and solvent followed by recrystallization gave the hydrochloride (Table I). Treatment of the hydrochloride with aqueous sodium hydroxide followed by extraction with chloroform (salted out with aqueous potassium carbonate) gave the free base which was dried either by heating in vacuo or azeotroping with chloroform. The amides I which contained chlorine were hydrogenated without added HCl since this was formed by hydrogenolysis. Hydrogenation of I*e* without added HCl gave material which furnished the hydrochloride of II*e* upon addition of ethanolic HCl or the hydrated base of II*e* upon recrystallization. The other amides I*a*-I*d*, when hydrogenated under neutral conditions, gave the *o*-aminoanilides which, when treated with ethanolic HCl in acetone, gave high yields of substituted benzimidazole hydrochlorides.

2′-Aminoformanilide. A mixture of 5.0 grams (0.03 mole) of 2′-nitroformanilide (*3*, *5*), 100 mg. of platinum oxide, and 150 ml. of ethyl acetate was shaken under hydrogen until about 0.095 mole had been absorbed. Removal of catalyst and solvent left a yellow solid which was recrystallized from ethyl acetate to yield 3.5 grams (85%) of white solid, m.p. 105–109° C. Recrystallization from benzene with minimal heating raised the m.p. to 107–110° C. When the product was refluxed in xylene for 6 hours, crude benzimidazole, m.p. and mixture m.p. 151–160° C., was obtained in 93% yield.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.77; H, 5.92; N, 20.58. Found: C, 61.96; H, 5.88; N, 20.70.

Benzimidazole-3-oxide (1-Hydroxybenzimidazole). When the above hydrogenation was carried out in absolute ethanol, crystallization of the crude product from ethyl acetate gave 0.61 gram (15%) of *N*-oxide, m.p. 199–205° C., literature m.p. 210° C. (*5*); hydrochloride m.p. 199.5–207° C., literature m.p. 200–214° C. dec. (*5*). Ultraviolet spectra of both the base and the hydrochloride were compatible with the published curves (*10*). Impure 2′-aminoformanilide (2.64 grams), contaminated with considerable benzimidazole, was obtained from the mother liquors.

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Characterization of the Diastereomers of 2,4-Dimethyl-3-oxapentane-1,5-diol

D. DAVID LAWSON
Jet Propulsion Laboratory, 4800 Oak Grove Drive, Pasadena, Calif. 91103

The diastereomeric forms of the 2,4-dimethyl-3-oxapentane-1,5-diol diprimary dipropylene glycol have been synthesized by two routes: reduction of the diethyl dilactate ester with lithium aluminum hydride; and replacement of chlorine by an acetoxy group on 1,5-dichloro-2,4-dimethyl-3-oxapentane. The diprimary glycol is then obtained by an ester interchange with methanol and diacetate ester. The glycol diastereomeric forms are readily purified by distillation and/or preparative gas chromatography.

PREPARATION of the three isomers of dipropylene glycol was reported by Sexton and Britton, but their consideration did not extend to the diastereomeric forms of the glycols (*5*).

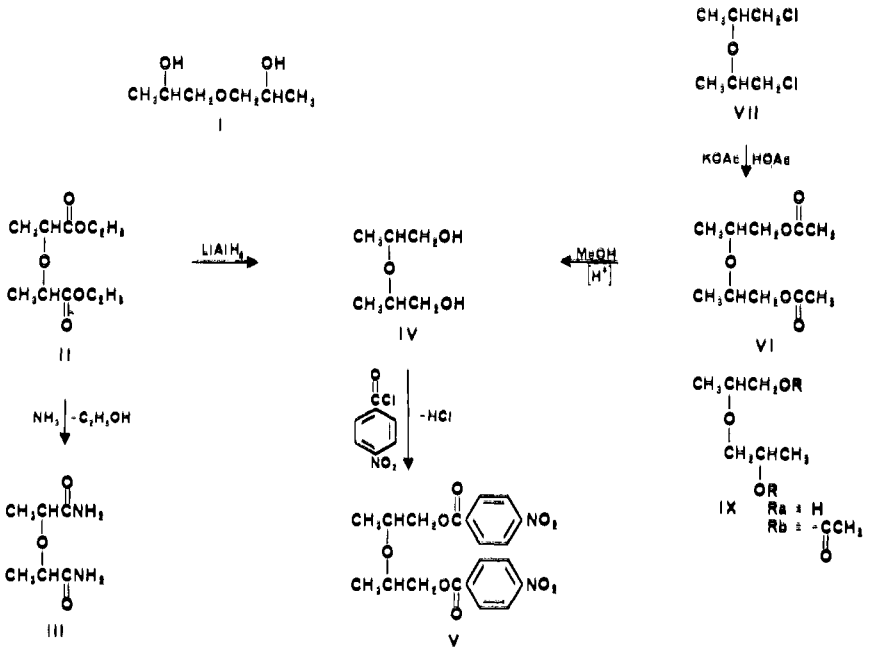
Later Summerbell, Jerina, and Grula reported the diastereomers of 4-oxaheptane-2,6-diol (I) (di-*sec*- dipropylene glycol) in connection with their studies of the conversion of glycols to dioxenes (*6*).

At this time, the authors report the preparation and characterization of the 2,4-dimethyl-3-oxapentane-1,5-diol (IV) (diprimary dipropylene glycol) diastereomeric forms.

In connection with the study of lactic acid metabolism, Vieles and coworkers (*7*) prepared a large number of derivatives of dilactic acid and determined their configurations relative to lactic acid. The authors also found in the case of diethyl dilactate (II), prepared from the sodium salt of ethyl lactate and ethyl α-bromopropionate, that the ratio of *dl* pairs to the meso form was 5 to 1 (*7*). The dilactate esters were separated by careful fractional distillation to obtain the lower boiling *dl* isomers. The meso ester remained in the residue and was further purified by preparative gas chromatography. To distinguish between the esters of the meso and *dl* forms, the diamides (III) were prepared by heating the appropriate diastereomeric ester with ammonia in a sealed tube and the melting points compared with those given by Vieles (*7*).

On reduction of both the *dl* and meso diethyl lactates (II) to the glycols (IV) with lithium aluminum hydride and dry diethyl ether, no apparent epimerization occurs. The course of this reduction was verified by gas chromatography using a Carbowax 20M column, which can be used to separate the esters or glycols easily. The bis-*p*-nitrobenzoate derivatives (Va) of the glycols were prepared by heating *p*-nitrobenzoyl chloride with either the meso or *dl* forms of IV (*2*).

Apparently, the melting points of the bis-*p*-nitrobenzoates



show that Sexton and Britton (5) prepared only the *dl*-2,4-dimethyl-3-oxapentane-1,5-diol.

A more convenient alternate synthesis of IV is to heat in an autoclave the 1,5-dichloro-2,4-dimethyl-3-oxapentane (VII) with potassium acetate and acetic acid to give the diacetate (VI). The glycol (IV) is then obtained by an ester interchange between methanol and VI. The chloro ether (VII) was readily obtained by the dehydration of secondary propylene chlorohydrin (VIII) with sulfuric acid.

Preparation of the secondary propylene chlorohydrin unfortunately results in a product which is contaminated with the primary chlorohydrin (~25%). Therefore, this yields a chloro ether which contains a small amount of 2-methyl-1,5-dichloro-3-oxahexane contaminant. The commercially available VII yields a diol acetate contaminated with about 10% of the primary-secondary diol acetate (IXb). This presents no problems, because diols IV and IXa are readily separated by distillation to give a mixture of the *dl* and meso forms of IV. The diastereomeric forms of IV are then separated by preparative gas chromatography using Carbowax 20M as the liquid phase. The gas chromatography data were reduced by a computer program (3), and plotted (Figure 1) according to the method of Littlewood, Phillips, and Price (4). It has been demonstrated that a plot of specific retention volume (Vg) *vs.* the reciprocal of the absolute temperature ($1/T$) for a given compound is linear and its slope is a function of the heat of solution

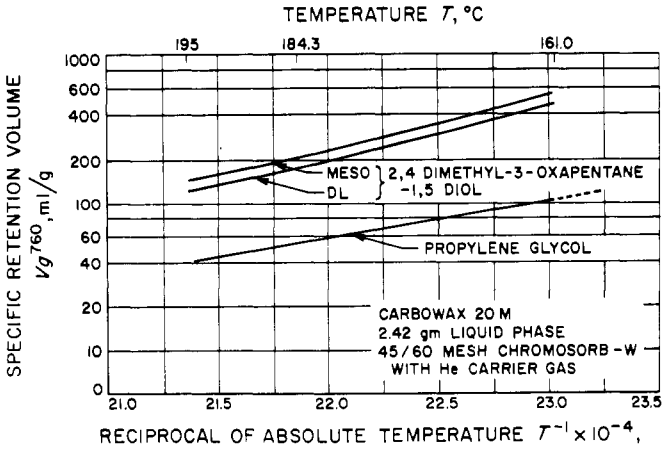


Figure 1. Gas-chromatography data as a function of specific retention volume *vs.* reciprocal of the absolute temperature

of the material in the liquid phase in the GLPC column (4). The results show the relative separation of the two diastereomers of IV as compared with propylene glycol.

The hydroxyl groups in IV were checked to verify that they were primary, by means of the different chemical shifts of the F^{19} NMR spectra of the glycol ditrifluoroacetate ester (1). This procedure allows an unequivocal characterization of the hydroxyl group in the diols.

EXPERIMENTAL

Care should be exercised in handling these materials because of possible peroxide formation.

Starting Materials and Equipment. All chemicals were used as received except for the 1,5-dichloro-2,4-dimethyl-3-oxapentane[bis(2-chloroisopropyl) ether], which was redistilled before use. The preparative gas chromatograph was a Wilkens A700 Autoprep unit with ⅜-inch by 6-foot column of 10% Carbowax 20M and Chromosorb W (30- to 40-mesh), with He as the carrier gas. Precision retention time data were obtained on an instrument of the author's design using 5-foot by ¼-inch columns; the technique will be described elsewhere. The ditrifluoroacetates were prepared by methods described by Ingham *et al.* (1) and the spectra obtained at 56.4 MHz at a 14-kilogauss field on Varian HR-60 high resolution NMR system with chemical shifts measured by side-band techniques. Distillations were run on a Wheeler spinning band distillation column (1 by 100 cm., Precision Distillation Apparatus Co., Woodland Hills, Calif.).

Preparation of 2,4-Dicarbethoxy-3-oxapentane (II). The procedure used was essentially that of Vieles, except that 2.2 moles of ethyl lactate and ethyl α-bromopropionate were used rather than 2.40 and 1.45 moles, respectively (7). The yield of 2,4-dicarbethoxy-3-oxapentane (V) was 389.7 grams (89.5%).

The diastereomers were then separated by careful distillation on a Wheeler spinning band distillation column to yield 234 grams of the *dl* ester, which was checked for purity by gas chromatography as the distillation proceeded. The compound had a boiling point range of 118-20° C. at 70 mm., $n_D^{28.1}$ 1.41435 and $d_0^{28.1}$ 1.023. This compares with literature values (7) of a boiling point of 124.0° at 2 mm., $n_D^{21.1}$ 1.4140 and $d_D^{28.1}$ 1.028. The remaining ester was purified by preparative gas chromatography to yield 70 grams of the meso ether with $n_D^{28.1}$ 1.41935 compared with 1.41892 (7).

2,4-Dicarbamyl-3-oxapentane from 2,4-Dicarbethoxy-3-oxapentane (II to III). In a 35-ml. bomb, 1.009 grams (0.005 mole) of *dl* or meso diethyl dilactate and 15 ml. of liquid ammonia were heated at 150° C. for 10 hours. The bomb was cooled to −20° C. and opened, and the excess ammonia allowed to escape. The crude diamide was then taken up in 10 ml. of boiling absolute ethanol, treated with charcoal, and filtered. The analytical samples were recrystallized three more times from acetone. The yield of *dl*-lactic acid diamide was 600 mg. (75%) of needles which melted at 182–83° C. The literature gives a melting point of 184° C. (*7*). Analysis. Calculated for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55 N, 17.49. Found: C, 45.08; H 7.95; N, 17.53. Mesolactic acid diamide: yield 550 mg. (69%) of plates which melted at 133-35° C. The literature gives a melting point of 136° C. (*7*). Analysis. Calculated for $C_6H_{12}N_2O_4$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.76; H, 7.84; N, 17.83.

Preparation of 2,4-Dimethyl-3-oxapentane-1,5-diol from 2,4-Dicarbethoxy-3-oxapentane (IV from II). The procedure was essentially that used by Sexton and Britton, except that the scale was one tenth (*5*). The reduction products were identical (by infrared) with the materials obtained from VII to the acetate (VI), and then to the glycol (IV). The course of the reduction was followed by gas chromatography using a Carbowax 20M column at 191° C.

Preparation of Bis-*p*-nitrobenzoate Esters of 2,4-Dimethyl-3-oxapentane-1,5-diol (IV to V). The *dl* or meso glycols (IV) were esterified by heating a mixture of the appropriate glycol (0.670 gram, 0.005 mole) and *p*-nitrobenzoyl chloride (1.856 grams, 0.01 mole) to 100° C. for 15 minutes with HCl evolution. After this, the reaction mixture was flushed with dry nitrogen and cooled. The crude esters were recrystallized from ethanol four times and dried at 1-torr vacuum at room temperature for 10 hours. The *dl*-ester yield was 2.0 grams (81%) with a melting point of 141-42° C. The literature melting point was 142–43° C. (*5*). Analysis. Calculated for $C_{20}H_{20}N_2O_8$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.57; H, 4.59; N, 6.34. The meso ester yield was 1.85 grams (75%) with a melting point of 115-16° C. Analysis. Calculated for $C_{20}H_{20}N_2O_9$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.47; H, 4.61; N, 6.63.

1,5-Diacetoxy-2,4-dimethyl-3-oxapentane (VI). In a 1.2-liter autoclave were placed 292.8 grams (1.7 moles) of bis(2-chloroisopropyl) ether, 400 grams of anhydrous potassium acetate, and 300 ml. of acetic acid. Before the autoclave was closed, the reaction mixture was stirred. The mixture was heated to 130° C. for 10 hours. The cold reaction mixture was dissolved in 2 liters of water and extracted three times with 200-ml. portions of diethyl ether. The combined extracts were washed with 100 ml. of water and dried over anhydrous sodium sulfate. The ether was removed with a rotary evaporator and a water bath (40° to 50° C.). The resultant diacetate was fractionated through a 20 × 1 cm. distillation column with metal packing to yield 150 grams (40.5%) at 118–19° C. at 9 mm. (sp. g. 25/25 1.041 n_D^{20} 1.4235). Analysis. Calculated for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.98; H, 8.40

Preparation of 1,5-Dihydroxy-2,4-dimethyl-3-oxapentane (IV). A mixture of 130 grams of 1,5-diacetoxy-2,4-dimethyl-3-oxapentane (0.596 mole), 100 ml. of absolute methanol, and one drop of concentrated sulfuric acid was refluxed for 10 hours and made basic with a concentrated solution of sodium hydroxide. Methanol was removed under reduced pressure to leave a residue of 89 grams of the crude glycol. Distillation with a Wheeler spinning band column of the crude product at 84° C. and 0.1 mm. gave 85 grams (91.4%) of IV. The separation of 10.0 grams of the mixture of the *dl* and meso forms of IV by preparative gas chromatography gave 3.2 grams of the *dl* glycol (IV) and 3.4 grams of the meso glycol (IV) (*dl* glycol n_D^{25} 1.4426. Analysis. Calculated for $C_6H_{14}O_4$: C, 53.71; H, 10.52. Found: C, 53.52; H, 9.90 meso glycol n_D^{25} 1.4356. Analysis. Calculated for $C_6H_{14}O_4$: C, 53.71; H, 10.52. Found: C, 53.46; H, 10.61. Literature n_D^{25} 1.440, b.p. 102° C. at 5 mm. (*5*).

The ditrifluoroacetates were prepared and carefully examined by F^{19} NMR spectroscopy for the presence of any secondary esters, none being observed in either the *dl* or meso glycols of IV. The chemical shifts of the fluorinated secondary diesters and the primary diesters are 75.82 ± 0.02 and 75.55 ± 0.02 p.p.m., respectively, relative to trichlorofluoromethane (*1*).

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Derivatives of Anthranilic Acid

BENJAMIN BLANK, SUZANNE R. COHEN, and DAVID W. SPIGGLE[1]
Research Division, Smith Kline and French Laboratories, Philadelphia, Pa. 19101

The preparation of carbamates and ureas derived from anthranilic acid, its methyl ester, and substituted anthranilic acids is described. A summary of the activity of these compounds in two anti-inflammatory screening assays is also presented.

CARBAMATES and ureas derived from anthranilic acid, its methyl ester, and substituted anthranilic acids were prepared because of their similarity to compounds with anti-inflammatory activity (*5, 6, 10, 11, 12*). The compounds prepared (Ia-x) together with appropriate analytical and physical data are listed in Table I. Ia-x were prepared by the procedures outlined in the experimental section.

In the preparation of Ia, d, and e, a second compound was formed. Infrared spectra and elemental analyses showed that these compounds were *N*-(*o*-alkoxycarbonylaminobenzoyl) anthranilic acids (IIa-c). The infrared spectra of IIa-c had a triplet in the carbonyl region—the most intense

[1] Deceased.