325. *The Question of Intramolecular Asymmetric Induction.*

By Alex. McKenzie and Alex. Duthie Wood.

The (—)menthyl and the (—)bornyl ester of 4 : 4′-dinitrodiphenic acid were prepared, and their rotatory powers were contrasted with those of the corresponding esters of *m*-nitrobenzoic acid and phthalic acid. These esters were all lævorotatory in the solvents chosen, and there was no evidence that intramolecular asymmetric induction of 4 : 4′-dinitrodiphenic acid had occurred under the directing influence of the optically active menthyl and bornyl groups. The conclusion is drawn that Kuhn's suggestion of " asymmetrische Umlagerung erster Art " with 4 : 4′-dinitrodiphenic acid under the influence of quinine must remain an open question meantime.

The isomeric optically inactive esters, (+)bornyl (—)bornyl 4 : 4′-dinitrodiphenate and *dl*-bornyl 4 : 4′-dinitrodiphenate, were prepared.

The conception of asymmetric induction as originally put forward by Erlenmeyer has been defined as " die Wirkung einer Kraft, die von asymmetrischen Molekülen ausgehend die Konfiguration veränderlicher Moleküle derart beeinflusst, dass diese aus einer ursprünglich symmetrischen in eine asymmetrische Form übergehen " (Kortüm, " Neuere Forschungen uber die optische Aktivität chemischer Moleküle," Samml. chem. u. chem.-tech. Vorträge, Stuttgart, 1932, 94). Some of the claims made by Erlenmeyer,* as, for example, that cinnamic acid and benzaldehyde were obtained in optically active forms, are based on faulty experimental evidence and cannot be accepted. Nevertheless, the conception, when it is extended to intramolecular change, has proved fruitful as an incentive to research, and interest in it has been revived within recent years, partly as a result of work carried out in this laboratory (McKenzie and Mitchell, *Biochem. Z.*, 1929, **208**, 456, 471; 1930, **221**, 1; 1930, **224**, 242; McKenzie and P. D. Ritchie, *ibid.*, 1931, **231**, 412; 1931, **237**, 1; 1932, **250**, 376; McKenzie, *Z. angew. Chem.*, 1932, **45**, 59; *Chem. and Ind.*, 1932, **10**, 491; Roger and P. D. Ritchie, *Biochem. Z.*, 1932, **253**, 239; Roger, J., 1932, 2168; P. D. Ritchie, " Asymmetric Synthesis and Asymmetric Induction," St. Andrews University Publications XXXVI, Oxford University Press, 1933; Roger and Gow, J., 1934, 130; Roger and McGregor, *ibid.*, p. 1545; McKenzie and Christie, *ibid.*, p. 1070; *Biochem. Z.*, 1935, **277**, 122, 426; McKenzie, *Ergebn. Enzymforsch.*, 1936, **5**, 49; McKenzie and A. Ritchie, *Ber.*, 1937, **70**, 23; Roger, this vol., p. 108).

The definition just given is somewhat restricted, and applies to *intermolecular*

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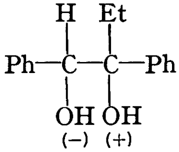
* References are given to Erlenmeyer's papers in the obituary notice (*Ber.*, 1921, **54**, *A*, 107). The question of asymmetric induction is discussed by Ebert and Kortüm (*Ber.*, 1931, **64**, 342).

asymmetric induction, for examples of which very few cases, if indeed any, are available. It is unlikely, for example, that the optical activation of racemic acid by the optically active malic acids (McKenzie, J., 1915, **107**, 440; McKenzie and Walker, J., 1922, **121**, 349; McKenzie, Plenderleith, and Walker, J., 1923, **123**, 2875; McKenzie and Christie, *Biochem. Z.*, 1935, **277**, 122) would come under this category. On the other hand, cases of *intramolecular* asymmetric induction have been accumulating, and the following considerations are adduced to make the meaning of this term clear.

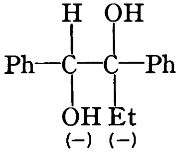
By the action of ethylmagnesium iodide on (—)benzoin, McKenzie and Wren (J., 1910, **97**, 473) obtained a dextrorotatory ethylhydrobenzoin, but the formation of the two diastereoisomerides was indicated :

(I.)



$$\begin{array}{c}\mathrm{H}\quad\mathrm{Et}\\ \mathrm{Ph{-}C{-}C{-}Ph}\\ \mathrm{OH}\;\mathrm{OH}\\ (-)\;(+)\end{array}$$

and

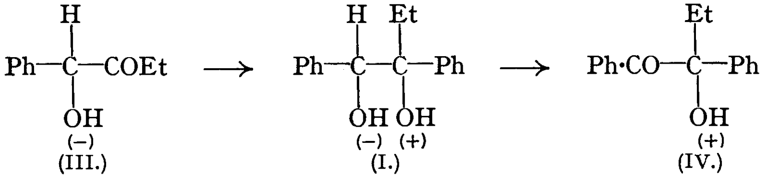


$$\begin{array}{c}\mathrm{H}\quad\mathrm{OH}\\ \mathrm{Ph{-}C{-}C{-}Ph}\\ \mathrm{OH}\;\mathrm{Et}\\ (-)\;(-)\end{array}$$

(II.)

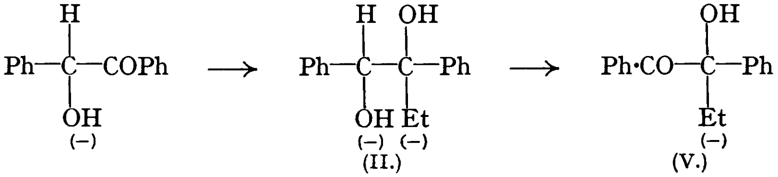
Only one glycol, subsequently designated as the β-form of +)ethylhydrobenzoin, was isolated from this reaction, whereas the α-form was obtained by Roger (*Helv. Chim. Acta*, 1929, **12**, 1060) by the action of phenylmagnesium bromide on (—)phenylpropionylcarbinol (III). It has been shown (Roger, J., 1937, 1048) that the α-form possibly has the structure (I), and that it can be converted into an optically active ethylbenzoin (IV) by solution in ethylmagnesium iodide and addition of benzaldehyde. (IV) is dextrorotatory in ethyl alcohol, and is the antimeride of the compound (V) which had been previously obtained by the action of phenylmagnesium bromide on (—)phenylethylglycollamide (McKenzie and A. Ritchie, *Ber.*, 1937, **70**, 23).

It will be noted that, in the action of phenylmagnesium bromide on (III), a second asymmetric carbon atom had been generated :



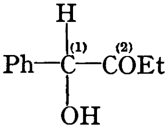
$$\begin{array}{c}\mathrm{H}\\ \mathrm{Ph{-}C{-}COEt}\\ \mathrm{OH}\\ (-)\\ \mathrm{(III.)}\end{array}\longrightarrow\begin{array}{c}\mathrm{H}\quad\mathrm{Et}\\ \mathrm{Ph{-}C{-}C{-}Ph}\\ \mathrm{OH}\;\mathrm{OH}\\ (-)\;(+)\\ \mathrm{(I.)}\end{array}\longrightarrow\begin{array}{c}\mathrm{Et}\\ \mathrm{Ph{\cdot}CO{-}C{-}Ph}\\ \mathrm{OH}\\ (+)\\ \mathrm{(IV.)}\end{array}$$

It is suggested that this new centre of optical activity is due to the carbonyl group in (III) having taken up a dissymetrical environment, and this would provide an example of *intramolecular* asymmetric induction. The extent of optical activity thus induced at the carbonyl group is assumed to be complete, and this activity is communicated to the glycol (I). Similarly, it has been shown (Roger, this vol., p. 108) that the β-form of (+)ethylhydrobenzoin (II) (McKenzie and Wren, *loc. cit.*) can be oxidised to (—)ethylbenzoin (V), so that the following changes can be effected :



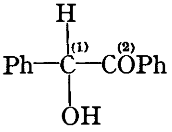
$$\begin{array}{c}\mathrm{H}\\ \mathrm{Ph{-}C{-}COPh}\\ \mathrm{OH}\\ (-)\end{array}\longrightarrow\begin{array}{c}\mathrm{H}\quad\mathrm{OH}\\ \mathrm{Ph{-}C{-}C{-}Ph}\\ \mathrm{OH}\;\mathrm{Et}\\ (-)\;(-)\\ \mathrm{(II.)}\end{array}\longrightarrow\begin{array}{c}\mathrm{OH}\\ \mathrm{Ph{\cdot}CO{-}C{-}Ph}\\ \mathrm{Et}\\ (-)\\ \mathrm{(V.)}\end{array}$$

In the optically active compounds



$$\begin{array}{c}\mathrm{H}\\ \mathrm{Ph{-}\overset{(1)}{C}{-}\overset{(2)}{C}OEt}\\ \mathrm{OH}\end{array}$$

and



$$\begin{array}{c}\mathrm{H}\\ \mathrm{Ph{-}\overset{(1)}{C}{-}\overset{(2)}{C}OPh}\\ \mathrm{OH}\end{array}$$

the inducing centre (1) is directly linked to the induced centre (2), and the effect produced by intramolecular asymmetric induction is suggested as being at a maximum.

Roger designates the conversion of (—)phenylpropionylcarbinol into (IV) and of (—)benzoin into (V) as examples of a " unilateral internal asymmetric synthesis." Also, Kenyon and Partridge (J., 1936, 1313) describe as an " asymmetric synthesis of a new type " the formation of (+)methyl αβ-dibromo-*n*-propyl ketone by the changes :

$$(-)CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}CH_3 \longrightarrow (+)CH_3{\cdot}CH(OH){\cdot}CHBr{\cdot}CHBr{\cdot}CH_3$$
$$\longrightarrow (+)CH_3{\cdot}CO{\cdot}CHBr{\cdot}CHBr{\cdot}CH_3$$

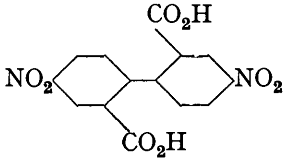
It must, however, be emphasised that in both of those cases where intramolecular asymmetric induction is possibly involved, the authors did not realise an asymmetric synthesis in the sense of the term as originated by Emil Fischer, Marckwald, and McKenzie (compare McKenzie and Walker, J., 1922, **121**, 350; McKenzie and Mitchell, *Biochem. Z.*, 1929, **208**, 460; McKenzie and Christie, J., 1934, 1070; McKenzie, *Ergebn. Enzymforsch.*, *loc. cit.*), who employ the term to distinguish it from " total (or absolute) asymmetric synthesis " carried out by physical asymmetric directing influences.

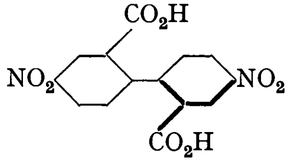
In this connexion it may be recalled that Fischer showed that, whilst mannose by the cyanohydrin reaction can theoretically yield both α- and β-mannoheptose, in practice only one of those isomerides was obtained. Similarly, only one manno-octose was isolated from this synthetic mannoheptose, and only one mannononose from the manno-octose. But it is forgotten by some authors that Fischer never designated those results as exemplifying asymmetric syntheses. They may, however, be regarded as providing examples of intramolecular asymmetric induction on the terminal aldehyde group. It may also be noted that the suggestion has been made, although with considerable reserve, that the asymmetric synthesis of, for example, (—)atrolactinic acid from (—)menthyl benzoylformate (McKenzie, J., 1904, **85**, 1249) provides in an intermediate phase of the synthesis an example of intramolecular asymmetric induction, if the carbonyl group in the α-position in (—)menthyl benzoylformate assumes a dissymmetrical environment giving rise to a mixture of the two esters,

$$C_6H_5{\cdot}\underset{(-)}{CO}{\cdot}CO{\cdot}O{\cdot}\underset{(-)}{C_{10}H_{19}} \quad \text{and} \quad C_6H_5{\cdot}\underset{(+)}{CO}{\cdot}CO{\cdot}O{\cdot}\underset{(-)}{C_{10}H_{19}}$$

in unequal amounts and containing a preponderance of the former.

As a consequence of our work in this field we have been led to study the work of Kuhn and Albrecht (*Annalen*, 1927, **455**, 272; compare also Bell and Robinson, J., 1927, 2234), who describe an abnormal effect with 4 : 4′-dinitrodiphenic acid. Those authors found that the quinine salt of this acid was deposited from an alcoholic solution, in a yield of over 80%, and that it was strongly *dextrorotatory*, giving $[\alpha]_{5893}$ + 108° in chloroform solution, whereas quinine itself is lævorotatory with $[\alpha]_{5893}$ — 177° under similar conditions. This result is in contrast with the optical behaviour of the quinine salts of phthalic and of *m*-nitrobenzoic acids, which are both lævorotatory and show no abnormality. The quinine salt of 4 : 4′-dinitrodiphenic acid is regarded by Kuhn and Albrecht as a homogeneous salt of the activated acid, and when the quinine was eliminated from the salt, racemisation was supposed to take place owing to the removal of groups which acted as obstacles to the free rotation of the benzene nuclei.





In a later paper (Kuhn, *Ber.*, 1932, **65**, 49) the abnormal rotatory power of the quinine salt is interpreted on the idea that complete transformation into one form of the two possible diastereoisomerides had occurred by the directing influence of the optically active quinine, and this is described by Kuhn as affording an example of " asymmetrische

Umlagerung erster Art." It is possible that we have here to deal with an example of intramolecular asymmetric induction.

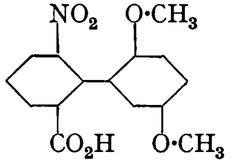
It was thought by us that an examination of the optically active menthyl and bornyl esters of 4 : 4′-dinitrodiphenic acid might give results in confirmation of Kuhn's suggestions. It appeared conceivable that the introduction of the heavy menthyl or bornyl group in place of the hydrogen atoms of the carboxyl groups might cause interference with the ortho-hydrogen atoms in the benzene nuclei, so that free rotation could not occur. It therefore seemed possible that intramolecular asymmetric induction might occur, and that evidence of this might be obtained, if the solutions of the esters were dextrorotatory and would resemble (—)menthyl benzoylformate in exhibiting mutarotation.

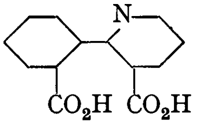
Both the acid and the normal (—)menthyl and (—)bornyl esters were accordingly prepared. A striking difference was observed in the rate of esterification of the acid with (—)borneol as compared with that with (—)menthol. Whilst a good yield of the bornyl ester was obtained by the usual procedure, the main product in the case of (—)menthol was the *acid* ester where the normal ester was expected (see experimental section). The esters were all *lævorotatory*, the normal esters having in each case a higher rotatory power than the acid esters. In no case was mutarotation observed, and the acid obtained from the saponification of the esters was optically inactive. For comparison, (—)menthyl *m*-nitrobenzoate, (—)dimenthyl phthalate, *(—)bornyl* m-*nitrobenzoate*, and (—)dibornyl phthalate were also examined. They were also all lævorotatory. There was thus no evidence that intramolecular asymmetric induction of 4 : 4′-dinitrodiphenic acid had occurred under the directing influence of the optically active menthyl and bornyl groups. But on the other hand the possibility that such an induction had occurred is not entirely excluded.

It had previously been found in this laboratory that, with esters of the type of (—)menthyl benzoylformate, mutarotation was accelerated by the presence of traces of catalysts. In the cases now examined, the failure to detect mutarotation may have been due to the presence of some unknown catalyst which may have caused the final stage of the induction to be reached almost instantaneously. On the other hand, it may be due to the complete absence of a suitable catalyst, so that mutarotation would proceed at an imperceptible speed.

With acids of the diphenyl group which can be isolated in optically active forms, occasional observations have been made, particularly by Adams, that their alkaloidal salts can definitely exhibit mutarotation, for example, with the brucine salt of 2′-nitro-2 : 5-dimethoxydiphenyl-6′-carboxylic acid (VI) (*J. Amer. Chem. Soc.*, 1932, **54**, 2966) :

(VI.)





(VII.)

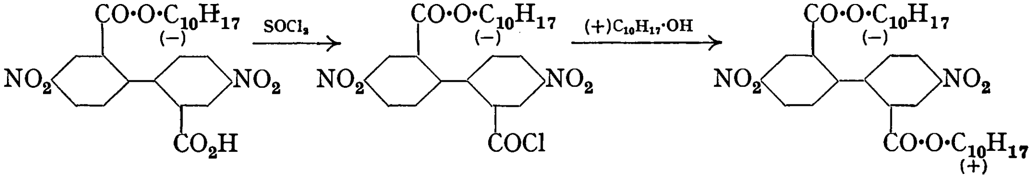
On the other hand, with some acids which are supposed to racemise so easily that they have not been isolated in an optically active form, the evidence cannot meantime be accepted as definite that their alkaloidal salts exhibit mutarotation. Thus, the salts of 2-phenylpyridine-2′ : 3-dicarboxylic acid (VII) with quinine, quinidine, cinchonine and cinchonidine are reported to exhibit mutarotation (Breckenridge and Smith, *Canadian J. Res.*, 1938, **16**, *B*, 109), although details are given for the quinidine salt only. The slight change in optical rotatory power in the latter case may have been due to sufficient precautions not having been taken to regulate the temperature conditions, and it is significant that data regarding temperature are not recorded. In this connexion the possibility of mutarotation occurring with quinine diphenate (Lesslie and Turner, J., 1934, 347) has been carefully examined in this laboratory, and the results will be published soon.

Kuhn and Albrecht (*loc. cit.*) found that the cinchonidine salt of 4 : 4′-dinitrodiphenic acid was strongly dextrorotatory, whereas cinchonidine itself is lævorotatory. We find that the quinine acid salt also is dextrorotatory, although not so markedly so as is the normal salt. The cinchonine salt is strongly lævorotatory, giving in chloroform $[\alpha]_{5893}^{18°}$ $-$ 153·1°, whereas cinchonine is dextrorotatory. The quinidine salt also is lævorotatory, giving in chloroform $[\alpha]_{5893}^{20·2°}$ $-$ 85·8°, whereas quinidine is dextrorotatory. It is perhaps significant that the salts of 4 : 4′-dinitrodiphenic acid with quinine, quinidine, cinchonine and cinchonidine possess rotations of the opposite signs to those of the alkaloids themselves. Similarly, Lesslie and Turner (*loc. cit.*) have observed that both quinine diphenate and cinchonidine diphenate are dextrorotatory whilst cinchonine diphenate and quinidine diphenate are lævorotatory.

The conclusion arrived at by Kuhn and Albrecht that the high dextrorotation of the quinine salt provides evidence of labile optical isomerism is criticised adversely by Hyde and Adams (*J. Amer. Chem. Soc.*, 1928, **50**, 2499; compare Kharasch, Senior, Stanger, and Chenicek, *ibid.*, 1934, **56**, 1646), who lay emphasis on the work of Hilditch (J., 1908, **93**, 1388; 1909, **95**, 331, 1570; 1911, **99**, 224). The last author observed anomalous effects on the rotatory power in the case of salts of various alkaloids with acids which cannot by any possible means be resolved into optical antimerides; thus, if there are conjugated systems close to the optically active centre of the molecule, the rotatory power is markedly influenced, whilst the nature of the groups, especially in the ortho-position, may induce anomalous rotations. We have confirmed the high dextrorotation of the quinine salt of 4 : 4′-dinitrodiphenic acid, and also the high yield of the salt noted by Kuhn and Albrecht. We find, however, that the rotatory power of the salt drops from $[\alpha]_{5893}$ + 102·4° to + 84·2° in chloroform, when the salt is crystallised from a mixture of chloroform and benzene. This observation cannot be attributed to partial racemisation of the salt, since free rotation round the central bond would presumably (if the interpretation of Kuhn and Albrecht is accepted) be prevented by the presence of the quinine, and the diastereoisomerides could only be formed by free rotation. The fall of rotatory power appeared to be due to the salt with the lower rotation containing benzene of crystallisation.

We therefore came to the conclusion that Kuhn's interesting suggestion of " asymmetrische Umlagerung erster Art " with 4 : 4′-dinitrodiphenic acid must remain an open question until further experimental evidence in its favour has been submitted. If the suggestion is correct, it is curious that abnormalities in rotatory power were lacking with the menthyl and bornyl esters which we have studied.

Arising from the work on the isomeric *optically inactive* bornyl fumarates (McKenzie and Abbot, J., 1934, 711; compare Abbot, McKenzie, and Ross, *Ber.*, 1937, **70**, 163; Abbot, Christie, and McKenzie, *Ber.*, 1938, **71**, 9; Abbot, McKenzie and Ross, *ibid.*, p. 16) we have prepared (+)*bornyl* (—)*bornyl* 4 : 4′-*dinitrodiphenate* according to the scheme :



This optically inactive ester melts at 212—213°, whereas the isomeric optically inactive *dl*-bornyl 4 : 4′-dinitrodiphenate, prepared by mixing equal quantities of (+)dibornyl 4 : 4′-dinitrodiphenate and (—)dibornyl 4 : 4′-dinitrodiphenate, melts at 200—201°. If in the preparation of (—)monobornyl 4 : 4′-dinitrodiphenate the assumption is made that intramolecular induction had occurred, then the optical activity of the ester would be due to two sources, (1) the optical activity of the (—)bornyl group and (2) the induced optical activity of the diphenyl group. In the event of the bornyl group being large enough to prevent free rotation about the central bond, the induced optical activity would be fixed, and, so long as the bornyl group is not removed, the optical activity could be neither increased nor decreased. When the (—)monobornyl ester is esterified by (+)borneol, the product would be (+)bornyl (—)bornyl 4 : 4′-dinitrodiphenate, and the optical activity due to the (+)bornyl group in the molecule would be neutralised exactly by that produced by the (—)bornyl group. If, therefore, the (+)bornyl (—)bornyl ester had shown any optical activity, this activity would be attributed to intramolecular asymmetric induction.

Since, on the other hand, the (+)bornyl (−)bornyl ester is optically inactive, we draw the conclusion that no intramolecular asymmetric induction had been brought about in the formation of the original monobornyl (−)ester.

In the event of the (−)menthyl or the (−)bornyl group exercising a blocking effect, it is possible that when 4 : 4′-dinitrodiphenic acid is esterified either by (−)menthol or by (−)borneol, a mixture of diastereoisomeric esters would be formed in each case, and such a mixture might be separable by fractional crystallisation. We encountered little evidence for this during the actual crystallisations. Nevertheless, a resolution may have taken place with the isolation of an ester either of the (+) or of the (−) acid, or the esters described (which are definite individuals and not mixtures) may be " partially racemic " compounds which, like (−)menthyl *r*-mandelate, cannot be separated into diastereoisomerides under the temperature conditions employed.

Some slight evidence, however, although not convincing, was afforded for the formation of diastereoisomerides. From the principle of Marckwald and McKenzie it follows that, if diastereoisomerides were formed during the esterification, they would be produced at different rates, and incomplete esterification would give a product with an optical rotatory power which would vary according to the extent of the esterification. Thus, when approximately half of the original acid was recovered unesterified by (−)borneol, the product (*a*) after one crystallisation had $[\alpha]_D - 26°$ ($c = 1{\cdot}7875$) in chloroform, whereas, when approximately one fifth of the acid was recovered, the product (*b*) after one crystallisation had $[\alpha]_D - 37°$ ($c = 1{\cdot}349$), the homogeneous ester having $[\alpha]_D - 41°$. When less than one twentieth of the original acid was recovered, the dibornyl ester (*c*) after one crystallisation was homogeneous with $[\alpha]_{5461} - 47{\cdot}2°$. Again, the solubilities of those various products (*a*), (*b*), and (*c*) differed in ethyl alcohol, (*a*) being rather easily soluble and (*c*) soluble with difficulty. (*c*) is a single individual, whilst (*a*) is perhaps a mixture of diastereoisomerides. If (*c*) is regarded as the ester of the (−)acid, (*a*) may contain some ester of the (+)acid.

EXPERIMENTAL.

Esterification of 4 : 4′-*Dinitrodiphenic Acid with* (−)*Menthol.*—The acid, m. p. 255—256°, was prepared by the oxidation of 2 : 7-dinitrophenanthraquinone (Schmidt and Kämpf, *Ber.*, 1903, **36**, 3738).

A mixture of the acid (10 g.) and (−)menthol (40 g.) was heated at 130° for 13 hours whilst hydrogen chloride was passed in at intervals. An ethereal solution of the product was washed with a concentrated solution of sodium bicarbonate. The aqueous solution was acidified by hydrochloric acid, and the precipitated solid crystallised from aqueous alcohol, 4 g. of unesterified acid being recovered. The ethereal solution was then washed three times with concentrated caustic soda solution, but from the aqueous solution only 0·2 g. of the acid ester was obtained. The ether and menthol were then removed from the ethereal solution by distillation in a current of steam. The residual solid was dried, dissolved in benzene, and the solution decolorised by charcoal. The addition of light petroleum (b. p. 40—60°) to the benzene solution caused the deposition of a solid (A), which was crystallised from benzene–light petroleum. Yield, 4 g. It is remarkable that this product was the acid ester and not the normal ester, and that it had not been removed by the treatment with caustic soda mentioned above.

(−)*Monomenthyl* 4 : 4′-*dinitrodiphenate* is an amorphous solid, m. p. 166—167° (Found : C, 61·1; H, 5·5; N, 6·2. $C_{24}H_{26}O_8N_2$ requires C, 61·2; H, 5·6; N, 6·0%).

No definite mutarotation was observed in ethyl-alcoholic solution. Attempts to obtain from this acid ester either a quinine salt or a salt of α-phenylethylamine were unsuccessful. On saponification with alcoholic potash the ester gave 4 : 4′-dinitrodiphenic acid, which was optically inactive in chloroform solution.

The mother-liquor from which solid (A) had separated gave on evaporation a viscous oil (3·8 g.), from which the normal ester was obtained in small amount by extraction with light petroleum–benzene and finally crystallised from aqueous methyl alcohol.

(−)*Dimenthyl* 4 : 4′-*dinitrodiphenate* separated from aqueous methyl alcohol as an amorphous solid, m. p. 61—62° (Found : C, 66·9; H, 7·2. $C_{34}H_{44}O_8N_2$ requires C, 67·1; H, 7·3%).

In a second esterification carried out by heating 15 g. of the acid with 60 g. of (−)menthol at 130° for 16 hours, the treatment with caustic soda adopted in the preceding preparation was omitted; 8·5 g. of the acid ester and 1·8 g. of the normal ester were obtained. When the heating of the acid with menthol was prolonged for 27 hours, the proportion of normal ester was increased; thus, from 11 g. of the acid and 44 g. of (—)menthol, 5·7 g. of the acid ester and 3·1 g. of the normal ester were obtained.

No mutarotation was detected, the rotatory power being constant after 40 days.

Saponification gave the optically inactive acid.

The dimenthyl ester was also synthesised as follows: (1) The monomenthyl ester was converted by means of thionyl chloride into its acid chloride, which was then heated at 185° for 15 minutes with (—)menthol to give the dimenthyl ester.

(2) 4 : 4′-Dinitrodiphenic acid (6·7 g.) was heated for 8 hours with thionyl chloride (175 g.) and pyridine (5 c.c.). The dichloride (6·4 g.) of 4 : 4′-dinitrodiphenic acid separated from benzene in crystals, m. p. 137°. 5·6 G. of the latter were heated with 12 g. of (—)menthol at 175° for 1 hour; the yield of pure dimenthyl ester was 3·1 g.

The latter ester, with which no mutarotation was detected, was saponified by alcoholic potash, and gave 4 : 4′-dinitrodiphenic acid, which in chloroform solution was optically inactive.

We prepared (—)menthyl *m*-nitrobenzoate (Cohen and Armes, J., 1905, **87**, 1190), b. p. 184°/2·4 mm., and (—)dimenthyl phthalate (Arth, *Ann. Chim. Phys.*, 1885, **7**, 485), m. p. 132°, and determined their rotations in ethyl alcohol, chloroform and benzene. The comparison of their rotatory powers with those of the esters of 4 : 4′-dinitrodiphenic acid is given in Table I.

TABLE I.

Ester.	Solvent.	*l*.	*c*.	$\alpha_D^{20°}$.	$[\alpha]_D^{20°}$.	$\alpha_{5461}^{20°}$.	$[\alpha]_{5461}^{20°}$.
(—)Monomenthyl 4 : 4′-dinitrodiphenate	Ethyl alcohol	2	1·04	—1·16°	— 55·8°	—1·31°	— 63°
	Chloroform	2	0·6768	—0·79	— 58·4	—0·87	— 64·3
	Benzene	2	0·598	—0·71	— 59·4	—0·78	— 65·2
(—)Dimenthyl 4 : 4′-dinitrodiphenate	Ethyl alcohol	2	0·7964	—	—	—1·43	— 89·8
		2	0·5676	—0·84	— 74	—	—
	Chloroform	2	0·734	—1·15	— 78·3	—1·40	— 95·4
	Benzene	2	0·8668	—1·45	— 83·6	—1·67	— 96·3
(—)Menthyl *m*-nitrobenzoate	Ethyl alcohol	2	1·4024	—2·28	— 81·3	—2·67	— 95·2
	Chloroform	2	1·5224	—2·55	— 83·7	—3·02	— 99·2
	Benzene	2	2·0815	—3·61	— 86·7	—4·22	—101·4
(—)Dimenthyl phthalate	Ethyl alcohol	2	0·5212	—1·01	— 96·9	—1·24	—119·0
	Chloroform	2	1·6032	—3·06	— 95·4	—3·65	—113·8
	Benzene	2	1·9815	—3·80	— 95·9	—	—
(—)Monomenthyl phthalate	Chloroform		—	—	— 91·4 *		
	Benzene		—	—	—107·5 †		

* Pickard and Littlebury, J., 1912, **101**, 109.

† Paoloni, *Atti R. Accad. Lincei*, 1919, **28**, II, 237.

Esterification of 4 : 4′-*Dinitrodiphenic Acid with* (—)*Borneol.*—A mixture of the acid (16 g.) and (—)borneol (48 g.) was heated at 165—175° for 18 hours, a current of dry hydrogen chloride being passed in at intervals. An ethereal solution of the product was washed with sodium bicarbonate solution, the aqueous solution being then separated and acidified by hydrochloric acid. The precipitated solid was crystallised from aqueous alcohol; 4 g. of 4 : 4′-dinitrodiphenic acid were isolated, but none of the acid ester was obtained.

The ethereal solution from which the acid had been obtained as just described was then evaporated, and the residue distilled in a current of steam to remove the excess of (—)borneol. The residual semi-solid was dissolved in benzene, the solution decolorised by charcoal, the bulk of the benzene evaporated, and light petroleum (b. p. 40—60°) added in excess. After two crystallisations from benzene–light petroleum and two further crystallisations from ethyl alcohol, the product (10·9 g.) was homogeneous. The ester was also prepared by the action of (—)borneol on the dichloride of 4 : 4′-dinitrodiphenic acid.

(—)*Dibornyl* 4 : 4′-*dinitrodiphenate* crystallised in rectangular plates, m. p. 201—202° (Found: C, 67·7; H, 6·7; N, 5·0. $C_{34}H_{40}O_8N_2$ requires C, 67·5; H, 6·7; N, 4·6%). In acetone ($l = 2$, $c = 1·434$): $\alpha_D^{20°}$ — 1·15°, $[\alpha]_D^{20°}$ — 40°; $\alpha_{5461}^{20°}$ — 1·38°, $[\alpha]_{5461}^{20°}$ — 48·1°.

A solution of this ester (10·9 g.) in aqueous alcohol was saponified with half the amount of caustic potash necessary for complete saponification; heating on the water-bath was conducted for 40 minutes until the solution was neutral to litmus. The alcohol was distilled off, and the residual oil stirred with ether. The solid which separated was washed thoroughly with ether.

It was then shaken with ether and dilute hydrochloric acid, in which it dissolved slowly. The ethereal solution was separated and dried over sodium sulphate, and the ether expelled. The resulting viscous oil was dissolved in hot benzene–light petroleum. The deposited solid was recrystallised from benzene–light petroleum. Yield, 4·1 g.

(—)*Monobornyl* 4 : 4′-*dinitrodiphenate* was obtained as an amorphous powder, m. p. 178—179° (Found : C, 61·9; H, 5·2; N, 6·0. $C_{24}H_{24}O_8N_2$ requires, C, 61·5; H, 5·2; N, 6·0%).

For comparison with the above esters in rotatory power, (—)*bornyl* m-*nitrobenzoate* was prepared by esterifying *m*-nitrobenzoic acid with (—)borneol by heating for 12 hours in the presence of hydrogen chloride. This ester crystallised from light petroleum in needles, m. p. 76—77° (Found : C, 67·2; H, 7·1; N, 4·8. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0; N, 4·6%).

(—)Dibornyl phthalate was prepared from phthalic anhydride and (—)borneol. It crystallised from ethyl alcohol in prisms, m. p. 104—105° (Found : C, 76·8; H, 8·7. Calc. for $C_{28}H_{38}O_4$: C, 76·7; H, 8·7%). Haller (*Compt. rend.*, 1889, **108**, 456) gives m. p. 101·1°.

The rotatory powers in the various solvents of the two bornyl esters described are given in Table II for comparison with those of (—)bornyl *m*-nitrobenzoate and (—)dibornyl phthalate. (—)Monobornyl 4 : 4′-dinitrodiphenate is very sparingly soluble in ethyl alcohol and its rotatory power was accordingly not determined in that solvent.

TABLE II.

Ester.	Solvent.	*l*.	*c*.	$\alpha_{D}^{20^\circ}$.	$[\alpha]_{D}^{20^\circ}$.	$\alpha_{5461}^{20^\circ}$.	$[\alpha]_{5461}^{20^\circ}$.
(—)Monobornyl 4 : 4′-dinitrodiphenate	Chloroform	2	2·1292	—1·23°	—28·9°	—1·42°	—33·3°
	Benzene	2	1·62	—0·81	—25	—0·96	—29·6
(—)Dibornyl 4 : 4′-dinitrodiphenate	Ethyl alcohol	2	0·2132	—0·20	—46·9	—0·24	—56·3
	Chloroform	2	1	—0·83	—41·5	—0·96	—48
	Benzene	2	0·533	—0·35	—32·8	—0·44	—41·3
(—)Bornyl *m*-nitrobenzoate	Ethyl alcohol	2	0·7284	—0·53	—36·4	—0·63	—43·2
	Chloroform	2	1·2475	—0·92	—36·9	—1·06	—42·5
	Benzene	2	2·0045	—1·31	—32·7	—	—
(—)Dibornyl phthalate	Ethyl alcohol	2	0·4582	—0·76	—82·9	—0·89	—97·1
	Chloroform	2	2	—2·71	—67·8	—3·23	—80·8
	Benzene	2	2·1695	—2·80	—64·5		
(—)Monobornyl phthalate	Ethyl alcohol				—58·3 *		
	Benzene				—42·72 †		

* Haller, *loc. cit.*

† Kenyon and Pickard, J., 1915, **107**, 35, give +42·72° for the (+)ester.

Alkaloidal Salts of 4 : 4′-*Dinitrodiphenic Acid.*—A mixture of the acid (6 g.) and cinchonine (13·2 g.) was heated with rectified spirit (1050 c.c.) for 1 hour. On cooling, cinchonine 4 : 4′-dinitrodiphenate (6 g.) separated in needles, which, after drying at the ordinary temperature under diminished pressure, gave in chloroform ($l = 2, c = 4{\cdot}0135$) : $\alpha_{D}^{18^\circ} - 12{\cdot}29^\circ$, $[\alpha]_{D}^{18^\circ} - 153{\cdot}1^\circ$; $\alpha_{5461}^{18^\circ} - 14{\cdot}84^\circ$, $[\alpha]_{5461}^{18^\circ} - 184{\cdot}9^\circ$. After recrystallisation from chloroform–ethyl alcohol it had $[\alpha]_{5461}^{20^\circ} - 183{\cdot}9^\circ$ ($c = 4{\cdot}001$). Crystals (1·5 g.) quickly separated from the mother-liquor from which the above 6 g. had been withdrawn, and these crystals had $[\alpha]_{5461}^{18^\circ} - 184{\cdot}5^\circ$ ($c = 4{\cdot}029$). From the filtrate after a few days 4·2 g. were removed and this gave $[\alpha]_{5461}^{20^\circ} - 185{\cdot}6^\circ$ ($c = 4{\cdot}025$) and m. p. 220—221°. No mutarotation was detected. The quinidine salt of 4 : 4′-dinitrodiphenic acid was obtained by heating a solution of the acid (2 g.) in ethyl alcohol (40 c.c.) with quinidine (4 g.). The crystals (5·2 g.), after being dried at 100° under diminished pressure, gave in chloroform ($l = 2$, $c = 2{\cdot}0445$) : $\alpha_{D}^{20{\cdot}2^\circ} - 3{\cdot}51^\circ$, $[\alpha]_{D}^{20{\cdot}2^\circ} - 85{\cdot}8^\circ$. After recrystallisation from chloroform–ethyl alcohol, the rotatory power in chloroform was $[\alpha]_{D}^{20{\cdot}5^\circ} - 87^\circ$ ($c = 2{\cdot}1325$).

The acid quinine salt of 4 : 4′-dinitrodiphenic acid was prepared by boiling the acid (2 g.) with ethyl alcohol (50 c.c.) and then adding a solution of quinine hydrate (2·3 g.) in ethyl alcohol (20 c.c.). The salt separated in rosettes of needles, m. p. 195—196°, and gave in a mixture of equal volumes of ethyl alcohol and chloroform ($l = 2$, $c = 1{\cdot}0185$) : $\alpha_{D}^{20{\cdot}7^\circ} + 0{\cdot}95^\circ$, $[\alpha]_{D}^{20{\cdot}7^\circ} + 46{\cdot}6^\circ$; $\alpha_{5461}^{20^\circ} + 1{\cdot}13^\circ$, $[\alpha]_{5461}^{20^\circ} + 55{\cdot}5^\circ$. There was no evidence of mutarotation having occurred with this solution after an interval of 10 days. The optical activity of the salt remained unaltered after recrystallisation.

A hot solution of 8 g. of 4 : 4′-dinitrodiphenic acid (1 mol.) in ethyl alcohol (200 c.c.) was mixed with a hot solution of 18·4 g. of quinine (2 mols.) in ethyl alcohol (160 c.c.). The crystals which separated on cooling were filtered off, washed with alcohol, and dried under reduced pressure at the ordinary temperature until constant in weight. The 21·6 g. (A) thus obtained had m. p. 229—231° (decomp.) and gave in chloroform $[\alpha]_{D}^{21^\circ}$ + 102·4°, $[\alpha]_{5461}^{21^\circ}$ + 119·6° (c = 1·998). On allowing the filtrate from this crop to remain at the ordinary temperature for 36 hours, a further deposition of crystals (1·5 g.) took place; these had m. p. 226—227° (decomp.), and gave in chloroform $[\alpha]_{D}^{20^\circ}$ + 108·5°, $[\alpha]_{5461}^{20^\circ}$ + 128·5° (c = 2·0084). (A) was crystallised three times from benzene–chloroform, the rotatory power of successive crops being $[\alpha]_{D}^{19^\circ}$ + 84·2° (c = 2·0016), $[\alpha]_{D}^{19^\circ}$ + 84·7° (c = 2·0012), and $[\alpha]_{D}^{20^\circ}$ + 85·2° (c = 2·001) in chloroform.

In a second experiment, carried out with 6 g. of the acid and 13·8 g. of quinine under similar conditions, the 13 g. of salt which separated on cooling were crystallised from a mixture of chloroform (120 c.c.) and benzene (120 c.c.). The crystals (B) which separated (6·1 g.) gave $[\alpha]_{D}^{19^\circ}$ + 87·9° (c = 2·001) in chloroform; the value of the crystals (2·2 g.) after two further crystallisations was practically identical, namely, $[\alpha]_{D}^{20^\circ}$ + 87·2° (c = 2·0015). A portion of (B) which had been crystallised from chloroform–benzene remained constant in weight when kept under diminished pressure over paraffin wax for 4 days. On heating, however, under diminished pressure at 100°, the loss in weight corresponded to a compound containing 1 mol. of the salt and 2 mols. of benzene. The rotation of the salt dried in this manner had risen to $[\alpha]_{D}^{20^\circ}$ +101° (c = 3·02).

The Isomeric Optically Inactive Bornyl 4 : 4′-*Dinitrodiphenates*.—(—)Monobornyl 4 : 4′-dinitrodiphenate (5·1 g.) was heated under reflux with thionyl chloride for 1 hour, and the excess of the thionyl chloride removed in a vacuum over caustic soda. The residual oil gradually solidified; the product was then triturated with benzene–light petroleum, and the *acid chloride* of (—)monobornyl 4 : 4′-dinitrodiphenate drained off. Yield, 4·1 g.; m. p. 48—49° (Found : C, 59·3; H, 5·0; N, 5·7. $C_{24}H_{23}O_7N_2Cl$ requires C, 59·2; H, 4·8; N, 5·8%).

A solution of this acid chloride (4·3 g.) in benzene (15 c.c.) was slowly added to a solution of optically pure (+)borneol (1·4 g.) in a mixture of benzene (10 c.c.) and pyridine (1·1 g.). After heating on the steam-bath for 30 minutes, the product was distilled in steam, the residue extracted with ether, the extract washed with sodium bicarbonate solution, and the product obtained from it crystallised from ethyl alcohol. The crystals (1·3 g.) were slightly lævorotatory in chloroform solution, giving $[\alpha]_{5461}^{20^\circ}$ — 6·6° (c = 2·4125). They were boiled with ether, the solution removed from undissolved residue, and this treatment was repeated twice. The residue (0·3 g.) was then optically inactive when dissolved in chloroform. (+)*Bornyl* (—)*bornyl* 4 : 4′-*dinitrodiphenate* crystallised from ethyl alcohol in rhombic prisms, m. p. 212—213° (Found : C, 67·3; H, 6·3. $C_{34}H_{40}O_8N_2$ requires C, 67·5; H, 6·7%).

(+)Dibornyl 4 : 4′-dinitrodiphenate, prepared from 4 : 4′-dinitrodiphenic acid by esterification with optically pure (+)borneol, crystallised in plates, m. p. 200—201°. In chloroform (l = 2, c = 0·86) : $\alpha_{5461}^{20^\circ}$ + 0·82°, $[\alpha]_{5461}^{20^\circ}$ + 47·7°. This value agrees with that found for the antimeride, namely, $[\alpha]_{5461}^{20^\circ}$ — 48°.

dl-*Dibornyl* 4 : 4′-*dinitrodiphenate*. A mixture of (+)dibornyl 4 : 4′-dinitrodiphenate (0·222 g.) and (—)dibornyl 4 : 4′-dinitrodiphenate (0·222 g.) was dissolved in chloroform, and the solvent evaporated. The residue was crystallised once from ethyl alcohol. *dl*-Dibornyl 4 : 4′-dinitrodiphenate melted at 200—201°. The mixture of it with the isomeric (+)bornyl (—)bornyl 4 : 4′-dinitrodiphenate melted indefinitely.

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