The Absolute Configuration of 2-Amino-2′-nitro-6,6′-dimethylbiphenyl and Related Constitutionally Unsymmetrical Biphenyls[1a]

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2-Amino-2′-nitro-6,6′-dimethylbiphenyl (1) has for the first time been resolved into the optically pure enantiomers. The absolute configuration of (1) has been established and reverses a previous assignment.

In an extension of our studies on the optical rotatory dispersion[2] and circular dichroism[3] of biaryls, we had occasion to prepare optically active 2-amino-2′-nitro-6,6′-dimethylbiphenyl (**1**) and a series of related constitutionally unsymmetrical biphenyls. 2-Amino-2′-nitro-6,6′-dimethylbiphenyl (**1**) was prepared as previously described[4] and was resolved with (+)- and (−)-tartaric acid. Although it had been previously reported that **1** could be resolved by fractional crystallization of the tartaric acid salt[5,6] or by chromatography of the racemic compound on lactose,[7] comparison of these earlier reports[5–7] with the results obtained in the present study (Table I) reveals that only partial optical fractionation had been achieved by the earlier workers.[5–7] It is noteworthy that narrow melting point ranges had been previously reported, even though the products were only partially resolved. Sharpness of melting point is therefore no criterion for optical purity in the case of **1**; indeed, the enantiomers of **1** form a continuous series of solid solutions (Figure 1).[8]

TABLE I

PHYSICAL CONSTANTS OF 2-AMINO-2′-NITRO-6,6′-DIMETHYLBIPHENYL (1)

Stereoisomeric form of **1**	M.p., °C.	$[\alpha]_D$, deg.	Ref.
Racemic	122–123	. . .	*a*
	123–124	. . .	*b, c*
	124–125	. . .	*d*
	123.6–125.6	. . .	Present study
(−) and (+)	122–123	±40^{e}	*a, f*
	122–123	±62^{e}	*g*
	111	±62^{h}	*b, i*
(−)	108.3–109.0	−74.6^{h}	Present study
		−187^{e}	Present study
(+)	108.7–109.1	+75.7^{h}	Present study
		+198^{e}	Present study

[a] Reference 6a. [b] Reference 5. [c] See also P. M. Everitt, S. M. Loh, and E. E. Turner, *J. Chem. Soc.*, 4587 (1960). [d] Reference 4. [e] In 0.2 *N* HCl. [f] Reference 7. [g] Reference 6b. [h] In 95–96% ethanol. [i] H. Mix, private communication.

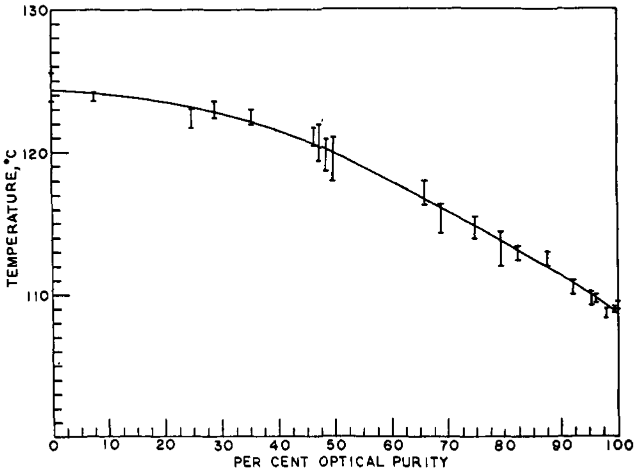

Figure 1.—Melting point range (vertical lines) *vs.* composition of enantiomeric mixtures of 2-amino-2′-nitro-6,6′-dimethylbiphenyl (1).

In the present study, when no further changes were observed to occur in the melting point and specific rotation of (+)- and (−)-**1** upon continued crystallization with (−)- and (+)-tartaric acid, respectively, each enantiomer was reduced to 6,6′-dimethylbiphenyl-2,2′-diamine (**2**), the absolute configuration of which had been previously determined.[9] The diamine **2** has been resolved (tartaric acid) by several independent groups of workers.[9,10] The physical constants (melting point, specific rotation) of optically pure **2** and the absolute configuration of **2** have been further established[9] by chemical correlation with the three diphenic acids, 6,6′-dinitro-2,2′-diphenic acid, 6,6′-dichloro-2,2′-diphenic acid, and 6,6′-dimethyl-2,2′-diphenic acid; these three diphenic acids have been independently resolved (with different resolving agents) and configurationally related to each other.[9b,11] The configurational characteristics of the reference compound **2** are therefore firmly secured.[12]

(−)-(*S*)-6,6′-Dimethylbiphenyl-2,2′-diamine[13] was formed from (−)-2-amino-2′-nitro-6,6′-dimethylbiphenyl,[13] and (+)-(*R*)-6,6′-dimethylbiphenyl-2,2′-diamine[13] was formed from (+)-2-amino-2′-nitro-6,6′-

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[2] (a) K. Mislow, M. A. W. Glass, R. E. O'Brien, P. Rutkin, D. H. Steinberg, J. Weiss, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1455 (1962); (b) K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962).

[3] E. Bunnenberg, C. Djerassi, K. Mislow, and A. Moscowitz, *J. Am. Chem. Soc.*, **84**, 2823, 5003 (1962); K. Mislow, E. Bunnenberg, R. Records, K. Wellman, and C. Djerassi, *ibid.*, **85**, 1342 (1963).

[4] S. Sako, *Bull. Chem. Soc. Japan*, **9**, 393 (1934).

[5] H. Mix, *Ann.*, **592**, 146 (1955).

[6] (a) A. Angeletti, *Gazz. chim. ital.*, **61**, 651 (1931); (b) A. Korolev and I. Bilik, *Compt. rend. acad. sci. USSR*, **29**, 586 (1940); A. I. Korolev and I. M. Bilik, *Organ. Poluprod. i Krasiteli, Nauchn.-Issled. Inst. Organ. Poluprod. Krasitelei, Sb. Statei*, **No. 1**, 113 (1959); *cf. Chem. Abstr.*, **55**, 19250*a* (1961).

[7] G. DiModica and E. Angeletti, *Ric. Sci.*, **22**, 715 (1952).

[8] Phase relations in which the enantiomers form a continuous series of solid solutions with the higher melting racemic modification have been previously described. A relatively recent example is 2,3-diacetoxybutane [H. J. Lucas, F. W. Mitchell, Jr., and H. K. Garner, *J. Am. Chem. Soc.*, **72**, 2138 (1950)].

[9] (a) K. Mislow, P. Rutkin, and A. K. Lazarus, *ibid.*, **79**, 2974 (1957); (b) F. A. McGinn, A. K. Lazarus, M. Siegel, J. E. Ricci, and K. Mislow, *ibid.*, **80**, 476 (1958).

[10] (a) J. Meisenheimer and M. Höring, *Chem. Ber.*, **60**, 1425 (1927); (b) E. D. Bergmann and S. Berkovic, *J. Org. Chem.*, **26**, 919 (1961); (c) W. Dethloff and H. Mix, *Chem. Ber.*, **82**, 534 (1949).

[11] M. Siegel and K. Mislow, *J. Am. Chem. Soc.*, **80**, 473 (1958).

[12] See also K. Mislow, *Angew. Chem.*, **70**, 683 (1958).

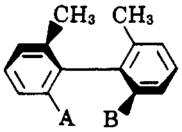
[13] Unless otherwise indicated, signs of rotation refer to ethanol at room temperature and to the sodium D line.

dimethylbiphenyl.[13] It follows that (−)-1 has the (*S*) configuration and (+)-1 the (*R*) configuration. The melting points and specific rotations of the diaminobitolyls **2** obtained from **1** indicated that the nitroaminobitolyl precursors (**1**) were essentially optically pure (see Experimental).

On the basis of the previously reported[5] conversion of (−)-**1** *via* (+)-2-bromo-2′-nitro-6,6′-dimethylbiphenyl (**3**) to (+)-2-bromo-2′-amino-6,6′-dimethylbiphenyl (**4**), and the report[14] that (−)-(**4**) had been converted to (−)-2,2′-dibromo-6,6′-dimethylbiphenyl (**5**) which has been shown[2a] to possess the (*S*) configuration, we had earlier been led to the conclusion[2a] that (−)-(**1**) has the (*R*) configuration, in direct conflict with the results of the present study. In order to resolve this discrepancy, we therefore repeated the work of the earlier workers.[5,14] The pertinent reaction sequences[13] have been summarized in Chart I.

CHART I

INTERCONVERSION REACTIONS OF SOME (*R*)-BIPHENYLS



Compd.	A	B	Sign of rotation[a] at 589 mμ in ethanol
2	NH_2	NH_2	+
↑			
1	NO_2	NH_2	+
↓			
3	NO_2	Br	−
↓			
4	NH_2	Br	+
↓			
→**5**	Br	Br	+

[a] Refers to the (*R*) configuration.

Optically pure (+)-(*R*)-**1** ($[\alpha]_D$ +76.6°) and (−)-(*S*)-**1** ($[\alpha]_D$ −73.3°) were converted by the Sandmeyer reaction to (−)-(*R*)-**3** ($[\alpha]_D$ −52.0°) and to (+)-(*S*)-**3** ($[\alpha]_D$ +52.9°), respectively. Stannous chloride reduction of (*R*)- and (*S*)-**3** gave (+)-(*R*)-**4** ($[\alpha]_D$ +4.2°) and (−)-(*S*)-**4** ($[\alpha]_D$ −3.4°), respectively. (+)-(*R*)-**4** was converted into (+)-(*R*)-**5** ($[\alpha]_D$ +12.7°) by the Sandmeyer reaction. Catalytic hydrogenation of (+)-(*R*)-**1** ($[\alpha]_D$ +75.6°) gave (+)-(*R*)-**2** ($[\alpha]_D$ +49.0° in ethanol and $[\alpha]_D$ −36.8° in 1 *N* HCl). We had earlier shown[2a] that (+)-(*R*)-**2** ($[\alpha]_D$ −35.9° in 1 *N* HCl) gives (+)-(*R*)-**5** ($[\alpha]_D$ +11.7°). The conversion of **1** into **5** by two independent pathways (**1** → **2** → **5** and **1** → **3** → **4** → **5**) therefore closes a reaction cycle and proves the internal consistency of all of our results. The displacement reaction **1** → **3** and **4** → **5** must occur with essentially complete (within experimental error) retention of optical purity as well as configuration, a result which is hardly unexpected since only one of the four *ortho* substituents is displaced at a time. In the conversion of **2** into **5**, both *ortho* substituents are displaced, again with complete (within experimental error) retention of optical purity as well as configuration; this follows from the near identity of the rotations of **5** obtained by the two independent pathways. In all such reactions,[15] the amino groups in **2** are most probably replaced consecutively rather than simultaneously.[16]

Our findings are clearly incompatible with those reported by Mix.[5] This author reported the preparation of **3** with $[\alpha]_D$ +73° and −73° starting from **1** with $[\alpha]_D$ −62° and +62°, respectively. The starting **1** is therefore only 82% optically pure, and the value of $[\alpha]_D$ 89° which may be calculated for optically pure **3** from the data of Mix[5] deviates markedly from the correct value of 52°.

Mix further reported[5] that reduction of **3** with $[\alpha]_D$ +73° gave **4** with $[\alpha]_D$ +8.5°, whereas in fact (see above) **3** with $[\alpha]_D$ +52.9° gives **4** with $[\alpha]_D$ −3.4°. Aside from the incorrect value of the specific rotation of **4**, the erroneous report[5] that **3** gives **4** with the *same* sign of rotation is now revealed as the source of the discrepancy in the assignment of absolute configuration to **1**.

In addition to the above discrepancies, our findings are also somewhat at variance with the report[14] of Angeletti and Migliardi that (−)-**4** with m.p. 77–78° and $[\alpha]_D$ −5.32° is converted to (−)-**5** with m.p. 109.0–110.0° and $[\alpha]_D$ −6.2° by the Sandmeyer reaction; we find that (+)-**4** with m.p. 81–84° and $[\alpha]_D$ +4.1° is converted to (+)-**5** with m.p. 108–109° and $[\alpha]_D$ +12.7°. The rotation of **5** reported earlier[14] is thus too low.

In conjunction with the work described above, (+)-(*R*)-2-nitro-6,6′-dimethylbiphenyl (**6**) and (−)-(*R*)-2-amino-6,6′-dimethylbiphenyl (**7**) were also prepared in optically active form, starting from (−)-(*S*)-**1**.[17]

Experimental

Optical Resolution of (+)-2-Amino-2′-nitro-6,6′-dimethylbiphenyl (1).—An excess of tartaric acid [with the more commonly available (+)-tartaric acid a ratio of 2 moles of (+)-tartaric acid to 1 mole of (±)-**1** was employed, while with (−)-tartaric acid an amount equal in weight to the amine was used] in boiling absolute ethanol was added to a solution of racemic **1** (m.p. 123.6–125.6°, prepared by the method of Sako[4] in 59% yield) in boiling absolute ethanol. The resulting reddish (usually turbid) solution was slowly cooled to room temperature and then overnight in a refrigerator at 5°. The resulting mass of white solid, which was interspersed with yellow crystals of free aminonitrobitolyl,[6a] was filtered and thoroughly washed with cold, anhydrous ethyl ether to remove the free aminonitrobitolyl and traces of tartaric acid. The white salt was recrystallized repeatedly from absolute ethanol to which (+)- or (−)-tartaric acid (whichever was appropriate) had been added; the quantity added was equal to about 10% of the weight of the salt.

The course of the resolution was roughly monitored by using the melting point of the salt as a guide. The highest melting points obtained for the relevant salts follow: (−)-aminonitrobitolyl (+)-tartrate, 157.1–159.1°; (+)-aminonitrobitolyl (−)-tartrate, 157.2–158.2°. The previously reported[6a] value for (−)-aminonitrobitolyl (+)-tartrate is 151°.

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(14) A. Angeletti and C. Migliardi, *Gazz. chim. ital.*, **65**, 819 (1935).

(15) Replacement by the Sandmeyer reaction of the amino groups in optically active **2** by chloro and cyano groups also proceeds with virtually complete retention of configuration and optical purity.[9b] Contrary to our experience,[2a] F. Bell and G. A. Dinsmore [*J. Chem. Soc.*, 3691 (1950)] reported that the Sandmeyer reaction of optically active **2** gives inactive **5**.

(16) It should be noted that even a tri-*ortho*-substituted biphenyl does not necessarily racemize in the course of a Sandmeyer reaction. Thus D. F. De Tar and J. C. Howard [*J. Am. Chem. Soc.*, **77**, 4393 (1955)] found that Sandmeyer replacement of the diazonium group from optically active 2-methyl-6-nitro-2′-aminobiphenyl with chloride and bromide resulted in little racemization.

(17) *The change in the configurational prefix does* not denote an inversion of configuration but is a consequence of the nomenclatural rules employed: R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

The course of the resolution was more accurately followed by decomposing the salt and examining the melting point and rotation of the aminonitrobitolyl **1**. The salt was dissolved in hot 4 N HCl, and the solution was cooled and made strongly alkaline with 7.5 N NH_3. The yellow precipitate of aminonitrobitolyl **1** was filtered, thoroughly washed with water, and dried *in vacuo* over concentrated sulfuric acid. The melting point and specific rotation of the crude amine were determined on the dried sample. The resolution was discontinued when essentially no further changes in rotation and melting point of **1** were observed.

After the resolution was complete, (−)-**2-amino-2′-nitro-6,6′-dimethylbiphenyl**, m.p. 108.2–109.2°, $[\alpha]^{23}_{\mathrm{D}}$ −73.5° (c 0.91, 95% ethanol), liberated from the (+)-tartaric acid salt, was recrystallized from 80% ethanol–water, to give yellow crystals: m.p. 108.3–109.0°, lit.[6a,b] m.p. 122–123° and 111° (H. Mix, private communication[5]); $[\alpha]^{22}_{\mathrm{D}}$ −74.6° (c 1.0, 95% ethanol), $[\alpha]^{22}_{\mathrm{D}}$ −187° (c 0.92, 0.2 N HCl), lit. $[\alpha]^{20}_{\mathrm{D}}$ −62° (96% ethanol),[5] $[\alpha]^{20}_{\mathrm{D}}$ −40°,[6a,7] $[\alpha]^{20}_{\mathrm{D}}$ −62° (0.2 N HCl).[6b]

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.26; H, 6.13; N, 11.85.

Similarly, (+)-2-amino-2′-nitro-6,6′-dimethylbiphenyl, m.p. 108.4–109.2°, $[\alpha]^{27}_{\mathrm{D}}$ +75.5° (c 0.92, 95% ethanol), liberated from the (−)-tartaric acid salt, was recrystallized from 80% ethanol–water, to give yellow crystals: m.p. 108.7–109.1°; $[\alpha]^{21}_{\mathrm{D}}$ +75.7° (c 0.93, 95% ethanol), $[\alpha]^{21}_{\mathrm{D}}$ +198° (c 0.91, 0.2 N HCl), lit. $[\alpha]^{20}_{\mathrm{D}}$ +62° (96% ethanol),[5] $[\alpha]^{20}_{\mathrm{D}}$ +40°,[6a,7] $[\alpha]^{20}_{\mathrm{D}}$ +62° (0.2 N HCl).[6b]

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.28; H, 5.66; N, 11.70.

(−)- **and** (+)-**2,2′-Diamino-6,6′-dimethylbiphenyl** (**2**).—A solution of (−)-2-amino-2′-nitro-6,6′-dimethylbiphenyl [**1**, 0.242 g., m.p. 108.1–108.9°, $[\alpha]^{22}_{\mathrm{D}}$ −72.6° (c 0.91, 95% ethanol)] in 30 ml. of absolute ethanol was hydrogenated over 63.5 mg. of 5% palladium on charcoal at atmospheric pressure and room temperature. The mixture was filtered and the clear, colorless filtrate was evaporated *in vacuo*. The white product (0.198 g., 93.5%), after drying *in vacuo* over phosphorus pentoxide, was dissolved in 4 ml. of benzene and chromatographed on 5.0 g. of Florisil. Elution with benzene afforded white crystals (care was taken to avoid recrystallization of the product, in order to prevent the possibility of optical fractionation) which melted at 157.9–158.8° (lit.[9a] m.p. 156–158°) and whose infrared spectrum was identical with that of authentic (−)-6,6′-dimethylbiphenyl-2,2′-diamine. The product had $[\alpha]^{25}_{\mathrm{D}}$ −48.1° (c 1.1, absolute ethanol), $[\alpha]^{26.5}_{\mathrm{D}}$ +38.6° (c 2.1, 1 N HCl), $[\alpha]^{26}_{\mathrm{D}}$ −100° (c 0.78, benzene), $[\alpha]^{26}_{\mathrm{D}}$ −114.5° (c 1.1, dioxane); lit.[9a] $[\alpha]^{24}_{\mathrm{D}}$ +34° (1 N HCl), $[\alpha]^{24}_{\mathrm{D}}$ −47° (absolute ethanol).

A similar reduction of (+)-2-amino-2′-nitro-6,6′-dimethylbiphenyl [0.247 g., m.p. 108.5–109.0°, $[\alpha]^{27}_{\mathrm{D}}$ +75.6° (c 0.78, 95% ethanol)] in 35 ml. of absolute ethanol over 71.8 mg. of 5% palladium on charcoal at atmospheric pressure and 22° yielded a white crystalline product (0.205 g., 95.5%) which was dissolved in 3 ml. of benzene and chromatographed on 5.5 g. of Florisil. Elution with benzene afforded white crystals: m.p. 157.8–159.0°; $[\alpha]^{25.5}_{\mathrm{D}}$ +49.0° (c 0.96, absolute ethanol), $[\alpha]^{25.5}_{\mathrm{D}}$ −36.8° (c 0.93, 1 N HCl), $[\alpha]^{25.5}_{\mathrm{D}}$ +101° (c 1.1, benzene), $[\alpha]^{25.5}_{\mathrm{D}}$ +114° (c 0.87, dioxane); lit.[9b] $[\alpha]^{24}_{\mathrm{D}}$ −36° (1 N HCl), $[\alpha]^{24}_{\mathrm{D}}$ +49° (absolute ethanol), $[\alpha]^{24}_{\mathrm{D}}$ +101° (benzene), $[\alpha]^{24}_{\mathrm{D}}$ +116° (dioxane).

(+)- **and** (−)-**2-Bromo-2′-nitro-6,6′-dimethylbiphenyl** (**3**).—A mixture of 4.80 g. of (−)-2-amino-2′-nitro-6,6′-dimethylbiphenyl [**1**, m.p. 109.4–110.0°, $[\alpha]^{21}_{\mathrm{D}}$ −73.3° (c 1.1, 95% ethanol)] and 20 ml. of 20% HBr was heated on a steam bath until all of the aminonitrobitolyl had dissolved. The solution was cooled in an ice–salt bath and the amine salt precipitated. A solution of 1.52 g. of sodium nitrite in 3 ml. of water was slowly added, with stirring. Separately, a solution of 3.17 g. of cuprous bromide in 30 ml. of 48.0% HBr was heated and stirred at about 95°. The ice-cold diazotized solution prepared above was slowly added, with vigorous stirring. The resulting mixture was heated for 10 min. on the steam bath, cooled in an ice bath, and extracted with ethyl ether. The ether extracts were combined and washed successively with 20% sulfuric acid, water, 10% sodium hydroxide solution, and finally with water. The ether solution was steam distilled and the distillate was extracted with ethyl ether. The ether extracts were evaporated, and the residue was dried over concentrated sulfuric acid to yield 2.54 g. of a light brown solid. A solution of this material in 5 ml. of benzene was chromatographed on 65 g. of Woelm acid-washed grade I alumina. Elution with benzene yielded 1.21 g. of pale yellow crystals, m.p. 116.5–122.0°. Recrystallization from 95% ethanol (charcoaling) afforded very pale yellow crystals: m.p. 123.7–124.6°, lit.[5] m.p. 124°; $[\alpha]^{27}_{\mathrm{D}}$ +52.9° (c 0.78, 95% ethanol), lit.[5] $[\alpha]^{20}_{\mathrm{D}}$ +73° (alcohol).

Anal. Calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; Br, 26.10; N, 4.58. Found: C, 55.02; H, 4.07; Br, 25.91; N, 4.55.

A similar preparation, starting from (+)-2-amino-2′-nitro-6,6′-dimethylbiphenyl [m.p. 108.6–109.5°, $[\alpha]^{25}_{\mathrm{D}}$ +76.6° (c 1.1, 95% ethanol)], yielded 4.33 g. of pale yellow crystals: m.p. 123.0–124.4° after recrystallization from 95% ethanol, lit.[5] m.p. 124°; $[\alpha]^{23.5}_{\mathrm{D}}$ −52.0° (c 0.90, 95% ethanol), lit.[5] $[\alpha]^{20}_{\mathrm{D}}$ −73.0° (alcohol).

Anal. Calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; Br, 26.10; N, 4.58. Found: C, 54.88; H, 3.93; Br, 26.23; N, 4.46.

(−)- **and** (+)-**2-Bromo-2′-amino-6,6′-dimethylbiphenyl** (**4**).—Anhydrous hydrogen chloride was bubbled into a stirred mixture of 3.105 g. of stannous chloride dihydrate and 10.5 ml. of glacial acetic acid until all the stannous chloride had dissolved. The clear, colorless solution was heated to about 50° and 1.035 g. of (+)-2-bromo-2′-nitro-6,6′-dimethylbiphenyl [**3**, m.p. 121.0–123.0°, $[\alpha]^{25}_{\mathrm{D}}$ +51.6° (c 0.83, 95% ethanol)] was slowly added. After all of the nitrobromobitolyl had been added, the clear, colorless solution was heated at 40–65° for about 1 hr. The solvent was evaporated and the white solid residue (and traces of acetic acid) was treated with about 50 ml. of 1 N HCl. The resulting white, turbid solution was extracted with ethyl ether and made strongly alkaline with sodium hydroxide solution. The alkaline solution was extracted with ethyl ether, and the combined ether extracts were washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the white crystals, tinged light brown, were dried over potassium hydroxide. The solid (0.354 g.) was dissolved in 3 ml. of benzene and chromatographed on 9.0 g. of Florisil. Elution with benzene yielded 0.340 g. of white crystals with a slight yellow tinge: m.p. 79.3–83.5°, $[\alpha]^{24}_{\mathrm{D}}$ −3.5° (c 2.5, 95% ethanol). Sublimation at 70–80° and 1.5–2.0 × 10^{-2} mm. afforded white crystals: m.p. 83.0–85.0°, $[\alpha]^{21}_{\mathrm{D}}$ −3.4° (c 2.0, 95% ethanol). Recrystallization from ligroin (b.p. 66–75°) also afforded white crystals: m.p. 83.8–84.8°, lit. m.p. 85°,[5] 77–78°[14]; $[\alpha]^{21}_{\mathrm{D}}$ −3.4° (c 2.1, 95% ethanol), lit. $[\alpha]^{18}_{\mathrm{D}}$ +8.5° (alcohol),[5] $[\alpha]^{20}_{\mathrm{D}}$ −5.32° (alcohol).[14]

Anal. Calcd. for $C_{14}H_{14}BrN$: C, 60.88; H, 5.11; Br, 28.94; N, 5.07. Found: C, 60.63; H, 5.24; Br, 29.23; N, 5.19.

A similar preparation, starting from (−)-2-bromo-2′-nitro-6,6′-dimethylbiphenyl [**3**, m.p. 122.0–123.5°, $[\alpha]^{23.5}_{\mathrm{D}}$ −54.4° (c 0.95, 95% ethanol)], afforded white crystals: m.p. 84.2–85.1°, lit. m.p. 85°,[5] 77–78°[14]; $[\alpha]^{25}_{\mathrm{D}}$ +4.1° (c 1.9, 95% ethanol), lit. $[\alpha]^{18}_{\mathrm{D}}$ −8.5° (alcohol),[5] $[\alpha]^{20}_{\mathrm{D}}$ +5.04° (alcohol).[14]

Anal. Calcd. for $C_{14}H_{14}BrN$: C, 60.88; H, 5.11; Br, 28.94; N, 5.07. Found: C, 60.83; H, 5.21; Br, 29.09; N, 5.38.

(+)-**2,2′-Dibromo-6,6′-dimethylbiphenyl** (**5**).—A suspension of 2.00 g. of (+)-2-bromo-2′-amino-6,6′-dimethylbiphenyl [**4**, m.p. 81.0–84.0°, $[\alpha]^{25}_{\mathrm{D}}$ +4.1° (c 2.2, 95% ethanol)] in 10 ml. of 20% HBr was heated to about 80° until all of the bromoaminobitolyl had dissolved. The solution was cooled to about −5° in an ice–salt bath (the white amine salt precipitated) and a solution of 0.525 g. of sodium nitrite in 3 ml. of water was added dropwise with vigorous stirring. A pale yellow solution resulted after the addition was complete. Separately, a suspension of 1.308 g. of cuprous bromide in 10 ml. of 47% HBr was heated to 95–100° and the diazotized solution, previously prepared above, was added with vigorous stirring at a rapid rate. The mixture was heated and stirred on the water bath at *ca.* 100° for about 15 min. A dark, gummy material separated out on the walls of the flask. The mixture was cooled (ice bath) and made strongly alkaline with concentrated aqueous ammonia. The mixture was extracted with ether and the combined ether extracts were washed with 10% sodium hydroxide and water, filtered, and evaporated. The residue was dried over concentrated sulfuric acid to yield 2.04 g. of a red semisolid material, which was dissolved in 10 ml. of 1:1 (v./v.) n-hexane–benzene and chromatographed on 60 g. of Woelm acid-washed alumina, grade I. Elution with 1:1 (v./v.) n-hexane–benzene, followed by rechromatography and elution with 4:1 (v./v.) n-hexane–benzene, afforded 0.574 g. of a waxy, white solid, which was sublimed at 3.5–6.5 × 10^{-3} mm. (oil bath at 95–105°) to yield 0.452 g. of slightly waxy, white solid, $[\alpha]^{22}\mathrm{D}$ +14.9° (c 1.0, absolute ethanol). This material was recrystallized from n-hexane followed by 95% ethanol to yield white crystals: m.p. 108.0–109.0°, lit. m.p. 109.0–110°,[14] 108.5–110.0°[2a]; $[\alpha]^{23}\mathrm{D}$ +12.7° (c 1.2, absolute ethanol), lit. $[\alpha]^{20}\mathrm{D}$ −6.2° for the enantiomer (alcohol),[14] $[\alpha]^{30}\mathrm{D}$ +11.7° (absolute ethanol).[2a]

The infrared spectrum was identical with that of (+)-2,2'-dibromo-6,6'-dimethylbiphenyl prepared from (+)-**2**.[2a,13]

(+)-2-Nitro-6,6'-dimethylbiphenyl (6).—A mixture of optically impure (−)-2-amino-2'-nitro-6,6'-dimethylbiphenyl [**1**, 2.40 g., m.p. 110.0–111.2°, $[\alpha]^{27}\mathrm{D}$ −67.6° (c 1.3, 95% ethanol)], 2.5 ml. of concentrated hydrochloric acid, and 10 ml. of water was heated on a steam bath until solution was complete. The mixture was cooled in an ice bath (the amine salt precipitated out at this point) and a solution of 0.76 g. of sodium nitrite in 1.5 ml. of water was added dropwise with vigorous stirring. To the resulting cherry-red solution was added 20 ml. of 50% hypophosphorous acid, previously cooled to 0°; there was considerable evolution of nitrogen. After 24 hr. the mixture was diluted with water and extracted with ethyl ether. The combined ether extracts were washed with water and dried, the ether was filtered and evaporated, and about 20 ml. of 15% sodium hydroxide solution was added to the red residue. The mixture was steam distilled, and the distillate was saturated with sodium chloride and extracted with ethyl ether. The ether extracts were combined, dried, filtered, and evaporated. The residue was recrystallized from 95% ethanol to give 1.48 g. (65.3%) of very pale yellow crystals, m.p. 64.0–67.4°. Recrystallization from 95% ethanol to a constant melting point gave white crystals: m.p. 67.4–68.0°, $[\alpha]^{25}\mathrm{D}$ +153.5° (c 0.82, 95% ethanol).

Subsequent preparations employing essentially optically pure 2-amino-2'-nitro-6,6'-dimethylbiphenyl gave virtually the same physical constants.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.75; H, 5.91; N, 6.34.

(−)-2-Amino-6,6'-dimethylbiphenyl (7).—A solution of (+)-2-nitro-6,6'-dimethylbiphenyl [**6**, 1.004 g., m.p. 65.5–67.3°, $[\alpha]^{27}\mathrm{D}$ +146° (c 1.0, 95% ethanol)] in 60 ml. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature, in the presence of platinum dioxide as catalyst. The mixture was filtered and the solvent was evaporated to give an oily white residue. Trituration with a small amount of 4 N HCl gave white crystals of amine salt. The amine salt was filtered, the filtrate was extracted with ether, and the amine salt was washed with ether. The aqueous acid filtrate and the amine salt were combined and enough water was added to dissolve all of the amine salt. The solution was cooled in an ice bath, made alkaline with 10% sodium hydroxide, and extracted several times with ether. The combined ether extracts were washed with water, dried, filtered, and evaporated to give an oily residue. After drying *in vacuo* over concentrated sulfuric acid this material solidified to give 0.693 g. of colorless product. Recrystallization from petroleum ether (b.p. 30–60°) afforded white crystals: m.p. 53.2–54.2°, $[\alpha]^{26}\mathrm{D}$ −26.3° (c 1.1, 95% ethanol).

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.17; H, 7.57; N, 7.31.

The Absolute Configuration of 2,2'-Dichloro-6,6'-dimethylbiphenyl-4,4'-diamine[1a]

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On the basis of a theoretical model the (S) configuration had been assigned by previous workers to (+)-2,2'-dichloro-6,6'-dimethylbiphenyl-4,4'-diamine (**3**). In an attempt to verify this assignment, (−)-**3** was deaminated to (−)-2,2'-dichloro-6,6'-dimethylbiphenyl (**5**). Since this reaction can only proceed with retention of configuration and since (−)-**5** has the (S) configuration, it has therefore been shown that (−)-**3** has the (S) configuration. Attempts to resolve **3** failed in our hands and optically active **3** was instead prepared by a series of transformations starting with optically active 2,2'-dimethyl-6,6'-dinitro-4,4'-diphenic acid (**4**).

In the course of previous investigations in these laboratories on the relative and absolute configurations of biphenyls,[2] the (R) configuration had been assigned to the dextrorotatory forms of 6,6'-dinitro-2,2'-diphenic acid (**1**)[3] and 6,6'-dimethylbiphenyl-2,2'-diamine (**2**).[4] These results reversed the absolute configurations predicted for these compounds by Kuhn and collaborators, which were based on qualitative[5] and semiquantitative[6] theoretical arguments. It thus became desirable to confirm the absolute configuration of 2,2'-dichloro-6,6'-dimethylbiphenyl-4,4'-diamine (**3**), which had been similarly assigned on theoretical grounds.[6]

An attempt to repeat the reported[6] resolution of racemic **3** was unsuccessful.[7] Synthesis of optically active **3** from optically active precursors was therefore undertaken. The starting material for this sequence was (−)-2,2'-dinitro-6,6'-dimethyl-4,4'-diphenic acid (**4**), which was converted into (−)-**3** and thence into (−)-(S)-2,2'-dichloro-6,6'-dimethylbiphenyl (**5**) by the steps outlined in Chart I and discussed in detail below. The product, (−)-(S)-**5**, also served as the absolute configurational standard in this series.[4]

Results and Discussion

The starting acid **4** was prepared and resolved according to a modification of the procedure developed by Mix,[8] who recorded a rotation of −20° for the presumably optically pure compound. In the present work, rotations no higher than −16.2, −16.3, and −16.3° were obtained in three separate resolutions; these samples therefore had an optical purity of 81% based on the figure reported by Mix. An incompletely resolved sample of **4**, $[\alpha]\mathrm{D}$ −7.0° (optical purity 35%), was converted to 2,2'-diamino-6,6'-dimethyl-4,4'-diphenic acid (**6**) by catalytic hydrogenation; the crude product had $[\alpha]\mathrm{D}$ −12.6°. Replacement of the amino groups of (−)-**6** by chlorine atoms using the Sandmeyer reaction, followed by esterification with diazomethane, gave **7**, $[\alpha]\mathrm{D}$ −7.2°.

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