The Synthesis of some Substituted Biphenyl-4-carboxylic Acids, 4-Biphenylylacetic Acids, and 4-Aminobiphenyls

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The synthesis of a range of substituted biphenyl-4-carboxylic acids and 4-aminobiphenyls is described. Preparations are included for the parent biphenyl-4-carboxylic acid, and for 4-biphenylylacetic acid and three substituted 4-biphenylylacetic acids.

THE substituted biphenyl-4-carboxylic acids, 4-biphenylylacetic acids, and 4-aminobiphenyls were required for the measurement of the ionisation constants which are discussed in the two preceding Papers. The characterisation and purity of the products was therefore of considerable importance, although the methods of preparation were standard and require no comment.

Several of the carboxylic acids were known compounds, and the majority were prepared by unambiguous routes. Potentiometric titration of the acids showed that the observed and calculated values of the neutralisation equivalents were in very close agreement, and satisfactory elemental analyses were obtained in all cases. Possible contamination with acids of similar molecular weight or with isomeric acids was excluded by esterification by standard methods, when the esters, except those containing nitrogen, were shown to be free from isomers and other impurities by gas–liquid chromatography. Satisfactory elemental analyses were obtained for those esters containing nitrogen. The physical constants of these esters will be reported in a future publication. Within each group of 2′-, 3′-, 4′-, and 2′,4′-substituted biphenyl-4-carboxylic acids, the infrared spectra were found to be closely similar, and this was taken as confirmatory evidence for the structures of those acids not prepared by unambiguous methods, and for the freedom from isomers of those acids containing nitrogen.

Satisfactory elemental analyses were obtained for all the substituted 4-aminobiphenyls, and those which were new compounds were obtained from biphenyl derivatives which have been adequately characterised. The infrared spectra of the amines confirmed the orientation of the substituents in the biphenyl system and indicated that that isomeric amines or other impurities were absent.

EXPERIMENTAL

Substituted Biphenyl-4-carboxylic Acids.—(i) *From substituted 4-acetylbiphenyls*. 3-Nitrobiphenyl was prepared by the Gomberg reaction,[1] and reduction of this compound [2] afforded 3-aminobiphenyl. Halogenobiphenyls were readily prepared from the corresponding aminobiphenyls, although 4-aminobiphenyl required a medium of equal parts (by volume) of acetic acid, concentrated hydrochloric acid, and water for diazotisation. 4-Methylbiphenyl was prepared from *p*-toluidine by the Gomberg reaction,[3] and 4-ethyl- and 4-t-butyl-biphenyl, although previously reported in the literature, were prepared by the following new methods.

4-*Ethylbiphenyl*. 4-Acetylbiphenyl (85 g.), diethylene glycol (450 ml.), 90% hydrazine hydrate (45 ml.), and potassium hydroxide (59 g.) were heated under reflux on a steam-bath until homogeneous, and for 1 hr. thereafter. The temperature of the mixture was then raised, and distillate collected until the temperature of the residue rose to 175°. The residue was then boiled under reflux for 3 hr., and cooled. The resultant liquid and the distillate were extracted with

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[1] J. Elks, J. W. Haworth, and D. H. Hey, *J. Chem. Soc.*, 1940, 1284.

[2] P. M. G. Bavin, *Org. Synth.*, 1960, **40**, 5.

[3] D. J. Byron, G. W. Gray, A. Ibbotson, and B. M. Worrall, *J. Chem. Soc.*, 1963, 2246.

ether; distillation of the combined extracts gave 4-ethylbiphenyl, 54 g. (60%), b. p. 115—120°/1 mm. (lit.,[4] b. p. 140°/15 mm.).

4-t-Butylbiphenyl. The Friedel–Crafts reaction between t-butyl chloride (14·8 g., 0·16 mole) and biphenyl (25 g., 0·16 mole) was carried out in carbon disulphide (125 ml.) at 25°, with ferric chloride (7·4 g., 0·045 mole) as catalyst. The 4-t-butylbiphenyl was distilled at 105—115°/0·05 mm., and crystallised from ethanol. The colourless plates, 10 g. (30%), had m. p. 49—50° (lit.,[5] m. p. 52·2°).

Friedel–Crafts acylation of substituted biphenyls. Method 1. Crushed, anhydrous aluminium chloride (0·59 mole) was suspended in dry carbon disulphide (160 ml.). Acetyl chloride (0·5 mole) and biphenyl or the substituted biphenyl (0·47 mole) were together dissolved in carbon disulphide (160 ml.) and added to the rapidly stirred suspension during 20 min. Stirring was continued for 30 min. more, and the mixture was then heated under reflux, with stirring, for a further 4 hr. Carbon disulphide was removed by distillation, and the residue was added to ice–water (500 ml.). The ketone was extracted with ether and distilled under reduced pressure. The product was crystallised to constant m. p. from appropriate solvents. Further data are given in Table 1.

TABLE 1

Substituted 4-acetylbiphenyls

Subst.	Reaction time (hr.)	Yield (%)	B. p.	M. p.	Cryst. from	Lit. m. p.	Found (%)			Formula	Required (%)		
							C	H	Hal		C	H	Hal
Method 1													
Unsubst.	—	93	130—140°/3 mm.	119—120°	A	120—121° [7]							
3′-F	—	90	145—150/0·3 mm.	90·5—92	B	—	78·5	5·1		$C_{14}H_{11}FO$	78·5	5·1	
3′-Br	—	92	158—163/0·3 mm.	45—46	C	40·3—40·9 [8]							
3′-I[a]	—	50	170—175/0·3 mm.	—		—	51·9	3·7	39·2	$C_{14}H_{11}IO$	52·2	3·4	39·4
3′-NO_2	—	80	185—190/10^{-4} mm.	110—111	C	109—110 [8]							
4′-Et	—	47	120—128/1 mm.	121—122	A	116[10]							
Method 2													
2′-F	18	42		85·5—86·5	B	—	78·6	5·1					
2′-Cl	18	47		54—56	D	—	72·7	4·8	15·4	$C_{14}H_{11}ClO$	72·9	4·8	15·4
2′-Br	18	50		81—82	B	—	61·0	4·0	29·0	$C_{14}H_{11}BrO$	61·1	4·0	29·1
2′-I	18	43		86·5—87·5	B	—	52·1	3·4	39·6				
2′-NO_2	18 [b]	50		110—111	C	110 [7]							
3′-Cl	24	87		52—53	D	—	73·1	4·8	15·1				
3′-Ph	5 [c]	39		103—104	C	104 [9]							
4′-F	6	74		105—106	D	—	78·7	5·2					
4′-Cl	6	74		103—104	D	102—103 [10]							
4′-Br	6	90		129—130	A	—	60·9	3·9	29·2				
4′-I	6	63		163—164	A	—	52·2	3·2	39·7				
4′-Me	6	90		121—122	B	122 [4]							
4′-Bu^{t}	6	74		132—133	B	—	85·8	8·1		$C_{18}H_{20}O$	85·7	8·0	
4′-NO_2	18 [b]	40		153—154	A	152—153 [7]							
4′-Ph	5 [c,d]	74		207—209	A	—	91·9	6·1		$C_{20}H_{16}O$	91·6	6·1	

Solvents: (A), acetone, then ethanol; (B), light petroleum (b. p. 40—60°); (C), methanol, then ethanol; (D), methanol.

[a] 4-Acetyl-3′-iodobiphenyl is an oil. [b] The reaction mixture was stirred at room temperature (12 hr.) and then at 50° (6 hr.). [c] The acetyl chloride was added at 28°, and the mixture was stirred at 45° for 5 hr. [d] Vol. of dry nitrobenzene, 1·5 l.

Method 2. Anhydrous aluminium chloride (14 g., 0·1 mole) and the substituted biphenyl (0·08 mole) were dissolved in dry nitrobenzene (85 ml.). Acetyl chloride (8·3 g., 0·1 mole) was added, usually at below 20°, and the dark solution was stirred at room temperature or above (Table 1) for the time indicated in Table 1. The solution was poured onto a mixture of ice (100 g.), water (25 ml.), and concentrated hydrochloric acid (50 ml.). The organic layer was separated and the nitrobenzene removed by steam distillation. The residue was cooled, and the ketone was crystallised from suitable solvents to constant m. p. Additional information is listed in Table 1.

4-Acetyl-o-terphenyl (59%), m. p. 92—93°, was prepared by the method of Allen and Burness.[6]

Oxidation of substituted 4-acetylbiphenyls. A solution of sodium hypobromite, prepared at 0° by dissolving bromine (15·6 g., 0·1 mole) in a solution of sodium hydroxide (14 g., 0·35 mole) in water (70 ml.), was added, with stirring, to a solution of the substituted 4-acetylbiphenyl (0·02 mole) in dioxan (50 ml.). The temperature was maintained at 35—40° throughout the addition and for 15 min. afterwards. The suspension was treated with enough aqueous sodium metabisulphite to remove the excess of hypobromite. Water (340 ml.) was added, and about 70 ml. of the liquid was distilled off. The residual suspension or solution was acidified with concentrated hydrochloric acid and cooled. The free acid was filtered off, and crystallised from appropriate solvents to constant m. p. Further data are given in Table 2.

(ii) *From methyl biphenylcarboxylates prepared by the Gomberg reaction.* The redistilled, substituted aniline (0·6 mole) was diazotised and the solution of the diazonium salt was added to methyl benzoate (1·2 l.) at 5°. The mixture was stirred vigorously and then made slightly alkaline with 10N-aqueous sodium hydroxide; stirring was continued at room temperature for 20 hr. The organic layer was separated, washed with water, dried, and the methyl benzoate was removed by distillation under vacuum. Reduced pressure (1 mm.) distillation of the residue gave an oily mixture

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[5] J. I. G. Cadogan, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 1954, 3352.

[6] C. F. H. Allen and D. M. Burness, *J. Org. Chem.*, 1949, **14**, 163.

TABLE 2

Substituted biphenyl-4-carboxylic acids prepared by oxidation of substituted 4-acetylbiphenyls

Subst.	Yield (%)	M. p.	Cryst. from	Lit. m. p.	Found (%)			Formula	Required (%)		
					C	H	Hal		C	H	Hal
Unsubst.	77	222—224°	A	225·8° [8]							
2′-*F*	89	232—233	A	—	72·2	4·3		$C_{13}H_9FO_2$	72·2	4·2	
2′-*Cl*	85	251·5—252·5	A	—	67·3	3·9	15·0	$C_{13}H_9ClO_2$	67·2	3·9	15·2
2′-Br	88	242—243	A	242 [11]							
2′-*I*	88	240·5—241·5	A	—	48·3	2·7	38·8	$C_{13}H_9IO_2$	48·1	2·8	39·2
2′-NO_2	86	253·5—254·5	B	250 [7]							
2′-Ph	80	201—202	A	202—203 [6]							
3′-*F*	80	240—241·5	A	—	72·0	4·4					
3′-*Cl*	88	249—250	A	—	67·1	4·1	15·1				
3′-Br	65	253—255	C	252·9—254·4 [8]							
3′-*I* [a]	80	250—253	C	—	47·9	2·9	39·3				
3′-NO_2	80	305—308	C	313—315 [8]							
3′-Ph	66	224—225	A	221[9]							
4′-*F*	88	236—238 [b]	A	—	72·1	4·2					
4′-Cl	90	286 [b]	C	290—293 [10]							
4′-Br	90	301·5—302·5	C	304 [11]							
4′-*I*	85	312—313	C	—	48·0	2·7	38·9				
4′-Me	89	248 [b]	A	243—245 [8]							
4′-*Et*	88	244—246 [b]	B	—	79·7	6·2		$C_{15}H_{14}O_2$	79·6	6·2	
4′-*Bu*^{t}	70	280—282	A	—	80·3	7·0		$C_{17}H_{18}O_2$	80·3	7·1	
4′-NO_2	72	338·5—340	C	336—338 [7]							
4′-Ph [c]	75	306—309 [b]	D	303—305 [12]							

Solvents: (A), acetic acid, then ethanol; (B), acetic acid, then ethanol–acetone; (C), acetic acid, then 2-methoxyethanol; (D), acetic acid.

[a] This acid was esterified and the ester purified and reconverted to the acid. [b] At the temperature quoted a nematic mesophase was produced. The nematic-isotropic transition temperatures were: 4′-F, 264·5—265·5°; 4′-Me, 275·5°; 4′-Cl, 290°; 4′-Et, 275°; 4′-Ph, 331°. [c] 200 ml. dioxan used; the acid was separated from unreacted ketone by sublimation (160—180°/0·5 mm.) and the residual acid purified by crystallisation.

TABLE 3

Substituted biphenyl-4-carboxylic acids prepared by the Gomberg reaction

Subst.	Sublimation temp. (at 1 mm.)	Yield (%)	M. p.	Cryst. from	Found (%)		Formula	Required (%)	
					C	H		C	H
2′-Me	—	6·2	186—187° [a]	A					
2′-*Et*	140—150°	2·3	178—180	B	79·6	6·0			
2′-*Pr*^{i}	150—160	1·6	179—180	B	79·9	6·5	$C_{16}H_{16}O_2$	80·0	6·7
2′-*MeO*	—	2·2	250—252	C	73·7	5·2	$C_{14}H_{12}O_3$	73·7	5·3
3′-*Me*	175—180	5·7	206—207	A	79·5	5·7	$C_{14}H_{12}O_2$	79·3	5·7
3′-*Bu*^{t}	195—200	2·9	198—200	C	80·2	6·9			
3′-*MeO*	175—180	4·3	197—198	C	73·9	5·4			
4′-Me [b]	—	7·5	248 [c, d]	A					
4′-*Pr*^{i} [b]	—	7·0	237 [d]	A	79·8	6·4			

Solvents: (A), acetic acid, then ethanol; (B), acetic acid, then benzene; (C), ethanol.

[a] Lit.,[12] m. p. 173—175°. [b] The oily distillate of isomeric esters solidified on standing. Crystallisation from light petroleum (b. p. 40—60°) gave the pure methyl substituted-biphenyl-4-carboxylate: 4′-Me, m. p. 118—118·5° (lit.,[13] m. p. 115—116°); 4′-Pr^i, m. p. 107°. [c] Lit.,[8] m. p. 243—245°. [d] At the temperatures quoted a nematic mesophase was produced. The nematic-isotropic transition temperatures were: 4′-Me, 275·5°; 4′-Pr^i, 256°.

of the methyl substituted-biphenyl-2-, -3-, and -4-carboxylates, which was usually hydrolysed by boiling with 80% aqueous methanol (250 ml.) containing potassium hydroxide (25 g. for each 10 g. of oil). The hydrolysate was diluted with water and acidified with concentrated hydrochloric acid. The tarry acids were filtered off and washed with a small volume of light petroleum (b. p. 40—60°) to remove a red impurity. After charcoal treatment, successive crystallisations from appropriate solvents gave the substituted biphenyl-4-carboxylic acid with constant m. p. In several cases, the acid was then sublimed *in vacuo*, and given one final crystallisation. In two instances it was possible to separate the pure methyl substituted-biphenyl-4-carboxylate by crystallisation of the mixture of isomeric esters. The purified ester was hydrolysed as described above, and the acid purified by crystallisation. Data for the acids are given in Table 3.

(iii) *From substituted* 4-*cyanobiphenyls*. The preparations of the required 4-amino-3-, -2-, -2′-, and -3′-chlorobiphenyls are discussed later.

Substituted 4-*cyanobiphenyls*. A solution of sodium cuprocyanide was prepared by adding cuprous cyanide (16·5 g., 0·185 mole) to sodium cyanide (18·1 g., 0·37 mole) in water (150 ml.). Benzene (100 ml.) was added, and the whole was stirred and cooled to 6°.

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[11] M. Gomberg and J. C. Pernert, *J. Amer. Chem. Soc.*, 1926, **48**, 1372.

[12] H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1939, 1283.

[13] M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 1954, 1941.

The finely powdered amine hydrochloride (0·1 mole) was diazotised, and the solution of the diazonium salt was neutralised (Congo Red) using solid sodium hydrogen carbonate, filtered, and added to the vigorously stirred solution of sodium cuprocyanide. After a short time, the emulsion failed to give a coupling reaction. The benzene layer was then separated, washed with aqueous sodium carbonate and water, and dried. The product was distilled at 0·5 mm. The red distillate was dissolved in light petroleum (b. p. 40—60°) and passed down a column of activated alumina (25 × 1·5 cm.). After elution with light petroleum (b. p. 40—60°), a dark red-brown band was left on the column. The eluate was evaporated to about 20 ml., and on cooling the required nitrile crystallised out. Data for the 4-cyanobiphenyls are listed in Table 4.

TABLE 4

Substituted 4-cyanobiphenyls

Subst.	Yield (%)	M. p.	Found (%) [a]			
			C	H	Cl	N
3-Cl [b]	30	101—101·5° [c]				
2-*Cl*	14	79—80	73·3	3·8	6·4	16·9
2′-*Cl*	10·5	93—94	73·2	3·6	6·7	16·7
3′-*Cl*	12	52—53	73·4	3·7	6·4	16·4

[a] $C_{13}H_8ClN$ requires C, 73·1; H, 3·8; Cl, 6·6; N, 16·6%. [b] Purification by chromatography unnecessary; the oil solidified after distillation and was crystallised from methanol. [c] Lit.,[14] m. p. 101—101·5°.

Hydrolysis of substituted 4-*cyanobiphenyls*. The substituted 4-cyanobiphenyl (6 g.) was dissolved in equal volumes (75 ml.) of ethanol and 10N-aqueous sodium hydroxide, and heated under reflux until no further evolution of ammonia occurred (6—36 hr.). The solution was poured into hot water (300 ml.), filtered, and the hot filtrate was acidified with concentrated hydrochloric acid. On cooling, the crude acid was filtered off, and, after charcoal treatment, crystallised from acetic acid and from ethanol to constant m. p. The yields after one crystallisation were 81—90%. (See Table 5).

TABLE 5

Substituted biphenyl-4-carboxylic acids prepared by hydrolysis of substituted 4-cyanobiphenyls

Subst.	M. p.	Found (%)		
		C	H	Cl
3-Cl	169·5—170° †			
2-*Cl*	203·5—204	67·3	3·8	15·0
2′-*Cl*	251·5—252 *	67·3	3·9	15·0
3′-*Cl*	249—250 *	67·1	4·1	15·1

† Lit.,[14] m. p. 166·6—167°. * No depression of m. p. on admixture with the product obtained by oxidation of the appropriate 4-acetylbiphenyl.

(iv) 2′-, 3′-, *and* 4′-*Cyanobiphenyl*-4-*carboxylic acids*. A mixture of the bromobiphenyl-4-carboxylic acid (0·005 mole), cuprous cyanide (0·65 g., 0·0074 mole), dimethylformamide (8 ml.), and pyridine (1 drop) was heated under reflux for 4 hr. The cooled reaction mixture set to a solid, which was dissolved in aqueous ammonia (8 ml., *d* 0·88). A saturated solution of ammonium chloride was added to precipitate the ammonium salt of the cyano-acid. This was filtered off, washed well with saturated aqueous ammonium chloride, and suspended in water. The free acid was filtered off after acidification, and crystallised to constant m. p. from nitrobenzene, dimethylformamide, or acetone. (See Table 6.)

TABLE 6

Cyanobiphenyl-4-carboxylic acids

Subst.	Yield (%)	M. p.	Found (%) [a]		
			C	H	N
2′-*CN*	54	317—320°	75·0	4·0	6·0
3′-*CN*	70	292—294	75·6	4·2	6·1
4′-*CN* [b]......	65	263—265 [c]	75·4	4·3	6·3

[a] $C_{14}H_9NO_2$ requires C, 75·3; H, 4·1; N, 6·2%. [b] Potentiometric titration showed the acid to contain about 10% of a non-acidic impurity, despite the satisfactory elemental analysis. [c] At the temperature quoted a nematic mesophase was produced. The nematic-isotropic transition temperature was 315°.

(v) 2′- *and* 4′-*Aminobiphenyl*-4-*carboxylic acid*. 2′- and 4′-Nitrobiphenyl-4-carboxylic acids were converted to the acid chlorides using thionyl chloride. Methanolysis of the acid chlorides gave the methyl esters, which were crystallised from benzene. Methyl 2′-nitrobiphenyl-4-carboxylate (76%) had m. p. 88—89° (lit.,[15] m. p. 84—85°) and methyl 4′-nitrobiphenyl-4-carboxylate (94%) had m. p. 190—191° (lit.,[16] m. p. 188—189°). The nitro-esters were reduced by iron pin dust in aqueous methanolic hydrochloric acid. *Methyl* 2′-*aminobiphenyl*-4-*carboxylate*, m. p. 129—130° (Found: C, 74·0; H, 6·0; N, 6·2. $C_{14}H_{13}NO_2$ requires C, 73·8; H, 5·8; N, 6·2%), was obtained in 91% yield after crystallisation from methanol, and methyl 4′-aminobiphenyl-4-carboxylate, m. p. 179—180° (lit.,[17] m. p. 182—183°), in 87% yield after crystallisation from benzene. The esters were hydrolysed by heating under reflux (2 hr.) with a 10% solution of potassium hydroxide in 80% aqueous methanol. The free amino-acids were precipitated from the cold hydrolysates with acetic acid. After charcoal treatment, the products were crystallised from aqueous ethanol and then from benzene to constant m. p. 2′-Aminobiphenyl-4-carboxylic acid (62%) had m. p. 173—175° (lit.,[18] m. p. 179°). 4′-Aminobiphenyl-4-carboxylic acid (67%) had m. p. 227—245°, but the purity of the product is difficult to assess by m. p. determination because the acid polymerises at or about its m. p., giving a polyamide of m. p. >360° (lit.,[8,19] m. p.s 227—236° and 241—241·5°).

(vi) *From ethyl biphenyl*-4-*carboxylates prepared by the Ullmann reaction*. The required *o*-halogenonitrobenzenes, and 4-bromo-3-nitro-anisole, -t-butylbenzene, and -toluene, were prepared by conventional methods.

Copper bronze (95 g., 1·5 g. atom) was added in small portions to a stirred mixture of ethyl *p*-iodobenzoate (138 g., 0·5 mole) and the appropriate *o*-halogenonitrobenzene (0·5 mole), preheated to 205°, at such a rate (over a period of 30 min. to 1 hr.) that undue rise in temperature was avoided. Heating and stirring were continued for a further 3 hr. after completion of the addition. The mass was left to cool and the organic matter was extracted with boiling acetone. The acetone was removed, and distillation of the residue at 190—210°/3 mm. yielded the oily ethyl

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[18] I. G. M. Campbell, *J. Chem. Soc.*, 1950, 3109.

[19] E. Boyland and J. W. Gorrod, *J. Chem. Soc.*, 1962, 2209.

TABLE 7

Substituted biphenyl-4-carboxylic acids prepared by the Ullmann reaction

Subst.	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
2′-NO_2,4′-*Me*	42	256—259°	65·3	4·1	5·6	$C_{14}H_{11}NO_4$	65·4	4·3	5·4
2′-NO_2,4′-*Bu*^{t}	61	225—228	68·1	5·8	4·9	$C_{17}H_{17}NO_4$	68·2	5·7	4·7
2′-NO_2,4′-*MeO*	42	240—243	61·5	3·9	5·3	$C_{14}H_{11}NO_5$	61·5	4·0	5·1

substituted-biphenyl-4-carboxylate. The esters were hydrolysed using methanolic potassium hydroxide, and the hydrolysate was diluted with water and acidified with concentrated hydrochloric acid. The precipitated acid was filtered off, and, after charcoal treatment, crystallised from acetic acid or acetone to constant m. p. Further data are listed in Table 7.

TABLE 8

Substituted 4-biphenylylthioacetmorpholides

Subst.	Yield (%)	M. p.	N (%) Found	Required
Unsubst.	94	142—144° *		
2′-*Ph*	73	113—116	3·5	3·7
4′-*Br*	85	165—167	3·6	3·7

* Lit.,[20] m. p. 142—143°.

*2′-Amino-4′-methoxybiphenyl-*4*-carboxylic acid.* Ethyl 4′-methoxy-2′-nitrobiphenyl-4-carboxylate (in methanol) was reduced catalytically (Raney nickel) at 50° and 100 atm. The autoclave was cooled after 10 hr., and the catalyst was filtered off from the warm solution. The amino-ester (75%), m. p. 136—138°, crystallised from the cooled filtrate and was hydrolysed as described above. Crystallisation of the crude acid from acetic acid and from ethanol gave the pure *2′-amino-4′-methoxybiphenyl-*4*-carboxylic acid* (62%), m. p. 223—225° (Found: C, 68·9; H, 5·5; N, 5·8. $C_{14}H_{13}NO_3$ requires C, 69·1; H, 5·4; N, 5·8%).

TABLE 9

Substituted 4-biphenylylacetic acids

Subst.	Yield (%)	M. p.	Found (%) C	H	Br	Formula	Required (%) C	H	Br
Unsubst.	95	162—164°†							
2′-*Ph*	78	168—169	83·5	5·9	—	$C_{20}H_{16}O_2$	83·3	5·6	
2′-*Br*	20 *	124—125	58·4	4·1	27·8	$C_{14}H_{11}BrO_2$	58·0	3·8	27·5
4′-*Br*	57	173—175	58·3	4·0	27·7				

† Lit.,[20] m. p. 164—165°. * Based on 4-acetyl-2′-bromobiphenyl.

Substituted 4-*Biphenylylacetic Acids*.—A mixture of the appropriate substituted 4-acetylbiphenyl (0·2 mole), sulphur (10·5 g.), and morpholine (65 ml.) was heated under reflux for 6 hr. The hot mixture was poured into methanol (250 ml.), and, after cooling, the solid was filtered off and washed with methanol. The crude thioacetmorpholide was crystallised from ethanol or 2-methoxyethanol to constant m. p. The product from 4-acetyl-2′-bromobiphenyl was an oil and was used in the next stage without purification.

The thioacetmorpholide (0·2 mole), 70% aqueous ethanol (380 ml.), and 50% aqueous sodium hydroxide (75 ml.) were heated under reflux for 8 hr. A volume of liquid equal to the volume of ethanol present was removed by distillation, and the residue was added to water and acidified with concentrated hydrochloric acid. The crude 4-biphenylylacetic acid was filtered off and crystallised in turn from acetic acid, ethanol, and benzene to constant m. p. (Table 9).

Substituted 4-*Aminobiphenyls*.—(i) *From the oximes of substituted* 4-*acetylbiphenyls*. A solution of the appropriate substituted 4-acetylbiphenyl (0·04 mole) and hydroxylamine hydrochloride (7·5 g., 0·11 mole) in a mixture of ethanol (19 ml.) and pyridine (55 ml.) was heated under reflux for 3 hr. The solvent was removed by distillation under reduced pressure, and the residue poured into water. The oxime was filtered off and crystallised from ethanol. The yields were 80—90%, and the m. p.s and analyses are given in Table 10.

The oxime (0·02 mole) was suspended in dry, AnalaR benzene (240 ml.). Phosphorus pentachloride (12 g.) was added, and the whole was heated under reflux for 15 min., cooled, added to a mixture of concentrated hydrochloric acid (24 ml.) and ethanol (480 ml.), and heated under reflux for 4 hr. The solvent was distilled off under reduced pressure, leaving a solid residue which was then suspended in water. The free amine, released by the addition of 2N-aqueous sodium hydroxide, was extracted with ether. The product was distilled under reduced pressure, and if the distillate solidified, it was crystallised from light petroleum (b. p. 40—60° or 80—100°) or from benzene to constant m. p. Further data are given in Table 11.

TABLE 10

Oximes of substituted 4-acetylbiphenyls

Subst.	M. p.	N(%) Found	Formula	N (%) Required
2′-*F*	147—148°	6·2	$C_{14}H_{12}FNO$	6·1
3′-*F*	158—160	6·3		
4′-*Br*	222—224	4·8	$C_{14}H_{12}BrNO$	4·8
2′-*I*	142—143	4·0	$C_{14}H_{12}INO$	4·2
4′-*Me*	206·5—208	6·4	$C_{15}H_{15}NO$	6·2
4′-Et	190—191 *			
4′-*Bu*^{t}	191—192	5·3	$C_{18}H_{21}NO$	5·2
2′-*Ph*	148—149	4·7	$C_{20}H_{17}NO$	4·9
3′-*Ph*	180—182	5·0		

* Lit.,[4] m. p. 189—190°.

(ii) *From substituted biphenyl-*4*-carbonamides*. 4-*Amino-2′-methylbiphenyl*. 2′-Methylbiphenyl-4-carboxylic acid (5·8 g.) was heated under reflux (15 min.) with enough

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[20] E. Schwenk and D. Papa, *J. Org. Chem.*, 1946, **11**, 798.

thionyl chloride to dissolve the solid. The excess of thionyl chloride was distilled off under reduced pressure, and the residual acid chloride was treated cautiously with aqueous ammonia (50 ml., *d* 0·88) and left to stand for 2 hr. The amide was filtered off and crystallised from ethanol. The colourless plates of 2′-*methylbiphenyl*-4-*carbonamide*, 4·6 g. (80%), had m. p. 190—192° (Found: N, 6·7. $C_{14}H_{13}NO$ requires N, 6·6%).

A solution of sodium hypobromite was prepared at 0° by adding bromine (1·3 ml., 0·025 mole) to a solution of sodium hydroxide (5 g., 0·126 mole) in water (42 ml.). To the cold solution was added the finely divided amide (4·4 g., 0·02 mole), and the mixture was stirred until dissolution was complete. The solution was warmed to 70—80°, and after 20 min. the mixture was steam distilled. The distillate was extracted with ether, and distillation gave 4-*amino*-2′-*methylbiphenyl* as a colourless oil, 1 g. (22%), b. p. 95—100°/0·1 mm. (Found: C, 85·4; H, 7·4; N, 7·6. $C_{13}H_{13}N$ requires C, 85·2; H, 7·2; N, 7·7%).

TABLE 11

Substituted 4-aminobiphenyls prepared by the Beckmann rearrangement

Subst.	B. p./0·1 mm.	Yield (%)	M. p.	Lit. m. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
2′-*F**	95—100°	60	50—52°	36° [21]	77·1	5·5	7·3	$C_{12}H_{10}FN$	77·0	5·4	7·5
2′-*I**	115—120	44	—		48·9	3·3	4·8	$C_{12}H_{10}IN$†	48·8	3·4	4·7
2′-Ph	165	39	116—118	117—118 [22]							
3′-*F*	115—120	37	44—46		77·3	5·5	7·2				
3′-Ph	200	63	101—102	101·5—102 [23]							
4′-Br	150—155	60	147—149	145·5 [24]							
4′-Me	130	74	99—100	99 [25]							
4′-*Et*	150	53	82—83		84·8	7·8	7·1	$C_{14}H_{15}N$	85·3	7·7	7·1
4′-*Bu*^{t}	130	57	89—91		85·2	8·5	6·3	$C_{16}H_{19}N$	85·3	8·5	6·2

* These products were oils, but 4-amino-2′-fluorobiphenyl solidified over a period of weeks. † Found: I, 43·2. $C_{12}H_{10}IN$ requires I, 43·0%.

4-*Amino*-4′-*isopropylbiphenyl*. 4′-*Isopropylbiphenyl*-4-*carbonamide* was prepared as described for the 2′-methyl derivative. The colourless plates (87%), had m. p. 257—259° (Found: N, 5·6. $C_{16}H_{17}NO$ requires N, 5·8%). The carbonamide (3·5 g., 0·014 mole), dissolved in 2-methoxyethanol (400 ml.), was mixed with a solution of sodium (0·7 g., 0·03 g. atom) in methanol (20 ml.). Bromine (0·84 ml., 0·016 mole) was added, and the resulting solution was heated on a steam-bath (10 min.), and then made slightly acid with acetic acid. The mixture was poured into an excess of water and the carbamate filtered off and crystallised from ethanol. The carbamate, 3·8 g. (96%), m. p. 179—180°, was hydrolysed by heating under reflux with a solution of potassium hydroxide (9 g.) in 80% aqueous methanol (90 ml.) for 2 hr. The hydrolysate was diluted with water and the precipitated amine was extracted with ether. Distillation gave 4-*amino*-4′-*isopropylbiphenyl*, b. p. 140°/0·1 mm., which crystallised from light petroleum (b. p. 40—60°) as colourless needles, 1·6 g. (57%), m. p. 66—68° (Found: C, 88·1; H, 8·2; N, 6·6. $C_{15}H_{17}N$ requires C, 88·2; H, 8·1; N, 6·6%).

(iii) *From substituted nitrobiphenyls.* 4-*Amino*-p-*terphenyl*. This was prepared from 4-nitro-*p*-terphenyl [26] by the method of Allen and Burness.[22]

4-*Amino*-2-, -2′-, -3′-, *and* -4′-*chlorobiphenyls*. 4-Chloro-4′-nitrobiphenyl was prepared by the chlorination of molten 4-nitrobiphenyl,[27] and the preparation and characterisation of the other three isomeric chloronitrobiphenyls have been described.[3]

The nitro-compounds were reduced by iron pin dust and ethanolic hydrochloric acid.[24] The crude amines were purified by fractional distillation under reduced pressure. 4-*Amino*-2-*chlorobiphenyl* (Found: C, 71·0; H, 5·0; Cl, 17·2; N, 7·1. $C_{12}H_{10}ClN$ requires C, 70·8; H, 5·0; Cl, 17·4; N, 6·9%) was an oil which was further purified by distillation (10^{-3} mm.), using a sublimation apparatus in which the usual cold finger had been replaced by one to the tip of which was attached a glass receiving cup. The other amines were purified by crystallisation, from light petroleum (b. p. 40—60°) in the case of the 2′-*chloro*-, m. p. 42—43° (Found: C, 71·0; H, 4·8; Cl, 17·4; N, 6·9%), and 3′-*chloro*-, m. p. 47—48° (Found: C, 70·9; H, 5·0; Cl, 17·4; N, 7·1%) *derivatives*, and from light petroleum (b. p. 80—100°) in the case of 4-amino-4′-chlorobiphenyl, m. p. 132·5° (lit.,[28] m. p. 134°).

(iv) 4-*Amino*-3-*chlorobiphenyl*. The preparation of this amine has been described.[3]

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