684. *Steric Effects in 2,2′-Bridged Diphenyls with a Heterocyclic Bridging Ring. Part II.* An Optically Active Tetrahydrodibenzazocine.*

By SHAKTI R. AHMED and D. MURIEL HALL.

1,2,7,8-Tetrahydro-3,4:5,6-dibenzazocine-1-spiro-1′-piperidinium picrate has been synthesised and obtained in optically active forms by crystallisation of the (+)- and (−)-α-bromocamphor-π-sulphonates. The compound is optically highly labile; Arrhenius parameters for racemisation have been determined. The optical stabilities of this and other 2,2′-bridged diphenyls are discussed.

THE optical stabilities of a number of diphenyls, in which two or three atoms join the 2- and the 2′-position to form part of a six- or seven-membered ring, have now been investigated.[1-7] In most of these compounds additional substituents (or parts of fused benzene rings) are present in the diphenyl 6- and 6′-positions.[3-7]

Chemical differences among the compounds studied have precluded comparisons of

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* Part I, *J.*, 1958, 3043.

[1] Iffland and Siegel, *J. Org. Chem.*, 1956, **21**, 1056; *J. Amer. Chem. Soc.*, 1958, **80**, 1947.

[2] Truce and Emrick, *ibid.*, 1956, **78**, 6130.

[3] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854.

[4] Hall and Turner, *J.*, 1955, 1242; Hall, *J.*, 1956, 3674.

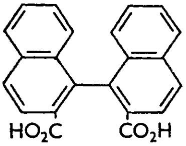
[5] Armarego and Turner, *J.*, (*a*) 1956, 3668; (*b*) 1957, 13.

[6] Badger, Jefferies, and Kimber, *J.*, 1957, 1837.

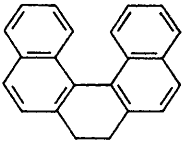
[7] Ahmed and Hall, *J.*, 1958, 3043.

optical stability under identical conditions but it is nevertheless possible to make certain generalisations.

(1) In the few cases [4,5,6] where reasonably valid comparisons can be made the bridged diphenyls (with a 6- or 7-membered ring) are optically *less* stable than unbridged compounds with somewhat similar blocking groups, presumably because the molecules of the bridged compound are held in a position which is already part of the way towards the transition state for racemisation. For example, compound (I) is optically more stable than (II) or (III) [4]; (IV) than (V); [5a] and (VI),[8] apparently, than (VII).[7] It is not, of course, possible to make a direct comparison; even if both (VIII) and (IX) happen to be available in optically active forms (the ditolyl being more suitable than the diphenic acid), the unbridged compound may racemise by either of two paths; in one of these, like groups pass each other (as indicated in IX), and in the other, unlike groups pass each other (as indicated in X). [In the case of (XI) [9] the second type of racemisation path is almost certainly the more important and, in fact, this compound is optically less stable than (XII) [3].] Further, the optical stability of (VIII) is undoubtedly influenced by the nature of the atom Y and by groups which may be attached to it.



(I)



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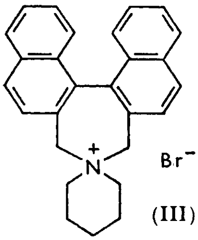
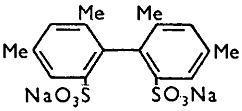


(III)



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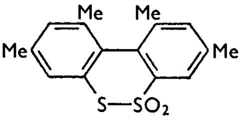
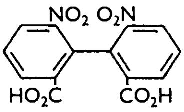
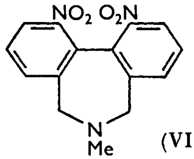


(V)

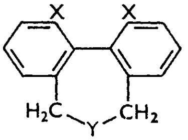


(VI)

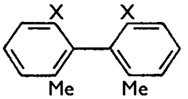


(VII)

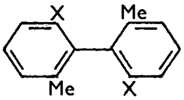
(2) Where both 6- and 7-membered ring compounds (with the same 6,6′-substituents) have been studied, the 6-membered ring compound is of a considerably lower optical stability than the 7-membered ring compound.[4,5b]



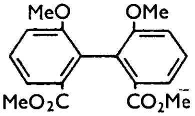
(VIII)



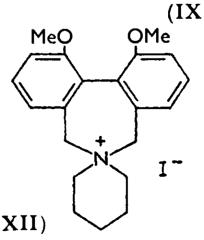
(IX)



(X)



(XI)



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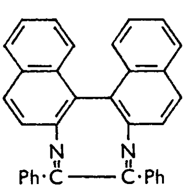
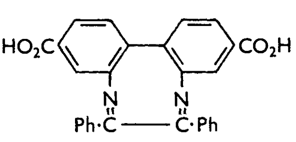


(XIII)



(XIV)

This suggested to us that compounds in which the bridge forms part of an 8-membered ring might be of yet higher optical stability. For some years such compounds showing optical activity were limited to two with an unsaturated heterocyclic bridge. Kuhn and Goldfinger [10] prepared the enantiomeric forms of the pentacyclic compound (XIII) from

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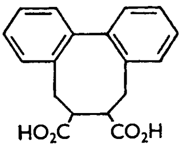
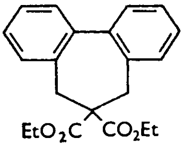
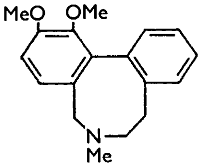
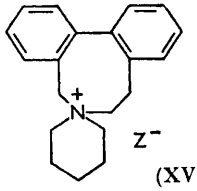
[8] Kuhn and Albrecht, *Annalen*, 1927, **455**, 272.
[9] Wittig and Petri, *ibid.*, 1933, **505**, 17.
[10] Kuhn and Goldfinger, *ibid.*, 1929, **470**, 183.

(+)- and (—)-2,2′-diamino-1,1′-dinaphthyl, and Bell[11] resolved the analogue (XIV), in which the 6- and the 6′-position are occupied only by hydrogen. In 1957 Mislow[12] obtained the two dibenzocyclo-octadiene acids (XV) in optically active forms and found that both compounds were optically highly labile, the *cis*-acid racemising and the *trans*-acid mutarotating at 31·5° in ethanolic solution with half-lives of 85 min. and 12 min. respectively.[13] They are thus of the same order of optical stability as the 7-membered ring homocyclic compound[1] (XVI) which has a half-life of 80 min. in cyclohexane at 32·5°. Bell's compound, however, is optically much more stable (undergoing resolution, not asymmetric transformation) and this may be attributed to the greater rigidity conferred on the molecule by the additional double bonds.


(XV)


(XVI)


(XVII)


(XVIII)

The recent synthesis of *OO*-dimethylapogalanthamine (XVII) by Kobayashi and Uyeo[14] provided a route to a heterocylic compound with an 8-membered ring. In the present work 2-(2-bromoethyl)-2′-bromomethyldiphenyl was prepared and condensed with (—)-ephedrine. Crystallisation of the quaternary iodide gave strong evidence of optical resolution but not of optical lability (at room temperature). The presence of a new asymmetric nitrogen atom is a complicating factor and, in view of this and of the initial low yield of the quaternary iodide, this compound was not investigated further.

Condensation of the dibromo-compound with piperidine gave a quaternary compound (XVIII), isolated as the iodide. The (+)-α-bromocamphor-π-sulphonate underwent asymmetric transformation by crystallisation, 93% of the salt crystallising as one diastereoisomer, which underwent rapid mutarotation in solution (*e.g.*, it had a half-life of about 3 min. in acetonitrile solution at 15·5°). The bromocamphorsulphonate and the iodide had similar solubilities in cold ethanol so that it was not possible to reprecipitate the iodide. However, the picrate was less soluble and accordingly the bromocamphorsulphonate was dissolved in ethanol at —10° and treated with a cold (—10°) saturated ethanolic solution of picric acid; (—)-1,2,7,8-tetrahydro-3,4:5,6-dibenzazocine-1-spiro-1′-piperidinium picrate [XVIII; $Z = C_6H_2(NO_2)_3O$] separated. (A preliminary account of this part of the work has already appeared.[15]) In order to obtain the other enantiomer the (—)-α-bromocamphor-π-sulphonate was prepared. Similar cold decomposition gave the (+)-picrate.

Racemisation of the optically active picrates was studied in acetone solution at 2° (half-life 24·5 min.), 10°, 16°, and 23° (half life 1·4 min.). The activation energy is 22·1 kcal. mole^{-1} and the non-exponential term *A* of the Arrhenius equation is $10^{14 \cdot 2}$ sec.$^{-1}$. The racemisation rate was also determined in acetonitrile at 2° and was, within experimental error, the same as in acetone at that temperature. It was not possible to determine the rate in ethanol as the solubility of the picrate in cold ethanol was too low.

The dibenzazocine compound is thus even less optically stable than Mislow's acids. The replacement of a carbon atom in the ring by the smaller positive nitrogen may be partly responsible for this, but the complexity of the factors contributing to optical stability

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[11] Bell, *J.*, 1952, 1527.

[12] Mislow, *Trans. New York Acad. Sci.*, 1957, **19**, 298.

[13] Dvorken, Smyth, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486.

[14] Kobayashi and Uyeo, *J.*, 1957, 638.

[15] Ahmed and Hall, *Chem. and Ind.*, 1958, 1329.

is clearly indicated by the Arrhenius parameters for the racemisation of Mislow's *cis*-acid in different solvents.[13] In ethanol E is 22·8 kcal. mole^{-1} and A is $10^{12\cdot5}$ sec.$^{-1}$; in 2·32N-sodium hydroxide, however, E is 25·4 kcal. mole^{-1} and A is $10^{14\cdot6}$ sec.$^{-1}$. Thus if our dibenzazocine compound in acetone is compared with the acid in ethanol, the greater optical stability of the latter is due mainly to its smaller value of A but, if the comparison is made with the acid in sodium hydroxide, then the greater optical stability of the homocyclic compound is largely the result of its higher activation energy. The picrate, like the acid in sodium hydroxide, will of course be ionised but in acetone it will not necessarily be highly dissociated.

de la Mare [16] and Harris [17] have recently drawn attention to the fact that the value of A for racemisation of diphenyls is often of the order of 10^{11} sec.$^{-1}$. In Harris's Table [18] (which includes various types of internally hindered compounds) values of A in the range 10^{13} to 10^{14} sec.$^{-1}$ are shown by two bridged compounds (II and IV) and by tri-*o*-thymotide. Since Mislow's *cis*-acid, the dibenzazocine compound, and 4',1''-difluoro-2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (A $10^{12\cdot7}$ sec.$^{-1}$) also have values of A of *ca.* 10^{13} sec.$^{-1}$ it seems possible that the two types of diphenyl, bridged and non-bridged, fall roughly into two classes as far as the non-exponential term in the Arrhenius equation is concerned. At present the information available is quite inadequate to decide whether the greater optical stability of the non-bridged compounds is due solely to the different range of values of A or whether, as surmised earlier in this paper, the non-bridged compounds do in general also have lower activation energies.

Compound (VII) with A $10^{11\cdot5}$ sec.$^{-1}$ is apparently an exception to this classification. Brooks, Harris, and Howlett [19] found, however, that the introduction of further nitro-groups into 6-nitrodiphenic acid increased the optical stability of the compound by reducing A without altering E and it is possible that the nitro-groups in compound (VII) are having a similar effect.

EXPERIMENTAL

(In all polarimetric readings $l = 2$.)

Rates of racemisation and mutarotation were determined by dissolving the finely ground solid as quickly as possible in solvent at approximately the right temperature and filtering the solution into a jacketted polarimeter tube round which water at the required temperature was circulating.

Methyl 2'-Carbomethoxymethyldiphenyl-2-carboxylate.—Diphenic anhydride (m. p. 225—226°) * was converted into methyl hydrogen diphenate,[21] and an Arndt–Eistert reaction carried out [22] on the acid chloride of the latter, with methanol as solvent for the decomposition of the diazo-ketone. The resulting ester was dimorphic (needles and prisms), both forms having the same m. p. (71—72°).

2-(2-*Hydroxyethyl*)-2'-*hydroxymethyldiphenyl* was obtained by reducing the above ester in ethereal solution with lithium aluminium hydride. It had m. p. 103·5—104° (from benzene) (Found: C, 79·1; H, 7·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1'-*piperidinium Iodide* (XVIII; Z = I).—The above diol (12 g.) was heated with 48% hydrobromic acid (570 c.c.) for ½ hr. at 126°. The acid was then decanted; another 570 c.c. of acid was added to the residue and the mixture was heated for a further ½ hr. The mixture was cooled and the acid again decanted. The residual dibromo-compound, which did not solidify, was dissolved in benzene and dried (Na_2SO_4). Piperidine (13 c.c., 2·3 mols.) was added and the solution kept at *ca.* 50° for 6 hr.

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* The highest m. p. given in the literature [20] is 222—224°; most references are to values below 220°.

[16] de la Mare, " Progress in Stereochemistry," Vol. I (Ed. Klyne), Butterworths, London, 1954.

[17] Harris, *ibid.*, Vol. II (Ed. Klyne and de la Mare), Butterworths, London, 1958, p. 173.

[18] Ref. 17, p. 174.

[19] Brooks, Harris, and Howlett, *J.*, 1957, 1934.

[20] Underwood and Kochmann, *J. Amer. Chem. Soc.*, 1923, **45**, 3071.

[21] *Idem, ibid.*, 1924, **46**, 2069.

[22] Marvel and Patterson, *ibid.*, 1941, **63**, 2218.

Solid separated and was filtered off and washed with warm benzene. It was very soluble and was therefore converted into the iodide by treating the cold aqueous solution with a saturated solution of potassium iodide. The quaternary *iodide*, crystallised from water, had m. p. 248° decomp. (7·5 g., 36%) (Found: C, 59·3; H, 6·5; N, 3·05; I, 31·5. $C_{20}H_{24}NI$ requires C, 59·3; H, 6·0; N, 3·5; I, 31·3%).

(−)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium* (+)-α-*Bromocamphor*-π-*sulphonate*.—The quaternary iodide (3·0 g.) was treated with silver (+)-bromocamphorsulphonate (3·1 g.) in aqueous alcohol. The filtered solution was evaporated to dryness and the residue was dissolved in a mixture of ethanol and ethyl acetate. 3·5 g. of salt gradually crystallised and another 0·5 g. of the same diastereoisomer was obtained from the mother-liquor (total yield 93%). The same diastereoisomer was obtained by crystallisation from acetonitrile. The (−)-dibenzazocine-1-spiro-1′-piperidinium (+)-α-bromocamphor-π-sulphonate had m. p. 201°, initial $[\alpha]_{5461}^{15\cdot5}$ +2·3° (by extrapolation) and final $[\alpha]_{5461}^{15\cdot5}$ +64·6° (*c* 0·747 in acetonitrile).

The mutarotation of this salt was studied (*a*) in ethanol at 7° (*c* 1·046), α_{5461} changing from +0·87° to +1·35° ($k = 8\cdot5 \times 10^{-4}$ sec.$^{-1}$), and (*b*) in acetonitrile at 15·5° (*c* 0·747), α_{5461} changing from +0·325° to +0·97° ($k = 3\cdot5 \times 10^{-3}$ sec.$^{-1}$).

(+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium* (−)-α-*Bromocamphor*-π-*sulphonate*.—This was obtained by using the quaternary iodide (0·9 g.) and silver (−)-α-bromocamphor-π-sulphonate (0·95 g.). 1·15 g. of the *salt* (88%) crystallised as one diastereoisomer and had initial $[\alpha]_{5461}^{15\cdot5}$ −4·0° (by extrapolation) and final $[\alpha]_{5461}^{15\cdot5}$ −65·1° (*c* 0·914 in acetonitrile) (Found: C, 60·9; H, 6·5. $C_{30}H_{38}O_4NBrS$ requires C, 61·2; H, 6·5%).

The mutarotation of this salt was studied in acetonitrile at 15·5° (*c* 0·914). α_{5461} changed from −0·53° to −1·19°; $k = 3\cdot7 \times 10^{-3}$ sec.$^{-1}$. (Average *k* for the two isomers $3\cdot6 \times 10^{-3}$ sec.$^{-1}$.)

(−)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrate*.—The finely ground (+)-bromocamphorsulphonate was dissolved in ethanol, precooled to −10°, and a saturated ethanolic solution of picric acid at −10° added to it. The (−)-picrate began to separate on scratching and was rapidly filtered and dried *in vacuo*. It racemised rapidly in solution and had initial $[\alpha]_{5461}^{2}$ −71° in acetone (by extrapolation to zero time) and initial $[\alpha]_{5461}^{2}$ −75° in acetonitrile.

(+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrate*.—Similar treatment of the (−)-bromocamphorsulphonate with picric acid at −10° gave the (+)-*picrate*, which had initial $[\alpha]_{5461}^{10}$ +62° in acetone (by extrapolation). For analysis a sample was crystallised from ethanol; it was then presumably racemic and had m. p. 196—197° (Found: C, 62·1; H, 5·0; N, 11·5. $C_{26}H_{26}O_7N_4$ requires C, 61·65; H, 5·2; N, 11·1%).

Racemisation of (−)- *and* (+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrates*.—Racemisation rates were measured in acetone solution, two determinations being made at each temperature (*c* 0·4—0·8; observed α_{5461} at first reading between 0·7° and 0·4°). At 2° $k = 4\cdot7 \times 10^{-4}$ sec.$^{-1}$; at 10° $k = 1\cdot33 \times 10^{-3}$ sec.$^{-1}$; at 16° $k = 3\cdot3 \times 10^{-3}$ sec.$^{-1}$; at 23° $k = 8\cdot45 \times 10^{-3}$ sec.$^{-1}$; whence $E = 22\cdot1$ kcal. mole^{-1}, and $A = 10^{14\cdot2}$ sec.$^{-1}$. The rate was also determined in acetonitrile solution at 2° and gave $k = 4\cdot8 \times 10^{-4}$ sec.$^{-1}$.

1,2,7,8-*Tetrahydro*-1-(β-*hydroxy*-α-*methylphenethyl*)-1-*methyl*-3,4:5,6-*dibenzazepinium Iodide*.—A solution in dry benzene of the dibromo-compound (from 15 g. of the diol) and (−)-ephedrine (from 26 g. of the hemihydrate) was kept at 50—60° during 40 hr.; the quaternary compound formed was extracted with water and precipitated as the *iodide* (4 g., 15%). After crystallisation from ethanol it had m. p. 224—225° (decomp.) (Found: C, 61·5; H, 6·15; I, 26·0. $C_{25}H_{28}ONI$ requires C, 61·9; H, 5·8; I, 26·15%). By controlled crystallisation from aqueous alcohol two fractions were obtained with $[\alpha]_{5461}^{18}$ +118° (*c* 0·214 in ethanol) and $[\alpha]_{5461}^{18}$ −60° (*c* 0·226 in ethanol) respectively. Their rotations were unchanged after their ethanolic solutions had been kept at 100° for 3 hr.

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