Tetrahedron. Vol 25. pp 2301 to 2311. Pergamon Press 1969. Printed in Great Britain

ABSOLUTE CONFIGURATIONS OF SOME 1,2-DIPHENYLETHANE DERIVATIVES[1]

N. D. BEROVA and B. J. KURTEV

Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria

(*Received in the UK* 3 *December* 1968; *Accepted for publication* 1 *January* 1969)

Abstract—The absolute configurations of two series of genetically related compounds with a general formula PhCH(X) – CH(Y)Ph are determined by chemical correlation with 2,3-diphenylpropanoic acid (V). It is demonstrated that all threo-isomers of absolute configuration *A* are laevorotatory and reasons are given that this is due to conformational asymmetry.

IN A previous paper[2] we reported that the reaction of hydrobenzamide with (−)-menthylphenyl acetate in presence of anhydrous aluminum chloride yields a mixture of the (−)-menthyl esters of the four 3-amino-2,3-diphenyl propanoic acids (I). These were successfully resolved in an optically pure state. Reduction of the esters with LAH gave two pairs of 3-amino-2,3-diphenyl-1-propanols (II), which on mixing yielded the racemates already described.[3] The assignment of the latter to one of the two steric series (erythro or threo) has been carried out by a number of independent methods.[3–5] The racemates and the optically active aminopropanols, on reaction with phosgene or *p*-nitrobenzaldehyde, gave 2-oxo- and 2-*p*-nitrophenyl-4,5-diphenyltetrahydro-1,2-oxazines, respectively.[6]

The preferred conformations of the above compounds were studied by NMR.[7] The data obtained allowed also the assignment of their absolute configurations[8] by means of Brewster's method of calculating optical rotations. The present study was undertaken with the view of correlating, by chemical means, the absolute configurations of the compounds mentioned above and some other 1,2-diphenylethane derivatives with the configuration of 2,3-diphenylpropanoic acid (V). It should also serve in substantiating experimentally the conclusions made by Fodor *et al.*[8] and could be useful in some further investigations of the relationship between configuration, conformation, and optical activity.

The absolute configuration of the standard compound chosen has reliably been assigned by several different methods. Pettersson was the first to show that (+)-V and (S)-(+)-2-phenylpropanoic acid are of like configuration, by applying the quasi-racemate method.[9] Sullivan *et al.*[10] determined the configuration of the methyl ester of (+)-2,3-diphenylpropanoic acid, (+)-VI, converting it into a partially racemized (+)-1,2-diphenyl propane whose configuration had been established earlier.[11] We obtained the same ester by esterification of (+)-2,3-diphenylpropanoic acid with diazomethane, thus confirming the conclusions made by Pettersson[9] and Sullivan *et al.*[10]

During the course of the present study, new evidence appeared in the literature concerning the absolute configuration of the (S)-(+)-V acid. Watson and Youngson[12] have correlated it chemically in a very conclusive manner with (−)-2-phenylpropanoic

acid, converting both acids into one and the same (+)-1,2-diphenylpropane of undoubtedly the highest optical purity. Cervinka and Hub have applied conversions analogous to Watson and Youngson[12] and compounds with rather low optical purity to correlate (S)-(+)-V again with (+)-1,2-diphenylpropane, whose configuration they further correlated with (S)-(+)-alanine.[13]

Primarily our problem was to investigate the (−)-menthylesters of the 3-amino-2,3-diphenylpropanoic acids (I, Table 1). The knowledge of their relative configurations made the task easier, reducing it to determining the absolute configurations of at least two of the eight dissymmetric C-atoms in the acid residues of the four β-aminoesters. By carrying out the conversions shown in Scheme 1, we correlated the carbon atoms in position 2 of the aminoesters (I) with those of the enantiomeric 2,3-diphenylpropanoic acids (V). The configuration of the dissymmetric carbon atoms in position 3 of the intermediate 3-bromoesters is evidently of no importance in the present case.

TABLE 1. ABSOLUTE CONFIGURATIONS, OPTICAL ROTATIONS AND MELTING POINTS OF (−)-MENTHYL ESTERS OF 3-AMINO-2,3-DIPHENYL-PROPANOIC ACID (I) AND 3-AMINO-2,3-DIPHENYL-1-PROPANOLS (II)

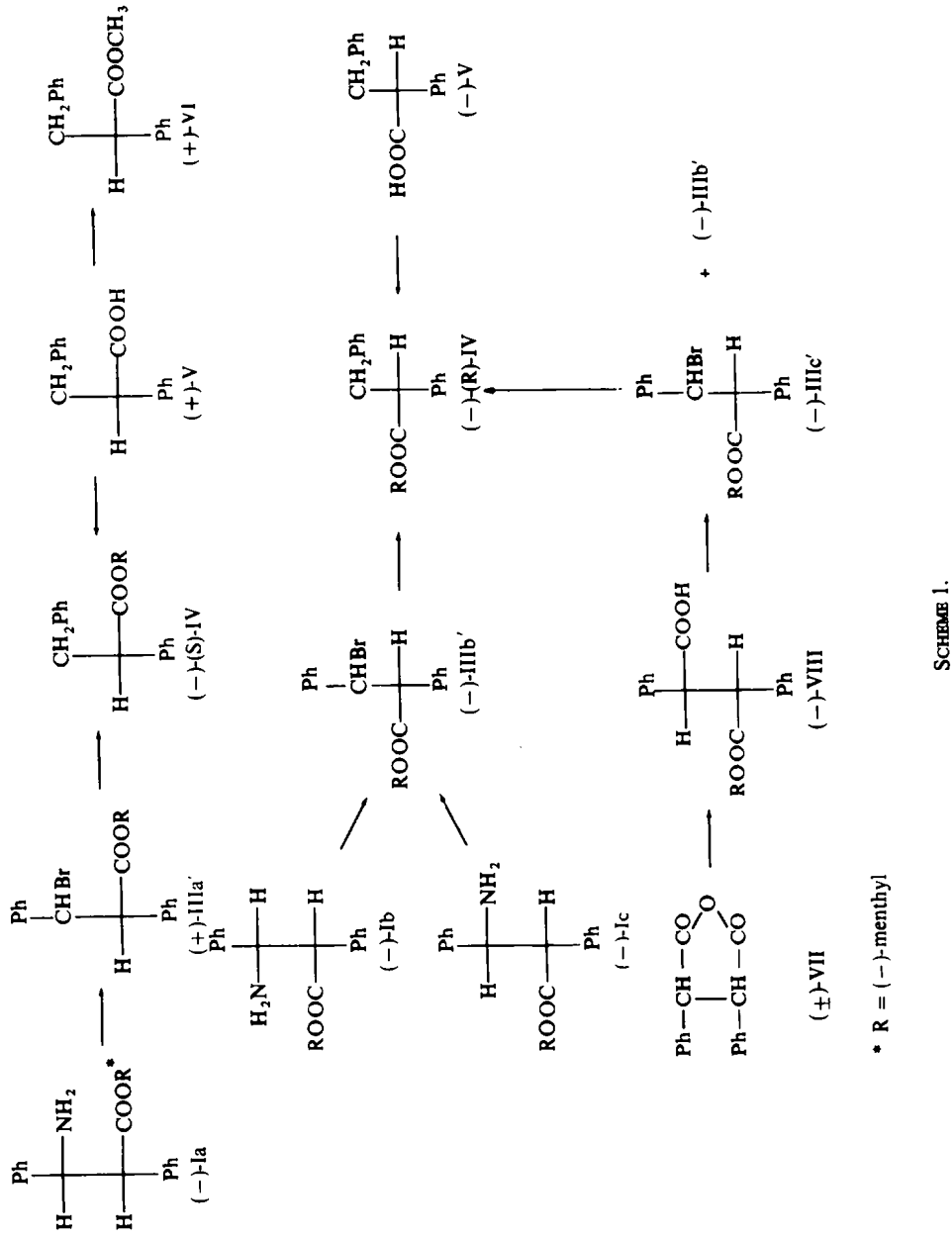
Compound		Abs. config.	$[\alpha]_D^{25}$*	m.p.
Erythro	Ia	2R:3R	−24·1	161–162°
	Ib	2S:3S	−66·9	119–120·5°
Threo	Ic	2S:3R	−153·4	96·5–97·5°
	Id	2R:3S	+49·4	65–66°
Erythro	IIa	2R:3R	+30·8	53–54°
	IIb	2S:3S	−30·6	53–54°
Threo	IIc	2S:3R	−72·3	63–65°
	IId	2R:3S	+71·9	63–65°

* 3% soln in $CHCl_3$.

The replacement of the amino group in position 3 by a bromine atom was carried out by treating the aminoesters with nitrosyl bromide. It is known that this reaction is accompanied with various side reactions. Among the latter, most troublesome is the formation of (−)-menthylester of the α-phenyl-*trans*-cinnamic acid, which on subsequent catalytic reduction could also be converted into a (−)-menthyl ester of the 2,3-diphenylpropanoic acid, however with a configuration in no way correlated with that of the initial amino ester.

Actually, in all experiments of replacing the amino group by bromine, together with the crystalline bromoesters mentioned below, isolated by several recrystallizations of the reaction mixtures, we obtained a predominating amount of oily products, containing bromine. The latter were not worked up any further, because even the crystalline bromoesters were purified with difficulty to a degree at which their IR spectrum showed no more absorption at ν_{max} 1650 cm^{-1} (evidence of the presence of an unsaturated product, most probably a menthylester of the α-phenyl-*trans*-cinnamic acid).

From the erythro-aminoester, Ia, we obtained the bromoester, IIIa′ with $[\alpha]_D^{25}$



* R = (−)-menthyl

SCHEME 1.

+53·8°. The erythro-aminoester, Ib, and the threo-aminoester, Ic, led to one and the same bromoester, IIIb′, with $[\alpha]_D^{22}$ −97·6° (starting from Ib) and $[\alpha]_D^{25}$ −99·2° (starting from Ic), respectively.

By catalytic hydrogenation over a palladium catalyst, the bromoester, IIIa′, yielded a product with $[\alpha]_D^{26}$ −17·2° which proved identical with the menthylester of (S)-(+)-2,3-diphenylpropanoic acid. The bromoester, IIIb′, was reduced to a product with $[\alpha]_D^{26}$ −97·7°, identical with the methylester of (−)-2,3-diphenylpropanoic acid. The menthylesters of 2,3-diphenylpropanoic acids have been prepared by Rupe and Kerkovins,[14] by esterification of samples with low optical purity; for the one diastereomer, $[\alpha]_D^{20}$ has been found −22° and for the other $[\alpha]_D^{20}$ −89·1°. According to[15] we obtained the two enantiomeric acids, V, with a higher optical purity and esterified them with (−)-menthol, following the method described in.[14] From (S)-(+)-V we prepared a methylester with $[\alpha]_D^{26}$ −18·0° and from the (R)-(−)-V acid, a menthylester with $[\alpha]_D^{26}$ −97·1°. Evidently our preparations possess rather a higher optical purity than the ones described by Rupe and Kerkovins.[14] The fact that the same esters were obtained with high optical purity from the bromoesters IIIa′ and IIIb′ proves that the catalytic reduction of the latter has taken place with practically no racemization.*

The results obtained proved unambiguously the absolute configurations of the aminoesters I and the aminopropanols II, shown in Table 1, as well as those of the remaining compounds described in Fodor *et al.*[8] (Experimental evidence is still lacking only about the configuration of the dissymmetric carbon atoms in position 2 of the four 2-*p*-nitrophenyl-4,5-diphenyl-tetrahydro-1,3-oxazines).

Our next task was to establish the absolute configuration of 2,3-diphenylsuccinic acid. The resolution of the (±)-acid has been realized a long time ago with brucine.[16a] Wren and Still[16b] have described the esterification of the (−)-antipode with menthol to the menthyl hydrogen ester (VIII). They obtained the same ester[16b] with a yield of 24% [calculated with respect to the (−)-acid], by esterification with (−)-menthol of the (±)-acid. We have considerably improved this method by treating the (−)-menthol with the (±)-anhydride (VII). In this case, the ester VIII is much more easily isolated in a pure state, with an almost quantitative yield.

We determined the absolute configuration of VIII by replacing the free carboxyl group with bromine, applying Hunsdiecker's reaction (cf. Scheme 1).

Hunsdiecker's reaction is accompanied by various side reactions, racemizations being also possible.[17] With the free (−)-2,3-diphenylsuccinic acid, it proceeds non-stereospecifically: from bromine and the silver salt of the acid, Bell and Smyth[18] obtained predominantly *meso*-1,2-dibromo-1,2-diphenylethane and about 15% of its racemic diastereomer. There are no data, however, about side reactions affecting the configuration of the neighbouring carbon atoms, e.g. in position 2 of the ester VIII.

Actually, the reaction of VIII with bromine led to a mixture of products, from which two crystalline diastereomeric bromoesters, III, were isolated. One of them, with $[\alpha]_D^{27}$ −98·1°, proved identical with the above described ester, IIIb′, while the other, with $[\alpha]_D^{21}$ −31·8°, has here been obtained for the first time and designated as IIIc′.

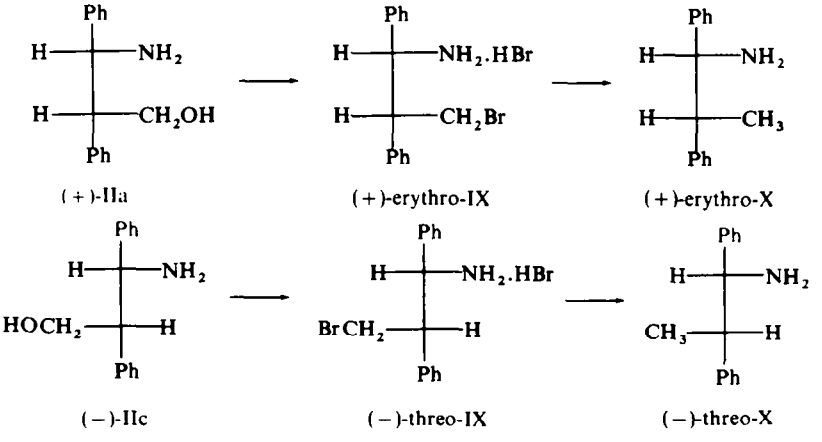
* According to Watson and Yongson[12], (+)-1,2-diphenylpropane, (−)-2-phenylpropanoic acid, and (−)-α-phenylethylamine are fully racemized when treated with freshly prepared Raney-nickel.

The catalytic hydrogenolysis of the latter gave the menthylester of the (−)-2,3-diphenylpropanoic acid, i.e. the same ester, already obtained from the bromoester IIIb'.

This proved that IIIb' and IIIc' are diastereomers with one and the same configuration of the carbon atom in position 2, identical with that of (−)-V. Thus, the absolute configuration of VIII, of the (−)-2,3-diphenylsuccinic acid and naturally of its enantiomer, as well as those of their known, optically active derivatives, is established.*

Establishing the absolute configurations of the aminoesters I and the aminopropanols II obtained from them, as well as that of the diphenylsuccinic acid, offers a possibility for the synthesis of other compounds with a predetermined absolute configuration. In connection with other investigations of ours, we carried out some syntheses, with the results stated below.

From erythro-aminopropanol, IIa, we prepared the hydrobromic salt of (+)-erythro-1(R),2(R)-3-bromo-1,2-diphenylpropylamine (IX) and from threo- IIc, the isomer, (−)-threo-IX, with a configuration 1(R),2(S). This replacement of the OH-group with a Br-atom was accomplished by analogy to the method applied in establishing the absolute configuration of L-valine.[19] Further, by catalytic reduction of (+)-erythro-IX we obtained (+)-erythro-1(R),2(R)-1,2-diphenylpropylamine, while from the (−)-threo-IX we prepared (−)-threo-X, with a configutation 1(R),2(S). The above conversions are summarized in Scheme 2.

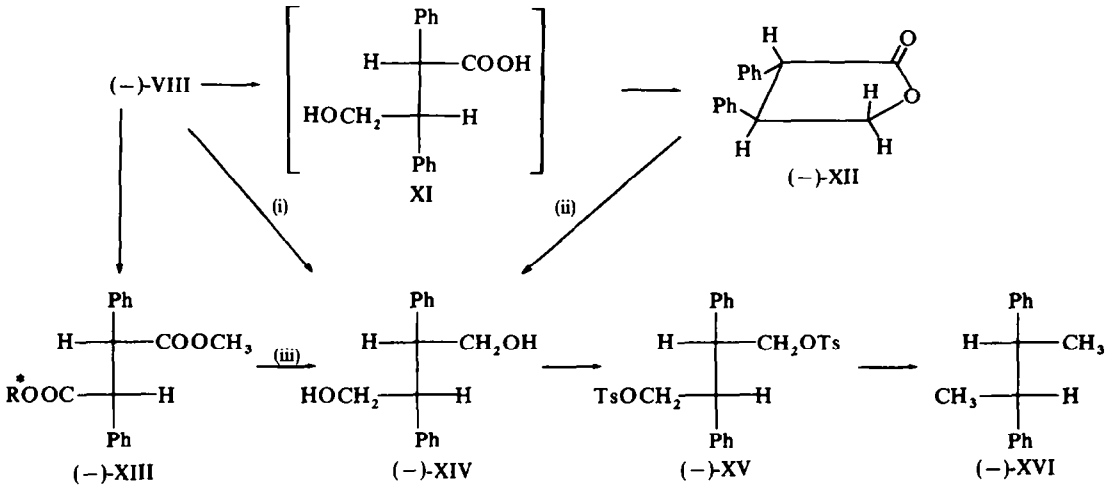


SCHEME 2.

An analogous reaction sequence was carried out, starting from (±)-erythro-II to (±)-erythro-X; the latter's constants coincided well with those reported for the same compounds obtained by another method.[20]

With the menthyl hydrogen ester of the diphenylsuccinic acid (VIII) which has thus become relatively easily available, we performed the syntheses, shown in Scheme 3.

* This conclusion of ours, reported for the first time by Berova and Kurtev[1b] has already been confirmed by R. Buchan and M. B. Watson (*J. Chem. Soc.* (C)2465 (1968)), who correlated (+)-2,3-diphenylsuccinic acid with (S)-(+)-2,3-diphenylpropanol.



* R = (−)-menthyl.

SCHEME 3.

Our attempt to reduce only the ester group in VIII and thus prepare the γ-hydroxy-acid (XI) or its lactone met with difficulties. On adding VIII to an equivalent amount of LAH, at room temperature, we obtained only (−)-2(R),3(R)-2,3-diphenyl-1,4-butanediol, (XIV), with a yield of about 50% (i). At −20°C, on addition of LAH to VIII, the main mass of the latter remained unchanged, with an insignificant admixture of lactone XII. According to Mirsa,[21] practically no reduction of a lactone to a diol takes place with LAH, in a mixture of ether–pyridine. This observation has been confirmed by our own experience: in an ether–pyridine medium we obtained a product, whose IR-spectrum is lacking the bands for the ester and hydroxyl-groups, whereas it shows an intensive absorption band at 1785 cm^{-1}. In absence of pyridine, lactone XII, obtained by us, is easily reduced with LAH to the diol XIV (ii).

The methyl-menthylester of (−)-2,3-diphenylsuccinic acid, XIII, prepared by esterification of VIII with diazomethane, proved unexpectedly inert with respect to LAH: it was reduced to XIV (iii), but rather more slowly than VIII (i). On hydrogenolysis of the di-*p*-toluenesulfonate, XV, prepared from diol XIV, (−)-2,3-diphenylbutane was isolated. In this way, it has unambiguously been confirmed that the configuration of this hydrocarbon is 2(R),3(R), as previously established by Verkade *et al.*[23] on the basis of the formation of the same enantiomer in a mixture of predominating quantities of racemic and *meso*-2,3-diphenylbutane (main product), by the reaction of (+)-(R)-1-phenylethyl chloride with lithium, sodium, or potassium in liquid ammonia.

2,3-Diphenylbutane described in the literature,[24] of highest optical purity, has shown $[\alpha]_D^{25}$ +98·8° (in ethanol). We found practically the same absolute value for our preparation, XVI. This proved that its parent compounds, XII–XV, not reported in the literature, must also be of high optical purity.*

* In this case, the correlation principle, namely that the optical purity of the starting compound Cabdc is at least equal to that of the compound Cabdf obtained from it, cannot be strictly applied, as we have to deal with compounds having more than one dissymmetric center and because in most cases purification was performed by recrystallization.

All the threo-1,2-diphenylethane derivatives described in the present paper, with an absolute configuration of the type depicted in Fig. A, are laevorotatory. This rather surprising correlation results from their strongly negative conformational asymmetries (computed after the formula $K_D = M_D - A_D$, cf. Ref. 8), while their pure atomic asymmetries are of different sign and have rather low absolute values; thus, for example, (−)-threo-IIc, IX, and X have an atomic asymmetry value of +43°. The conformers, contributing most to the negative conformational asymmetries are the ones shown in Fig. B, since the substituents possessing the highest refractivity (in the present case, the phenyls) are (−)-synclinal.

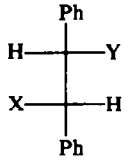


FIG. A.

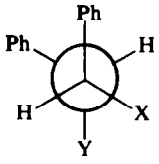


FIG. B.

This has been already shown to be the case for the compounds (−)-threo-Ic and (−)-threo-IIc by means of computations, carried out (cf. Ref. 8) after Brewster's method. It was previously shown, with the aid of NMR spectroscopy[7] that the preferred conformation of the latter compound is of the type B. Instead of (−)-threo-Ic, we examined the NMR spectrum of methyl ester of (±)-threo-3-amino-2,3-diphenylpropanoic acid[3,4] and obtained the following values for the coupling constant—in $CDCl_3$ 10·2 Hz and in DMSO-D_6 10·5 Hz; for the erythro isomer we got 9·6 Hz and 9·8 Hz respectively. We can, therefore, assume that also for (−)-threo-Ic, the preferred conformation is B. According to Bothner-By and Naar-Colin[25] the conformation B in the case of (±)-2,3-diphenylbutane does not exceed 40%. This value is rather low, but nevertheless sufficient to allow us to predict, using Brewster's method, negative rotation for (−)-XVI on the condition that the other two conformers are present in equal amounts ($A_D = 0$, $K_{D\,calc.} = -36°$).

A more extensive study of the relationship between configuration, conformation and optical activity in the group of 1,2-diphenylethane derivatives is taking place at present in our laboratories.

EXPERIMENTAL

Optical rotations were measured in 0·5 dm. tubes on a Quick-polarimeter Roussel-Jouan. M.p's, unless specifically stated, were determined in capillaries and are uncorrected.

1. *Menthyl esters of* 3-*amino*-2,3-*diphenylpropanoic acids* (I) *and* 3-*amino-diphenyl*-1-*propanols* (II)

Optically pure samples were prepared according to Berova *et al.*[2] Their specific rotations are shown in Table 1.

2. *Preparation of menthyl esters of* 3-*bromo*-2,3-*diphenylpropanoic acids* (III)

(a) *From* I *by treatment with nitrosyl bromide.*

General procedure. A soln of I (0·002–0·0004 mole) in chloroform (25–50 ml) was cooled to −40° and a chloroform soln of nitrosyl bromide was added dropwise until the appearance of a strong yellow colouration. The mixture was kept under cooling for 3 hr, then allowed to warm up to room temp. The resulting soln was washed several times with water (until the removal of colouration) and dried over $MgSO_4$. After removing the chloroform, the residue was recrystallized.

Menthyl ester of 2(S)-3-*bromo*-2,3-*diphenylpropanoic acid* (IIIa'). Amino ester Ia (1·52 g) gave after several recrystallizations from ethanol pure IIIa' (380 mg, 22%), m p. 188·5–191°, $[\alpha]_D^{25}$ +53·8° (*c*, 0·278 in benzene). (Found: Br 17·40; $C_{25}H_{31}BrO_2$ requires Br 18·02%).

Menthyl ester of 2(*R*)-3-*bromo*-2,3-*diphenylpropanoic acid* (IIIb'). Amino ester Ib (0·76 g) afforded after four recrystallizations from ethanol pure IIIb' (134 mg, 16%), m.p. 151–152°, $[\alpha]_D^{22}$ −97·6° (*c*, 0·246 in acetone). (Found: Br 17·05%).

The same ester IIIb' was obtained from Ic (1·52 g). The crude product was recrystallized four times from ethanol and once more from *n*-hexane, giving pure IIIb' (86 mg, 5%), m.p. 150–151·5°, $[\alpha]_D^{25}$ −99·2° (*c*, 0·244 in acetone).

(b) *From menthyl hydrogen ester of* (−)-2(*R*)3(*R*)-2,3-*diphenylsuccinic acid* (VIII) *by the Hunsdiecker reaction*

Menthyl esters of 2(*R*)-3-*bromo*-2,3-*diphenylpropanoic acids* (IIIb' *and* IIIc'). To a refluxed and stirred slurry of the silver salt of VIII (1·17 g, 0·0023 mole) in tetrachloromethane (20 ml dried over P_2O_5), a soln of bromine (equimole amount) in tetrachloromethane (20 ml) was dropped slowly. The mixture was refluxed and stirred for 5½ hr. The organic layer was then washed with 5% $NaHSO_3$ aq, water, 10% NaOH aq and again with water. After drying and removing the tetrachloromethane, the residue was recrystallized from *n*-pentane (8 ml) and then from ethanol.

The resulting crystalline product (58 mg, 6%) was identified as IIIb', m.p. 149·5–151°, $[\alpha]_D^{27}$ −98·2° (*c*, 0·232 in acetone), $[\alpha]_D^{27}$ −98·1° (*c*, 0·353 in chloroform). On partial evaporation two melting over a long range crystalline fractions were obtained from the *n*-pentane mother liquor, which were not worked up further, due to their insignificant amounts. The residual oil, after complete evaporation of the *n*-pentane, was purified by chromatography on silica gel. The fractions (242 mg, 24%), eluted with *n*-hexane–benzene (1:1), have m.p. 92·5–94° (Kofler), $[\alpha]_D^{20}$ −32·7° (*c*, 0·232 in acetone) and afforded on recrystallization from dilute ethanol 181 mg, m.p. 93–95°, $[\alpha]_D^{21}$ −31·8° (*c*, 0·264 in acetone), $[\alpha]_D^{27}$ −32·8° (*c*, 0·320 in chloroform). This product was assigned as IIIc'. (Found: C, 67·42; H, 7·16. $C_{25}H_{31}BrO_2$ requires: C, 67·71; H, 7·04%).

3. *Menthyl esters of the* 2,3-*diphenylpropanoic acids* (IV)

(a) *By esterification of optically active* 2,3-*diphenylpropanoic acid* (V) *with* (−)-*menthol*

The (±)-acid, V, was prepared from α-phenyl-*trans*-cinnamic acid by reduction over Pd/C catalyst. The enantiomeric (+)-V and (−)-V were obtained by resolving (±)-V according to Pettersson.[15]

(+)-V has m.p. 82–83°; $[\alpha]_D^{25}$ +129·5° (*c*, 0·251 in acetone);[15] $[\alpha]_D^{25}$ +133·8 (*c*, 0·553 in acetone);[12] $[\alpha]_D^{20}$ +133·7° (*c*, 0·535 in acetone).

The methyl ester, (+)-VI, was prepared from (+)-V and diazomethane in ether. The crude ester was distilled under reduced pressure, b.p. 111–113°/0·18 mm, n_D^{25} 1·5517, $[\alpha]_D^{20}$ +123·9° (*c*, 0·223 in chloroform). (Found: C, 79·65; H, 6·85; calc. for $C_{16}H_{16}O_2$: C, 79·97; H, 6·71%)[10] b.p. 123–124°/0·20 mm, n_D^{25} 1·5518, $[\alpha]_D^{25}$ +90·5° (*c*, 4·6 in chloroform).

(−)-V has m.p. 81·5–82·5°, $[\alpha]_D^{25}$ −131·8° (*c*, 0·224 in acetone,[15] $[\alpha]_D^{25}$ −134·3° (*c*, 0·491 in acetone).

The menthyl esters, IV, were prepared according to Rupe and Kerkowins[14] from pure enantiomeric acids by esterification with (−)-menthol. Menthyl ester of (+)-V has m.p. 97·5–98°, $[\alpha]_D^{26}$ −18·0° (*c*, 0·311 in benzene). (Found: C, 82·39; H, 9·03; calc. for $C_{25}H_{32}O_2$: C, 82·37; H, 8·85%),[14] m.p. 100–101°, $[\alpha]_D^{20}$ −22·0° (in benzene). Menthyl ester of (−)-V has m.p. 73–74·5° (Kofler), $[\alpha]_D^{26}$ −97·1° (*c*, 0·304 in benzene). (Found: C, 82·10; H, 8·95%)[14] m.p. 58–62°, $[\alpha]_D^{20}$ −89·1° (in benzene).

(b) *By reduction of the menthyl esters of* 3-*bromo*-2,3-*diphenylpropanoic acid* (III)

General procedure. A soln of 160 mg of ester III in ethanol (30 ml) was shaken under H_2 with 120 mg 5% palladium on carbon and 0·60 g sodium bicarbonate at atm. pressure and room temp. until uptake was complete. Filtration from the catalyst followed by evaporation under reduced pressure afforded the crude ester IV. It was recrystallized from dilute ethanol.

From ester IIIa', according to procedure (3b) and after two recrystallizations from EtOH aq, pure menthyl ester of (+)-V was obtained (in 70% yield), m.p. 96·5–97·5°, $[\alpha]_D^{26}$ −17·2 (*c*, 0·302 in benzene).

In the same manner both esters IIIb' and IIIc' yielded the menthyl ester of (−)-V: m.p. 72·5–73·5° (Kofler), $[\alpha]_D^{26}$ −97·7° (*c*, 0·232 in benzene), 54% yield (from IIIb'); m.p. 73–74°, $[\alpha]_D^{19}$ −101·5° (*c*, 0·256 in benzene), 70% yield (from IIIc'), respectively.

By comparison with authentic samples (prepared by procedure 3a) m.p's of mixtures were undepressed and IR spectra were the same throughout the whole range.

4. Menthyl hydrogen ester of (−)-2(R)3(R)-2,3-diphenylsuccinic acid (VIII)

Reimer has indicated the possibility of preparing (±)-2,3-diphenylsuccinic acid from the *meso*-acid by heating the latter with barium hydroxide soln.[25] Modifying his method, we obtained the (±)-acid in 70% yield by heating the *meso*-acid for 12 hr at 210° with twice mole excess of barium hydroxide aq. soln. The resulting mixture was worked up according to Torf *et al.*[27] and (±)-acid was converted into its anhydride VII (in 95% yield, m.p. 114–116°) as described by Wren and Still.[16a]

Menthyl hydrogen ester VIII was prepared by a modification of Wren and Still's method.[16b] Solution of (±)-anhydride VII (9·55 g) and (−)-menthol (11·8 g) in dry pyridine (15 ml) was heated at 100° for 8 hr. The resulting mixture of menthyl hydrogen esters, converted in potassium salts as in Wren and Still[16b] was refluxed and stirred in the presence of dry ether (250 ml) for ½ hr. The undissolved part was filtered off and treated in the same manner with fresh ether several times (about 5–6) until the optical rotation of a small sample (after decomposition with HCl) reached a $[\alpha]_D$-value of −235°. Then all the amount of extracted product was converted into hydrogen menthyl ester, according to Wren and Still.[16b] After crystallization from ethanol and drying at 100° to constant weight, 7·6 g pure VIII was obtained (in 96% yield against the available (−)-acid, m.p. 158–159°, $[\alpha]_D$ −267·3° (*c*, 0·202 in acetone),[16b] m.p. 158–159·5°, $[\alpha]_D^{19}$ −266·9° (*c*, 1·3095 in acetone).

5. Preparation of 3-bromo-1,2-diphenylpropylamine hydroboromides (IX)

General procedure. 1·45 g (0·006 mole) of aminopropanol II hydrochloride (II, HCl) was mixed with dry acetic acid (15 ml) and cooled at −15°. A moderate stream of dry hydrogen bromide was passed through the cooled slurry for 15 min. The resulting mixture was heated at 125° for 10 hr in a sealed tube. The acetic acid was removed completely by evaporation over a steam bath and the residue was washed several times with ether to remove the coloured impurities. Its further purification is shown below.

(+)-*Erythro*-1(*R*)2(*R*)-IX was prepared from erythro IIa, HCl. The resulting crude product was recrystallized several times from abs. ethanol affording a crystalline product in 55% yield, m.p. 240–241° (decomp. in sealed capillary tube), $[\alpha]_D^{24}$ +0·47° (*c*, 0·212 in ethanol), $[\alpha]_D^{23}$ +3·45° (*c*, 0·318 in methanol). ν_{max} (OH) absent. (Found: Br, 42·80. $C_{15}H_{17}Br_2N$ requires: Br 43·06%).

(−)-*Threo*-1(*R*)2(*S*)-IX was obtained from threo IIc, HCl. The crude product was purified by dissolving in abs. ethanol and slow precipitation with ether to give a crystalline product in 54% yield, m.p. 218·5–219·5° (decomp. in sealed capillary tube), $[\alpha]_D^{24}$ −26·8° (*c*, 0·261 in ethanol) ν_{max} (OH) absent. (Found: N, 3·61. $C_{15}H_{17}Br_2N$ requires: N, 3·77%).

6. 1,2-Diphenylpropylamines (X)

(±)-*Erythro*-X was prepared from (±)-erythro-II, HCl by the procedures (5) and (3b). Product recrystallized from *n*-pentane has m.p. 125–126°, Lit[20] m.p. 127°.

(+)-*Erythro*-1(*R*)2(*R*)-X. 300 mg (+)-erythro-IX was hydrogenated over palladium–carbon catalyst, following procedure (3b). The crude amine was purified by two recrystallizations from dilute ethanol to give 112 mg (67% yield), m.p. 120–121·5°, $[\alpha]_D^{23}$ +47·7° (*c*, 0·276 in chloroform). IR absorption (CCl_4) at 1380 (CH_3) and 3400 (NH) cm^{-1}. The resulting (from another run) crude (+)-erythro-X was converted into its hydrochloride. The latter was purified by recrystallization from ethanol–ether, $[\alpha]_D^{24}$ +3·0° (*c*, 0·232 in ethanol), $[\alpha]_D^{24}$ +22·7° (*c*, 0·220 in water). (Found: Cl, 13·96. $C_{15}H_{18}ClN$ requires Cl, 14·31%).

(−)-*Threo*-1(*R*)2(*S*)-X. 300 mg (−)-threo-IX, according to procedure (3b) afforded crude threo-X in 77% yield. The latter was converted into its hydrochloride and purified from ethanol–ether. The pure (−)-threo X, HCl has $[\alpha]_D^{24}$ −116·5° (*c*, 0·218 in ethanol). (Found: Cl, 13·95%). After treating with 30% soln of sodium hydroxide and extraction with ether, the solvent was evaporated to afford (−)-threo-X as a colourless oil. n_D^{25} 1·5653, $[\alpha]_D^{25}$ −58·1° (*c*, 0·224 in chloroform). IR absorptions at 1385 (CH_3) and 3395 (NH) cm^{-1} (CCl_4).

7. Lactone of 2(R)3(R)-4-hydroxy-2,3-diphenylbutanoic acid (XII)

To a stirred soln of 1·16 g of VIII in dry ether (30 ml) and dry pyridine (8 ml) a suspension of 0·21 g of LAH in ether (30 ml) was dropped slowly. The mixture was stirred at room temp for 6 hr and hydrolyzed by careful addition of water. The resulting precipitate, upon filtration was washed with ether (20 ml) and suspended in 8% HCl (20 ml).

After removing the ether from the combined extracts, the residue weighed 250 mg (37%, considered as lactone XII). Its IR spectrum (CCl_4) exhibited ν_{max} (C=O) only at 1785 cm^{-1} (γ-lactone). The crude lactone was chromatographed over Si-gel with *n*-hexane–benzene. The compound emerged as colourless crystals

(150 mg, 23% yield). m.p. 92·5–95°. Recrystallization from dilute ethanol afforded 130 mg, m.p. 96·5–98°, $[\alpha]_D^{23}$ −196·7° (*c*, 0·231 in chloroform). (Found: C, 81·33; H, 6·42. $C_{16}H_{14}O_2$ requires: C, 80·64; H, 5·92%).

8. *Menthyl–methyl ester of* (−)-2(*R*)3(*R*)-2,3-*diphenylsuccinic acid* (XIII)

Prepared from the hydrogen ester VIII with diazomethane in ether. Recrystallized from *n*-hexane. m.p. 129–130°, $[\alpha]_D^{23}$ −266·6° (*c*, 0·270 in chloroform). (Found: C, 76·86; H, 8·34. $C_{27}H_{34}O_4$ requires: 76·74; H, 8·11%).

9. 2(*R*)3(*R*)-2,3-*diphenyl*-1,4-*butanediol* (XIV) (cf. Scheme 3)

(i) *From ester* XIII. To a stirred slurry of LAH (2·3 g) in ether (50 ml) the ester XIII (2·5 g) soln in ether (100 ml) was dropped slowly and stirring continued for 24 hr at room temp. After general work up, the resulting mixture was distilled with steam, to remove the (−)-menthol. The clear aqueous soln obtained was evaporated under reduced pressure to dryness. Crude diol XIV (in 63% yield) was recrystallized twice from *n*-hexane to give 0·70 g (49%) of needles, m.p. 101–102°; $[\alpha]_D^{24.5}$ +4·8 (*c*, 0·330 in ethanol); $[\alpha]_D^{21}$ −48·3° (*c*, 0·356 in chloroform). (Found: C, 79·52; H, 7·69. $C_{16}H_{18}O_2$ requires: C, 79·31; H, 7·49%).

(ii) *From ester* VIII. Solution of 410 mg VIII in ether (15 ml) was dropped to 80 mg LAH in ether (10 ml). Stirring was continued for 4 hr at room temp. After work up, as described above, 120 mg (50%) diol XIV was obtained, m.p. 100·5–102°, $[\alpha]_D^{20}$ −48·0° (*c*, 0·312 in chloroform).

(iii) *From lactone* XII. Solution of 73 mg lactone XII in ether (10 ml) was added dropwise to a stirred slurry of 118 mg LAH in ether (10 ml). The mixture was stirred for 6 hr at room temp and worked up as above. The yield of the recrystallized diol XIV was 54 mg (72%), m.p. 101–102°, $[\alpha]_D^{27.5}$ +4·7° (*c*, 0·298 in ethanol), $[\alpha]_D^{21}$ −48·2° (*c*, 0·249 in chloroform).

10. *Di*-p-*toluenesulfonate of* 2(*R*)3(*R*)-2,3-*diphenyl*-1,4-*butanediol* (XV)

Anhyd. pyridine (3 ml) was added slowly to a stirred mixture of 480 mg diol XIV and 1·44 g *p*-toluenesulfonyl chloride at −15°. The mixture was stirred at −10° for 4 hr and then kept at 0° for 20 hr. After pouring into 50 g ice-water, the resulting oil solidified in ½ hr. It was filtered off and washed consecutively with water, 2% HCl, 2% NaOH, and water. Yield of the crude di-*p*-toluenesulfonate, XV, was 0·97 g (88%). Recrystallization from benzene-*n*-hexane afforded 0·90 g (82%), m.p. 108–109°, $[\alpha]_D^{23}$ −8·1 (*c*, 0·234 in benzene). IR absorption at 1180, 1370 cm^{-1} (S=O). (Found: C, 65·58; H, 5·88. $C_{30}H_{30}O_6S_2$ requires: C, 65·43; H, 5·49%).

11. (−)-2(*R*)3(*R*)-2,3-*Diphenylbutane* (XVI)

Solution of 0·90 g XV in THF (50 ml) was added dropwise to a stirred slurry of 0·50 g LAH in THF (25 ml). The mixture was refluxed with stirring for 6 hr, then hydrolyzed by careful addition of water. The organic layer was completely evaporated to dryness and the residue taken up in ether (45 ml). Ether soln. was washed with 10%aq Na_2CO_3 and water. After drying and removing the ether, the crude oil-product was chromatographed over Si-gel with *n*-hexane. Yield of the pure hydrocarbon XVI was 250 mg (72%). $[\alpha]_D^{21}$ −100·1° (*c*, 0·424 in ethanol), $[\alpha]_D^{24}$ −108·6° (*c*, 0·433 in chloroform). (Found: C, 91·38; H, 8·69; calc. for $C_{16}H_{18}$: C, 91·37; H, 8·63%). The (+)-enantiomer of highest purity has $[\alpha]_D^{25}$ +98·8° (ethanol).[24]

REFERENCES

[1] Preliminary communications: N. Berova and B. Kurtev;
[a] *C. R. Acad. Bulg. Sci.* **20**, 931 (1967);
[b] *Ibid.* **21**, 557 (1968) (Russ).

[2] N. Berova, J. Stefanovsky, B. Kurtev, M. Chaimova and N. Mollov, *C.R. Acad. Bulg. Sci.* **17**, 41 (1964); C.A. **61**, 10609 (1964).

[3] B. Kurtev, N. Mollov and A. Orahovats, *Monatsh. Chem.* **95**, 64 (1964).

[4] J. Stefanovsky and B. Kurtev, *Ibid.* **95**, 603 (1964).

[5] E. Varga, B. Kurtev and A. Orahovats, *Comm. Depart. Chem. Bulg. Acad. Sci.* **1**, 79 (1968).

[6] G. Fodor, J. Stefanovsky and B. Kurtev, *Chem. Ber.* **98**, 705 (1965).

[7] G. Fodor, R. Reavill, J. Stefanovsky, B. Kurtev and H. Bernstein, *Tetrahedron* **22**, 237 (1966).

[8] G. Fodor, J. Stefanovsky and B. Kurtev, *Chem. Ber.* **100**, 3069 (1967).

[9] K. Pettersson, *Arkiv Kemi* **10**, 297 (1956).

[10] H. R. Sullivan, J. R. Beck and A. Pohland, *J. Org. Chem.* **28**, 2381 (1963).

[11] R. A. Barnes and B. R. Juliano, *J. Am. Chem. Soc.* **81**, 6462 (1959).
[12] M. B. Watson and G. W. Youngson, *J. Chem. Soc.* (C) 258 (1968).
[13] O. Červinka and L. Hub, *Coll. Czech. Chem. Comm.* **33**, 1911 (1968).
[14] H. Rupe and W. Kerkovins, *Chem. Ber.* **45**, 1398 (1912).
[15] K. Pettersson, *Arkiv Kemi*, **7**, 339 (1954).
[16] H. Wren and Ch. J. Still, (a) *J. Chem. Soc.* **444**, 1449 (1915); (b) *Ibid.* 513 (1917).
[17] C. V. Wilson, *Org. Reaction* **9**, 332 (1957).
[18] F. Bell and T. F. B. Smyth, *J. Chem. Soc.* 2372 (1949).
[19] F. Barrow and G. Ferguson, *Ibid.* 410 (1935).
[20] H. Christol, A. Laurent and G. Solladie, *Bull. Soc. Chim. France* 877 (1963).
[21] R. Mirsa, *Current Sci. India* **21**, 195 (1952); *Chem Abstr.* **47**, 10545 (1953).
[22] Tsuji and T. Nogi, *J. Am. Chem. Soc.* **88**, 1289 (1966).
[23] P. E. Verkade, K. S. De Vries and B. M. Wepster, *Rec. Trav. Chim.* **83**, 1149 (1964).
[24] H. H. Richmond, E. J. Underhill, A. G. Brook and G. E. Wright, *J. Am. Chem. Soc.* **69**, 937 (1947).
[25] A. A. Bothner-By and C. Naar-Colin, *Ibid.* **84**, 743 (1962).
[26] C. L. Reimer, *Chem. Ber.* **14**, 1802 (1881).
[27] S. F. Torf and N. W. Chromow-Borissow, *Zh. Obshch. Khim.* **25**, 858 (1956).