J_{AB}$ = 12 Hz), 7.3–7.7 (6 H, m), 7.9–8.2 (4 H, m).

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.33; H, 6.00.

Similarly, **dibenzoate 2** (7) (other diastereomer) was converted into 8 (other diastereomer): noncrystalline glass; NMR ($CDCl_3$) $\delta$ 1.17 (3 H, d, $J$ = 5.9 Hz), 1.1–2.7 (5 H, m), 2.70 (1 H, d, $J$ = 8.8 Hz), 4.04 (1 H, d, $J$ = 10.3 Hz), 4.78 and 5.11 (2 H, AB, $J_{AB}$ = 12.5 Hz), 7.3–8.1 (10 H, m); mass spectrum (EI), $m/z$ 382.1444 ($C_{22}H_{22}O_6$ requires 382.1416).

Similarly **dibenzoate 3** (**4b**) was converted into **5b**: NMR ($CDCl_3$) $\delta$ 0.8–2.8 (5 H, m), 1.28 (3 H, d, $J$ = 6 Hz), 4.73 (1 H, dd, $J_1$ = 7 Hz), 4.76 and 5.03 (2 H, AB, $J_{AB}$ = 12 Hz), 7.3–7.7 (6 H, m), 7.9–8.2 (4 H, m); mass spectrum (EI), $m/z$ 382.1399 ($C_{22}H_{22}O_6$ requires 382.1416).

**3-(Benzoyloxy)-3-((benzoyloxy)methyl)cyclohexane-1,2-dione (1a), 3-(Benzoyloxy)-3-((benzoyloxy)methyl)-5-methylcyclohexane-1,2-dione (1b) and 3-(Benzoyloxy)-3-((benzoyloxy)methyl)-6-methylcyclohexane-1,2-dione (9).** Trifluoroacetic anhydride (104 $\mu$L, 0.7 mmol) was added over 5 min to a solution of $Me_2SO$ (70 $\mu$L, 0.9 mmol) in dry $CH_2Cl_2$ (1.1 mL) at −70 °C under Ar. After the mixture was stirred 20 min at −70 °C, **5a** (192 mg, 0.5 mmol) was added over 5–10 min, and stirring was continued for 30 min. Triethylamine (20 $\mu$L) was added over 10–15 min, giving a light yellow color. The solution was allowed to warm to room temperature, and $H_2O$ was added. The mixture was extracted with ether, and the extract was washed with 5% HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (100–200 mesh, 15 g). Elution with 10% EtOAc–hexane gave **1a**: prisms from MeOH; 125 mg (65%); mp 159–161 °C; NMR ($CDCl_3$) $\delta$ 2.3–3.1 (4 H, m), 4.70 and 4.82 (2 H, AB, $J_{AB}$ = 12 Hz), 5.93 (1 H, s, $D_2O$ exchangeable), 6.23 (1 H, dd, $J_1$ = 5.6 Hz, $J_2$ = 2.8 Hz), 7.4–8.1 (10 H, m); FAB mass spectrum, $m/z$ (relative intensity) 389 (10; M + Na), 367 (25; M + H; $C_{21}H_{18}O_6$ + H requires 367), 349 (8; 367 − $H_2O$), 305 (7; 349 − $CO_2$), 245 (100; M − $C_7H_5O_2$), 123 (60; $C_7H_6O_2$ + H), 122 (50; $C_7H_6O_2$).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.91; H, 5.10.

In a similar manner, **5b** was converted to **1b**, light yellow glass. (The reaction mixture was quenched with water without being first warmed to room temperature.): NMR ($CDCl_3$) (equilibrated solution 24 h after dissolution) $\delta$ 1.18 (3 H, d, $J$ = 6.5 Hz), 1.9–2.9 (4 H, m), 4.65 and 4.76 (2 H, AB, $J_{AB}$ = 12 Hz), 6.05 (1 H, br s, $W_{1/2}$ = 3 Hz), 7.3–7.7 (6 H, m), 7.9–8.2 (4 H, m). In a freshly prepared solution, the AB pattern above appeared instead as a pair of closely spaced lines, $\delta$ 4.76 and 4.77, and the vinylic H signal, $\delta$ 6.05, was greatly reduced in intensity. FAB mass spectrum:[13] $m/z$ 381.1341 ($C_{21}H_{20}O_6$ + H requires 381.1338).

Similarly, 8 (each diastereomer) was converted to **9**: light yellow glass; product from **dibenzoate 1**, NMR (diketo form) ($CDCl_3$) $\delta$ 1.28 (3 H, d, $J$ = 6 Hz), 2.17–2.76 (5 H, m), 4.71 and 4.78 (2 H, AB, $J_{AB}$ = 12 Hz), 7.4–8.1 (10 H, m); product from dibenzoate 2, NMR (diketo form) ($CDCl_3$) $\delta$ 1.25 (3 H, d, $J$ = 6 Hz), 1.8–2.9 (5 H, m), 4.82 and 5.00 (2 H, AB, $J_{AB}$ = 12 Hz), 7.2–8.3 (10 H, m); NMR (enolic form) ($CDCl_3$) $\delta$ 1.97 (3 H, s), 1.3–2.8 (4 H, m), 4.68 and 4.88 (2 H, AB, $J_{AB}$ = 12 Hz), 7.3–8.3 (10 H, m); FAB mass spectrum,[13] $m/z$ 381.1333 ($C_{22}H_{20}O_6$ + H requires 381.1338).

**Quinoxaline Derivatives 10 and 11.** Diketone **1b** (140 mg, 0.37 mmol) in EtOH (5 mL) and acetic acid (0.5 mL) was treated with a solution of *o*-phenylenediamine (60 mg, 0.55 mmol) in EtOH (3 mL).[18] The mixture was refluxed for 2 h under $N_2$, then cooled, and neutralized with dilute NaOH. The solvent was removed under reduced pressure, and $H_2O$ was added. The mixture was extracted with ether, and the extract was washed with $H_2O$, dried ($Na_2SO_4$), and evaporated under reduced pressure. The resultant oil was chromatographed on a column of silica gel (100–200 mesh, 30 g). Elution with 20% EtOAc–hexane gave the quinoxaline derivative **10**: 110 mg (60%); prisms from ether–hexane; mp 143–144 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (3 H, d, $J$ = 6.3 Hz), 2.36 (1 H, m), 2.61 (2 H, d, $J$ = 7.1 Hz), 3.13 and 3.32 (2 H, AB, $J_{AB}$ = 15 Hz, with $\delta$ 3.13 further coupled, 151.05 = 12 Hz, and $\delta$ 3.32 further coupled, $J$ = ca. 1–2 Hz), 4.79 and 5.17 (2 H, AB, $J_{AB}$ = 12 Hz), 7.3–8.3 (14 H, m); on irradiation at $\delta$ 2.36, the upfield signals became $\delta$ 1.25 (s), 2.61 (sl br s), 3.13 (sl br d, $J$ = 15 Hz), 3.32 (sl br d, $J$ = 15 Hz), and 4.79 and 5.17 (unchanged); $^{13}C$ NMR ($CDCl_3$, off-resonance decoupled multiplicity) $\delta$ 21.90 (qu), 27.57

(18) Schweizer, H. R. *Helv. Chim. Acta* **1969**, *52*, 322–329.

(d), 37.22 (t), 41.44 (t), 68.34 (t), 81.18 (s), 128.32, 128.43, 128.52, 128.94, 129.28, 129.73, 129.98, 130.37, 133.02 (d), 133.25 (d), 141.40 (s), 141.50 (s), 151.05 (s), 153.90 (s), 164.90 (s), 166.08 (s).

Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35. Found: C, 74.16; H, 5.42.

Similarly, diketone **9** was converted to quinoxaline derivative **11**: cubes from ether–hexane; mp 150 °C; NMR ($CDCl_3$) $\delta$ 1.68 (3 H, d, $J$ = 7 Hz), 2.08 (1 H, d, $J$ = 12 Hz), 2.31 (1 H, dd, $J_1 = J_2$ = 12 Hz), 2.51 (1 H, d, $J$ = 12 Hz), 3.05 (1 H, dd, $J_1 = J_2$ = 12 Hz), 3.45 (1 H, m), 4.80 and 5.10 (2 H, AB, $J_{AB}$ = 12 Hz), 7.3–8.2 (14 H, m). Irradiation at $\delta$ 3.45 caused the methyl group doublet to collapse to a singlet. All other signals were unchanged as shown by a difference spectrum.

Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32, H, 5.35. Found: C, 74.27; H, 5.50.

**Bis(phenylhydrazone) Derivatives 13 and 14.** Diketone **1b** (50 mg, 0.13 mmol), EtOH (5 mL), and acetic acid (10.5 mL) was treated with phenylhydrazine (150 mg, 1.38 mmol). The solution was stirred and refluxed under $N_2$ for 5 h. The solution was cooled, diluted with $H_2O$, and centrifuged. The precipitate was dissolved in ether, and the solution was washed with $H_2O$, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed by preparative TLC (solvent 30% EtOAc–hexane) followed by a second chromatography on a column of silica gel (100–200 mesh, 10 g) gave **13**: 20 mg; yellow plates from EtOH; mp 157–158 °C; NMR ($CDCl_3$) $\delta$ 1.15 (3 H, m), 0.9–3.1 (5 H, m), 4.75 (2 H, s), 7.0–8.3 (22 H, m); UV (95% EtOH) $\lambda_{max}$ ($\epsilon$) 232 (3.4 × $10^4$), 273 (sh, 4.3 × $10^3$), 282 (sh, 3.1 × $10^3$), 385 (1.8 × $10^4$) nm. Cyclohexane-1,2-dione bis(phenylhydrazone)[16] had UV (95% EtOH): $\lambda_{max}$ ($\epsilon$) 230 (1.3 × $10^4$), 261 (1.9 × $10^4$), 309 (1.1 × $10^4$), 390 (1.6 × $10^4$) nm.

Anal. Calcd for $C_{34}H_{32}N_4O_4$: C, 72.84; H, 5.75. Found: C, 71.73; H, 5.64.

Similarly **9** was converted to **14**: yellow noncrystalline glass; NMR ($CDCl_3$) $\delta$ 1.38 (3 H, d, $J$ = 6 Hz), 1.1–3.3 (5 H, m), 4.76 (2 H, s), 6.8–8.3 (22 H, m).

**Single-Crystal X-ray Diffraction Analysis of Quinoxaline Derivative 11.** A roughly cubic crystal with dimensions of 0.8 × 0.7 × 0.5 mm was selected for study. Preliminary X-ray photographs displayed monoclinic symmetry and accurate lattice constants of $a$ = 13.985 (3), $b$ = 11.133 (2), and $c$ = 14.385 (2) Å and $\beta$ = 92.90 (1)° were determined from a least-squares fit of 15 diffractometer measured $2\theta$ values. Systematic extinctions and crystal density (1.65 g/cm$^3$) were uniquely consistent with space group $P2_1/n$ with one molecule of formula $C_{28}H_{24}O_4N_2$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were recorded on a computer-controlled four-circle diffractometer with a variable speed 1° $\omega$ scan and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.541 78 Å). Of the 3140 independent reflections surveyed in this manner, 2822 (90%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. A phasing model was found uneventfully by direct methods.[19] Block-diagonal, least-squares refinements with anisotropic heavy atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.05 for the observed reflections. Additional crystallographic parameters have been deposited with this paper as supplementary material.

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**Registry No.** **1a**, 90369-58-7; **1b**, 90369-59-8; **2a**, 533-60-8; **3a**, 1004-52-0; **3b**, 90369-60-1; **4a**, 90369-61-2; **4b**, 90369-62-3; **5a**, 90369-63-4; **5b**, 90369-64-5; **6**, 90369-65-6; **7** (isomer 1), 90369-66-7; **7** (isomer 2), 90369-67-8; **8a**, 90369-68-9; **8b**, 90369-69-0; **9**, 90369-70-3; **10**, 90369-71-4; **11**, 90369-72-5; **13**, 90369-73-6; **14**, 90369-74-7; 2-hydroxy-4-methylcyclohexanone dimer, 35326-28-4; *o*-phenylenediamine, 95-54-5; leucogenenol, 29101-95-9.

**Supplementary Material Available:** Tables of fractional coordinates, thermal parameters, and bond distances and bond angles for quinoxaline derivative **11** (5 pages). Ordering information is given on any current masthead page.

(19) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were as follows: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78 and 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

# A Liquid Chromatographic Method for Resolving Chiral Lactams as Their Diastereomeric Ureide Derivatives

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Chiral type 1 lactams react with chiral isocyanates (e.g., $\alpha$-phenylethyl isocyanate) to afford diastereomeric ureides that are readily separable by chromatography on silica. The elution order and sense of NMR nonequivalence of a pair of diastereomeric ureides can be used to assess relative (and hence absolute) configuration of the lactam enantiomers which are readily retrievable from the separated ureides. The enantiomeric purity and absolute configuration of these lactams may also be ascertained by NMR using chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent.

Lactam functionality is fairly common among natural products and compounds of pharmacological interest. Consequently, the need to determine enantiomeric purity and absolute configuration of chiral lactams or, alterna-

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