711. *Some αω-Di(phenanthridin-6-yl)alkanes.*

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The preparation of some *NN'*-di-(2-biphenylyl)alkylenediamines and their cyclisation to the corresponding αω-di(phenanthridin-6-yl)alkanes are described.

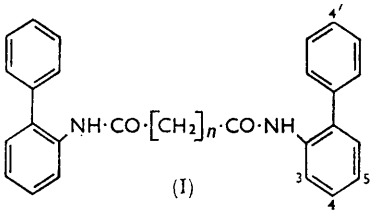
Some αω-di(phenanthridin-6-yl)alkanes, which are structurally similar to emetine and were required for biological study as possible amœbicides, have been prepared.

Morgan and Walls [1] prepared 6-substituted phenanthridines by cyclisation of 2-acylamidobiphenyls with phosphorus oxychloride. Ritchie [2] extended this method to *NN'*-di-(2-biphenylyl)adipamide (I; $n = 4$) obtaining 1,4-di(phenanthridin-6-yl)butane (II; $n = 4$) in low yield, together with a second, unidentified compound. We now find that, when ring closure is effected by phosphorus oxychloride in nitrobenzene, 1,4-di-(phenanthridin-6-yl)butane is formed in 50% yield, without the second compound described by Ritchie.[2] The pentane, hexane, heptane, octane, and decane compounds (II; $n = 5$—8, 10) have now been prepared similarly in 55—80% yield, but the glutaramide derivative (I; $n = 3$) resisted attempts at ring closure, even under experimental conditions that led to extensive resinification (cf. Ritchie [2]).

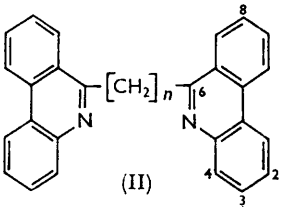
Attempts to prepare amino-derivatives of compounds (II) by extending the ring closure to nitro-derivative of adipamide (I; $n = 4$) failed. This was not entirely unexpected, as Walls [3] had shown that cyclisation of 2-acetamido-4'-nitrobiphenyl gives only a negligible yield of 6-methyl-8-nitrophenanthridine, presumably owing to the deactivating influence of the nitro-substituent. Aminophenanthridines were later prepared by Petrow [4] and by Walls [5] by reducing 2-acylamido-nitrobiphenyls and protecting the amino-group by benzoylation or by ethoxycarbonylation before cyclisation.

[1] Morgan and Walls, *J.*, 1931, 2447.
[2] Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1944, **78**, 155.
[3] Walls, *J.*, 1932, 2229.
[4] Petrow, *J.*, 1945, 18.
[5] Walls, *J.*, 1947, 67.

Accordingly the 5-nitro-2-biphenylyl-amide was reduced and benzoylated, but this product and its 4′-benzamido-isomer resisted cyclisation by phosphorus oxychloride alone or in nitrobenzene. The desired ring closures were achieved, however, by using the 5- and the 4′-ethoxycarbonylamino-derivatives.



(I)



(II)

The di(phenanthridin-6-yl)alkanes (II) are fairly high-melting, rather insoluble compounds, readily form quaternary salts and picrates, and exhibit the characteristic phenanthridine blue fluorescence in sulphuric acid. The quaternary salts are somewhat unstable in solution and have no biological activity.

1,4-Di(phenanthridin-6-yl)butane has slight action against *Entamoeba histolytica in vivo* and *in vitro*.

Experimental

The following acid chlorides were prepared by refluxing the acids with an excess of thionyl chloride in benzene and were repeatedly distilled under reduced pressure: glutaroyl, b. p. 103—104°/11 mm., n_D^{20} 1·47178, adipoyl, b. p. 118—119°/12 mm., n_D^{20} 1·47172, pimeloyl, b. p. 135—136°/11 mm., $n_D^{20\cdot5}$ 1·47005, suberoyl, b. p. 147—148°/11 mm., $n_D^{20\cdot5}$ 1·46923, azeloyl, b. p. 158—159°/12 mm., n_D^{20} 1·46749, sebacoyl, b. p. 168—169°/12 mm., n_D^{20} 1·46864, and dodecanedioyl dichloride, b. p. 192—193°/11 mm., $n_D^{20\cdot5}$ 1·46814.

NN′-*Di*-(2-*biphenylyl*)*adipamide*.—2-Aminobiphenyl (17·75 g.), adipoyl dichloride (9·2 g.), and dry benzene (70 ml.) were gently refluxed until evolution of hydrogen chloride had ceased (~3 hr.). The products were made alkaline with aqueous ammonia and again refluxed for a short time. The solution was evaporated to dryness, and the solid obtained was suspended in 50% aqueous alcohol and refluxed for 15 min. After cooling, the precipitated solid was collected. It formed needles (from ethanol), m. p. 174—175° (Found: C, 80·3; H, 6·3; N, 6·5. Calc. for $C_{30}H_{28}N_2O_2$: C, 80·3; H, 6·3; N, 6·3%) (yield 95%). Ritchie [2] gives m. p. 171°.

The *compounds* in Table 1 were prepared similarly. The following notes apply:

No. 1: Ritchie gives m. p. 162°.

No. 7: This was prepared from adipoyl dichloride and 2-amino-4-methylbiphenyl [6] in toluene.

No. 8: This was prepared from 2-amino-4-chlorobiphenyl [6] in toluene.

No. 12: This was prepared from the 4′-nitro-compound by use of reduced iron in aqueous ethanol.

No. 13: An identical compound was prepared by reaction of adipoyl dichloride with 2-amino-4′-ethoxycarbonylaminobiphenyl [6] in benzene.

No. 14: This was prepared by reaction of adipoyl dichloride with 2-amino-4′-benzamidobiphenyl [6] in chlorobenzene, and by benzoylation (Schotten–Baumann) of No. 12.

No. 16: This was prepared from the 5-nitro-compound by use of reduced iron in aqueous ethanol.

1,4-*Di*(*phenanthridin*-6-*yl*)*butane*.—The amide (I; $n = 4$) (30 g.), dry nitrobenzene (100 ml.), and phosphorus oxychloride (36 ml.) were heated at 180° until evolution of hydrogen chloride, which at first was vigorous, had practically ceased (~1 hr.). The cooled product was poured on ice (300 g.) and neutralised with aqueous ammonia. The collected solid was heated in 50% aqueous alcohol for 30 min. The solid residue was collected and crystallised from pyridine. 1,4-Di(phenanthridin-6-yl)butane formed very pale yellow needles, m. p. 215° (Found: C, 86·8; H, 5·8; N, 6·7. Calc. for $C_{30}H_{24}N_2$: C, 87·4; H, 5·7; N, 6·8%) (yield 50%). Ritchie [2] gives m. p. 214°. It is soluble in pyridine, nitrobenzene, and glacial acetic acid, but only sparingly soluble in other organic solvents.

The *dimethosulphate*, white needles, m. p. 287° (decomp.) (Found: S, 9·6. $C_{34}H_{36}N_2O_8S_2$

[6] Hollingsworth and Petrow, *J.*, in the press.

TABLE 1. *Amides of type* (I).

Number	Subst.†	*n*	Form	Solvent for crystn.*	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
1	None	3	Needles	EtOH	160—161°	90	80·1	6·0	6·3	$C_{29}H_{26}N_2O_2$	80·2	6·0	6·45
2	None	5	Needles	EtOH	167—168	90	80·2	6·6	5·8	$C_{31}H_{30}N_2O_2$	80·6	6·5	6·1
3	None	6	Needles	EtOH–H_2O	148—149	70	80·5	6·6	6·0	$C_{32}H_{32}N_2O_2$	80·7	6·7	5·9
4	None	7	Plates	EtOH–Pet	118—119	85	80·9	6·7	5·5	$C_{33}H_{34}N_2O_2$	80·8	6·95	5·7
5	None	8	Plates	EtOH	142—143	90	80·8	6·9	5·4	$C_{34}H_{36}N_2O_2$	81·0	7·15	5·55
6	None	10	Needles	EtOH–H_2O	114—115	70	81·1	7·4	5·3	$C_{36}H_{40}N_2O_2$	81·2	7·5	5·3
7	4-Me	4	Needles	EtOH	210	90	80·6	8·0	6·1	$C_{32}H_{32}N_2O_2$	80·7	8·1	5·9
8	4-Cl	4	Needles	Py–EtOH	229—230	80	69·5	5·1	5·2	$C_{30}H_{26}Cl_2N_2O_2$	69·6	5·0	5·4
9	5-Br	4	Plates	Py–EtOH	234—235	85	59·2	4·2	4·6	$C_{30}H_{26}Br_2N_2O_2$	59·4	4·3	4·6
10	3,5-Br_2	4	Needles	Py–EtOH	267—268	87·5	47·3	3·0	3·6	$C_{30}H_{24}Br_4N_2O_2$	47·1	3·1	3·7
11	4′-NO_2	4	Needles	Py	285—286	50	67·2	4·9	10·6	$C_{30}H_{26}N_4O_6$	66·9	4·8	10·4
12	4′-NH_2	4	Needles	EtOH–Pet	186	20	74·8	6·5	11·4	$C_{30}H_{30}N_4O_2$	75·2	6·3	11·7
13	4′-NH·CO_2Et	4	Powder	EtOH	231—232	50	68·9	6·0	8·8	$C_{36}H_{38}N_4O_6$	69·4	6·1	9·0
14	4′-NHBz	4	Plates	EtOH–Pet	220	50	76·5	5·6	8·0	$C_{44}H_{38}N_4O_4$	77·0	5·5	8·2
15	5-NO_2	4	Plates	Py	266	65	67·2	5·0	10·6	$C_{30}H_{26}N_4O_6$	66·9	4·8	10·4
16	5-NH_2	4	Needles	EtOH–Pet	224—225	60	75·5	6·4	11·6	$C_{30}H_{30}N_4O_2$	75·2	6·3	11·7
17	5-NH·CO_2Et	4	Cubes	EtOH	190—191	75	69·6	6·2	8·9	$C_{36}H_{38}N_4O_6$	69·4	6·1	9·0
18	5-NHBz	4	Needles	EtOH–Pet.	245	80	76·8	5·4	8·3	$C_{44}H_{38}N_4O_4$	77·0	5·5	8·2
19	3,5-$(NO_2)_2$	4	Needles	EtOH–$COMe_2$	239—240	70	57·3	3·7	13·2	$C_{30}H_{24}N_6O_{10}$	57·3	3·8	13·4
20	5,4′-$(NO_2)_2$	4	Needles	Py	308—309	50	57·4	3·7	13·7				

* Pet. = Light petroleum (b. p. 80—100°), Py = Pyridine. † In both nuclei.

TABLE 2. *αω-Di(phenanthridin-6-yl)alkanes* (II).

Number	Subst.†	*n*	Form	Solvent for crystn.*	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
1	None	5	Needles	Py	135—136°	55	86·9	6·0	6·3	$C_{31}H_{26}N_2$	87·3	6·1	6·6
2	None	6	Needles	Py	171—172	70	87·5	6·1	6·55	$C_{32}H_{28}N_2$	87·3	6·4	6·4
3	None	7	Needles	Py	139—140	65	87·3	6·75	6·2	$C_{33}H_{30}N_2$	87·3	6·6	6·2
4	None	8	Needles	Py	166—167	75	87·2	6·9	6·0	$C_{34}H_{32}N_2$	87·2	6·9	6·0
5	None	10	Fawn needles	Py–EtOH	146	80	87·1	7·5	5·4	$C_{36}H_{36}N_2$	87·1	7·3	5·6
6	3-Me	4	Needles	Py–EtOH	194	45	87·4	6·6	6·4	$C_{32}H_{28}N_2$	87·3	6·35	6·35
7	3-Cl	4	Cream needles	Py	248—249	45	74·8	4·8	5·5	$C_{30}H_{22}Cl_2N_2$	74·85	4·8	5·5
8	2-Br	4	Yellow plates	Py–EtOH	217—218	30	62·9	3·9	4·8	$C_{30}H_{22}Br_2N_2$	63·2	3·9	4·9
9	2,4-Br_2	4	Cream needles	Py–EtOH	290—291	20	49·6	2·8	4·0	$C_{30}H_{20}Br_4N_2$	49·5	2·9	3·85
10	8-NH·CO_2Et	4	Cream needles	Py–EtOH	286—287	60	73·5	5·9	9·8	$C_{36}H_{34}N_4O_4$	73·7	5·8	9·6
11	2-NH·CO_2Et	4	Needles	Py–EtOH	210—211	65	73·4	6·0	9·4	$C_{36}H_{34}N_4O_4$			

* Py = Pyridine.

requires S, 9·6%) after crystallisation from aqueous alcohol, was prepared by use of dimethyl sulphate in nearly boiling nitrobenzene (yield 80%). With aqueous potassium iodide it gave the yellow *dimethiodide* (95%), m. p. 278 –280° (decomp.) [from alcohol–light petroleum (b. p. 80—100°)] (Found: I, 36·1. $C_{30}H_{24}N_2,2CH_3I$ requires I, 36·5%). On repeated recrystallisation this formed the *monomethiodide*, also yellow, m. p. 274° (decomp.) (Found: I, 23·2. $C_{30}H_{24}N_2,CH_3I$ requires I, 22·9%), that with wet silver chloride in boiling absolute alcohol gave the white *monomethochloride*, needles (60%) (from alcohol–ether), m. p. 228 –229° (decomp.) (Found: Cl, 7·5. $C_{30}H_{24}N_2,CH_3Cl$ requires Cl, 7·7%).

1,5-*Di*(*phenanthridin*-6-*yl*)*pentane di-isethionate*, white prisms (from alcohol–acetone), m. p. 173—174° (Found: S, 9·3. $C_{35}H_{38}N_2O_8S_2$ requires S, 9·4%), was obtained (70%) by treating the base with isethionic acid in boiling alcohol: it was easily soluble in alcohol and water, but practically insoluble in non-ionic solvents.

The *compounds* in Table 2 were prepared similarly. Compound 10 was recovered unchanged after 5 hours' refluxing in fuming hydrochloric acid, and after 2 hours' in 70% sulphuric acid at 150°.

This work was commenced at Queen Mary College (University of London), during the period 1946—1948.

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