

## Relative Abundance of Racemic and *meso*-Diastereoisomers of 3,3'-Diphenylbiphtalid-3-yl arising from the Corresponding Chemically and Photochemically Generated Free Radicals

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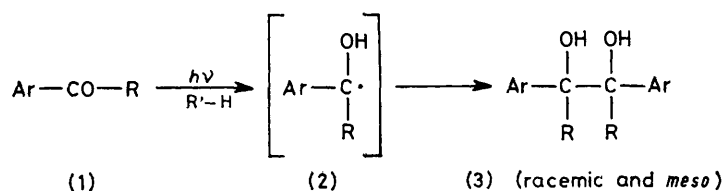
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Contrary to previously reported results we have shown by quantitative  $^{13}\text{C}$  n.m.r. analysis of the crude reaction product, that racemic and *meso*-diastereoisomers of 3,3'-diphenylbiphtalid-3-yl are formed in equivalent quantities by the coupling of the corresponding free radicals; the latter were generated by the chemical and photochemical reduction of 2-benzoylbenzoic acid as well as by photolysis of the acid amides. We have also shown that the low melting diastereoisomer can be thermally converted into the other diastereoisomer; this result helps to explain the disagreement between our observations and those previously reported.

THE photochemical reductive coupling of non-symmetrical carbonyl compounds (1) <sup>1</sup> in a hydrogen donor solvent yields both racemic and *meso*-diastereoisomers of the corresponding glycols (3).<sup>2</sup> The relative abundance of these diastereoisomers depends on the approach and coupling modes of free radicals (2) (Scheme 1). Previous

product cannot be seriously considered in the general case.

Another source of error can come from the irradiation conditions, since it has been shown, at least for the acetophenone pinacols, that the latter can be photochemically destroyed at short wavelengths with the



SCHEME 1

literature sometimes mentions that one of the diastereoisomers may be isolated in >50% yield.<sup>3</sup> Seldom are the purity criteria of the isolated more abundant compound well defined; they generally consist only of the observation of a narrow and constant melting range, which would not be, *in this instance*, sufficient proof of purity.

Moreover it is now established that some pinacols are thermally unstable and revert to type (2) free radicals. At least in the case of the acetophenone pinacols it has been shown that the racemic isomer is more easily cleaved than the *meso*-isomer; after recombination, the net effect is a diminution of the racemic : *meso* ratio.† According to the conditions used disproportionation of the free radicals arising from the cleavage can also occur, yielding the corresponding ketone and alcohol.<sup>4,5</sup>

It appears from the above that any quantitative analysis which is not applied to the crude reaction

† For example, after heating a pure sample of the racemic isomer for seven days at 160 °C in pentan-2-ol, a racemic : *meso* ratio of 0.11 is obtained.<sup>4</sup>

<sup>1</sup> A. Schönberg, 'Preparative Organic Photochemistry,' Springer, New York, 1968, p. 203; J. G. Calvert and J. N. Pitts, jun., 'Photochemistry,' Wiley, New York, 1966, p. 528; P. Heinrich in 'Methoden der organischen Chemie (Houben-Weyl), Photochemie II, Band 4, Teil 5b,' Georg Thieme, Stuttgart, 1975, p. 813.

<sup>2</sup> E.g., C. Weizmann, E. Bergmann, and Y. Hirshberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1530; W. L. Bencze, C. A. Burckhardt, and W. L. Yost, *J. Org. Chem.*, 1962, **27**, 2865; S. G. Cohen, D. A. Laufer, and W. V. Sherman, *J. Amer. Chem. Soc.*, 1964, **86**, 3060.

<sup>3</sup> E.g., F. Bergmann and Y. Hirshberg, *J. Amer. Chem. Soc.*, 1943, **65**, 1429.

formation of unidentified products; moreover the *meso*-diastereoisomer reacts faster than the racemate.<sup>6</sup> It thus appears necessary to run the photopinacolisations with filtration of the wavelengths lower than the  $n,\pi^*$  absorption range of the carbonyl compounds which are involved.

A precise quantitative analysis of diastereoisomeric compounds has been achieved by Stocker *et al.*<sup>4,7</sup> These authors have investigated the isolated reaction products from a series of ketones (1), produced not only photochemically but also by electroreduction or by use of peroxides.

The pinacols (3; R = H, Ar = Ph) have also been obtained by other workers from benzyl alcohol utilising either  $\gamma$ -<sup>8</sup> or u.v. irradiation of the neat compound or of an acetone solution,<sup>9</sup> and also by heating of this alcohol in the presence of t-butyl peroxide.<sup>9</sup>

Matsuura<sup>10</sup> has studied the photoreduction of six compounds of the type (1), five of which had also been investigated by Stocker.<sup>4,7</sup>

Quantitative analyses have been accomplished by

<sup>4</sup> J. H. Stocker and D. H. Kern, *J. Org. Chem.*, 1970, **35**, 1708.

<sup>5</sup> D. C. Neckers and D. P. Colenbrander, *Tetrahedron Letters*, 1968, 5045.

<sup>6</sup> J. H. Stocker and D. H. Kern, *J. Org. Chem.*, 1966, **31**, 3755.

<sup>7</sup> J. H. Stocker, R. M. Jenevein, and D. H. Kern, *J. Org. Chem.*, 1969, **34**, 2810, and references therein; J. H. Stocker and R. M. Jenevein, *Coll. Czech. Chem. Comm.*, 1971, **36**, 925.

<sup>8</sup> G. A. Swan and D. Wright, *J. Chem. Soc.*, 1958, 4673.

<sup>9</sup> W. G. Brown, *Tetrahedron Letters*, 1966, 1845.

<sup>10</sup> T. Matsuura and Y. Kitaura, *Bull. Chem. Soc. Japan*, 1968, **41**, 2483.

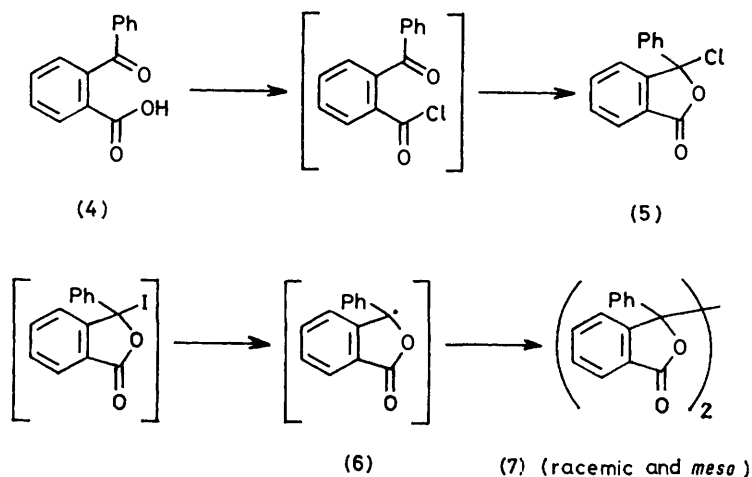
isotope dilution techniques,<sup>4,7,8,\*</sup> <sup>1</sup>H n.m.r.,<sup>4,7,10</sup> or by g.l.c. of the silylated products.<sup>9</sup>

Configurational assignments of the pure isolated diastereoisomers is also a problem. In the past it was generally agreed that the pinacol of higher m.p. is the *meso*-isomer, but exceptions to this empirical rule are now known.† The configurational assignment for alkyl aryl ketone pinacols has been investigated by the use of i.r.,<sup>13</sup> <sup>1</sup>H n.m.r.,<sup>14,15</sup> and in some specific cases by X-ray analysis.<sup>15,16</sup>

It appears from Stocker's work<sup>4,7</sup> that in neutral or slightly acidic medium, the racemic : *meso* ratio of the diastereoisomers obtained has a value near unity, with

rationalises this result by postulating a stronger hydrogen bond than in the usual case, during the coupling of free radicals (2).

Since these previous studies, Bhatt *et al.* have published<sup>17</sup> a study concerning the relative abundance of the diastereoisomers (7) arising from the coupling of the free radicals (6) formed by reduction of the chlorophthalide (5) using sodium iodide in acetone; the chlorophthalide was prepared from *o*-benzoylbenzoic acid by treatment with thionyl chloride (see Scheme 2). These authors have extended this reaction to four other examples in which the phenyl group is replaced by *p*-Br-, *p*-Cl-, *p*-NO<sub>2</sub>-, and *p*-NMe<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>.



SCHEME 2

a slight but systematic predominance of the racemate. The authors argue that formation of the *meso*-isomer should be favoured since coupling of free radicals (2) has minimal steric hindrance when the three identical groups are in opposition. In order to rationalise the observed inverse result however, the authors propose that a hydrogen bond between the hydroxy-groups facilitates the coupling which yields the D or L enantiomer. The net balance of these adverse influences gives rise to the formation of the two diastereoisomers in almost equal quantities.

Swan<sup>8</sup> and Brown<sup>9</sup> also observe a racemic : *meso* ratio close to unity with a slight predominance, however, of the *meso* compound in the latter work. Matsuura's results<sup>10</sup> agree with Stocker's,<sup>4,7</sup> showing a value near unity for the racemic : *meso* ratio.

The only example where both these authors observe a racemic : *meso* ratio distinctly different from 1.0 (1.25) is for the irradiation of *p*-methoxyacetophenone; Stocker<sup>4,7</sup>

\* This method has the disadvantage of requiring several recrystallisations. In Stocker's examples,<sup>4,7</sup> the solvents which are used are of low enough b.p. to prevent the risk of obtaining erroneous results due to thermal interconversion of the diastereoisomers.

† Acetophenone pinacols;<sup>11</sup> *p*-tolualdehyde pinacols.<sup>12</sup>

‡ In one case (2-*p*-bromobenzoylbenzoic acid) the structure of the high melting diastereoisomer of type (7) has been shown by X-ray analysis to be the *meso*-compound.<sup>16</sup> For other cases, the assignments are not known.

Yields of the diastereoisomers obtained indicate that the ratio of low to high melting compound ‡ varies from 0.23 to 0.40 for the five compounds studied. These yields of the isolated diastereoisomers, however, were obtained by recrystallisation of the crude mixture of biphtalidyls (7) from xylene; for example with 2-benzoylbenzoic acid (4), the high melting isomer (A) of mixture (7) is obtained in 65.4% yield, and after evaporation of the mother liquors and recrystallisation, the low melting isomer (B) is isolated in 25.7% yield [(B) : (A) 0.39].

From quantitative i.r. analysis of the crude product of this same reaction the yield of isomer (B) was calculated to be 32 ± 1% by measuring the intensity of the band at 970 cm<sup>-1</sup> which is absent in the other isomer.

We show in this report that at least for compound (4),

<sup>11</sup> D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81**, 2748.

<sup>12</sup> J. Grimshaw and J. S. Ramsey, *J. Chem. Soc. (C)*, 1966, 653.

<sup>13</sup> W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, 1963, **28**, 2154.

<sup>14</sup> H. Agahigian, J. F. Moraveck, and H. Gauthier, *Canad. J. Chem.*, 1963, **41**, 194.

<sup>15</sup> J. N. Brown, R. N. Jenevein, J. H. Stocker, and L. M. Trefonas, *J. Org. Chem.*, 1972, **37**, 3712 and references therein.

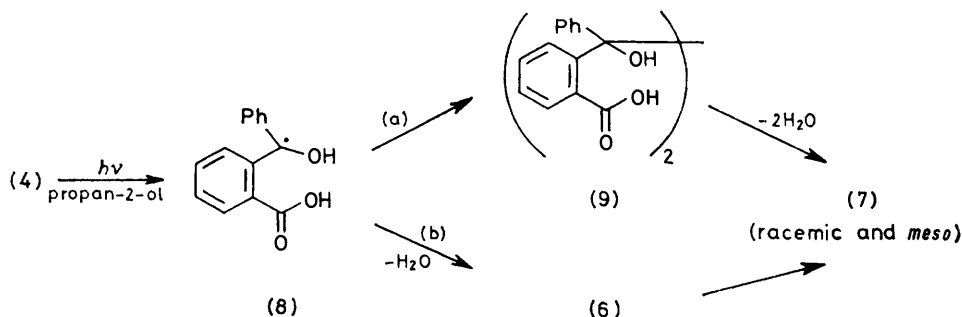
<sup>16</sup> H. Manohar, V. Kalyani, M. V. Bhatt, and K. M. Kamath, *Tetrahedron Letters*, 1966, 5413; V. Kalyani, H. Manohar, and N. V. Mani, *Acta Cryst.*, 1967, **23**, 272.

<sup>17</sup> M. V. Bhatt, K. M. Kamath, and M. Ravindranathan, *J. Chem. Soc. (C)*, 1971, 3344.

the racemic : *meso* ratio of the biphthalidyls (7), as determined by  $^{13}\text{C}$  n.m.r. analysis of the crude reaction product, has in fact a value close to unity as in the aforementioned cases.

#### RESULTS

The biphthalidyls (7) have not only been obtained by repetition of the sequence in Scheme 2, but also by photopinacolisation-lactonisation of compound (4) (Scheme 3) and by photolysis of amides (10) (Scheme 4).



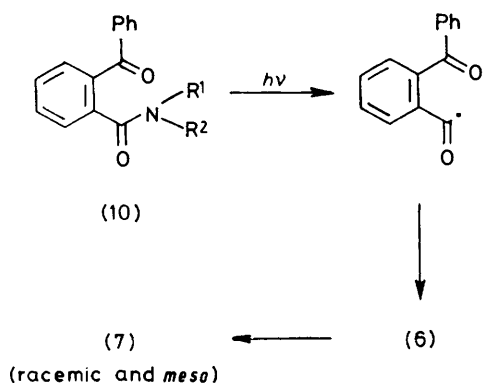
SCHEME 3

**Preparation of Biphthalidyls (7).—Method 1: from the pseudo-acid chloride (5) (Scheme 2).** The experimental procedure of Bhatt *et al.*<sup>17</sup> was scrupulously followed up to obtaining the crude mixture (7) which was then used directly for analysis.

**Method 2: by photopinacolisation-lactonisation of acid (4) (Scheme 3).** It has been reported<sup>18</sup> that irradiation with sunlight of compound (4) in ethanol allowed the isolation of a product (50%), m.p. 265–266 °C, to which formula (7) was attributed.

We have, however, through irradiation at 360 nm of a propan-2-ol solution of acid (4), obtained a quantitative yield of biphthalidyls (7), isolation of the material being achieved simply by filtration and ambient temperature evaporation of the solvent. The isomer ratio of this material was then determined without further purification.

**Method 3: by photolysis of amides (10) (Scheme 4).** This



SCHEME 4

photochemical reaction is the subject of a separate report.<sup>19</sup> The isomer ratio determination was performed on the crude reaction mixture.

**Physical Properties of Biphthalidyls (7).**—The properties

<sup>18</sup> D. B. Limaye, *J. Univ. Bombay*, 1932, **1**, pt. 2, 52 (*Chem. Abs.*, 1933, **27**, 2097).

<sup>19</sup> J. C. Gramain and M. F. Lhomme, to be submitted.

of the diastereoisomers (7), in particular their m.p.s (Table 1) and  $^{13}\text{C}$  n.m.r. spectra (Table 2), were obtained for the individual compounds purified by t.l.c., without subsequent recrystallisation. Indeed, we have observed that refluxing the low melting diastereoisomer (B) in xylene partially isomerises it to the other diastereoisomer (A), in agreement with the observations reported in the introduction for related systems.

**Quantitative  $^{13}\text{C}$  n.m.r. analysis of biphthalidyls (7).** Chemical shifts measured for the various carbons of the

biphthalidyls (7) [(A) and (B)] and for the model compounds (C) (phthalide), (D) (3-phenylphthalide) and (E) (3,3-diphenylphthalide) are reported in Table 2.

TABLE 1  
M.p.s (°C) of diastereoisomers (7)

	Diastereoisomer	
	A	B
This study	289–290	284–285
Ref. 17	275–278	269–270

TABLE 2  
 $^{13}\text{C}$  N.m.r. chemical shifts <sup>a</sup> of compounds (A)–(E)

Carbon atom	(A)	(B)	(C) <sup>b</sup>	(D)	(E)
1	168.67	169.20	170.4	170.50	169.65
3	90.07	90.84	69.5	82.66	91.59
4	125.52	124.52	122.0	122.89	124.16
5	134.16	134.58	133.6	134.32	134.11
6	129.67	129.74	128.5	129 { <sup>24</sup> / <sub>34</sub> <sup>c</sup>	129.33
7	125.13	125.59	124.9	125.53	125.96
3a	149.01	149.03	146.3	149.69	151.94
7a	126.25	125.74	125.2	125.53	125.48
<i>ipso</i>	134.99	136.68		136.43	140.82
<i>ortho</i>	126.84	126.33		126.94	127.04
<i>meta</i>	127.81	128.09		128.95	128.46
<i>para</i>	128.49	128.35		129 { <sup>34</sup> / <sub>24</sub> <sup>c</sup>	128.46

<sup>a</sup> Chemical shifts in  $\delta$  (p.p.m.) relative to tetramethylsilane,  $\text{CDCl}_3$  solvent. <sup>b</sup> Ref. 20. <sup>c</sup> Assignments may be reversed.

Assignments were made (i) from chemical shifts and intensities observed in totally decoupled spectra; (ii) taking account the shifts induced by  $\text{Eu}(\text{fod})_3$  shift reagents and the shape of the signals in the off-resonance spectra (C-7).

It may be noted on one hand that the shifts for C-3 and -4 are very sensitive to the degree of substitution of the C-3 and on the other hand that the C-1, -3, -5, and *ipso*-signals are different enough to allow a quantitative analysis of biphthalidyls (A) and (B).

Results for crude mixtures of biphthalidyls (7) obtained

<sup>20</sup> D. W. Hughes, H. L. Holland, and D. B. Maclean, *Canad. J. Chem.*, 1976, **54**, 2252.

by methods 1—3 indicate in the three cases that the (B) : (A) ratio is equal to  $1.00 \pm 0.03$ . Moreover, when a mixture of biphthalidyls (7) having an initial ratio of (B) : (A) = 4.00 is refluxed in xylene for 14 h, the (B) : (A) ratio changes to  $1.30 \pm 0.03$ .

To check the photostability of the diastereoisomers, irradiations at 360 nm were also performed within the same conditions of method 2 with solutions of pure diastereoisomer (A) and of a mixture of known composition of diastereoisomers (A) and (B). In both cases, no changes were noticed in the  $^{13}\text{C}$  n.m.r. analyses, showing that no interconversion of the diastereoisomers nor preferential destruction of one of them is possible at the wavelength employed.

#### DISCUSSION

The difference between our results and those of Bhatt *et al.*<sup>17</sup> is probably due to the fact that the high melting compounds isolated by these authors in >50% yield are in reality mixtures of both diastereoisomers; indeed for biphthalidyls (7), the m.p. reported for isomer (A) is *ca.* 10° lower than the one we have observed for the same chromatographically purified compound (Table I). Moreover, our thermal experiments indicate that the recrystallisations from xylene performed by these authors have probably enriched their mixtures in the high melting diastereoisomer.

As for their i.r. determination of the yield of compound (B) performed on the crude mixture (7), we believe that in this case the method may be unreliable because of the very low intensity of the 970  $\text{cm}^{-1}$  absorption.

Although our results (racemic : *meso ca.* 1) agree with those obtained by other authors for similar examples as reported in the Introduction, Stocker's arguments<sup>4,7</sup> cannot be invoked in our case, since no hydrogen bond can facilitate any coupling leading to the racemic diastereoisomer; \* thus one should observe for biphthalidyls (7) a preponderance of the *meso*-compound; as this is not the case, we admit however that the systems under comparison are distinct enough and that in example (7), both types of free radical coupling (6), leading to diastereoisomers (A) or (B) are equally probable.

*Conclusions.*—It is clear that a study of the relative abundance of diastereoisomeric pinacols or related systems should be undertaken with great care. Indeed it is an absolute must to determine the isomer ratio of the crude reaction mixture to avoid the risk of thermal interconversion. Moreover, for the same reason, each diastereoisomer must be isolated and purified more rigorously than by mere recrystallisation.

This study has also shown that  $^{13}\text{C}$  n.m.r. analysis is perfectly suited to the isomer ratio determination of this type of compound and is easier than the other

\* If path (a) is followed in the photopinacolisation reaction (method 2, Scheme 3) this argument could be invoked; however similar results obtained with methods 1 and 3 invalidate the point. On the contrary, it may be deduced from these results that path (b) is probably followed by the reaction described in Scheme 3, since it leads to the same intermediate (6) as in the other cases.

methods which have been used previously, such as the isotopic dilution techniques.

#### EXPERIMENTAL

Mass and i.r. spectra were taken on AEI MS 30 and Perkin-Elmer 457 spectrometers, respectively.

*Syntheses of Biphthalidyls (7).*—Method 1 was that of ref. 17 without recrystallisation of the crude product.

*Method 2.* A solution of 2-benzoylbenzoic acid (4) (5.0 g; recrystallised from xylene), m.p. 127—128°, and propanol-2-ol (115 ml) was introduced into a Pyrex tube. Irradiation was performed with a preparative Rayonet reactor equipped with eight RUL 350 nm lamps and a fan (*T ca.* 35 °C) after bubbling nitrogen for 5 min into the solution. Crystals formed were periodically filtered off, † washed with propan-2-ol, dried at ambient temperature, and combined (total 3.84 g). When no further precipitate was formed (total irradiation time 24 h), the solution was evaporated to dryness at ambient temperature with a rotary evaporator (solid residue 0.81 g). The total yield of biphthalidyls (7) is thus 4.65 g (100%). T.l.c. on silica (eluent  $\text{CH}_2\text{Cl}_2$ ) showed that the isolated solids consisted only of the biphthalidyls (7) [ $R_F$  of isomer (B) slightly greater than that of isomer (A)]. Only in the evaporated residue was there a slight trace of starting material (4) and a slight trace of an unidentified product. It should be noted that 3-phenylphthalide (D) is totally absent. ‡

Non-quantitative recrystallisation of the filtered crystals in a large excess of xylene, allowed the isolation of diastereoisomer (A) contaminated with < 2% of the other isomer ( $^{13}\text{C}$  n.m.r. analysis); solvent evaporation followed by recrystallisation of the residue in a small quantity of benzene after hot filtration, allowed the isolation of diastereoisomer (B) containing < 5% of the other isomer. Both crystalline fractions were then chromatographed on thin silica plates (three successive  $\text{CH}_2\text{Cl}_2$  elutions) to obtain pure diastereoisomers (A) and (B), without subsequent recrystallisation. Isomer (A)  $\text{C}_{28}\text{H}_{18}\text{O}_4$  (*M* 418.42) had m.p. (instantaneous) 289—290 °C,  $\nu_{\text{max}}$  ( $\text{CS}_2$ ) 1 785 (C=O)  $\text{cm}^{-1}$ , *m/e* 210 (19%), 209 (100), 152 (14), and 105 (12). Isomer (B), had m.p. (instantaneous) 284—285 °C,  $\nu_{\text{max}}$  ( $\text{CS}_2$ ) 1 785 (C=O)  $\text{cm}^{-1}$ , *m/e* 210 (16%), 209 (100), 152 (12), and 105 (9).

For quantitative analysis, acid (4) (0.15 g) was irradiated under the same conditions in propan-2-ol (3.5 ml) in a conical Pyrex tube for 2 h 30 min. The suspension thus obtained was evaporated to dryness at ambient temperature and the residue was further dried in a desiccator on  $\text{P}_2\text{O}_5$ .

Method 3 was taken from ref. 19.

*Isomerisation of Biphthalidyl (B).*—A homogenous mixture of pure biphthalidyls (A) and (B) (0.175 g; 1 : 4) was divided in two portions. One was analysed directly by  $^{13}\text{C}$  n.m.r. and the other was refluxed in xylene (10 ml) for 14 h. After evaporating to dryness followed by further drying, this residue was also analysed.

*Photostability of Biphthalidyls (7).*—Saturated solutions [*ca.* 0.09 g in propan-2-ol (250 ml)] of pure biphthalidyl (A) and of a 1 : 4 mixture of biphthalidyls (A) and (B) were irradiated in Pyrex tubes (250 ml) for 2 h 30 min under the conditions of method 2. The solutions were then evaporated, dried, and analysed.

† The last filtered fraction consists almost exclusively of diastereoisomer (A) (t.l.c.).

‡ It is also worth noting that the  $R_F$  of this compound lies near those of (7) [ $R_F(\text{A}) < R_F(\text{D}) < R_F(\text{B})$ ] in spite of the fact that it is only half the molecular weight.

*Quantitative Analyses of Biphthalidyls (7).*— $^{13}\text{C}$  N.m.r. analyses were performed on the crude mixtures of biphthalidyls (7) obtained by methods 1—3 as well as on the mixtures described in the preceding paragraphs. Spectra were taken on a Varian CFT 20 spectrometer operating at 20 MHz. Analyses of biphthalidyls (80—100 mg mixtures)

in solution in  $\text{CDCl}_3$  (*ca.* 1 ml) in the presence of a small quantity of  $\text{Cr}(\text{acac})_3$  were performed by using the gated decoupling-NOE suppressed mode; 4000 Hz spectral width, 1 s acquisition time, 19 s delay.

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