618. *Steric Effects in 2 : 2′-Bridged Diphenyls with a Heterocyclic Bridging Ring. Part I. Optically Active Dihydrodibenzazepines.*

By Shakti R. Ahmed and D. Muriel Hall.

2 : 2′-Bisbromomethyl-6 : 6′-dinitrodiphenyl has been condensed with (−)-ephedrine and the resulting quaternary bromide separated into two diastereoisomers. Hofmann degradation of the two bromides gave (−)- and (+)-2 : 7-dihydro-1-methyl-4′ : 1″-dinitro-3 : 4-5 : 6-dibenzazepine with $[\alpha]_{5461}^{19}$ −1343° and +1333° respectively. The cyclic amines are optically stable in benzene solution up to about 100° and racemise slowly at 125°. Similar condensation of 2 : 2′-bisbromomethyl-6 : 6′-difluorodiphenyl with (−)-ephedrine, followed by Hofmann degradation of the diastereoisomeric bromides, gave optically active (but probably not optically pure) (−)- and (+)-4′ : 1″-difluoro-2 : 7-dihydro-1-methyl-3 : 4-5 : 6-dibenzazepine. The hydrochlorides of the fluoro-amines racemise in aqueous acid at 80° with a half-life of 6·5 hr.

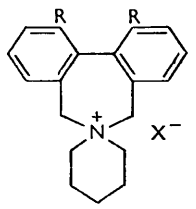
Optical activity has been demonstrated in compounds of the types (I) and (II) only when *ortho*-substituents [or fused benzene rings as in (III) and (IV)] are present.[1,2] In view of the high optical stability and very low specific rotation of the dimethoxy-compound (I*a*) ($[\alpha]_{5461}^{22}$ +4·0° and −3·8°), this failure to resolve compounds of types (I*b*) and (II), in which R = H, was originally attributed to experimental difficulties rather than to lability of configuration. Support for this view came from the greatly increased specific rotations (presumably associated with their different light-absorbing properties) of the dinaphthyl compounds (III) and (IV) which have $[\alpha]_{5461}^{20}$ +306·5° and +205·3° respectively.

However, more recent work on diphenyls with other types of bridging rings suggests that in the absence of other *ortho*-substituents compounds with a bridge of three or four atoms possess only low optical stability.[3,4,5] At the same time further evidence of the low optical rotation associated with this type of structure has been obtained. Thus compound (V) [3] had $[\alpha]_{D}^{32\cdot5}$ +2·25° and compound (VI) [4] had $[\alpha]_{D}^{25}$ +3·1°.

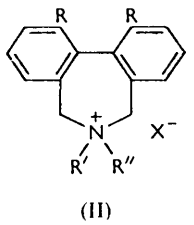
In order to extend our knowledge of the configurational stability of 2 : 2′-bridged diphenyls we have therefore begun a study of the effects of various *ortho*-substituents on the optical stability of compounds of the types (I) and (II). At the same time it seemed desirable to facilitate the detection of optical resolution or asymmetric transformation, if either of them occurred, by using compounds of higher specific rotation. With this in

[1] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854.
[2] Hall and Turner, *J.*, 1955, 1242.
[3] Iffland and Siegel, *J. Org. Chem.*, 1956, **21**, 1056.
[4] Truce and Emrick, *J. Amer. Chem. Soc.*, 1956, **78**, 6130.
[5] (*a*) Mislow, *Trans. New York Acad. Sci.*, 1957, [2], **19**, 298; (*b*) Dvorken, Smyth, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486.

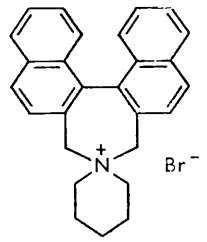
view we selected nitro-groups as suitable *ortho*-substituents for preliminary study, as their bathochromic effect on the electronic absorption bands might be expected to increase the optical rotatory power in the region in which it can most easily be measured. They have the further advantage of being a suitable starting point for the introduction of other groups and, in addition, a certain amount is already known about their steric [6] and other [6,7] effects on the optical stability of *unbridged* diphenyls.



(I*a*) : R = OMe, X = I.
(I*b*) : R = H, X = I.
(I*c*) : R = NO_2, X = I.
(I*d*) : R = F, X = I.



(II)



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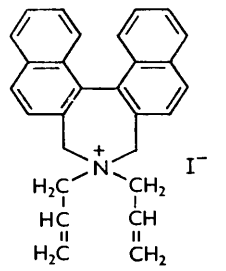
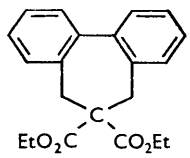
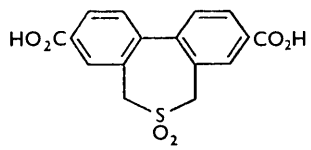


(IV)



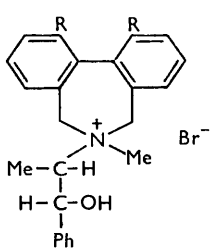
(V)

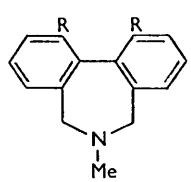


(VI)

Accordingly 2 : 2′-dimethyl-6 : 6′-dinitrodiphenyl was prepared and was brominated by *N*-bromosuccinimide in the presence of benzoyl peroxide, a method used by Wenner [8] for other ditolyls. Interaction of the resulting 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl * with piperidine gave the *spiro*-piperidinium compound (I*c*) which was isolated as the iodide. However, the camphorsulphonate failed to crystallise for nearly a year. The dibromo-compound was meanwhile condensed with (—)-ephedrine and, after repeated crystallisation, two diastereoisomeric bromides (VII*a*) were isolated. The one which was less soluble in ethanol had $[\alpha]_{5461}^{23}$ —709° and by a Hofmann degradation gave (—)-2 : 7-dihydro-1-methyl-4′ : 1″-dinitro-3 : 4-5 : 6-dibenzazepine (VIII*a*), with $[\alpha]_{5461}^{19}$ —1343°. The

(VII*a*) : R = NO_2
(VII*b*) : R = F





(VIII*a*) : R = NO_2
(VIII*b*) : R = F

quaternary bromide which was more soluble in ethanol, had $[\alpha]_{5461}^{18}$ +689° and, in a similar way, gave the (+)-azepine with $[\alpha]_{5461}^{19}$ +1333°.

The azepine was optically stable in benzene solution up to about 100°. The yellow

* Shortly after we had first made this compound its preparation by a different method was announced by Iffland and Siegel [3] and by Mislow and Newman.[9]

[6] Stanley and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 1200; Adams and Yuan, *Chem. Rev.*, 1933, **12**, 261; and many other papers.
[7] Brooks, Harris, and Howlett, *J.*, 1957, 1934.
[8] Wenner, *J. Org. Chem.*, 1952, **17**, 523.
[9] Mislow and Newman, *J. Amer. Chem. Soc.*, 1957, **79**,1769.

solution became very dark when heated at 110° in the air and it was therefore not possible to follow the racemisation by direct observation of a solution in a jacketed polarimeter tube at a suitable temperature. Instead, a solution of the azepine in benzene was heated in a number of sealed tubes in a thermostat-controlled oil-bath, and tubes were withdrawn at suitable intervals for polarimetric examination. In this way the dinitroazepine in benzene solution was found to have a half-life of 16 hr. at 125° and of 2·6 hr. at 145°, whence the activation energy is 30 kcal. mole^{-1}. Rather surprisingly the dinitroazepine appears to be much less optically stable than the dimethoxyazepinium compound (I*a*), which was only partly racemised after 8 hr. in boiling *cyclo*hexanol solution (160°).[1] However, the difference in the valency state of the nitrogen atom in the two compounds may well affect their relative optical stabilities, as may the alteration in type of solvent. To test this, the methiodide (II; R = NO_2, R′ = R″ = Me, X = I) of the (−)-dinitroazepine was made. It racemised in acetone solution (sealed tubes) at 145° with a half-life of 4·75 hr. It is thus nearly twice as optically stable as the tertiary amine at that temperature, but still not as stable as the quaternary dimethoxy-compound.

The slight steric effect of fluorine, compared with that of any other (necessarily larger) atom or group, is apparent from extensive studies [10] of optical stabilities in non-bridged hindered diphenyls and also from recent spectroscopic work.[11] We therefore prepared 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl [12] and brominated it with peroxide-catalysed *N*-bromosuccinimide. In this case the dibromo-compound failed to crystallise and was condensed without isolation with piperidine, giving the salt (I*d*), and with (−) ephedrine, giving the salt (VII*b*). The latter was crystallised from ethanol and the less soluble bromide obtained as needles with $[\alpha]_{5461}^{18\cdot5}$ +50°. Its diastereoisomer crystallised from aqueous ethanol in hydrated cubes with $[\alpha]_{5461}^{18\cdot5}$ −55°. In view of the expected optical instability of these compounds, Hofmann degradation was carried out at the lowest temperature practicable, *viz.*, about 70°. The resulting azepines (VIII*b*) were liquid and were therefore examined in dilute hydrochloric acid solution without isolation. Approximate concentrations of the deliquescent hydrochlorides were determined subsequently by evaporation. The azepine hydrochlorides had $[\alpha]_{5461}^{18\cdot5}$ +45° and $[\alpha]_{5461}^{18\cdot5}$ −41·5° respectively. They racemised in aqueous hydrochloric acid solution with a half-life of 6·5 hr. at 80° and of 2·0 hr. at 91°. At lower temperatures the rate was too slow for convenient measurement; at higher temperatures the solvent was too near its boiling point. These rates give a value of about 28 kcal. mole^{-1} for the activation energy but the data are inadequate for accurate assessment of *E*. It is, however, clear that the compound is much more optically stable than the hydrocarbon ester (V), which was inactive after 5 hr. at 32·5°.[3] Slight racemisation (perhaps a few units per cent.) probably occurred during the Hofmann degradation.

The quaternary ephedrinium iodide [1] without *ortho*-substituents (VII; R = H) was also re-examined. It showed no mutarotation in chloroform solution at temperatures in the range 0—50°.

Experimental

(In all polarimetric readings, unless otherwise stated, $l = 2$.)

2 : 2′-*Bisbromomethyl*-6 : 6′-*dinitrodiphenyl*.—2 : 2′-Dimethyl-6 : 6′-dinitrodiphenyl was prepared by the method of Carlin and Foltz,[13] except that it was found preferable to carry out the Ullmann reaction at 150° instead of 200°. The dinitroditolyl, m. p. 110·5—112° (10·7 g.), was heated under reflux in dry carbon tetrachloride (64 c.c.) with *N*-bromosuccinimide (14·3 g.) and benzoyl peroxide (0·1 g.) for 5 hr. A little more (0·05 g.) catalyst was washed in with carbon tetrachloride (20 c.c.) and heating continued for another 3 hr. The hot solution was filtered and concentrated; crude dibromide separated on cooling. Some of it had also crystallised with the succinimide and was isolated by washing out the latter with much cold water.

[10] Kleiderer and Adams, *J. Amer. Chem. Soc.*, 1931, **53**, 1575; 1933, **55**, 4219; Stanley, McMahon, and Adams, *ibid.*, p. 706; Stoughton and Adams, *ibid.*, 1932, **54**, 4426.
[11] Beaven and Hall, *J.*, 1956, 4637.
[12] Bell, *J.*, 1934, 835.
[13] Carlin and Foltz, *J. Amer. Chem. Soc.*, 1956, **78**, 1997.

The product was crystallised from dry benzene (yield, 9·5 g., 64%).* Recrystallisation gave pure 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl as pale yellow pointed prisms, m. p. 184—185° (Found: C, 39·3; H, 2·1; N, 6·2; Br, 37·4. Calc. for $C_{14}H_{10}O_4N_2Br_2$: C, 39·1; H, 2·3; N, 6·5; Br, 37·2%). The use of slightly impure dinitroditolyl greatly reduced the yield of brominated product.

2 : 7-*Dihydro*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—Piperidine (3·74 g., 2·2 mols.) was added to a solution of the dinitro-dibromide (8·6 g., 1 mol.) in benzene at 50° and the mixture kept at this temperature for 3½ hr. The solution was then decanted from the gum, which was washed with warm benzene and triturated with cold water. The bromide crystallised from water as a pale cream solid, m. p. 302—303° (decomp.) (5·6 g., 65%). It darkened rapidly in light and was therefore converted into the *iodide*, which crystallised from water in deep yellow prisms, m. p. 306—308° (decomp.) (Found: C, 47·4; H, 3·9; N, 8·85; I, 26·8. $C_{19}H_{20}O_4N_3I$ requires C, 47·4; H, 4·2; N, 8·7; I, 26·4%).

(−)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—A solution of (−)-ephedrine hemihydrate (12 g., 2·3 mols.) in benzene was dried (Na_2SO_4) and added to a solution of 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl (12·9 g., 1 mol.) in dry benzene at 50°. The mixture became cloudy; it was kept at *ca.* 50° for 35 hr., during which a gum gradually separated. The gum solidified on treatment with water; it was washed with warm benzene and then with cold water (crude yield, 10·3 g.) and crystallised repeatedly from absolute ethanol. The less soluble quaternary (−)-*bromide* (2·5 g.) was obtained as yellow needles, m. p. 248° (decomp.), $[\alpha]_{5461}^{23}$ −709°, $[\alpha]_D^{23}$ −544° (*c* 0·994 in MeCN, *l* = 1) (Found: C, 56·3; H, 4·6; N, 8·25; Br, 15·6. $C_{24}H_{24}O_5N_3Br$ requires C, 56·0; H, 4·7; N, 8·2; Br, 15·5%).

(+)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—After separation of most of the (−)-isomer, ethanol was removed from the mother-liquor and the impure quaternary (+)-bromide obtained as a gum. Three crystallisations from acetonitrile gave the (+)-*bromide* as yellow needles, m. p. 228° (decomp.), $[\alpha]_{5461}^{18}$ +689°, $[\alpha]_D^{18}$ +533° (*c* 0·273 in MeCN) (Found: C, 55·6; H, 4·8; N, 8·1; Br, 15·2%). The sparing solubility of this isomer in acetonitrile meant that only very dilute solutions could be examined polarimetrically.

(−)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—A solution of the (−)-bromide (1·3 g.) in ethanol was kept on a steam-bath and treated, during 1 hr., with an aqueous suspension of silver oxide. After filtration, ethanol, water and β-methylstyrene oxide were removed under reduced pressure, a short period of heating at 120° being necessary to ensure complete removal of the epoxide. The residue was dissolved in ether, and the (−)-*amine* extracted with dilute hydrochloric acid and precipitated with ammonia. It crystallised from benzene–light petroleum (b. p. 60—80°) in yellow needles (0·5 g.), m. p. 169—170°, $[\alpha]_{5461}^{19}$ −1343° ± 5°, $[\alpha]_D^{19}$ −1030° ± 5° (*c* 0·197 in C_6H_6) (Found: C, 60·4; H, 4·2; N, 13·8. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·4; N, 14·05%).

(+)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—Similar treatment of the (+)-bromide (1·1 g.) gave the (+)-*amine* (0·4 g.), m. p. 169—170°, $[\alpha]_{5461}^{19}$ +1333° ± 2°, $[\alpha]_D^{19}$ +1024° ± 2° (*c* 0·454 in C_6H_6) (Found: C, 59·8; H, 4·8; N, 14·1%).

Racemisation of (+)- *and* (−)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—The (+)-amine (0·198 g.) in benzene solution (100 c.c.) with $\alpha_{5461}^{18\cdot5}$ +2·64° was sealed in 8 tubes and heated in a thermostat at 125°. Tubes were removed at intervals, then chilled, and rotations read at 18·5°. During 15·25 hr. the rotation fell to +1·36°; $k = 1\cdot2 \times 10^{-5}$ sec.$^{-1}$. Heating of the last tube was continued for a few days; the solution was then inactive. Similar experiments at 145° gave $k = 7\cdot4 \times 10^{-5}$ sec.$^{-1}$; $E = 30$ kcal. mole^{-1}; $A = 10^{11\cdot5}$ sec.$^{-1}$.

(−)-2 : 7-*Dihydro*-1 : 1-*dimethyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium iodide*, prepared from the (−)-amine, crystallised from ethanol and had m. p. 252—254° (decomp.), $[\alpha]_{5461}^{19}$ −813° in acetone (*c* 0·089) (Found: C, 43·1; H, 3·7; N, 9·5; I, 29·0. $C_{16}H_{16}O_4N_3I$ requires C, 43·5; H, 3·7; N, 9·5; I, 28·8%). Racemisation of an acetone solution in sealed tubes at 145° gave $k = 4\cdot05 \times 10^{-5}$ sec.$^{-1}$.

2 : 2′-*Difluoro*-6 : 6′-*dimethyldiphenyl*.[12]—2 : 2′-Dimethyl-6 : 6′-dinitrodiphenyl was reduced[15]

* Newman, Rutkin, and Mislow[14] report that they also tried this method of preparation of the dibromide (cf. ref. 9) but only obtained a 10% yield.

[14] Newman, Rutkin, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 465.

[15] Kenner and Stubbings, *J.*, 1921, **119**, 593.

and the resulting diamine converted into the tetrazonium borofluoride. Thermal decomposition at 100°, followed by steam-distillation, gave 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl in 37% yield * (from the borofluoride), m. p. 44—45° (from methanol).

(+)- *and* (−)-4′ : 1″-*Difluoro*-2 : 7-*dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—A solution of 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl (10 g.) in carbon tetrachloride (32 c.c.) was heated under reflux with *N*-bromosuccinimide (16·5 g.) and benzoyl peroxide (0·1 g.) for 8 hr. (Contrary to Wenner's experience [8] we found that the use of larger amounts of catalyst, with consequent liberation of bromine, did not improve the yield.) The hot solution was filtered and solvent removed from the filtrate. The residual dibromo-compound was a gum and was dissolved in dry benzene and used without further purification. A solution of (−)-ephedrine hemihydrate (16·5 g., 2·2 mols.) in benzene (175 c.c.) was dried (Na_2SO_4) and added to the solution of the dibromo-compound at 50°; the mixture was kept at 50° for 10 hr. Needles and a gum separated. The needles (presumably ephedrine hydrobromide) dissolved in water; the gum solidified (10·5 g., 50%) and was repeatedly crystallised from ethanol. The less soluble quaternary *bromide* separated as fluffy needles, m. p. 233—234° (decomp.), $[\alpha]_{5461}^{18\cdot5}$ +50°, $[\alpha]_{D}^{18\cdot5}$ +37·5° (*c* 0·439 in EtOH) (Found: C, 62·2; H, 5·3; N, 3·5; Br, 17·2. $C_{24}H_{24}ONBrF_2$ requires C, 62·6; H, 5·25; N, 3·0; Br, 17·4%).

Dilution of the mother-liquor with water gave the more soluble quaternary *bromide* as hydrated cubes, m. p. 230—232° (decomp.), $[\alpha]_{5461}^{18\cdot5}$ −55°, $[\alpha]_{D}^{18\cdot5}$ −41° (*c* 0·509 in EtOH) (Found: C, 60·6; H, 5·5; N, 2·9; Br, 16·6. $C_{24}H_{24}ONBrF_2,H_2O$ requires C, 60·3; H, 5·5; N, 2·9; Br, 16·7%).

(+)- *and* (−)-4′ : 1″-*Difluoro*-2 : 7-*dihydro*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine*.—The (+)-quaternary bromide (1 g.) was dissolved in ethanol and the warm solution treated with freshly prepared silver oxide during 45 min. After filtration the solution was kept at about 70° while ethanol, water, and the epoxide were removed under reduced pressure. The residue was dissolved in 10% hydrochloric acid, and the solution washed with ether until the washings were no longer optically active. The solution had $\alpha_{5461}^{18\cdot5}$ +0·79° and $[\alpha]_{5461}^{18\cdot5}$ +45° (*c* of hydrochloride determined by subsequent evaporation, 0·877).

Similar treatment of the (−)-quaternary bromide (1 g.) gave (−)-amine. Its solution in 10% hydrochloric acid had $\alpha_{5461}^{18\cdot5}$ −0·47° and $[\alpha]_{5461}^{18\cdot5}$ −41·5° (*c* of hydrochloride, 0·566).

The *methiodide* [made from the (±)-amine after racemisation] crystallised from ethanol in prisms, m. p. 253—254° (Found: I, 32·7. $C_{16}H_{16}NIF_2$ requires I, 32·8%).

Racemisation of (+)- *and* (−)-4′ : 1″-*difluoro*-2 : 7-*dihydro*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine*.—The solutions in 10% hydrochloric acid obtained from the Hofmann degradation were observed in a jacketed polarimeter tube round which water from a thermostat was circulating. At 80° $k = 2{\cdot}95 \times 10^{-5}$ sec.$^{-1}$; at 91° $k = 9{\cdot}75 \times 10^{-5}$ sec.$^{-1}$; whence E = 27·8 kcal. mole^{-1} and $A = 10^{12\cdot7}$ sec.$^{-1}$.

4′ : 1″-*Difluoro*-2 : 7-*dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—2 : 2′-Difluoro-6 : 6′-dimethyldiphenyl (4·36 g.) was brominated and the resulting dibromide treated in benzene solution with piperidine. The piperdinium bromide formed was very soluble in water and was converted into the less soluble *iodide*, which crystallised from water in needles (5·2 g., 60%), m. p. 268—270° (decomp.) (Found: C, 53·3; H, 4·3; N, 3·0; I, 29·35. $C_{19}H_{20}NIF_2$ requires C, 53·4; H, 4·7; N, 3·3; I, 29·7%).

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* No other recognisable product was isolated. However an attempt to convert 2-amino-2′-methyldiphenyl into the corresponding fluoro-compound failed and gave fluorene as the only product (cf. Mascarelli and Gatti [16]).

[16] Mascarelli and Gatti, *Atti IV Congr. naz. Chim. pura applicata*, 1933, 503.