S 14. *Esters of* N-*Substituted Phthalamic Acids. Preparation and Use in the Optical Resolution of Alcohols and Amines.*

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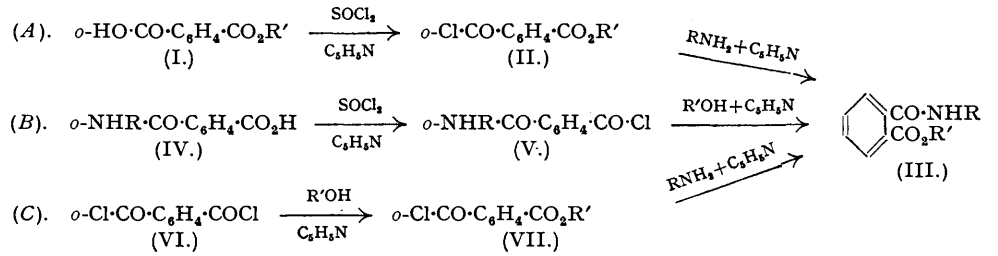
Methods of preparation of esters of the type *o*-NHR·CO·C_6H_4·CO_2R′ are described, which give good yields for a wide range of groups R and R′. The esters are stable solids of good crystallising power. Successful resolutions of (±)-*trans*-2-methyl*cyclo*hexanol, (±)-*trans*-3-methyl*cyclo*hexanol and (±)-2-butanol through their (−)-*N*-menthylphthalamic esters are described.

Very few esters of *N*-monosubstituted phthalamic acids are recorded in the literature, and usually these have not been made from the acids by normal esterification procedures, because of the ease of cyclisation of those acids under a variety of conditions to give *N*-substituted phthalimides (*e.g.* Tingle and Rolker, *J. Amer. Chem. Soc.*, 1908, **30**, 1882). Clark and Read (*J.*, 1934, 1775) found that (−)-*N*-menthylphthalamic acid suffered cyclisation during attempts at esterification with (−)-menthol. The reaction of an alkyl iodide with the silver salt of an acid has been used to prepare a few esters, such as methyl phthalanilate (van der Meulen, *Rec. Trav. chim.*, 1896, **15**, 347), but this method is of limited value.

The following three fairly general methods enabled good yields of esters of the above type to be obtained for a wide range of alcohol and amine components. Each of the methods involved the formation of an intermediate acid chloride which was generally too unstable to be isolated, and the chlorides were prepared and used in dilute solution in the cold, by the method of Carré and Liebermann (*Compt. rend.*, 1934, **199**, 1422), which used exactly one mole each of pyridine and thionyl chloride. Human and Mills (*Nature*, 1946, **158**, 877) have elsewhere noted the value of this method.



Method (*A*). The hydrogen phthalate (I) of an alcohol was converted into the acid chloride (II), which was then coupled with an amine to give the desired ester (III), using either pyridine or an excess of amine as hydrogen chloride acceptor. Drew and Hatt (*J.*, 1937, 16) used essentially this method treating *o*-carbomethoxybenzoyl chloride (II; R′ = Me) with hydrazine, but they isolated the acid chloride. The method gave 70—97% yields of ester from a number of hydrogen phthalates, but failed completely with (−)-*trans*-4-*iso*propyl*cyclo*hex-2-enyl hydrogen phthalate, therefore it may not be applicable to the hydrogen phthalates derived from αβ-unsaturated alcohols and others which readily undergo dehydration. When concentrated aqueous ammonia was used in the second stage, esters of phthalamic acid (III; R = H) were obtained.

Method (*B*). A substituted phthalamic acid (IV) was esterified directly, the acid chloride (V) being prepared by the action of equimolecular amounts of thionyl chloride and pyridine, and treated with with an alcohol in the usual way. This result was surprising in view of the ease of cyclisation of most monosubstituted phthalamic acids, but it seemed to be fairly general. Acid chloride formation and esterification took place almost exclusively with cyclo*hexylphthalamic acid* (IV; R = *cyclo*hexyl), as well as with menthyl- and *neo*menthyl-phthalamic acids (IV; R = menthyl), and the corresponding phthalimides were not detected in the product. The chlorides of these three acids seemed to be stable in ether solution up to its boiling point. Phthalanilic acid (IV; R = Ph) and phthalamic acid (IV; R = H) also gave esters (III), but in rather poor yields, and they were difficult to purify because of the presence of large quantities of the products of cyclisation. The low solubility of the last two acids in the solvents used may have contributed to the unsatisfactory results.

This method gave good results with an αβ-unsaturated alcohol and a glycol, and probably would be applicable to phenols, and is therefore, in part, complementary to (*A*). It should also provide a route to mixed phthalamides of the type *o*-RNH·CO·C_6H_4·CO·NHR′, of which very few examples are known.

Method (*C*). *s*-Phthaloyl chloride (VI) was treated with one mole each of an alcohol and of pyridine, to give the ester-acid chloride (II), which was treated with an amine, as in method (*A*). This method was not much investigated, in view of the success of (*A*) and (*B*), as the chance of by-product formation was greater, but a good yield of ester was obtained when R = R′ = menthyl.

The esters prepared were all solids of good crystallising power, with melting points mainly in the range of 100—200°, and all were stable to heat up to the melting point. Hydrolysis with a slight excess of alkali regenerated the alcohols and phthalamic acids, and the amines were recoverable by decomposing the phthalamic acids with hydrazine (Ing and Manske, *J.*, 1926, 2348); it was not necessary to cyclise the acids before treatment with hydrazine.

When the amine RNH_2 is optically active, and the alcohol R′OH is racemic, the ester (III) represents a diastereoisomeric mixture theoretically capable of separation, and the optical resolution of three alcohols by this method was examined, using (−)-menthylamine as the active amine. Initial preparation of the esters usually was by method (*A*), and the (−)-menthyl-phthalamic acid recovered after hydrolysis of the esters was used again by method (*B*). The diastereoisomeric mixtures separated very slowly, and long and tedious fractional crystallisations

were necessary. Eventually, quite good yields of one active component were obtained from (±)-2-butanol and (±)-*trans*-3-methyl*cyclo*hexanol (in each case the form which is less readily available by other methods of resolution), but only 8% of the theoretical amount of *lævo*-epimer was obtained from (±)-*trans*-2-methyl*cyclo*hexanol. Replacement of (−)-menthylamine by (+)-*neo*menthylamine in the latter case showed no advantage.

Use of the esters (III) also presents the possibility of resolving a racemic amine with an active alcohol. An attempt to resolve (±)-α-phenylethylamine with (−)-menthol showed that a resolution was proceeding, but it had to be abandoned because of its slowness.

Experimental.

Typical examples of the three methods of preparation of the esters (III) are given below. The choice of solvent for the reaction did not greatly affect the yield, and at different times ether, chloroform, benzene, and carbon tetrachloride were used. Ether probably gave the best yields, but was the most difficult to make and keep pure and anhydrous. Purified chloroform was attractive because of its high solvent power, in particular for pyridine hydrochloride, but unless it was distilled from phosphoric oxide the rapid formation of carbonyl chloride on storage was a disadvantage.

Method (A).—(±)-*trans*-2-Methyl*cyclo*hexyl hydrogen phthalate (Gough, Hunter, and Kenyon, *J.*, 1926, 2052) (2·00 g.) was dissolved in dry ether (25 ml.) and to the solution were added pure anhydrous pyridine (0·616 ml.; 1·0 mol.) and pure thionyl chloride (0·554 ml.; 1·0 mol.); the mixture was shaken and left protected from moisture at 20° for 4 hours, during which granular pyridine hydrochloride separated. *cyclo*Hexylamine (0·755 g.; 1·0 mol.) and pyridine (0·616 ml.) were dissolved in ether (5 ml.) and added to the mixture, which was left overnight at 20°. More ether was added to dissolve some ester which had crystallised out, and the ethereal solution was washed to remove pyridine and a little unreacted hydrogen phthalate. Removal of the ether left a slightly impure ester (III; R = *cyclo*hexyl, R′ = 2-Me-*cyclo*hexyl), m. p. 146°, in 83% yield. (Pure sample, see below.)

Method (B).—(−)-*N*-Menthylphthalamic acid (IV; R = menthyl) (Clark and Read, *loc. cit.*) (4·34 g.) was dissolved in dry ether (40 ml.), containing pyridine (1·15 ml.; 1·0 mol.), in a flask fitted for stirring and protected from moisture. Thionyl chloride (1·04 ml.; 1·0 mol.) dissolved in ether (10 ml.) was dropped in during 30 minutes at 25°. The dropping funnel was rinsed with ether (5 ml.) and the mixture left for 45 minutes. Pyridine hydrochloride separated. A solution of (−)-*trans*-4-*iso*propyl*cyclo*hex-2-enol (Gillespie, Macbeth, and Mills, *J.*, 1948, 996) (2·0 g.; 1·0 mol.) and pyridine (1·15 ml.) in ether (15 ml.) was dropped in during 30 minutes; the mixture was left at 25° for one hour and then refluxed for 30 minutes. During the working up a sodium carbonate washing recovered unchanged (−)-menthylphthalamic acid (10%). The yield of crude ester (III; R = menthyl, R′ = *iso*propyl*cyclo*hexenyl), m. p. 122°, was 89% (5·45 g.), hence very little (−)-*N*-menthylphthalimide, m. p. 109°, could have been formed. (Pure ester below.)

In the above case the acid chloride (IV; R = menthyl) showed so little tendency to cyclisation that it was immaterial whether the pyridine or thionyl chloride was added first, or both together, but for very readily cyclised acids they were mixed in the proper amount and added slowly. With the acid (IV; R = *cyclo*hexyl) refluxing was omitted, and for (IV; R = Ph) and (IV; R = H) the whole reaction was carried through with ice-water cooling in two hours.

Method (C).—*s*-Phthaloyl chloride (5·1 g.) was dissolved in dry benzene (15 ml.) and to the solution was slowly added a solution of (−)-menthol (3·9 g.; 1·0 mol.) and pyridine (2·0 g.; 1·0 mol.) in benzene (15 ml.), with shaking and cooling. After standing for 2 hours, the solution was poured from the pyridine hydrochloride into a mixture of (−)-menthylamine (3·9 g.; 1·0 mol.) and pyridine (2·0 g.) in benzene (15 ml.). After 2 hours' standing the product was worked up as usual. The ester (III; R = R′ = menthyl) (90% yield) was deeply coloured and rather impure (pure ester below).

New Compounds.—Data in parentheses show the substituents in the general formula (III), the method of preparation, the solvent in which it was done, and the yield before recrystallisation. Excepting those prepared by method (*C*), the crude esters required about two crystallisations to reach analytical purity. Some of the yields recorded were obtained during preliminary work, and may not be the highest attainable.

cyclo*Hexyl phthalamate* (R = H, R′ = *cyclo*hexyl; *A*, using aqueous ammonia, benzene, 50%; *B*, chloroform, poor yield), needles from light petroleum (b. p. 60—90°), m. p. 96° (Found: C, 68·3; H, 6·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9%). cyclo*Hexyl phthalanilate* (R = Ph, R′ = *cyclo*hexyl; *A*, benzene, 97%; *B*, chloroform, poor yield; *C*, carbon tetrachloride, 60%), needles from light petroleum, m. p. 111·5—112° (Found: C, 74·2; H, 6·5. $C_{20}H_{21}O_3N$ requires C, 74·3; H, 6·6%). (±)-trans-2-*Methyl*cyclo*hexyl* N-cyclo*hexylphthalamate* (R = *cyclo*hexyl, R′ = 2-Me-*cyclo*hexyl; *A*, ether, 83%; *B*, chloroform, 90%), minute needles from light petroleum (b. p. 100—120°), m. p. 147—148° (Found: C, 73·4; H, 8·5. $C_{21}H_{29}O_3N$ requires C, 73·4; H, 8·6%). *Ethyl* (−)-N-*menthylphthalamate* (R = menthyl, R′ = Et; *B*, ether, 84%), minute needles from light petroleum (b. p. 60—90°), m. p. 116—116·5°, $[\alpha]_D^{16°}$ −41·9° (in chloroform, *c*, 2·6) (Found: N, 4·2. $C_{20}H_{29}O_3N$ requires N, 4·2%). n-*Amyl* (−)-N-*menthylphthalamate* (R = menthyl, R′ = *n*-amyl; *B*, ether, 87%), needles from light petroleum (b. p. 40—60°), m. p. 101—102°, $[\alpha]_D^{17°}$ − 35·9° (in chloroform, *c*, 4·5) (Found: N, 3·9. $C_{23}H_{35}O_3N$ requires N, 3·8%). *Allyl* (−)-N-*menthylphthalamate* (R = menthyl, R′ = allyl; *B*, ether, 62%), needles from light petroleum (b. p. 40—60°), m. p. 98·5°, $[\alpha]_D^{19°}$ − 43·0° (in chloroform, *c*, 3·0) (Found: N, 4·1. $C_{21}H_{29}O_3N$ requires N, 4·1%). cyclo*Hexyl* (−)-N-*methylphthalamate* (R = menthyl, R′ = *cyclo*hexyl; *A*, benzene, 70%), needles from light petroleum (b. p. 60—90°), m. p. 164—164·5° (Found: N, 3·7. $C_{24}H_{35}O_3N$ requires N, 3·6%). (−)-*Menthyl* (−)-N-*menthylphthalamate* (R = R′ = menthyl; *B*, ether, 60%; *C*, benzene, 90%), needles from aqueous alcohol, m. p. 154°, $[\alpha]_D^{17°}$ − 86·8° (in chloroform, *c*, 3·2) (Found: N, 3·1. $C_{28}H_{43}O_3N$ requires N, 3·2%). (−)-trans-4-iso*Propyl*cyclo*hex*-2-*enyl* (−)-N-*menthylphthalamate* (R = menthyl, R′ = *iso*propyl*cyclo*hexenyl; *A*, various conditions, nil; *B*, ether, 89%);

minute needles from light petroleum (b. p. 50—80°), m. p. 130°, $[\alpha]_D^{19°} - 126°$ (in chloroform, *c*, 4·4) (Found : N, 3·3. $C_{27}H_{39}O_3N$ requires N, 3·3%). *Ethylene glycol bis-*(−)-N-*menthylphthalamate* $[(C_{10}H_{19}\cdot NH\cdot CO\cdot C_6H_4\cdot CO_2\cdot CH_2)_2$; *B*, chloroform, 89%], crystalline powder from acetone, m. p. 239—241°, sparingly soluble in most solvents (Found : N, 4·5. $C_{38}H_{52}O_6N_2$ requires N, 4·6%).

*N-cyclo*Hexylphthalimide was prepared by mixing equimolecular quantities of phthalic anhydride and *cyclo*hexylamine in chlorobenzene, and, after the spontaneous reaction subsided, heating until no more water was evolved. After recrystallisation from alcohol it formed glistening large plates, m. p. 170—171°, not 168° (Vanags, *Chem. Abs.*, 1940, **34**, 1983). Warming with a slight excess of methyl-alcoholic potassium hydroxide gave N-cyclo*hexylphthalamic acid* (IV; R = *cyclo*hexyl), shining platelets from aqueous alcohol, m. p. 160—161° (sealed tube) (Found : N, 5·6. $C_{14}H_{17}O_3N$ requires N, 5·7%).

Resolution of (±)-trans-3-*Methyl*cyclo*hexanol.*—(±)-*trans*-3-Methyl*cyclo*hexyl hydrogen phthalate (Macbeth and Mills, *J.*, 1945, 709) (59 g.) was dissolved in pure ether (600 ml.) and converted into acid chloride as in method (*A*), the thionyl chloride being added dropwise to the refluxing solution during one hour. After a further 30 minutes the acid chloride was treated with (−)-menthylamine during one hour and the whole left overnight. More ether was added and the products worked up as usual, giving the diastereoisomeric mixture, m. p. 120—130°, in 92% yield. This was recrystallised systematically in 4 fractions from aqueous alcohol (80—90% ; about 8 ml./g.). Initially rapid, the separation became slow after the m. p. reached 163—168°, corresponding to 80% *dextro-* and 20% *lævo*-epimer, and 23 series of recrystallisations were necessary before pure (+)-trans-3-*methyl*cyclo*hexyl* (−)-N-*menthylphthalamate* (III; R = menthyl, R′ = 3-Me-*cyclo*hexyl) (Found : N, 3·6. $C_{25}H_{37}O_3N$ requires N, 3·5%), fine needles, m. p. 183°, $[\alpha]_D - 25·0°$ (in chloroform), was obtained (16·5 g., 41% of theory). Hydrolysis was effected by refluxing the ester with methyl-alcoholic potassium hydroxide (4% ; 1·3 mols.) for 40 minutes. After working up and recovering the alcohol by continuous ether extraction, (+)-trans-3-*methyl*cyclo*hexanol*, b. p. 88°/15 mm., $\alpha_D^{14°} + 3·70°$ (homogeneous, *l* = 1), was obtained (80% recovery). Acidification of the alkaline solution from the hydrolysis gave (−)-*N*-menthylphthalamic acid (93% recovery).

For (−)-*trans*-3-methyl*cyclo*hexanol Macbeth and Mills (*J.*, 1947, 205) recorded $\alpha_D^{28°} - 3·62°$ (homogeneous, *l* = 1). From this was prepared (−)-trans-3-*methyl*cyclo*hexyl* (−)-N-*menthylphthalamate* (Found : C, 75·4; H, 9·8%), needles from aqueous alcohol, m. p. 135—136°, $[\alpha]_D - 44·4°$ (chloroform).

Resolution of (±)-trans-2-*Methyl*cyclo*hexanol.*—(±)-*trans*-2-Methyl*cyclo*hexyl hydrogen phthalate in ether was combined with (−)-menthylamine as in the preceding resolution, giving the diastereoisomeric mixture, m. p. 155—160°, $[\alpha]_D^{30°} - 25°$ (chloroform), in 79% yield. For each of the large number of solvents tried the rate of resolution was always found to be very slow. Best results were obtained by using the smallest possible amount (7—8 ml./g.) of a mixture (30 : 70) of chlorobenzene and light petroleum (b. p. 50—80°), and doing 23 bulk recrystallisations, followed by 12 recrystallisations from aqueous alcohol. (−)-trans-2-*Methyl*cyclo*hexyl* (−)-N-*menthylphthalamate* (III; R = menthyl, R′ = 2-Me-*cyclo*hexyl) (Found : N, 3·6. $C_{25}H_{37}O_3N$ requires N, 3·5%) formed matted fine needles from light petroleum, m. p. 171°, $[\alpha]_D^{18·5°} - 74·0°$ (in chloroform, *c*, 4·7) (10% yield). Hydrolysis of the ester gave (−)-*trans*-2-methyl*cyclo*hexanol, b. p. 90°/15 mm., $\alpha_D^{19°} - 35·5°$ (homogeneous, *l* = 1) (80% recovery, 8% overall yield). Gough, Hunter, and Kenyon (*loc. cit.*) reported $\alpha_D^{20°} - 35·6°$ (homogeneous).

(±)-*trans*-2-Methyl*cyclo*hexyl hydrogen phthalate was also converted into (±)-trans-2-*methyl*cyclo*hexyl* (+)-neo*menthylphthalamate* (Found : N, 3·5%), m. p. 145—151°, $[\alpha]_D + 18·4°$ (in chloroform), in 79% yield, but separation of the diastereoisomeric mixture was also very slow, and was not pursued far.

Resolution of (±)-2-*Butanol.*—(±)-2-Butyl hydrogen phthalate in ether was converted into (±)-2-*butyl* (−)-N-*menthylphthalamate*, m. p. 110—130°, in 82% yield, and the same ester was obtained in 90% yield from (−)-*N*-menthylphthalamic acid in ether and (±)-2-butanol by method (*B*). The mixed ester was recrystallised systematically in 3 fractions, 10 times from aqueous alcohol (85% ; 3 ml./g.) then 13 times from light petroleum (b. p. 80—140° ; 12 ml./g.), resulting in (−)-2-*butyl* (−)-N-*menthylphthalamate* (III; R = menthyl, R′ = 2-Bu) (Found : N, 4·0. $C_{22}H_{33}O_3N$ requires N, 4·0%), b. p. 169·5—170°, $[\alpha]_D^{15°} - 47·6°$ (in chloroform, *c*, 3·5), obtained as small needles in 47% yield.

The ester was hydrolysed, the methyl alcohol separated by an efficient column, the residue steam distilled, the (−)-2-butanol salted out of the distillate with potassium carbonate, and extracted with light petroleum (b. p. 20—40°). Fractionation and redistillation gave a product, b. p. 98—99°, $\alpha_D^{20°} - 10·88°$ (homogeneous, *l* = 1), whence $[\alpha]_D^{20°} - 13·5°$. Pickard and Kenyon (*J.*, 1911, **99**, 45) recorded $[\alpha]_D^{20°} + 13·87°$ for (+)-2-butanol.

Partial Resolution of (±)-α-*Phenylethylamine.*—(−)-Menthyl hydrogen phthalate (Pickard and Littlebury, *J.*, 1912, **101**, 111) was converted into the acid chloride in ether by method (*A*) and coupled with (±)-α-phenylethylamine (Ingersoll, *Org. Synth.*, Coll. Vol. II, 1943, p. 503) giving (−)-*menthyl* (±)-N-α-*phenylethylphthalamate* (III; R = α-phenylethyl, R′ = menthyl) (Found : N, 3·5. $C_{26}H_{33}O_3N$ requires N, 3·4%), m. p. 70—100°, $[\alpha]_D^{26°} - 70°$ (in chloroform), in 85% yield. Recrystallisation from light petroleum or aqueous methyl alcohol caused slow changes in the physical constants, until, when only 10% of the starting material was left, the m. p. appeared to be nearly constant at 127°, $[\alpha]_D^{18·5°} - 51°$ (in chloroform). This material was hydrolysed and the *N*-α-phenylethylphthalamic acid (IV; R = α-phenylethyl) recovered (6·5 g.) was crystallised once from aqueous alcohol to give a sparingly soluble fraction (2·7 g.) and a much more soluble fraction (3·6 g.). On refluxing with hydrazine hydrate (Ing and Manske, *loc. cit.*) for 3 hours, the 2 fractions yielded samples of α-phenylethylamine with $\alpha_D^{20°}$ (homogeneous, *l* = 1) +4° and +18° respectively. Ingersoll (*loc. cit.*, p. 506) gives $[\alpha]_D^{25°} + 39·2°$ to +39·7°. The data of Mann and Watson (*J.*, 1947, 505) suggest that (±)-*N*-α-phenylethylphthalamic acid is much less soluble than the active forms, as is indicated by the above result.

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