436. *Steric Effects in 2,2'-Bridged Biphenyls with a Heterocyclic Bridging Ring. Part IV.[1] Some Dibenzodiazocines.*

By D. Muriel Hall and Joan M. Insole.

The enantiomeric forms of 4',1''-dimethyl-5,6:7,8-dibenzo-1,4-diazocine have been prepared from (+)- and (−)-2,2'-diamino-6,6'-dimethylbiphenyl. As expected, the diazocine is highly stable optically but some loss of optical activity occurs at *ca.* 350° in diphenyl ether. Arrhenius parameters for the racemisation of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3''-dicarboxylic acid in ethyl benzoate solution in the temperature range 247—288° have been determined.

2,2'-Bridged biphenyls with an unsaturated heterocyclic bridge appear to show optical stabilities of a higher order than those found in similar compounds with saturated bridges.[2] Thus Bell[3] resolved 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3''-dicarboxylic acid (I; R = Ph), which must therefore be optically stable up to at least 78° (the brucine salt was crystallised from ethanol), whereas the related compounds (II) (*cis* and *trans*) and (III), with saturated bridges forming parts of eight-membered rings, are

optically highly labile. The *cis*-acid (II) racemises and the *trans*-acid mutarotates in ethanolic solution at 31·5° with half-lives of 85 and 12 minutes, respectively;[4] the dibenzazocine picrate[2] (III) has a half-life in acetone solution at 23° of 1·4 minute. The only other optically active diazocine known is (IV), prepared by Kuhn and Goldfinger[5] by the condensation of (+)- or (−)-2,2'-diamino-1,1'-binaphthyl with benzil at *ca.* 200°. Here the comparison is less clear-cut since the binaphthyl system confers considerable optical stability on the system in any case. The diazocine must be optically stable at

least up to 200° (its temperature of formation); 2,7-dihydrodinaphtho(2',1':3,4)(1'',2'':5,6)-azepinium-1-spiro-1'''-piperidinium bromide[6] (V) has a half-life of the order of 26 hours at 172°.

[1] Part III, Ahmed and Hall, *J.*, 1960, 4165.
[2] Ahmed and Hall, *J.*, 1959, 3383.
[3] Bell, *J.*, 1952, 1527.
[4] Dvorken, Smyth, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486.
[5] Kuhn and Goldfinger, *Annalen*, 1929, **470**, 183.
[6] Hall and Turner, *J.*, 1955, 1242.

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In the present work it was hoped to determine the Arrhenius parameters for some diazocines, as has been done for many compounds with saturated bridges.[2,4,6-9] The first compound selected for study was 4′,1″-dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine (VI; R = Ph), since the racemic compound had already been prepared[5] and the racemisation of the related unbridged compound, 2,2′-diamino-6,6′-dimethylbiphenyl, very thoroughly studied.[10]

Condensation of the (±)-diamine and benzil failed to occur under the conditions described by Kuhn and Goldfinger[5] (20 min. at 180—200°) but could be brought about by longer heating (4 hr.) at 220—230°. A cleaner product was obtained by heating the two compounds together in boiling propionic acid (an adaptation of Allinger and Youngdale's use of acetic acid[11] in the preparation of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine). Similar condensations of the (+)- and (−)-diamines[12] gave, respectively, the (−)- and (+)-diazocines.

Attempts to racemise the diazocine in boiling solvents were unsuccessful. The rotation of a solution in tetralin was unchanged after boiling under reflux (207°) for $9\frac{1}{2}$ hours and that of a solution in diphenyl ether similarly unchanged after 4 hours at the boiling point (259°). Some loss of optical activity occurred when solutions of the diazocine in diphenyl ether were heated in sealed tubes. For example, 24% of the optical activity was lost after heating gradually to approximately 350° and maintaining at this temperature for 5 hours; the solutions darkened and it was not possible to determine whether the loss of optical activity was due solely to racemisation or at least in part to thermal decomposition. With the apparatus available more precise measurements were not practicable.

Kistiakowsky and Smith[10] studied the racemisation of 2,2′-diamino-6,6′-dimethylbiphenyl in diphenyl ether solution (in sealed tubes) and in the gas phase. In solution the diamine lost 42% of its optical activity after being heated at 355° for 5·15 hours and 30% of its optical activity after 31 minutes at 385°. Qualitatively, it thus appears that the (bridged) diazocine is optically somewhat more stable than the closely related unbridged diamine; previous experience[6] among compounds with saturated bridges has been the reverse of this. However, the high temperatures necessary to permit study of loss of optical activity in the diazocine and the diamine may invalidate this conclusion. It is possible that the diazocine is virtually non-racemisable by the types of molecular distortions normally involved in the racemisations of biphenyls and binaphthyls and that what is being studied here involves bond-breaking in thermal decomposition.

The preparation of 2,3-dimethyl-diazocines, by the use of biacetyl instead of benzil, was also investigated. Acid conditions cannot be used here but the condensation with 2,2′-diaminobiphenyl proceeded satisfactorily in ethylene glycol. However, as the condensation with (±)-2,2′-diamino-6,6′-dimethylbiphenyl gave only a low yield of 2,3,4′,1″-tetramethyl-5,6:7,8-dibenzo-1,4-diazocine (VI; R = Me), the reaction was not carried out with resolved diamine.

It was hoped that a dibenzodiazocine without additional *ortho*-substituents would undergo racemisation at a temperature at which satisfactory rate measurements could be made. Accordingly, 2,2′-diaminobiphenyl-4,4′-dicarboxylic acid was synthesised by the improved method of Chua Cheung King Ling and Harris[13] and condensed with biacetyl in ethylene glycol; the resulting diazocine (I; R = Me) was only obtained in an impure form and as it failed to give crystalline salts with various alkaloids was not

[7] Ahmed and Hall, *J.*, 1958, 3043.
[8] Mislow and Glass, *J. Amer. Chem. Soc.*, 1961, **83**, 2780.
[9] Mislow, Hyden, and Schaefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1449.
[10] Kistiakowsky and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1043.
[11] Allinger and Youngdale, *J. Org. Chem.*, 1959, **24**, 306.
[12] Meisenheimer and Höring, *Ber.*, 1927, **60**, 1425.
[13] Chua Cheung King Ling and Harris, *J.*, 1964, 1825.

investigated further. Condensation with benzil in acetic acid solution gave the diazocine acid (I; R = Ph), which was readily resolved as described by Bell.[3]

Preliminary experiments showed that temperatures above 200° would be required to racemise the diphenyl compound (I; R = Ph). The method used to determine the racemisation rates was to seal up a solution of the compound in a number of glass tubes, each having a hook made in the end at the time of sealing. By means of pieces of wire threaded through the hooks the tubes were suspended down a long wide air condenser into a flask containing a liquid of suitable boiling point. The liquid was heated to boiling and, after thermal equilibrium had been reached, the tubes were removed at intervals and cooled; polarimetric readings of the contents were made at room temperature. The high specific rotation of the compound ($[\alpha]_{5461}^{24}$ −2100°, $[\alpha]_{5461}^{18\cdot5}$ +2050° in dimethylformamide) made it possible to take accurate readings with very dilute solutions.

The racemisation was first studied in dimethylformamide solution. Slow racemisation was observed at ~210° and the diphenyldiazocine had a half-life of the order of 350—400 minutes at 245°. However, the racemisation was erratic with fluctuations in rate; this was probably due to decomposition of the solvent as considerable pressure developed inside the tubes. It seems likely that some dimethylamine was formed and that, as a result, both diazocine-acid and its ions were present, not necessarily racemising at the same rate. Both rates might also be affected by the progressive change in medium. It was not possible to determine the rate of racemisation of the disodium salt of the diazocine in aqueous solution as the tubes did not stand up to the internal pressure at 245°.

Ethyl benzoate was then used as solvent. Racemisation was not observed below 240° so that the compound is much more stable optically in this solvent than in dimethylformamide. Solutions of the diazocine-acid in ethyl benzoate darkened after being heated at 247° for a few hours but this could be avoided by removing air from the tubes before sealing; in this way racemisation rates were determined over the temperature range 247—288° (Table). In several experiments there was a tendency for the later readings to deviate slightly from the straight line plot of $\log_{10}\alpha_t$ against time; in all cases these readings were of solutions which had been heated for many hours at a high temperature and in which slight decomposition of the solvent had occurred, leading to increase in pressure in the tubes.

Racemisation of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3''-dicarboxylic acid in ethyl benzoate.

Temp.	α_{5461} at first reading	$k \times 10^6$ (sec.$^{-1}$)	$t_{\frac{1}{2}}$ (hr.)
247·0°	+2·85	3·67	52·5
261·5	−2·69	9·14	21·1
268·5	−2·77	15·4	12·5
274·0 *a*	−2·64	22·0	8·76
288·0	−2·70	46·7	4·13

±1°, other temperatures ±0·5°.

A solution of the diazocine-acid in ethyl benzoate was completely racemised by heating it at 283·5° for 40 hours. Considerable pyrolysis of the solvent to benzoic acid and ethylene occurred under these conditions and it was not possible to recover the diazocine-acid. From the ethyl benzoate solution a small amount of neutral material was recovered. This appeared to be the diazocine ester since its infrared spectrum showed the C=O and C–O stretching frequencies of the ester of an aromatic acid and also a band at 1621 cm.$^{-1}$, indicative of the C=N group. [Bacon and his co-workers [14,15] attribute a peak or peaks in the 1600—1630 cm.$^{-1}$ region in a variety of 4,5:6,7-dibenzo-1,2-diazocines, *e.g.*, (VII), to the C=N group of the heterocyclic ring, and the 5,6:7,8-dibenzo-1,4-diazocines (I) R = Ph) and (VIII) also show a peak in this region (at 1623 and 1616 cm.$^{-1}$, respectively).]

[14] Bacon and Lindsay, *J.*, 1958, 1382.
[15] Bacon and Bankhead, *J.*, 1963, 839.

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From the racemisation* data the energy of activation is found to be 36 kcal. mole^{-1} and the non-exponential term, A, of the Arrhenius equation to be $10^{9\cdot9}$ sec.$^{-1}$. The corresponding transition state functions are $\Delta F^{\ddagger}$ 44 kcal. mole^{-1} (at 268·5°), $\Delta H^{\ddagger}$ 35 kcal. mole^{-1}, and $\Delta S^{\ddagger}$ −16·5 e.u.
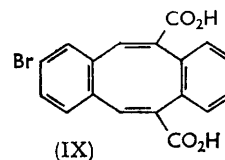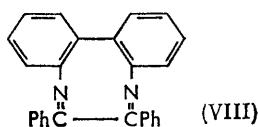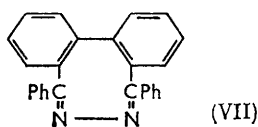
The high energy of activation for racemisation must be due largely to the configurational rigidity provided by the two carbon–nitrogen double bonds. Distortions of the type [8,9] which lead to ready racemisation of similar compounds with a saturated homocyclic or heterocyclic bridge cannot occur in the dibenzodiazocine system unless the high resistance to twisting of the double bonds can first be overcome. The activation energies for racemisation of compounds (II) [3] and (III) [2] are 22·8 and 22·1 kcal. mole^{-1}, respectively; it thus appears that the presence of the double bonds in (I; R = Ph) demands an additional 13—14 kcal. mole^{-1} for the racemisation process.

Configurational changes in a rather similar ring system have been studied by Mislow and Perlmutter,[16] who resolved the dibenzocyclo-octatetraene derivative (IX). Racemisation was studied in the temperature range 120—140°, and the energy of activation is 27 kcal. mole^{-1}. It is unlikely that the exchange of C=C for C=N will make very much difference to the configurational stability of the eight-membered ring. Probably the major difference between the racemisation processes for the compounds lies in the proximity in (I; R = Ph) of the two benzene rings which form part of the diazocine ring. Rotation of the single bond between them is a more sterically hindered process than rotation of the single bonds in (IX), where interaction of carboxyl with the adjacent aromatic ring can be minimised by twisting of the carboxyl group. The " racemisation barrier " in biphenyl itself has been calculated [17] as 3·9 kcal. mole^{-1} which, added to the value for (IX), would give approximately 31 kcal. mole^{-1} for (I; R = Ph). Some loss of conjugation in the transition state between the substituent phenyl groups (in the 2- and the 3-position) and the adjacent double bonds of the heterocyclic ring probably accounts for part of the remaining 5 kcal. mole^{-1} of the activation energy of the diazocine-acid.

Another feature of the racemisation process of the latter acid is the large negative entropy of activation.† Bridged biphenyls generally appear to have positive or small negative entropies of activation, those known so far [18,8,9,19] lying within the range from −8·3 to +8·6 e.u. The value for the diazocine-acid ($\Delta S^{\ddagger}$ −16·5 e.u.) lies well outside this range, *i.e.*, its racemisation is much less " favoured " than that of other bridged biphenyls. The difficulty of racemisation is reflected by the temperature range in which it occurs.

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* *Added in Proof.*—Since this Paper was submitted it has been shown by Allinger, Szkrybalo, and DaRooge, *J. Org. Chem.*, 1963, **28**, 3007, that the diazocine acid undergoes thermal rearrangement in mesitylene at 278° to give 6-phenylphenanthridine-3,8-dicarboxylic acid and benzonitrile; similar behaviour by the dimethyl ester was studied at 242°. If the same process occurs in ethyl benzoate, our data for loss of optical activity will in fact apply not to racemisation but to thermal rearrangement. Nevertheless, the value of 36 kcal. mole^{-1} for the energy of activation sets a lower limit to the energy which would be required to invert the configuration of the diazocine ring.

† This is not a surprising result if the reaction is decomposition and not racemisation; cf. previous footnote.

[16] Mislow and Perlmutter, *J. Amer. Chem. Soc.*, 1962, **84**, 3591.
[17] Howlett, *J.*, 1960, 1055.
[18] Hall and Harris, *J.*, 1960, 490, and references cited therein.
[19] Hall and Poole, unpublished.

EXPERIMENTAL

(In all polarimetric readings $l = 1$ unless otherwise stated.)

(±)-*4',1''-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine* (VI;   R = Ph).—2,2'-Di-amino-6,6'-dimethylbiphenyl (0·5 g., 1 mol.) obtained by the reduction [20] of the dinitro-compound,[7,21] was heated with benzil (0·5 g., 1 mol.) in boiling propionic acid (10 c.c.) for 3 hr. Most of the solvent was removed by distillation and the residue crystallised twice from ethanol, giving 0·2 g. (20%) of the yellow diazocine, m. p. 209—210° (Kuhn and Goldfinger give m. p. 213°); $\lambda_{min.}$ 231·5 (ε 24,000), $\lambda_{max.}$ 254·5 (ε 32,000), $\lambda_{infl.}$ 327 mμ ($\varepsilon_{infl.}$ 4150) (in 96% ethanol).

Optical Resolution of 2,2'-Diamino-6,6'-dimethylbiphenyl.—This was carried out through the tartrate by the method of Meisenheimer and Höring [12] and gave the active amines with $[\alpha]_{5461}^{20}$ +63·7° ($l = 2$; c, 0·6905 in CHCl$_3$), m. p. 156—158°, and $[\alpha]_{5461}^{19}$ −63·8° ($l = 2$; c, 0·5255 in CHCl$_3$), m. p. 155—157°, respectively.

(−)-*4',1''-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.*—The (+)-diamine (0·5 g.) and benzil (0·5 g.) were heated in boiling propionic acid (10 c.c.) for 5 hr. The solvent was removed and the residue dissolved in hot ethanol. Some benzil separated from the cooled solution and was filtered off. The filtrate was evaporated and the residue ground twice with a little light petroleum (b. p. 60—80°) and then crystallised from light petroleum (b. p. 60—80°). The (−)-diazocine (0·1 g., 10%) was obtained as yellow prisms, m. p. 179—180°, $[\alpha]_{5461}^{22}$ −2080° (c, 0·445 in CHCl$_3$) (Found: C, 86·7; H, 5·7; N, 7·5. $C_{28}H_{22}N_2$ requires C, 87·0; H, 5·7; N, 7·25%).

(+)-*4',1''-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine* was obtained similarly from the (−)-diamine; it had m. p. 179—180°, $[\alpha]_{5461}^{19}$ +2060° (c, 0·630 in CHCl$_3$) (Found: C, 87·0; H, 5·7; N, 7·2%).

attempted Racemisation of (−)-*4',1''-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.*—The (−)-diazocine (0·025 g.), dissolved in diphenyl ether (*ca.* 3 c.c.), was heated in a sealed tube. The temperature gradually rose to approximately 350° (furnace temperature) and was maintained there for 5 hr. The tube was removed from the furnace and allowed to cool. The solution had darkened and α_{5791}^{23} had changed from −4·66 to −3·52°, corresponding to 24% loss of optical activity. (The diazocine used was contaminated with benzil but was free from diamine.)

2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine.—2,2'-Diaminobiphenyl (1 g.) and biacetyl (0·5 g.) were heated in ethylene glycol solution at 130—135° for 1 hr. The cooled solution was poured into water, and the mixture extracted with ether. Ether was removed, after being dried, and the residue dissolved in dry benzene and purified by chromatography on alumina. The *diazocine* (0·5 g., 39%) had m. p. 129—130° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 82·2; H, 6·15. $C_{16}H_{14}N_2$ requires C, 82·0; H, 6·0%).

2,3,4',1''-Tetramethyl-5,6:7,8-dibenzo-1,4-diazocine (VI; R = Me).—2,2'-Diamino-6,6'-di-methylbiphenyl (1 g., 1 mol.) and biacetyl (0·4 g., 1 mol.) were heated in ethylene glycol (25 c.c.) in a bath kept at 160—170° for 1 hr. The cooled solution was poured into water, and the gum extracted with ether and dried (Na$_2$SO$_4$). Solvent was removed and the residue dissolved in dry benzene and passed through alumina, being eluted with more benzene. A pale yellow solid was obtained from one of the fractions of eluate and, on crystallisation from light petroleum (b. p. 80—100°), gave the *tetramethyldiazocine* (∼0·1 g.), m. p. 138—140° (Found: C, 82·1; H, 6·8. $C_{18}H_{18}N_2$ requires C, 82·4; H, 6·9%).

2,2'-Diaminobiphenyl-4,4'-dicarboxylic Acid.—Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarb-oxylate was obtained by an Ullmann reaction and reduced [13] with hydrazine hydrate in the presence of Raney nickel. Hydrolysis gave the amino-acid, m. p. 323° (decomp.).

2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine-2',3''-dicarboxylic Acid (I; R = Me).—2,2'-Di-aminobiphenyl-4,4'-dicarboxylic acid (2 g.) and biacetyl (0·7 g.) were heated in ethylene glycol (20 c.c.) at 130—140° for 1 hr., with frequent shaking. The hot solution was filtered and the solid washed with ethanol and crystallised from ethylene glycol. The diazocine-acid (1·4 g., 59%) was obtained as yellow plates, m. p. 360°, still smelling slightly of biacetyl (Found: C, 65·4; H, 4·35; N, 8·4. $C_{18}H_{14}N_2O_4$ requires C, 67·1; H, 4·4; N, 8·7%).

[20] Kenner and Stubbings, *J.*, 1921, **119**, 593.
[21] Carlin and Foltz, *J. Amer. Chem. Soc.*, 1956, **78**, 1997.

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2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2′,3″-dicarboxylic Acid (I; R = Ph).—2,2′-Di-
aminobiphenyl-4,4′-dicarboxylic acid (1 g.) and benzil (0·78 g.) were heated in boiling glacial
acetic acid (70 c.c.) for 25 hr. The hot solution was filtered and the filtrate concentrated to
~1/3 of its volume. Hot water was added until yellow solid began to crystallise. This was
taken through the sodium salt to remove any benzil and the acid then crystallised from aqueous
acetic acid. The diazocine-acid (0·4 g., 24%) had m. p. >360° (Bell [3] gives m. p. 348°).

Optical Resolution of 2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2′,3″-dicarboxylic Acid.—
This was achieved through the brucine salt [3] which was repeatedly extracted with boiling
ethanol until a constant rotation of $[\alpha]_{5461}^{22}$ $-750°$ (l = 2; c, 0·458 in $CHCl_3$) was obtained.
A chloroform solution of the salt was extracted with 10% sodium hydroxide solution, and the
(−)-acid was precipitated from it and crystallised from aqueous acetic acid from which it
separated in a solvated form. After being heated at 100° it had a rather variable first m. p.
of *ca.* 225° but resolidified on further heating and then melted sharply at 276—277°; $[\alpha]_{5461}^{24}$
$-2100°$ $[\alpha]_{5791}^{24}$ $-1670°$ (c, 0·170 in Me_2NCHO) (Found, after being dried at 100° *in vacuo*:
C, 75·1; H, 4·3; N, 6·4; O, 14·4. Calc. for $C_{28}H_{18}N_2O_4$: C, 75·3; H, 4·1; N, 6·3; O, 14·3%).
Similar treatment of the original-mother-liquor of the brucine salt gave the (+)-acid with
similar melting behaviour; $[\alpha]_{5461}^{24}$ $+2050°$, $[\alpha]_{5791}^{24}$ $+1620°$ (c, 0·226 in Me_2NCHO) (Found,
after being dried at 100° *in vacuo*: C, 75·35; H, 4·2; N, 6·25; O, 14·55%).

*Racemisation of (+)- and (−)-2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2′,3″-dicarboxylic
Acid in Ethyl Benzoate.*—Racemisation rates were determined as follows: the active diazocine-
acid (~0·03 g.) in ethyl benzoate (20 c.c.) was sealed, under vacuum, in 10 tubes. The tubes
were suspended in a flask of 1-methylnaphthalene and the solvent heated to boiling (247·0°).
The tubes were removed at intervals and plunged into hot and then cold water. Polarimetric
readings were taken in a 1-dm. micro-tube at room temperature; α_{5461} fell from 2·85 to 1·46°
during 55·5 hr. Rates were similarly determined in the following boiling liquids: diphenyl ether
(261·5°), diphenylmethane (268·5°), ethyl cinnamate (274·0°), and dimethyl phthalate (288·0°).

One tube of solution was heated for 40 hr. at 283·5°. Considerable pressure developed in
the tube and, when it was opened, benzoic acid crystallised out. Some ethyl benzoate
remained but much more pyrolysis had occurred than in any of the solutions used to determine
rates. The mixture was treated with 10% sodium hydroxide solution and a little ether and
the organic and aqueous layers separated. Both were optically inactive. Removal of ethyl
benzoate from the organic layer gave a small residue, thought to be the diazocine ester.[*]
Acidification of the aqueous layer gave a precipitate but in view of the large amount of benzoic
acid present it was not practicable to determine whether chemically unchanged diazocine-
acid remained.

Attempts to recover solute from partially racemised solutions gave an acid with an infrared
spectrum showing the features of the benzoic acid spectrum together with some of the peaks
of the diazocine-acid.

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* More probably the 6-phenylphenanthridine ester; cf. asterisked footnote on p. 2329.