Irradiation of 1-Acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]-cyclopropane (3).—A solution of 1.11 g of 1-acetyl-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropane (**3**) (57% *trans*–43% *cis*; the sample also contained 9% ethyl crysanthemumate and 1% another impurity but these compounds were stable to the irradiation conditions and did not interfere) in 170 ml of *t*-butyl alcohol (0.039 *M*) was irradiated 4 hr using Corex-filtered light. The vpc monitor showed the formation of one major photoproduct with the following percentages at the end of the irradiation: 52% product A (retention time relative to *cis* **3** equaled 0.38), 1% a minor unidentified product (retention time relative to *cis* **3** equaled 0.79), 17% *cis* **3**, 12% *trans* **3** (retention time relative to *cis* **3** equaled 0.96), and *ca.* 18% nonmonomeric material. Also, the monitor showed that *trans* **3** disappeared faster than *cis* **3**.

Solvent was removed and the photoproduct, isolated by vpc of the colorless oil (0.71 g) on a 25% Carbowax 20M column (9 ft × 3/8 in.), was identified as 2-[1′-(2-methylpropenyl)]-3,3,5-trimethyl-Δ^4-dihydrofuran (**6**) on the basis of the following data: mass spectrum, last peak at 166, peaks at 151, 137, 109, base peak at 123; ν_{max} 1672 (s), 1380 (s), 1248 (s), 1009 (s), 948 (s), 735 cm^{-1} (s); uv$^{abs\ EtOH}$ $\epsilon_{220\ m\mu}$ 4620, $\epsilon_{210\ m\mu}$ 7410; nmr (τ, ppm, $CDCl_3$) 4.59 (1.0 H, broad doublet, J = 10 Hz, side chain vinylic H), 5.25 (0.9 H, doublet, J = 10 Hz, H which is both allylic and geminal to the oxygen), 5.45 (0.8 H, broad singlet, vinylic H at C_4), 8.10–8.31 (8.8 H, multiplet, vinylic methyl H), 8.92 and 9.08 (6.5 H, two singlets, methyl H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; Hr, 11.19.

An nmr specrtrum of recovered **3**, vpc collected, showed no indication that any ester photoproduct similar to **7** had been formed.

Irradiation of 2-[1′-(2-Methylpropenyl)]-3,3-dimethyl-Δ^4-dihydrofuran (4).—A solution of 33 mg of **4** in 15 ml of cyclohexane (0.014 *M*) was irradiated in a quartz flask for 0.5 hr using light from a 100-W Hanovia lamp (Model 608A-36). Vpc monitoring of the irradiation showed three photoproducts with retention times relative to starting material of 2.61, 4.31, and 4.97. The final yields were 51% starting material, 3, 4, and 8% photoproducts, in order of glpc elution, and 34% nonmonomeric material. The 4 and 8% products had identical vpc retention times as *trans*- and *cis*-2,2-dimethyl-3-[1′-(2-methylpropenyl)]cyclopropylcarboxaldehyde (**1**), respectively. The 3% product was not identified and the irradiation was not investigated further.

Irradiation of **4** with a 450-W lamp (21 mg, 10 ml of cyclohexane, 0.014 *M*, quartz flask, 0.75 hr) resulted in almost complete polymerization of both starting material and photoproducts.

Registry No.—*trans* **1**, 20104-05-6; *cis* **1**, 20104-06-7; *trans* **2**, 20104-07-8; *cis* **2**, 20104-08-9; *trans* **3**, 20104-09-0; *cis* **3**, 20104-10-3; **4**, 20104-11-4; **5**, 20104-12-5; **6**, 20104-13-6; **7**; 20104-14-7; **8**, 20104-15-8; *trans* **9**, 20104-16-9; *cis* **9**, 20104-17-0; *trans* **10**, 20104-18-1; *cis* **10**, 20104-19-2.

Acknowledgment.—The authors would like to thank Mr. P. Porcaro (Givaudan) for aid in some of the analytical work.

The Synthesis of Racemic *threo*- and *erythro*-β-Hydroxylysines

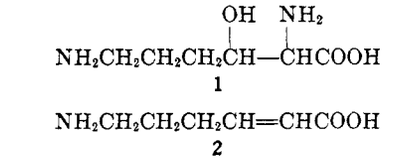
CHARLES H. STAMMER[1] AND RONALD G. WEBB[2]

Department of Chemistry, University of Georgia, Athens, Georgia 30601

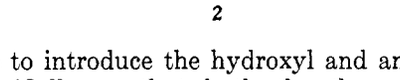
Received December 30, 1968

The synthesis of both *threo*- and *erythro*-β-hydroxy-DL-lysines from an *erythro*-β-methoxy-α-bromohexanoic acid derivative has been accomplished. Amination of this acid in ammonium hydroxide proceeded with retention while treatment with sodium azide proceeded with inversion of the configuration at the α-carbon atom giving intermediates convertible into the two diastereomeric amino acids.

In connection with our program on the synthesis of cycloserines, the unknown β-hydroxylysine (**1**) was a required intermediate. β-Hydroxyamino acids have been synthesized in the past by (1) the condensation of acid chlorides with diazoacetates and azlactones followed by several steps,[3] (2) condensation of aldehydes with glycine[4] and esters of acetamidomalonic and nitroacetic acids, and (3) multistep formation of the α-amino-β-hydroxy structure from the appropriate α,β-unsaturated acid.[5] After several attempts to use the second method, the longer surer approach through the α,β-unsaturated acid led to the desired compound. In this reaction sequence, a 6-amino-2-hexenoic acid (**2**) derivative was required which could be converted into **1** by the introduction of the appropriate functional groups. Two stereoisomers of **1** are possible and it was



1



2

desirable to introduce the hydroxyl and amino groups stereospecifically so that both the *threo* and *erythro* isomers would both be available.

The synthesis of **2** appeared feasible by the Doebner condensation[6] of an N-substituted γ-aminobutyraldehyde with malonic acid. The problem, then was to synthesize the required aldehyde. N-Benzoyl-γ-aminobutyraldehyde had been reported as quite unstable,[7] possibly owing to a tendency toward ring closure giving a pyrrolidine. Attempts to prepare N-benzoyl-γ-aminobutyric acid chloride had indeed led to the ring-closed product, N-benzoyl-2-pyrrolidone. Consequently, it seemed necessary to block the amino function with a group such as phthaloyl which would effectively pro-

(1) To whom inquiries should be addressed.

(2) Taken from the Ph.D. Thesis of R. G. Webb which was presented to the University of Georgia Graduate School, Oct 1968.

(3) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957); H. E. Carter, J. B. Harrison, and D. Shapiro, *J. Amer. Chem. Soc.*, **75**, 4705 (1953); J. M. Stewart and D. W. Wooley, *ibid.*, **78**, 5336 (1956).

(4) T. Wieland, H. Cords, and E. Keck, *Ber.*, **87**, 1312 (1954); T. T. Otani and M. Winitz, *Arch. Biochem. Biophys.*, **102**, 464 (1963); M. Sato, K. Okawa, and S. Akabori, *Bull. Chem. Soc. Jap.*, **30**, 937 (1957); H. Mix and F. W. Wilcke, *Z. Physiol. Chem.*, **337**, 40 (1964); H. Hellmann and H. Piechota, *ibid.*, **318**, 66 (1960); H. Hellmann and H. Piechota, *Ann. Chem.*, **631**, 175 (1960); S. Umezawa and S. Zen, *Bull. Chem. Soc. Jap.* **36**, 1143 (1963); D. I. Weisblatt and D. A. Lyttle, U. S. Patent 2,570,297 (1951).

(5) (a) W. Schrauth and H. Geller, *Chem. Ber.*, **55**, 2783 (1922); (b) H. D. West and H. E. Carter, *J. Biol. Chem.*, **119**, 103 (1937); (c) H. D. West, G. S. Krummel and H. E. Carter, *ibid.*, **122**, 605 (1937); (d) H. E. Carter and C. L. Zirkle, *ibid.*, **178**, 709 (1949); (e) K. Pfister, III, E. E. Howe, C. A. Robinson, A. C. Shabica, E. W. Pietrusza, and M. Tishler, *J. Amer. Chem. Soc.*, **71**, 1096 (1949); (f) T. Kanebo and H. Katsura, *J. Chem. Soc. Jap.* **36**, 899 (1963).

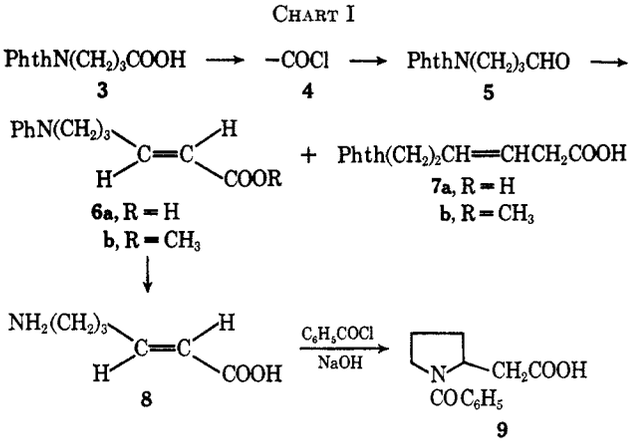
(6) J. R. Johnson, *Org. Reactions*, **1**, 226 (1942).

(7) S. Sugasan and Y. Zusshi, *J. Pharm. Soc. Jap.*, **550**, 1044 (1927).

hibit reactions at that site. N-Phthaloyl-γ-aminobutyric acid (**3**) was readily prepared by treating γ-aminobutyric acid directly with phthalic anhydride as previously described.[8] This acid was readily converted into the known acid chloride (**4**) which could be reduced without purification by the Rosenmund[9] procedure to the desired N-phthaloyl-γ-aminobutyraldehyde (**5**). The reduction proceeded under scrupulously dry conditions to evolve *ca.* 80% of the theoretical yield of hydrogen chloride using a $Pd/BaSO_4$ catalyst and afforded an acceptable yield of crude aldehyde. Many purification methods including recrystallization, chromatography, bisulfite adduct formation, conversion into the aldehyde diacetate, etc., gave aldehyde of variable purity. Finally, an acceptably pure material, which afforded a 2,4-dinitrophenylhydrazone of correct melting point,[10] was obtained by short-path vacuum distillation in about 50% yield. Either the crude or the purified aldehyde could be used in the next step with good results.

Doebner condensation (Chart I) of the aldehyde with malonic acid gave a product which by all indications was a mixture of acids. Extraction of the crude product

CHART I

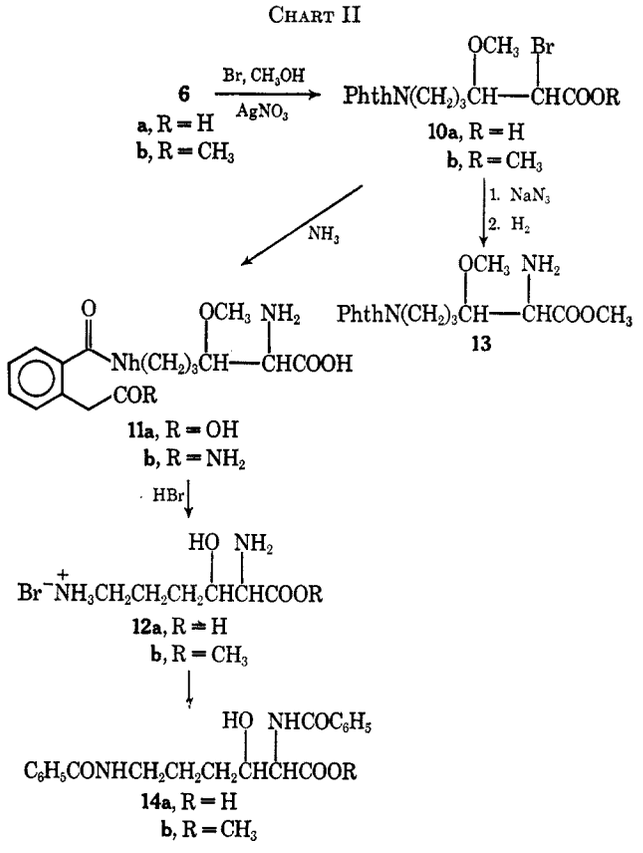


Phth = Phthaloyl

with successive portions of hot water separated it into a low-melting (126–127°) more soluble material and a high-melting (153–156°) less soluble product. The latter was shown to be the expected *trans*-6-phthalimido-2-hexenoic acid (**6a**) while the former **7a** was thought to be the *cis* isomer. Attempts to convert this low-melting product into **6a** by known isomerization procedures, *i.e.*, irradiation in the presence of iodine and melting in the presence of iodine, gave mixtures of **6a** and **7a**. It was found that dephthaloylation of **6a** gave the crystalline amino acid **8** which showed a vinylic coupling constant consistent with the *trans* configuration in its nmr spectrum, as did that of the parent **6a**. When an attempt was made to benzoylate **8** under Schotten–Baumann conditions, only **9** (N-benzoylpyrrolidine-2-acetic acid) was obtained, resulting from an internal Michael addition of the ω-amino group to the α,β-unsaturated system[11] followed by benzoylation. If the low-melting compound (**7a**) were the *cis* isomer of **6a** it should undergo this same series of reactions resulting in the formation of **9**. A low yield of **9** was actually obtained from **7a** but a definite structural assignment was not possible. Esterification of the low-melting isomer in boiling methanolic hydrogen chloride gave a considerable amount of the highly insoluble *trans* methyl ester (**6b**) and **7b**, the methyl ester of **7a**. Its nmr spectrum showed clearly the α-methylene doublet and a complex multiplet in the vinyl region as would be expected of the β,γ-unsaturated ester. The esterification process allowed a separation of **6a** and **7a** owing to a difference in solublility of the methyl esters. It was clear also that **7** was being partially converted into **6** under the acid conditions of the esterification. Diazomethane esterification of both **6a** and **7a**, however, gave noncrystalline products of indeterminate structure.

The *trans* acid (**6a**), now in hand, was converted into α-bromo-β-methoxy-ω-phthalimidohexanoic acid (**10a**) by the method of Carter[5c] (Chart II). This compound

CHART II



was difficult to purify and molecular distillation followed by recrystallization was used to obtain an analytical sample. Attempts to make the simple α-bromo-β-hydroxy analog of **10a** by the addition[5d] of HOBr to **6a** give only unchanged starting material. Amination of the crude bromoethoxy compound (**10a**) in concentrated ammonium hydroxide gave a product showing two or three ninhydrin positive spots. The multiplicity of spots was probably due to the formation of ring-opened phthalamic acids (**11a** and **11b**), since it is well

(8) S. Gabriel and J. Coleman, *Chem. Ber.*, **41**, 513 (1908); J. H. Villman and W. F. Harting, *J. Amer. Chem. Soc.*, **70**, 1473 (1948); see also R. Laliberté and L. Berlinguet, *Can. J. Chem.*, **38**, 1933 (1960).

(9) E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, Chapter 7 (1948).

(10) K. Balenovic, I. Jambresic, and I. Furic, *J. Org. Chem.*, **17**, 1459 (1952).

(11) B. R. Baker, R. E. Schaub, and J. N. Williams, *ibid.*, **17**, 124 (1952).

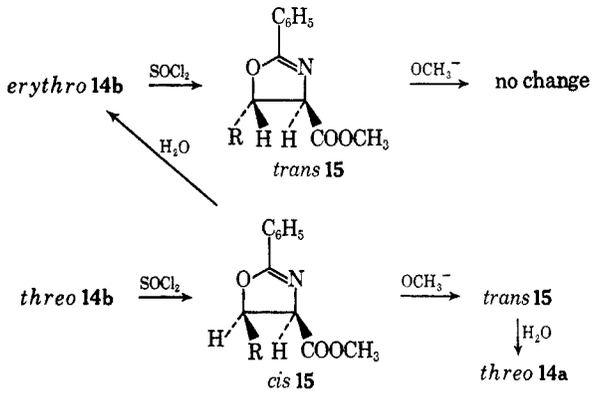
known that phthalimide derivatives are very sensitive to base.[12] The crude phthalamic acid mixture was hydrolyzed without separation in refluxing 48% hydrobromic acid. Paper chromatographic analysis of the hydrolysis reaction mixture showed that the phthaloyl group was removed in less than 1 hr, while 4-hr reflux gave the best yield of the demethylated amino acid (**12**). The product was isolated after conversion into the monohydrobromide salt with pyridine and the monohydrobromide was convertible into the monohydrochloride by passage through IRA-400 on the chloride cycle. Dissatification with the losses involved in the purification of the bromomethoxy acid (**10a**) led us to study a number of alternate methods for the addition of methyl hypobromite and of hypobromous acid to **6a** and its methyl ester. N-Bromosuccinimide (NBS) in aqueous dimethyl sulfoxide and dimethoxyethane gave essentially unreacted acid as did N-bromoacetamide (NBA). The methyl ester (**6b**), however, gave reasonable yields of bromomethoxy ester (**10b**) when it was treated with bromine in a methanolic silver nitrate solution. Methanolic NBS and NBA in the presence of hydrogen bromide or hydrogen chloride also gave **10b** in somewhat lower yields.

The addition of the elements of methyl hypobromite to α,β-unsaturated acids has been shown to occur both regiospecifically[13] and stereospecifically[5c,e] by its addition to crotonic (*trans*) and isocrotonic (*cis*) acids to give allothreonine (*erythro* configuration) and threonine (*threo* configuration), respectively. We could, consequently, assign the *erythro* configuration to **10a** by analogy with this early work. We showed that the ester obtained by the bromomethoxylation of ester **6b** was the same **10b** obtained when the acid **10a** was esterified. Thus, the regio- and stereospecificity of the bromomethoxylation was unaffected by esterification of the **6a** carboxyl function. Amination of **10a** with ammonia should, by analogy with Pfister's work on threonine,[14] be accomplished with retention of configuration at the α-carbon atom giving the acid **11** with an *erythro* configuration. Our amino acid (**12a**) derived from **11** could thus be assigned the *erythro* configuration.

When the ester **10b** was treated with sodium azide in dimethyl sulfoxide solution[15] followed by reduction of the intermediate azide ester, a β-methoxylysine ester (**13**) was obtained. Since the reaction of the halo ester with azide ion is known[16] to invert the configuration of the α-asymmetric center, the lysine derivative **13** had the *threo* configuration and was diastereomeric with **11** and **12a** prepared earlier. In spite of this, hydrolysis of **13** gave an amino acid having the same R_f values as **12a** in three paper chromatography systems. However, both the acid hydrobromides and corresponding methyl ester hydrochlorides were shown to be different by infrared and nmr spectral comparison. The *erythro* isomer showed an unexpected resistance to esterification by the usual methods, *i.e.*, dry HCl/CH_3OH or dimethyl sulfite–methanol, and **12b** was obtained in only 15% yield. The *threo* ester, however, was isolated in 78% yield using the standard HCl/CH_3OH procedure. For further comparison, the N,N′-dibenzoyl derivatives (**14a**) of both isomers were synthesized and the comparison of these again showed that the two amino acids were indeed isomeric.

Confirmation of both the structural and stereochemical assignments made above was obtained by physical and chemical means. An nmr study of both *erythro* **12** and *threo* **12** as their monohydrobromide salts showed that the doublet characteristic of the α proton shifted 0.54 ppm upfield when the pH was increased, while the multiplet absorption for the β proton shifted only 0.32 ppm. Deprotonation of the ammonium ion must be responsible for the greater diamagnetic shift of the α proton since the carboxyl function was ionized both before and after the pH increase. These data support the α-amino-β-hydroxy structure. Substantiation of the configurations assigned was obtained by use of the well-known[17] oxazoline method. This method is based on the known steric course of oxazoline formation from α,β-amino alcohols and the fact that *cis*-4,5-disubstituted 2-oxazolines isomerize to the *trans* isomers under basic conditions. This reaction sequence involving the new hydroxylysines is shown in Chart III. Treatment

CHART III



of the dibenzoyl esters (**14b**) of the isomeric amino acids with thionyl chloride converted each into a 2-oxazoline. This process is known to occur with inversion of configuration at the β-carbon atom[17b,c] requiring that the *erythro* isomer should form the *trans*-4,5-disubstituted oxazoline (*trans* **15**) and the *threo* isomer should give *cis* **15**. *trans* **15**, formed from *erythro* **14b**, was in fact an oil which was unchanged upon treatment with methanolic sodium methoxide as shown by solution infrared. *cis* **15**, as prepared from the *threo* isomer, was a crystalline solid whose nmr spectrum showed a coupling of 9 Hz between the 4 and 5 protons, consistent with the *cis* configuration. When *cis* **15** was treated with methanolic sodium methoxide it isomerized to

(12) L. R. Caswell, P. L. Wright, and D. D. Adams, *Texas J. Sci.*, **17**, 334 (1965); L. R. Caswell and P. C. Atkinson, *J. Org. Chem.*, **29**, 3151 (1964).

(13) This term refers to the *direction* of methyl hypobromite addition, *i.e.*, α-bromo-β-methoxy *vs.* α-methoxy-β-bromo; *cf.* A. Hassner, *ibid.*, **33**, 2684 (1968).

(14) According to early work on the amination of α-bromo acids, β-substituted α-bromo acids undergo amination with retention of configuration, while β-unsubstituted α-bromo acids aminate with inversion. A modern study of these reactions has apparently not been done. For a complete discussion of this, see J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol 1, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 165–167.

(15) R. A. Strojny and H. C. White, *J. Org. Chem.*, **28**, 1942 (1963).

(16) P. Brewster, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 178 (1950).

(17) (a) M. Pankova and J. Sicher, *Collect. Czech. Chem. Commun.*, **30**, 388 (1965); (b) A. F. Wagner, *J. Amer. Chem. Soc.*, **79**, 3240 (1957); (c) J. M. Stewart, *ibid.*, **83**, 435 (1961); (d) D. F. Elliot, *J. Chem. Soc.*, (1949); (e) D. F. Elliot, *ibid.*, 62 (1950); (f) W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, **72**, 2187 (1950); (g) S. H. Pines, S. Karaday, M. A. Kozlowski, and M. Sletzinger, *J. Org. Chem.*, **33**, 1762 (1968).

trans **15** which (without isolation) was hydrolyzed to the *threo*-dibenzoyl acid (*threo* **14a**) almost quantitatively. Since hydrolysis of 2-oxazolines does not change the configurations of the asymmetric centers, the formation of the *threo*-amino acid proved that *cis* **15** had been isomerized by the methoxide treatment. Indeed, hydrolysis of *cis* **15** without prior base treatment gave *erythro* **14a** showing that a single inversion had occurred during the thionyl chloride reaction.

Our work thus confirmed earlier reports that amination of β-substituted α-bromo acids proceeded with retention of configuration while azide displacement gave the diastereomeric configuration. The stereospecificity of these reactions can be used to allow the synthesis of both isomers of a given amino acid from a single bromo acid intermediate. Consequently, the use of an α,β-unsaturated acid of known configuration and its subsequent bromomethoxylation becomes an attractive method for the synthesis of *both* diastereomers of any desired β-hydroxyamino acid.

Experimental Section

All melting points were determined using the capillary method and are uncorrected. Petroleum ether refers to a 30–60° boiling fraction. For circular paper chromatography, Whatman No. 1 paper (32-cm diameter with a 2-cm center hole) was used. BAW is the upper phase which separates when *n*-butyl alcohol, acetic acid, and water are mixed in a volume ratio of 5:1:4, respectively; PW is a 65:35 mixture of pyridine and water; MPW is a 20:5:8 mixture of methyl ethyl ketone, pyridine, and water. The amino acids were visualized with ninhydrin reagent. The infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 or Model 237B using a polystyrene standard. The nmr spectra were obtained on a Varian A-60 or HA-100 instrument with TMS (tetramethylsilane) as standard except in D_2O where TMS*, 3-(trimethylsilyl)propanesulfonic acid sodium salt, was used. The majority of the nmr spectra were calibrated by the usual techniques. All elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

γ-Phthalimidobutyraldehyde (5).—When 16.5 g (0.066 mol) of γ-phthalimidobutyryl chloride (**4**) was reduced under Rosenmund conditions[9] (Quinoline-S poison was unnecessary), 15.4 g of a gummy product was obtained. After sublimation *in vacuo* at 90–120° for 50–60 hr, 7.7 g (37%) of **5** was obtained: mp 69–72° (lit.[10] mp 72–73°); ir (Nujol) 1770 (imide C=O), 1706 (imide C=O), 1315, 1125, 1050, and 860 cm^{-1}; nmr ($CDCl_3$) δ 7.74 (m, C_6H_4), 3.75 (t, N-CH_2), 2.25 (m, α,β-CH_2CH_2), 9.75 (s, CHO). The 2,4-dinitrophenylhydrazine derivative had mp 184–185° (lit.[18] mp 185°).

6-Phthalimido-2-hexenoic Acid (6a).—A solution of 72.5 g (0.3 mol) of γ-phthalimidobutyraldehyde or an equivalent amount (based on HCl evolution) of crude aldehyde and 62.5 g (0.6 mol) of malonic acid in 150 ml of pyridine was heated for 12–24 hr in an oil bath at 65–86° until evolution of CO_2 ceased. The cooled solution was diluted with five volumes of water and 10% sulfuric acid was added until no more oil or solid formed. The supernate was decanted and the product was washed twice with water and recrystallized from 50% ethanol, mp 115–140°. This material was further recrystallized from 2-propanol and then from ethanol giving 12.7 g (15%): mp 153–155°; ir (Nujol) 1770 (imide C=O), 1725 (acid C=O), 1695 (imide C=O), 1670, 1631 cm^{-1}; nmr (DMSO-d_6) δ 7.76 (m, C_6H_4), 3.54 (t, NCH_2), 1.90 (m, γ, δ-CH_2CH_2–), 6.8 (pentuplet, $J_{\alpha,\beta}$ = 16 Hz, $J_{\beta,\gamma}$ = 6 Hz, –CH_2CH=CH), 5.73 (d, J = 16 Hz, CH=CHCOOH). The analytical sample was obtained by recrystallization of a portion of this material from ethanol, mp 156–158°.

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.25; N, 5.46.

6-Amino-*trans*-2-hexenoic Acid Hydrochloride (8).—6-Phthalimido-2-hexenoic acid (**6a**, 3.3 g, 12.8 mmol) was dissolved in 30 ml of 1 *N* NaOH and allowed to stand at room temperature for 30 min. The addition of 4.3 ml (52 mmol) of concentrated HCl caused a precipitate to form which dissolved when the mixture was refluxed for 1 hr. The solution was cooled in ice and the precipitated phthalic acid (89%) was removed by filtration. The remaining solution was evaporated under vacuum and held at oil-pump vacuum overnight. The resulting solid was extracted with two 25-ml portions of boiling ethanol leaving behind 1.6 g of sodium chloride. The ethanol extract was evaporated to give 2.2 g solid, mp 140–155°, which was recrystallized from 40 ml of isopropyl alcohol, giving 1.3 g of product: mp 150–157°; ir (Nujol) 3100, 1700 (acid C=O), 1645, C=C), 980 cm^{-1} (*trans* C=C; nmr (D_2O) δ 3.05 (t, NCH_2), 1.90 (m, δ-CH_2), 2.32 (t, CH_2CH=CH), 7.05 (two t, $J_{\alpha,\beta}$ = 16 Hz, $J_{\beta,\gamma}$ = 7 Hz, CH_2-CH=CH), 5.95 (d, J = 16 Hz, CHCOOH); MPW, R_f 0.35 (blue); PW, R_f 0.70 (pink); BAW, R_f 0.62 (pink). The analytical sample was obtained by two crystallizations from ethanol, mp 156–159°.

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; Cl, 21.41; N, 8.46. Found: C, 43.26; H, 7.25; Cl, 21.12; N, 8.49.

N-Benzoylpyrrolidine-2-acetic Acid (9).—A sample of 6-amino-*trans*-2-hexenoic acid hydrochloride (**8**) was benzoylated according to Baker[11] giving a crystalline product, mp 134° (lit.[11] mp 134°). Paper chromatography of a basic aqueous solution of the amino acid **8** (MPW, R_f 0.35, blue spot) showed an immediate change to the pyrrolidine acetic acid (MPW, R_f 0.39, yellow spot) before benzoylation.

Methyl 6-Phthalimido-2-hexenoate (6b).—6-Phthalimido-2-hexenoic acid (**6a**, 35.1 g, 10.13 mol) was dissolved in 350 ml of methanol and the solution was saturated with hydrogen chloride without external cooling and then refluxed 1 hr. On cooling the solution to room temperature, the ester crystallized and was collected and washed with cold methanol: weight 22.7 g (61%); mp 90–92°, ir (Nujol) 1775 (imide C=O), 1720 (ester C=O), 1705 cm^{-1} (imide C=O); nmr ($CDCl_3$) δ 7.75 (m, C_6H_4), 3.70 (t, NCH_2–), 2.08 (m, γ, δ-CH_2CH_2–), 6.94 (two t, $J_{\alpha,\beta}$ = 15 Hz, $J_{\beta,\gamma}$ = 7 Hz, CH_2CH=CH), 5.80 (d, J = 15 Hz, CH=CH-$COOCH_3$), 3.65 (s, $COOCH_3$). A second crop of 6.3 g, mp, 82–84°, was obtained on cooling the mother liquor.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.74; H, 5.74; N, 5.30.

***erythro*-α-Bromo-β-methoxy-ε-phthalimidocaproic Acid (10).**—From a dropping funnel, 72.3 g (0.28 mol) of 6-phthalimido-2-hexenoic acid (**6a**) in 1100 ml of methanol was added over 1.5 hr to a rapidly stirred suspension of 46.8 g (0.28 mol) of silver nitrate in 750 ml of methanol in a 3-l. ice-cooled beaker. Concurrently 15.2 ml (0.28 mol) of bromine was bubbled into the solution in a stream of air. After stirring an additional 2 hr in ice the mixture was filtered and evaporated under vacuum giving 101.2 g of red oil. The residue was dissolved in about 1 l. of ether, and the solution was washed with three 500-ml portions of water. After drying over sodium sulfate, the solution was evaporated to dryness giving 77.7 g of light yellow oil. After three crystallizations of 1.2 g of the crude oil from 10, 3.5, and 5 ml of benzene, 0.58 g of material, mp 108–116°, was obtained. Molecular distillation of 200 mg of this product at 0.01 mm and 160° gave 0.174 g of analytical sample: mp 115–118°; ir (Nujol) 1758, 1710 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 7.76 (m, C_6H_4), 4.15 (d, J = 8 Hz, α proton), 3.68 (t, NCH_2–), 3.38 (s, OCH_3), 1.80 (m, γ, δ-CH_2CH_2–).

Anal. Calcd for $C_{15}H_{16}BrNO_5$: C, 48.66; H, 4.36; Br, 21.59; N, 3.78. Found: C, 48.88; H, 4.53; Br, 21.63; N, 3.55.

***erythro*-β-Hydroxy-DL-lysine Hydrobromide (*erythro* 12a).**—Crude α-bromo-β-methoxy-ε-phthalimidocaproic acid (**10a**, 74 g) was divided into four approximately equal portions and placed in four 500-ml hydrogenation bottles. Concentrated ammonium hydroxide (300 ml) was added to each, a rubber stopper was securely wired in place, and the bottles were stored in an oven at 50° for 3.5 days. After cooling in ice, the solutions were filtered and the combined filtrates were evaporated under vacuum. The crude α-amino-β-methoxy-ε-phthalimidocaproic acid–ammonium bromide mixture was a yellow glass (79 g). Paper chromatography of this material showed the following ninhydrin positive materials: MPW, R_f 0.14, BAW, R_f 0.30, 0.46, 0.59.

The crude α-amino-β-methoxy-ε-phthalimidocaproic acid (70.8 g) was treated with 470 ml of refluxing 48% hydrobromic acid for 4 hr. The hydrobromic acid was evaporated under vacuum, 200 ml of water was added to the residue, and 18.5 g of phthalic acid was collected by filtration. The filtrate was treated with Norit and evaporated under vacuum, and the solid residue was dissolved in 40 ml of hot water. Pyridine (28 ml) was added and,

(18) F. E. King, P. L'Ecuyer, and H. T. Openshaw, *J. Chem. Soc.*, 1477 (1933).

after cooling to room temperature, the solution was filtered. The filtrate was heated, 800 ml of hot ethanol was added, and the solution was filtered and allowed to cool. After standing at 0° overnight, 14.0 g of crude β-hydroxylysine hydrobromide was collected on a filter. This was dissolved in 14.0 ml of hot water, and 35 ml of hot ethanol was added in portions. At the cloud point, an oil formed which was separated. The supernate was cooled to −5° overnight and deposited 4.3 g of white solid, mp 224° dec. The separate oil was diluted with 15 ml of ethanol and scratched with a glass rod until crystalline (3.6 g). The spectral properties of these two materials were identical: ir (Nujol) 3450 (OH), 1670, 1590 (COO^-), 1490 cm^{-1} (NH_3^+); nmr (D_2O) δ 4.62 (m, 1, β proton), 4.37 (d, 1, J = 4 Hz, α proton), 3.56 (t, 2, NCH_2–), 2.15 (m, 4, γ, δ-CH_2CH_2–); MPW, R_f 0.13; BAW, R_f 0.28.

The analytical sample was the product which melted at 224° with decomposition.

Anal. Calcd for $C_6H_{15}BrN_2O_3$: C, 29.63; H, 6.22; Br, 32.87; N, 11.52. Found: C, 29.53; H, 6.41; Br, 32.70; N, 11.38.

The hydrochloride of *erythro* **12** could be prepared from the above hydrobromide by passing a sample through an IRA-400 ion exchange column: mp 227° dec; MPW, R_f 0.22.

A dihydrochloride was obtained when the monohydrochloride was treated with 3 *N* HCl followed by a crystallization from methanol–ether, mp 194° dec.

Methyl *erythro*-β-Hydroxylysinate Dihydrochloride (*erythro* **12b**).—The monohydrobromide of *erythro*-β-hydroxylysine (*erythro* **12a**, 0.702 g, 2.89 mmol) was converted in aqueous solution into the nitrate by addition of silver nitrate (0.46 g, 2.98 mmol). The precipitated silver bromide was filtered, and the filtrate was evaporated to a yellow oil. The oil was dissolved in a methanolic solution of dimethyl sulfite prepared from 0.32 ml (4.5 mmol) of thionyl chloride and allowed to stand overnight at room temperature. Evaporation of the methanol and reconcentration several times with fresh solvent left an oil. This oil was dissolved in methanol and the solution was saturated with HCl gas and refluxed 15 min. The oil which resulted from removal of the solvent gave crystals from methanol–ether (0.12 g), and the product was recrystallized from 1.2 ml methanol and 5 ml ether giving an analytical sample: 0.105 g (15%); mp 184–186° dec; ir (Nujol) 3370, 1740 ($COOCH_3$), 1235, and 1050 cm^{-1}; nmr (D_2O) δ 4.10 (d, J = 2.5 Hz, α proton), 3.94 (m, β proton), 3.70 (s, $COOCH_3$), 2.90 (m, NCH_2–), 1.67 (m, γ, δ-CH_2CH_2); MPW, R_f 0.54; BAW, R_f 0.37 (pink); PW, R_f 0.83 (pink).

Anal. Calcd for $C_7H_{18}Cl_2N_2O_3$: C, 33.74; H, 7.28; N, 11.24. Found: C, 33.46; H, 7.43; N, 11.39.

***erythro*-N,N′-Dibenzoyl-β-hydroxylysine** (*erythro* **14a**).—Schotten–Baumann benzoylation of 595 mg of *erythro* **12a** gave 787 mg (86%) of crude product, mp 162–166°. Recrystallization from 40% aqueous ethanol gave an analytically pure sample: mp 166–167°; ir (Nujol) 3375 and 3280 (NH), 1720 (acid C=O), 1680 (amide C=O), 1635, 1545 and 1250 cm^{-1}; nmr (DMSO-d_6) δ 8.50 (m, C_6H_5CONH), 7.94 (m, C_6H_5, α-benzamido), 7.56 (m, C_6H_5, ε-benzamido).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.44; N, 8.06.

Methyl *erythro*-ε-Phthalimido-α-bromo-β-methoxycaproate (**10b**).—Methyl 6-phthalimido-2-hexenoate (**6b**, 22.5 g, 82.4 mmol) was suspended in 138 ml of ice-cooled methanol and 14.8 g (83 mmol) of N-bromosuccinimide was added in one portion. After stirring for 5 min, 1.4 ml of methanol which had been saturated with hydrogen bromide gas at 0° was added to the suspension. The solution immediately turned orange. After 1 hr the mixture was taken out of the ice bath and allowed to come to room temperature for 1 hr. It was then heated and stirred at no more than 35–40° while all of the solid dissolved to give a clear red solution which was allowed to stand for an additional 5 hr at room temperature. After filtering a trace of solid, the solution was stored in the cold overnight. The solution and the precipitate which had formed were stirred in an ice bath for 5 hr to complete the crystallization. After filtration and drying, 20.8 g of solid was obtained, mp 73–75°. The crude product was recrystallized from 50 ml of methanol: 19.0 g (60%); mp 72–75°; ir (Nujol) 1770 (imide C=O), 1735 (ester C=O), 1720 (imide C=O), and 1395 cm^{-1}; nmr ($CDCl_3$) δ 7.80 (d, phthaloyl phenyl), 4.20 (d, J = 9 Hz, α-H), 3.80 (s, $COOCH_3$), 3.40 (s, methyl ether), 1.83 (m, γ δ-CH_2CH_2).

Anal. Calcd for $C_{16}H_{18}BrNO_5$: C, 50.01; H, 4.72; Br, 20.80; N, 3.65. Found: C, 49.93; H, 4.74; Br, 21.07; N, 3.73.

Methyl *threo*-Nω-Phthaloyl-β-methoxylysinate Hydrochloride (**13**).—After dissolving 6.5 g (100 mmol) of sodium azide in 83 ml of dimethyl sulfoxide, 18.9 g (49 mmol) of methyl ε-phthalimido-β-methoxy-α-bromocaproate (**10b**) was added with stirring. After the solid dissolved, the solution was kept at 65° for 8 hr. The solution was diluted with water and the resulting precipitated yellow oil was extracted with three 50-ml portions of chloroform. The combined chloroform extracts were washed with 100 ml of water, dried (Na_2SO_4), and evaporated under vacuum. After 1 hr at oil-pump vacuum, 17.8 g of crude methyl ε-phthalimido-β-methoxy-α-azidocaproate was obtained as a light yellow oil: ir (neat) 2100 (N_3), 1745 (ester C=O), and 1770, 1710 cm^{-1} (imide C=O); nmr ($CDCl_3$) δ 3.40 (s, OCH_3), (s, $COOCH_3$) 7.64 (m, phenyl). The azide was dissolved in 100 ml of methanol contained in a 500-ml round-bottomed flask cooled in an ice bath. The catalyst (1.2 g of 5% palladium on carbon) was added as a slurry in 75 ml of methanol, and a slow stream of hydrogen was bubbled through the magnetically stirred solution. After adding 4.1 ml (49 mmol) of concentrated HCl, the ice bath was removed and the solution was allowed to come to room temperature. The course of the reaction was followed by periodically removing a small sample of the reduction mixture and determining the ir spectrum of the products after filtration and evaporation. The azide absorption at 2100 cm^{-1} completely disappeared after 22 hr. The solution was filtered, evaporated under vacuum, and the 15.8 g of yellow glass was dissolved in 38 ml of methanol and slowly diluted with 100 ml of ether. After crystallization was induced by scratching, 100 ml of ether was added and the mixture was kept in the cold. Filtration and drying under vacuum at 46° gave 10.9 g (63%) of **13**: mp 164–166° dec; ir (Nujol) 1765 (imide C=O), 1735 (ester C=O), 1710 (imide C=O), 1395 cm^{-1}; nmr (D_2O) δ 3.52 (s, methyl ether), 3.97 (s, methyl ester), 4.33 (d, J = 4 Hz, α proton), 7.87 (s, phenyl); MPW, R_f 0.98; BAW, R_f 0.78; PW, R_f 0.99.

The analytical sample was obtained by recrystallization from methanol–ether, mp 166–167° dec.

Anal. Calcd for $C_{16}H_{21}ClN_2O_5$: C, 53.85; H, 5.93; Cl, 9.94; N, 7.85. Found: C, 54.00; H, 6.05; Cl, 10.14; N, 7.98.

***threo*-β-Hydroxylysine Hydrobromide** (*threo* **12a**).—Methyl Nω-phthaloyl-β-methoxylysinate hydrochloride (**13**, 10.2 g, 28.6 mmol) was refluxed with 42 ml of 48% HBr for 4 hr and the solution was allowed to stand at room temperature overnight. The clear supernate was decanted from the precipitated phthalic acid and the filtrate was extracted with four 50-ml portions of ether to remove dissolved phthalic acid. The aqueous layer was evaporated *in vacuo* giving an oil which was evaporated three times with 50 ml of acetone and twice with 50 ml of benzene. The resulting red oil, after pumping, was dissolved in 70 ml of hot ethanol, and 20 ml of pyridine was added to the hot solution. An oil separated which became granular after refluxing the solution for 5 hr. After filtration and drying, 5.6 g (80%) of light brown solid was obtained: mp 211° dec; ir (Nujol) 3085 (NH_3^+), 1625, 1575 cm^{-1}; nmr (D_2O) δ 4.60 (m, 1, β-H), 4.17 (d, 1, J = 5 Hz, α-H), 3.5 (t, 2, NCH_2–), 2.24 (m, 4, γ, δ-CH_2CH_2–); MPW, R_f 0.17; BAW, R_f 0.16; PW, R_f 0.48.

An analytical sample was obtained by crystallization of the crude *threo*-β-hydroxylysine hydrobromide from aqueous ethanol, mp 218–222° dec.

Anal. Calcd for $C_6H_{15}BrN_2O_3$: C, 29.63; H, 6.22; Br, 32.87; N, 11.52. Found: C, 29.35; H, 6.15; Br, 32.76; N, 11.73.

***threo*-N,N′-Dibenzoyl-β-hydroxylysine** (*threo* **14a**).—Schotten–Baumann benzoylation of 0.21 g of crude *threo* **14a** gave 141 mg (64%) of product, mp 167–169°. Recrystallization from aqueous ethanol afforded an analytical sample: mp 167–168°; ir (Nujol) 3480, 3375 (shoulder), 3310, 1715 (acid C=O), 1630 cm^{-1} (amide C=O's); nmr (DMSO-d_6) δ 7.94 (m, C_6H_5, α-benzamide), 7.52 (m, C_6H_5, ε-benzamide).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.32; N, 7.81.

Methyl *threo*-β-Hydroxylysinate Dihydrochloride (*threo* **12b**).—A suspension of the *threo* acid (*threo* **12a**) (0.53 g, 2.2 mmol) in 50 ml of methanol was saturated with HCl gas and allowed to stand 24 hr. The solvent was evaporated and the residue was dissolved in 2 ml of methanol and precipitated by the addition of ether giving 0.55 g of crude ester, mp 178–179° dec. The crude ester was redissolved in 10 ml of methanol, and after saturation with HCl gas the solution was allowed to stand 24 hr. It was then refluxed 1 hr, cooled, and centrifuged giving 0.43 g (78%) of analytically pure product: mp 189–191° dec; ir (Nujol) 3375, 1740 (ester C=O), 1235, and 1025 cm^{-1}; nmr (D_2O) δ

1.76 (m, γ, δ-CH_2CH_2), 4.32 (d, J = 3 Hz, α-H), 4.25 (m, β-H), 3.86 (s, $COOCH_3$); MPW, R_f 0.55 (pink); PW, R_f 0.87.

Anal. Calcd for $C_7H_{13}Cl_2N_2O_3$: C, 33.74; H, 7.28; Cl, 28.46; N, 11.25. Found: C, 33.86; H, 7.41; Cl, 28.66; N, 11.22.

Sodium Methoxide Treatment of Oxazoline (*cis* **15**).—Pure oxazoline (*cis* **15**) (68 mg, 0.18 mmol) was dissolved in 10 ml of dry methanol, 1.0 ml of 0.88 *N* sodium methoxide was added, and the solution was allowed to stand for 20 min. Then 2.5 ml of water was added and the solution was refluxed for 30 min. When cooled, the solution was acidified to congo red with concentrated HCl and allowed to stand for 4 hr. The pH of the solution was adjusted to *ca.* 10 which after 10 min was reacidified with concentrated HCl and evaporated at 40° under vacuum until an oil began to form in the liquid. Methanol was added until the oil dissolved. Water was then added and the solution was scratched to induce crystallization. The product was collected by centrifugation and dried under vacuum at 46°: weight 62 mg (93%); mp 172–173° dec. The infrared spectrum was identical with that of *threo*-N,N′-dibenzoyl-β-hydroxylysine (*threo* **14a**), the starting material from which this oxazoline was prepared.

Direct Acid Hydrolysis of Oxazoline (*cis* **15**).—The oxazoline (*cis* **15**) (83 mg, 0.23 mmol) was dissolved in 10 ml of methanol, 1.2 ml of 1 *N* HCl was added, and the solution was allowed to stand 18 hr to convert the oxazoline into the O-benzoyl compound. After the solution had been made basic with about 1.2 ml of *N* NaOH and had stood 10 min, enough base was added to bring the total volume of base to 3 ml and the solution was refluxed 30 min. The solution was then cooled to room temperature, acidified with concentrated HCl, and evaporated to an oily solid residue. After washing the residue twice with water, it was dissolved in 2 ml of methanol and diluted with 8 ml of water. This solution was then evaporated under vacuum to about 3 ml, after which a solid slowly crystallized from the solution. After centrifugation and drying at 46° under vacuum, 14 mg of *erythro*-N,N′-dibenzoyl-β-hydroxylysine (*erythro* **14a**) was collected, mp 159–162° dec. The infrared spectrum of this product was identical with *erythro* **14a**.

Registry No.—**6a**, 19991-86-7; **6b**, 19991-87-8; **8** hydrochloride, 19991-88-9; **10a**, 19991-89-0; **10b**, 19991-90-3; *erythro* **12a** hydrobromide, 19991-91-4; *threo* **12a** hydrobromide, 19991-92-5; *erythro* **12b** dihydrochloride, 19991-93-6; *threo* **12b** dihydrochloride, 19991-94-7; **13** hydrochloride, 19991-95-8; *erythro* **14a**, 19991-96-9; *threo* **14a**, 19991-97-0.

Synthetic Furocoumarins. IX. A New Synthetic Route to Psoralen[1]

LEONARD R. WORDEN,[2a] KURT D. KAUFMAN, JAMES A. WEIS, AND THOMAS K. SCHAAF[2b]

Department of Chemistry, Kalamazoo College, Kalamazoo, Michigan 49001

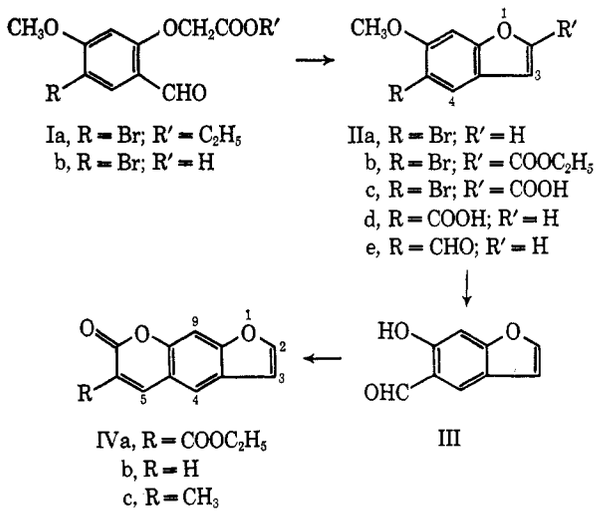
Received December 4, 1968

Practical syntheses of psoralen (IVb) and 3-methylpsoralen (IVc) from β-resorcylaldehyde are described. Bromination of ethyl (2-formyl-5-methoxyphenoxy)acetate gave the 4-bromo derivative Ia, which was saponified and simultaneously cyclized and decarboxylated to 5-bromo-6-methoxybenzofuran (IIa). Lithium–bromine interchange and then formylation and demethylation gave 5-formyl-6-hydroxybenzofuran (III), which was condensed with diethyl malonate to furnish psoralen after hydrolysis and decarboxylation of the Knoevenagel product IVa. Condensation of III with propionic anhydride furnished 3-methylpsoralen (IVc) directly.

Unfavorable directive effects associated with syntheses of psoralens unsubstituted in the 9 position have limited yields of the naturally occurring phototoxin psoralen (IVb, Scheme I) to 1–4% over-all from resorcinol or β-resorcylaldehyde.[3] However, Chatterjee and Sen recently reported a 15% conversion of resorcinol into psoralen.[4] Although their scheme now is the route of choice to psoralen itself, the synthesis lacks the versatility of the novel Scheme I, which represents a 14% conversion of β-resorcylaldehyde into psoralen.

Ethyl (4-bromo-2-formyl-5-methoxyphenoxy)acetate (Ia) was prepared both by bromination of ethyl (2-formyl-5-methoxyphenoxy)acetate[5] and by alkylation of 5-bromo-2-hydroxy-*p*-anisaldehyde.[6] Saponification of the ester Ia and then decarboxylative cyclization in acetic acid–acetic anhydride[7] gave the bromobenzofuran IIa and a trace quantity of a carboxylic acid identified as IIc by the independent synthesis of IIc from the ester Ia by base-catalyzed cyclization.

SCHEME I



To investigate the lithium–halogen interchange, the bromobenzofuran (IIa) was treated with butyllithium and then Dry Ice. This gave the carboxylic acid IId in quantitative yield. Earlier investigation of direct metalation with butyllithium of 6-methoxybenzofuran[8] and then carbonation (Dry Ice) indicated (thin layer chro-

(1) Part VIII: K. D. Kaufman, R. C. Kelly, and D. C. Eaton, *J. Org. Chem.*, **32**, 504 (1967). Preliminary communication: L. R. Worden and K. D. Kaufman, presented at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967.

(2) (a) To whom inquiries should be directed. (b) National Science Foundation Undergraduate Research Participant (Grant No. GE-4097).

(3) (a) E. Späth, B. L. Manjunath, M. Pailer, and H. S. Jois, *Ber.* **69**, 1087 (1936); (b) E. C. Horning and D. B. Reisner, *J. Amer. Chem. Soc.*, **70**, 3619 (1948); (c) R. T. Foster, A. Robertson, and A. Bushra, *J. Chem. Soc.*, 2254 (1948); (d) T. R. Seshadri and M. S. Sood, *Indian J. Chem.*, **1**, 291 (1963).

(4) D. K. Chatterjee and K. Sen, *Sci. Cult.* (Calcutta), **33**, 528 (1967).

(5) R. Andrisano, F. Duro, and G. Pappalardo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **14**, 96 (1956).

(6) M. G. S. Rao, C. Srikantia, and M. S. Iyengar, *J. Chem. Soc.*, 1578 (1929); *Chem. Abstr.*, **23**, 4681 (1929).

(7) A. W. Burgstahler and L. R. Worden, *Org. Syn.*, **46**, 28 (1966).

(8) H. Dumont and St. v. Kostanecki, *Ber.*, **42**, 911 (1909).