Preparation of Some Dibenz[*b*,*f*][1,4]oxazepines and Dibenz[*b*,*e*]azepines

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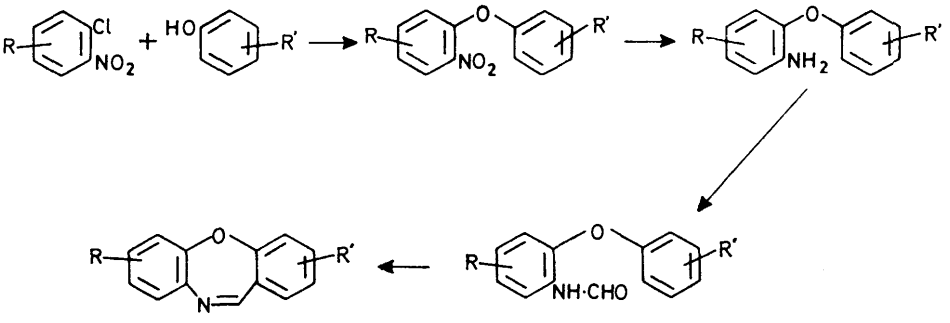
Some dibenz[*b*,*f*][1,4]oxazepines and dibenz[*b*,*e*]azepines, variously substituted in the aromatic rings but not substituted at the azomethine group, are described.

DIBENZ[*b*,*f*][1,4]OXAZEPINE (1d) † has intense lachrymatory and skin irritant properties,[1,2] and the corresponding azepine and thiazepine are also extremely irritant to the skin, mucous membrane, and eyes.[2] Preliminary biological examination of dibenz[*b*,*f*][1,4]-oxazepine showed that its powerful irritant properties were coupled with very low mammalian toxicity; various biological investigations of dibenz[*b*,*f*][1,4]-oxazepine have been reported recently.[3] Concurrent with the biological evaluation, a series of derivatives of synthesis of the tricyclic ring system are not novel. However, most of the products described are new, with the synthetic interest arising principally from the selection of suitable routes to afford the required substituent pattern. Also, in contrast to most work reported elsewhere, the products all contain an unsubstituted azomethine system, which seems to be a requirement for irritancy.

The procedure (A) used for the synthesis of dibenz-[*b*,*f*][1,4]oxazepine and its derivatives is essentially that



SCHEME 1

that compound and the azepine analogue substituted in the benzene rings were prepared in an attempt to find whether there was any relation between irritancy and structure. In this paper the syntheses of these derivatives are reported; none was significantly more potent than dibenz[*b*,*f*][1,4]oxazepine.

Following the discovery of the antidepressant activity of imipramine,[4] there has been considerable interest in the synthesis of tricyclic systems wherein a central seven-membered ring is flanked by two aromatic rings. In particular much work on the synthesis of dibenzoxazepines and dibenzazepines has been reinvestigated, and new synthetic procedures have been reported.[2,5-10] Accordingly the routes described in this paper for the described previously by other workers,[1,2] and is illustrated in Scheme 1. The required nitro-phenoxybenzene (Table 1), prepared by Ullman-type reaction between suitably substituted 1-chloro-2-nitrobenzenes and phenols, was reduced to the corresponding amine (Table 2) with steam and iron filings or catalytically. Formylation of the phenoxyanilines afforded the corresponding formamides (Table 3), which were converted

† In formula numbers (1)—(20) (Tables 1—4), suffix 'a' refers to the 1-nitro-2-phenoxybenzenes, 'b' to the 2-phenoxyanilines, 'c' to the *N*-(2-phenoxyphenyl)formamides, and 'd' to the dibenz[*b*,*f*][1,4]oxazepines.

[1] R. Higginbottom and H. Suschitzky, *J. Chem. Soc.*, 1962, 2367.

[2] F. Hunziker, F. Kunzle, O. Schindler, and J. Schmutz, *Helv. Chim. Acta*, 1964, **47**, 1163.

[3] B. Ballantyne, F. W. Beswick, and D. P. Thomas, *Medicine, Science, and the Law*, 1973, **13**, 265; B. Ballantyne and D. W. Swanston, *Acta Pharmacol. et Toxicol.*, 1974, **35**, 412; P. Holland, *Brit. J. Dermatol.*, 1974, **90**, 657; D. G. Upshall, *Tox. Appl. Pharmacol.*, 1974, **29**, 301; R. E. Pattle, C. Schock, P. Dirnhuber, and J. M. Creasey, *Brit. J. Exp. Path.*, 1974, **55**, 213.

[4] R. Kuhn, *Schweiz. Med. Wochschr.*, 1957, **87**, 1135.

[5] C. I. Brodrik, M. L. Donaldson, J. S. Nicholson, W. F. Short, and D. G. Webberley, *J. Chem. Soc.*, 1953, 1079.

[6] M. Allen and R. Y. Moir, *Canad. J. Chem.*, 1959, **37**, 1799.

[7] (*a*) F. Hunziker, F. Kunzle, and J. Schmutz, *Helv. Chim. Acta*, 1963, **46**, 2337; (*b*) F. Hunziker and O. Schindler, *ibid.*, 1965, **48**, 1590; (*c*) F. Hunziker, F. Kunzle, and J. Schmutz, *ibid.*, 1966, **49**, 244, 1433; (*d*) J. Schmutz, F. Kunzle, F. Hunziker, and R. Gauch, *ibid.*, 1967, **50**, 245; (*e*) F. Hunziker, E. Fischer, and J. Schmutz, *ibid.*, p. 1588; (*f*) F. Kunzle and J. Schmutz, *ibid.*, 1969, **52**, 622.

[8] (*a*) K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni, and R. K. Shah, *Indian J. Chem.*, 1974, **12**, 227; (*b*) K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni, A. N. Goud, and R. K. Shah, *ibid.*, p. 236; (*c*) K. Nagarajan, C. L. Kulkarni, and A. Venkateswarlu, *ibid.*, p. 247; (*d*) K. Nagarajan, V. R. Rao, A. Venkateswarlu, and R. K. Shah, *ibid.*, p. 252; (*e*) K. Nagarajan, C. L. Kulkarni, A. Venkateswarlu, and R. K. Shah, *ibid.*, p. 258; (*f*) K. Nagarajan and R. K. Shah, *ibid.*, p. 268.

[9] (*a*) M. Nakanishi and T. Oe, Jap. P. 7,016,951 (*Chem. Abs.*, 1970, **73**, 131,055b); (*b*) G. Schmidt, U.S.P. 3,546,214 (*Chem. Abs.*, 1971, **74**, 141,907r); (*c*) G. Schmidt, S. Afr. P. 6,804,436 *Chem. Abs.* 1969, **71**, 50,016w); (*d*) L. H. Werner and A. P. A. Rossi, Belg. P. 632,563 (*Chem. Abs.*, 1964, **61**, 8325); (*e*) J. O. Jilek, J. Pomykacek, and M. Protiva, Czech. P. 111,215 (*Chem. Abs.*, 1963, **62**, 14,707); (*f*) C. F. Howell and E. V. Greenblatt, U.S.P. 3,660,406 (*Chem. Abs.*, 1972, **77**, 62,038s).

[10] A. M. Islam, I. B. Hannout, E. A. Hassan, and A. E. Ihsan, *J. prakt. Chem.*, 1972, **314**, 727.

into dibenzoxazepines (Table 4) on treatment with polyphosphoric acid (Bischler–Napieralski reaction [11]).

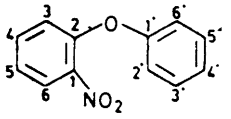
With the exception of the 3-methyldibenzoxazepine and the oxazepine formed from *N*-[2-(2-naphthyloxy)-phenyl]formamide (20c), the positions of substitution in the dibenzoxazepines followed from the structure of the formamido precursors. However treatment of the *N*-[2-(3-methylphenoxy)phenyl]formamide (4c) with polyphosphoric acid could afford both 1- and 3-methyldibenzoxazepines. In practice the 3- and 1-isomers were formed in the ratio 7 : 3 (ratio of methyl n.m.r. signals). The major 3-isomer was purified by fractional crystallisation. The 1-isomer was prepared by unequivocal synthesis (Scheme 2), thereby establishing the structures of both derivatives. The preponderant formation of the 3-methyl derivative probably occurs as a result of steric control favouring attack at a carbon atom with one *ortho*-substituent rather than at a carbon atom with both *ortho*-positions substituted (leading to the 1-isomer).

The most interesting feature of the sequence in Scheme 2 was the selective reduction of the nitro-aldehyde to the amino-aldehyde which underwent spontaneous cyclisation to give the Schiff's base directly. Dibenz[*b*,*f*][1,4]oxazepine itself was also prepared by the route exemplified in Scheme 2.

The ring closure of *N*-[2-(2-naphthyloxy)phenyl]-formamide (20c) yielded the angular system (20d) rather than the isomeric linear structure (21). The ^{1}H n.m.r.

TABLE 1

1-Nitro-2-phenoxybenzenes *



Compd.	Subst.	Reactants	B.p. (°C; mm Hg) [M.p.]	Yield (%)
(1a) *		Phenol, 1-chloro-2-nitrobenzene	152; 2	80
(3a) [b]	4′-Me	*p*-Cresol, 1-chloro-2-nitrobenzene	132; 0.01 [42]	71
(4a) [b]	3′-Me	*m*-Cresol, 1-chloro-2-nitrobenzene	130; 0.01	83
(5a) [c]	2′-Me	*o*-Cresol, 1-chloro-2-nitrobenzene	125; 0.04	50
(6a)	3-Me	Phenol, 2-bromo-3-nitrotoluene [d]	[65]	66
(7a)	4-Me	Phenol, 3-chloro-4-nitrotoluene [e]	142; 0.15 [57]	61
(8a)	5-Me	Phenol, 4-chloro-3-nitrotoluene	132; 0.01	60
(9a)	6-Me	Phenol, 3-bromo-2-nitrotoluene [f]	100; 0.03	40
(10a) [c]	3′,6′-Me_2	2,5-Xylenol, 1-chloro-2-nitrobenzene	136; 0.05	67
(11a) [c]	3′,5′-Me_2	3,5-Xylenol, 1-chloro-2-nitrobenzene	[56]	52
(12a) [c]	2′,4′-Me_2	2,4-Xylenol, 1-chloro-2-nitrobenzene	[58]	88
(13a)	2′,3-Me_2	*o*-Cresol, 2-bromo-3-nitrotoluene [d]	126; 0.03	43
(14a)	3,6-Me_2	Phenol, 2-bromo-1,4-dimethyl-3-nitrobenzene	130; 0.2 [69]	64
(15a) [g]	4′-Cl	*p*-Chlorophenol, 1-chloro-2-nitrobenzene	151; 0.1	62
(16a) [g]	4-Cl	Phenol, 1,3-dichloro-4-nitrobenzene	[85]	24
(17a) [h]	4′,5-Cl	4-Chlorophenol, 1,4-dichloro-2-nitrobenzene	[66]	61
(20a)	3′,4′-Benzo †	β-Naphthol, 1-chloro-2-nitrobenzene	[56]	37

* Superscript letters denote references in which products or intermediates are described. † 1-Naphthyloxy-2-nitrobenzene.

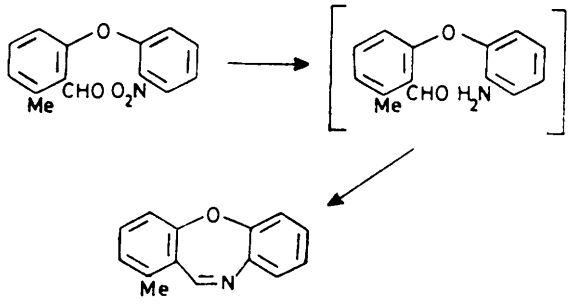
[a] R. Higginbottom and H. Suschitzky, *J. Chem. Soc.*, 1962, 2367. [b] R. V. Henley, *J. Chem. Soc.*, 1930, 1222. [c] J. D. C. Mole and E. E. Turner, *J. Chem. Soc.*, 1939, 1720. [d] D. F. DeTar and J. C. Howard, *J. Amer. Chem. Soc.*, 1955, **77**, 4395. [e] L. A. Elson, C. S. Gibson, and T. D. A. Johnson, *J. Chem. Soc.*, 1929, 2735. [f] A. Tomisek, B. Graham, A. Griffiths, C. S. Pease, and B. C. Christensen, *J. Amer. Chem. Soc.*, 1948, **68**, 1587. [g] E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1925, 2004. [h] L. G. Groves, E. E. Turner, and and G. I. Sharp, *J. Chem. Soc.*, 1929, 512.

TABLE 2

2-Phenoxyanilines

Compd.	Subst.	Method of reduction *	B.p. (°C; mm Hg) [M.p.]	Yield (%)
(1b)		*y*	[40]	70
(3b)	4′-Me	*x*	115; 0.15	78
(4b)	3′-Me	*x*	124; 0.01	67
(5b)	2′-Me	*x*	110; 0.015	71
(6b)	3-Me	*y*	[72]	80
(7b)	4-Me	*y*	128; 0.2	83
(8b)	5-Me	*y*	128; 0.1	79
(9b)	6-Me	*y*	84; 0.04	75
(10b)	3′,6′-Me_2	*x*	120; 0.03	73
(11b)	3′,5′-Me_2	*x*	[54]	73
(12b)	2′,4′-Me_2	*x*	120; 0.1	70
(13b)	2′,3-Me_2	*y*	108; 0.04	78
(14b)	3,6-Me_2	*x*	[54]	42
(15b)	4′-Cl	*x*	118; 0.1	80
(16b)	4-Cl	*x*	98; 0.01	40
(17b)	4′,5-Cl_2	*x*	[61]	30
(18b)	5-Cl	(Supplied by I.C.I.)		
(19b)	4′-CF_3	(Supplied by I.C.I.)		
(20b)	3′,4′-Benzo †	*y*	79	70

* *x*, iron filings and steam; *y*, H_2, Pd–C. † 2-(2-Naphthyloxy)aniline.



SCHEME 2

[11] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 74.

spectrum did not allow definitive assignment of structure, although the azomethine proton exhibited an unusually low-field resonance [δ 9.26; *cf.* 8.5 for (1d)] which favoured structure (20d). (This presumably reflects a compound (21) could not be detected in the ^{13}C spectrum of crude (20d), indicating that the stereospecificity of the ring closure was >95%. The preponderant formation of (20d) was not unexpected because ring closure

TABLE 3

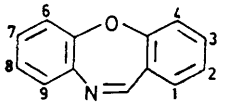
N-(2-Phenoxyphenyl)formamides

Compd.	Subst.	M.p. (°C) (from ethanol)	Yield (%)	Analysis (%) (Reqd./Found) C	H	N
(1c)		94	90			
(3c)	4'-Me	90	95	74.0/74.1	5.8/6.1	6.1/6.2
(4c)	3'-Me	91	96	74.0/74.1	5.8/5.9	6.1/6.2
(5c)	2'-Me	127	94	74.0/74.1	5.8/6.0	6.1/6.4
(6c)	3-Me	119	94	74.0/74.3	5.8/5.9	6.1/6.2
(7c)	4-Me	78	82	74.0/74.2	5.8/5.7	6.1/6.2
(8c)	5-Me	73	91	74.0/73.8	5.8/6.0	6.1/6.5
(9c)	6-Me	105	82	74.0/73.8	5.8/5.8	6.1/6.3
(10c)	3',6'-Me_2	93	94	74.7/74.9	6.3/6.4	5.8/5.9
(11c)	3',5'-Me_2	90	89	74.7/74.9	6.3/6.5	5.8/5.9
(12c)	2',4'-Me_2	87	96	74.7/74.6	6.3/6.3	5.8/6.0
(13c)	2',3-Me_2	132	96	74.7/74.5	6.3/6.4	5.8/5.8
(14c)	3,6-Me_2	137	84	74.7/74.6	6.3/6.4	5.8/6.0
(15c)	4'-Cl	101	95	63.0/63.1	4.1/4.2	5.7/5.5
(16c)	4-Cl	101	96	63.0/63.0	4.1/4.2	5.7/5.7
(17c)	4',5'-Cl_2	104	75	55.3/55.6	3.2/3.3	5.0/4.6
(18c)	5-Cl	128	88	63.0/63.2	4.1/4.4	5.7/5.6
(19c)	4'-CF_3	91	96	59.8/59.7	3.6/3.5	5.0/4.9
(20c)	3',4'-Benzo †	94	81	77.5/77.3	5.0/5.1	5.3/5.0

† *N*-[2-(2-Naphthyloxy)phenyl]formamide.

TABLE 4

Dibenz[*b*,*f*][1,4]oxazepines



Compd.	Subst.	M.p. (°C) [b.p. (°C; mm Hg)]	Yield (%)	Analysis (%) (Reqd./Found) C	H	N
(1d)		72	88	80.0/79.8	4.6/4.8	7.2/7.4
(3d)	2-Me	60	86	80.4/80.3	5.3/5.3	6.7/6.6
(4d)	3-Me	85	80 *	80.4/80.4	5.3/5.6	6.7/6.7
(5d)	4-Me	[100; 2]	57	80.4/80.1	5.3/5.6	6.7/7.0
(6d)	6-Me	40	51	80.4/80.7	5.3/5.6	6.7/6.5
(7d)	7-Me	44	29	80.4/80.1	5.3/5.6	6.7/6.9
(8d)	8-Me	40	51	80.4/80.4	5.3/5.2	6.7/7.1
(9d)	9-Me	70	71	80.4/80.6	5.3/5.5	6.7/6.8
(10d)	1,4-Me_2	82	80	80.7/81.4	5.9/6.0	6.3/6.2
(11d)	1,3-Me_2	122	71	80.7/80.4	5.9/6.2	6.3/6.3
(12d)	2,4-Me_2	[128; 0.04]	57	80.7/80.9	5.9/6.1	6.3/6.4
(13d)	4,6-Me_2	77	31	80.7/80.4	5.9/6.0	6.3/6.4
(14d)	6,9-Me_2	51	57	80.7/81.0	5.9/6.1	6.3/6.0
(15d)	2-Cl	94	56	68.0/68.1	3.5/3.4	6.1/6.2
(16d)	7-Cl	94	50	68.0/67.8	3.5/3.6	6.1/6.2
(17d)	2,8-Cl_2	145	44	59.2/59.2	2.7/2.6	5.3/5.4
(18d)	8-Cl	75	76	68.0/67.8	3.5/2.5	6.1/6.1
(19d)	2-CF_3	68	19	63.9/64.0	5.3/5.2	3.1/3.4
(20d)	1,2-benzo. †	128	64	83.2/83.0	4.6/4.7	5.7/5.5

* Yield of crude product (mixture of 1- and 3-isomers); yield of 3-isomer aftr three crystallisations, 62%. † Naphtho[2,1-*b*]-[1,5]benzoxazepine.

van der Waals interaction with the proton at the adjacent α-position on the naphthalene ring system resulting in a mutual deshielding.) The ^{13}C n.m.r. spectrum,[12] however, gave unequivocal proof of structure, showing the azomethine carbon signal as a simple doublet (J 179.7 Hz) indicative of a $^1J_{CH}$ interaction only. This is consistent only with structure (20d). [The azomethine carbon atom in (21) would give a four-line resonance ($^1J_{CH}$ and $^3J_{CH}$) action.] Further, in the Bischler–Napieralski reaction occurs by electrophilic substitution, and naphthalene usually undergoes electrophilic substitution preferentially in the α-position.

Dibenz[*b*,*e*]azepines may be prepared by essentially the same procedures as used for the dibenz[*b*,*f*][1,4]-oxazepines, provided that suitably substituted intermediates are available. In many cases, however, lack of suitable intermediates has necessitated the use of

[12] C. Brown, personal communication.

alternative procedures. The procedures (C—F) used for the synthesis of the dibenz[*b*,*e*]azepines listed in

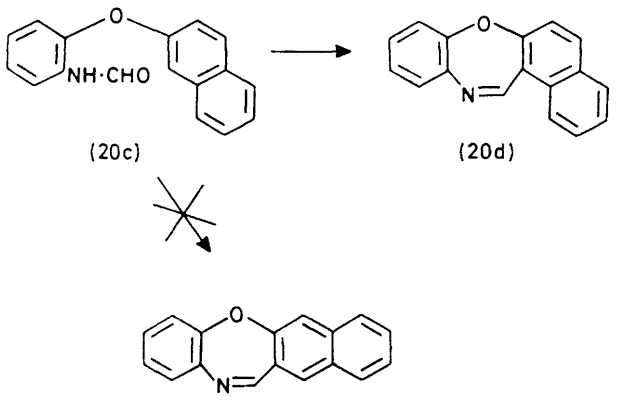


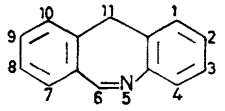
Table 5 are outlined in Schemes 3—6. In Scheme 3, the synthesis of 4-methyldibenz[*b*,*e*]azepine (24) is given as an example of procedure C. Treatment of 2,8-dimethyl-3,1-benzoxazin-4-one [13] with phenylmagnesium bromide afforded 2-acetamido-3-methylbenzophenone; [14] this was followed by deacetylation, reduction, formylation, and ring closure by the Bischler–Napieralski reaction.

An alternative procedure for converting 2-aminoacetophenone derivatives (procedure D) is illustrated in Scheme 4. In this sequence, exemplified by the synthesis of 10,11-dimethyldibenz[*b*,*e*]azepine (29), the bridgehead carbon atom was substituted by Grignard reagent addition,[14] and deoxygenated by treatment with red phosphorus and hydriodic acid. Ring closure by formation of an amide bridge was effected *via* an isocyanate intermediate.[15] The 5,11-dihydro-10,11-dimethyldibenz[*b*,*e*]azepin-6-one was converted into 10,11-dimethyldibenz[*b*,*e*]azepine (29) by sequential reduction with lithium aluminium hydride and dehydrogenation with sulphur. Other methods of dehydrogenation involving the use of tetrachloro-*p*-benzoquinone [2] or mercury(II) acetate [7a] have been described.

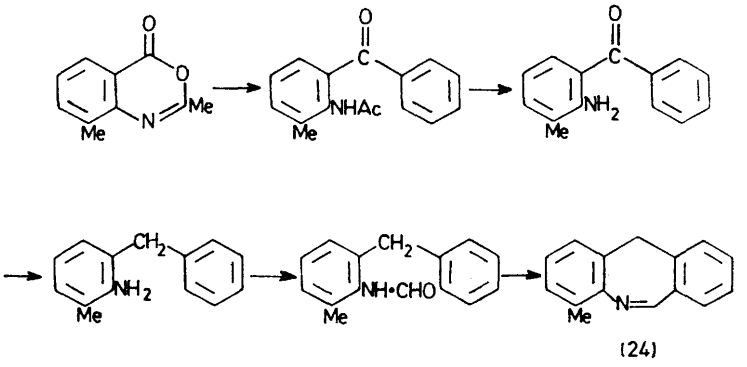
Procedure E, illustrated in Scheme 5, involves the formation of anthraquinone derivatives and subsequent Schmidt ring expansion of the anthraquinone to morph-

TABLE 5

Dibenz[*b*,*e*]azepines



Compd.	Subst.	Procedure	M.p. (°C) [B.p. (°C; mm Hg)]	Yield (%)	Analysis (%) (Reqd./Found) C	H	N
(22)		E	62	65	87.0/87.1	5.7/6.0	7.3/7.4
(23)	1-Me	C	45	25	86.9/86.8	6.3/6.7	6.8/6.4
(24)	4-Me	C	68	43	86.9/86.7	6.3/6.6	6.8/6.5
(25)	10-Me	C	[102; 2]	50	86.9/86.8	6.3/6.6	6.8/6.7
(26)	11-Me	F	69	79	86.9/87.0	6.3/6.6	6.8/6.7
(27)	1,4-Me_2	E	80	50	86.8/86.8	6.8/6.9	6.3/6.1
(28)	7,10-Me_2	C	91	85	86.8/86.6	6.8/6.6	6.3/6.7
(29)	10,11-Me_2	D	75	49	86.8/86.7	6.8/7.0	6.3/6.2
(30)	1,4,11-Me_3	F	81	50	86.8/86.5	7.3/7.3	6.0/5.7
(31)	11-Et	D	61	69	86.1/86.1	7.7/7.9	6.3/6.3

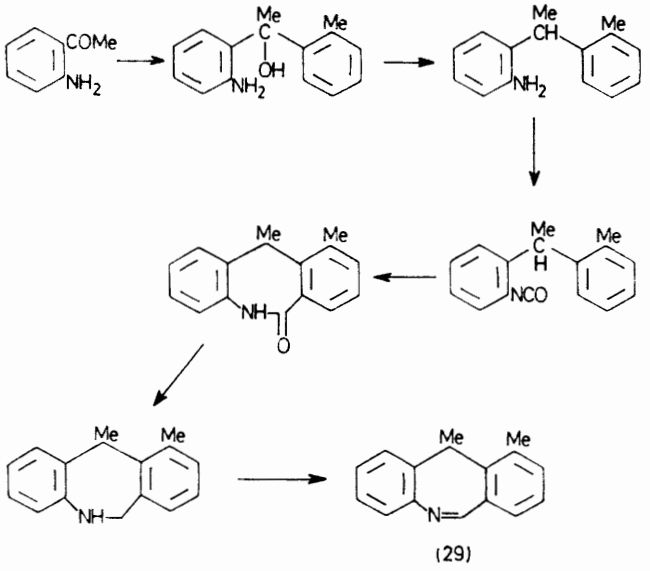


SCHEME 3

anthridinones, followed by reduction and dehydrogenation to give the dibenzazepines. The applicability of this procedure is limited by the ease of formation of the required anthraquinones [16] and by the stereoselectivity

[13] W. C. Lothrop and P. A. Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 365.
[14] H. Hart and J. R. Kosak, *J. Org. Chem.*, 1962, **27**, 116.
[15] J. Schmutz, F. Kunzle, F. Hunziker, and A. Burki, *Helv. Chim. Acta*, 1965, **48**, 336.
[16] G. Baddely, G. Holt, and S. M. Makar, *J. Chem. Soc.*, 1952, 2415.

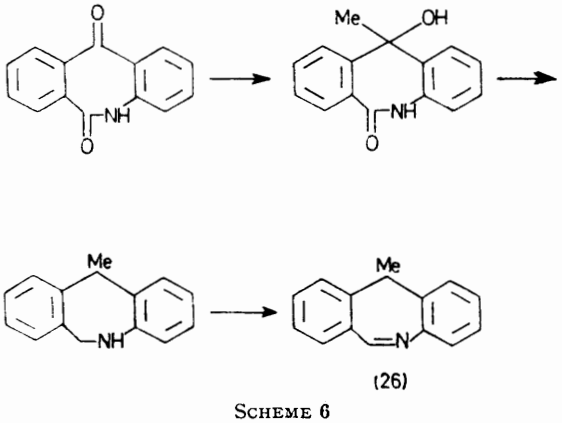
of the reaction between the anthraquinones and sodium azide. A number of examples of the Schmidt reaction



(29)

SCHEME 4

in the formation of monosubstituted morphanthridine-6,11-diones have been described.[17] In most cases yields were low and mixtures of the four possible isomers were obtained. The Schmidt reaction with 1,4-dimethylanthraquinone however was highly stereoselective, affording essentially only one product (t.l.c. and n.m.r. evidence). The structure of that product (1,4-dimethylmorphanthridine-6,11-dione) was established by converting the dione into 2-(2,5-dimethylbenzoyl)benzoic acid by a procedure [17] involving successive alkaline hydrolysis, diazotisation, and hydrolysis. It is not easy to determine why the Schmidt reaction with 1,4-dimethylanthraquinone should be highly stereoselective whereas other reactions in this series are not. Ring expansion of fluorenones to phenanthridones have been studied in far greater detail but no clear appreciation of the relative importance of steric and electronic effects has been forthcoming.[18]



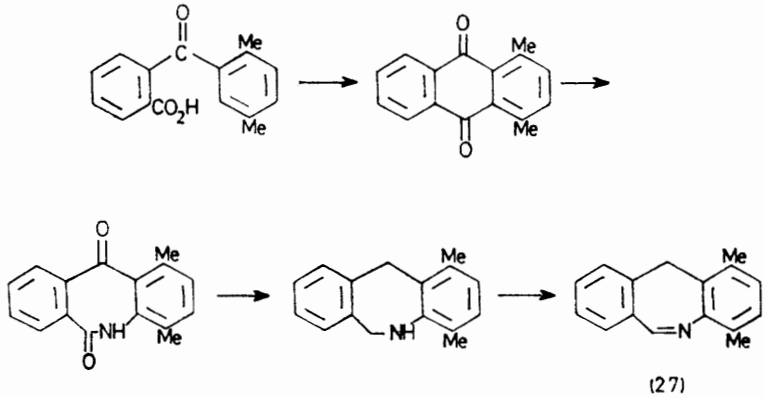
(26)

SCHEME 6

Procedure F, used for the preparation of compounds (26) (illustrated in Scheme 6) and (30) involved treatment of the appropriate morphanthridine-6,11-dione with methylmagnesium iodide to give a tertiary alcohol which could be reduced with lithium aluminium hydride to a 6,11-dihydro-11-methyldibenz[*b*,*e*]azepine. The dihydro-derivatives were then dehydrogenated with sulphur.

EXPERIMENTAL

Procedure A.—As an example of the sequence of reactions illustrated in Scheme 1, the synthesis of the dibenzoxazepine



(27)

SCHEME 5

(1d) is described. All the products listed in Tables 1—4 were obtained by corresponding procedures.

2-*Phenoxyaniline* (1b). (*a*) A solution of 1-nitro-2-phenoxybenzene (1a) [1] (50 g) in ethanol (100 ml) was hydrogenated over palladium–charcoal. The solution was filtered and concentrated and the product distilled (b.p. 126° at 1 mmHg) to afford, on cooling, a buff-coloured solid (m.p. 40°; 30 g, 70%).

(*b*) This reduction procedure was also applicable to substituted diphenyl ethers which were susceptible to catalytic hydrogenation. A mixture of the nitro-derivative (1a) (81 g) and iron powder (121 g) in water (81 ml) containing a few drops of acetic acid was heated at 100 °C for 70 min. The solution was cooled and filtered, and the solid residue and filtrate both extracted with ether. The

[17] L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Medicin. Chem.*, 1965, **8**, 74.
[18] H-L. Pan and T. L. Fletcher, *J. Heterocyclic Chem.*, 1970, **7**, 313.

combined extracts were dried and concentrated and the product distilled as above to afford (1b), m.p. 41—42° (50 g, 71%).

N-(2-*Phenoxyphenyl*)*formamide* (1c). A solution of the amine (1b) (10 g) in formic acid (100 ml) was boiled under reflux for 4 h, then concentrated, and the product was recrystallised from methanol; m.p. 94° (10.3 g, 90%) (lit.,[1] 92.5°; lit.,[2] 94—95°).

Dibenz[b,f][1,4]*oxazepine* (1d). A stirred mixture of the amide (1c) (53.5 g, 0.25 mol), polyphosphoric acid (426 g), and phosphoryl chloride (142 g) was heated to an oil-bath temperature of 100 °C for 2 h. The mixture was cooled, neutralised with ammonia solution (s.g. 0.880), diluted with water, and extracted with chloroform. The product (1d) (43 g, 88%) had m.p. 72.5° (from ethanol) (lit.,[1] 72°; lit.,[2] 71—72°).

One intermediate, 2-*bromo*-1,4-*dimethyl*-3-*nitrobenzene* [required for the synthesis of (14a)], was prepared by sequential nitration, diazotisation, and copper bromide treatment of 2,5-dimethylaniline;[19] m.p. 62° (from methanol) (Found: C, 41.7; H, 3.7; N, 5.6. $C_8H_8BrNO_2$ requires C, 41.8; H, 3.5; N, 6.1%).

Procedure B.—1-*Methyldibenz*[b,f][1,4]*oxazepine* (2d). 2-Methyl-6-hydroxybenzaldehyde[20] (30 g) was heated to 80 °C under nitrogen, and potassium hydroxide pellets (12.4 g) and 1-chloro-2-nitrobenzene (91 g) were added to the stirred liquid. The mixture was heated at 200 °C for 3.5 h and the excess of 1-chloro-2-nitrobenzene was removed by steam distillation. A solution of iron(II) sulphate (375 g) in ethanol (350 ml) and ammonia (s.g. 0.880; 300 ml) was added, and the mixture was boiled under reflux for 50 min, stored overnight at room temperature, and concentrated. The residue was steam distilled and the distillate extracted with ether. The extract was dried, concentrated, and distilled (b.p. 90—92° at 0.04 mmHg) and the yellow solid obtained was recrystallised from ethanol to afford the *product* (2d) (2.2 g, 5%), m.p. 101° (Found: C, 80.4; H, 5.6; N, 6.9. $C_{14}H_{11}NO$ requires C, 80.4; H, 5.3; N, 6.7%).

Procedure C. Preparation of 4-*Methyldibenz*[b,e]*azepine* (24).—2,8-*Dimethyl*-3,1-*benzoxazin*-4-*one*. A solution of 2-amino-3-toluic acid (104 g) in acetic anhydride (210 g) was heated under reflux for 1 h, then concentrated; the product crystallised from benzene as yellow *needles*, m.p. 133° (92 g, 77%) (Found: C, 68.9; H, 5.4; N, 7.7. $C_{10}H_9NO_2$ requires C, 68.2; H, 5.2; N, 8.0%).

2-*Acetamido*-2-*methylbenzophenone*. The Grignard reagent prepared from bromobenzene (78.5 g) and magnesium (12 g) in ether (300 ml) was added to a solution of 2,8-dimethyl-3,1-benzoxazin-4-one (87.5 g) in dry benzene (1 l). The solution was heated at 30—40 °C for 1 h, then cooled, and dilute hydrochloric acid was added. The organic phase was separated, dried, and concentrated and the residue recrystallised from benzene to afford the *product*, m.p. 145° (95 g, 79%) (C, 75.7; H, 6.1; N, 5.7. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%).

2-*Benzyl*-6-*methylaniline*. A solution of the above acetamido-derivative (50 g) in glacial acetic acid (300 ml) and concentrated hydrochloric acid (65 ml) was boiled under reflux for 16 h. The solution was cooled, diluted with water, and basified with ammonium hydroxide, and the precipitated product was filtered off and recrystallised from methanol to afford 2-amino-3-methylbenzophenone, m.p. 38° (30 g, 75%). A solution of the benzophenone (42 g) in ether (400 ml) was added dropwise to a suspension of lithium aluminium hydride (35.6 g) in ether (1 400 ml), and the mixture was boiled under reflux for 6 h. The solution was cooled, the excess of lithium aluminium hydride and alkoxides was destroyed with water, and the solids were removed. The filtrate was concentrated and the residue distilled (b.p. 88—90° at 0.027 mmHg) to afford the *product* (22 g, 61%), which on cooling solidified; m.p. 30—32° (Found: C, 84.8; H, 8.0; N, 6.8. $C_{14}H_{15}N$ requires C, 85.2; H, 7.7; N, 7.1%).

N-(2-*Benzyl*-6-*methylphenyl*)*formamide*. A solution of the above amine (22 g) in formic acid (88 ml) was boiled under reflux for 4 h, then concentrated, and the residue was recrystallised from methanol to afford the *product* (20 g, 80%), m.p. 92° (Found: C, 80.1; H, 6.8; N, 6.3. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2%).

4-*Methyldibenz*[b,e]*azepine* (24). A mixture of the above formamido-derivative (15 g), polyphosphoric acid (120 g), and phosphoryl chloride (32 g) was stirred at 120 °C for 1.5 h. The mixture was cooled, diluted with water, made alkaline with aqueous potassium hydroxide, and extracted with ether. The extract was dried and concentrated and the residue distilled (b.p. 100° at 0.025 mmHg) to afford, on cooling, yellow *needles*, m.p. 68° (6 g, 43%).

In a similar fashion 1-*methyldibenz*[b,e]*azepine* (23) was prepared from 2,5-dimethyl-3,1-benzoxazin-4-one. Key intermediates were 2-*amino*-6-*methylbenzophenone*, m.p. 73° (from methanol) (Found: C, 79.6; H, 6.2; N, 6.4. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.4%) and 2-*benzyl*-3-*methylaniline*, m.p. 63—65° (from methanol) (Found: C, 85.0; H, 7.8; N, 7.1. $C_{14}H_{15}N$ requires C, 85.2; H, 7.7; N, 7.1%).

2-*Amino*-2′-*methylbenzophenone*[13] was prepared from 2-tolylmagnesium bromide and 2-methyl-3,1-benzoxazin-4-one. Reduction afforded 2-(2-*methylbenzyl*)*aniline*, m.p. 68° (from ethanol) (Found: C, 85.4; H, 7.9; N, 7.3. $C_{14}H_{15}N$ requires C, 85.2; H, 7.7; N, 7.1%). Formylation and ring closure afforded 10-*methyldibenz*[b,e]*azepine* (25).

2-(2,5-*Dimethylbenzyl*)*aniline*, m.p. 94° (from ethanol) (Found: C, 80.1; H, 7.3; N, 5.7. $C_{15}H_{17}NO$ requires C, 80.4; H, 7.2; N, 5.9%), was prepared by treating 2-methyl-3,1-benzoxazin-4-one with *p*-xylylmagnesium bromide, followed by deacetylation and reduction. Formylation and ring closure afforded 7,10-*dimethyldibenz*[b,e]*azepine* (28).

Procedure D. 10,11-*Dimethyldibenz*[b,e]*azepine* (29).—1-(2-*Aminophenyl*)-1-(2-*tolyl*)*ethanol*. A solution of 2-aminophenyl methyl ketone (72 g) in ether (600 ml) was added to a solution of the Grignard reagent prepared from 2-bromotoluene (364.5 g), magnesium (52.5 g), and ether (1 l), and the mixture was boiled under reflux for 2 h. The mixture was cooled and poured into aqueous ammonium chloride, and the ether layer was separated, dried, and concentrated. The residue was distilled to afford a yellow solid, which was crystallised from methanol to give a product, m.p. 79—81° (68 g, 58%).

2-(2,α-*Dimethylbenzyl*)*aniline*. A mixture of the above carbinol (93 g), hydroiodic acid (56%; 620 ml), and red phosphorus (144 g) in acetic acid (2.5 l) was boiled under reflux for 18 h. The mixture was concentrated, and the residue was dissolved in aqueous sodium hydroxide and extracted with ether. The extract was dried and concentrated and the residue distilled *in vacuo* to afford, on cooling, a solid product, m.p. 47—48° (69 g, 79%).

2-(2,α-*Dimethylbenzyl*)*phenyl isocyanate*. A solution of

[19] E. Noeting and G. Thesmar, *Ber.*, 1902, **35**, 640.
[20] F. Tiemann and C. Schotten, *Ber.*, 1878, **11**, 767.

phosgene (35.4 g) in toluene (177 ml) was added to a solution of the above amine (38 g) in toluene (80 ml) at −10 to 0 °C. The solution under phosgene was then heated under reflux for 30 min and stored overnight at room temperature. The solution was concentrated and the residue distilled (b.p. 94—96° at 0.04 mmHg) to afford the *product*, which solidified; m.p. 51° (38 g, 89%) (Found: C, 81.2; H, 6.4; N, 5.7. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.3; N, 5.9%).

5,11-*Dihydro*-10,11-*dimethyldibenz*[b,e]*azepin*-6-*one*. A solution of the isocyanate derivative (38 g) in 1,2-dichlorobenzene (130 ml) was added to a mixture of aluminium chloride (21.7 g) in 1,2-dichlorobenzene (200 ml) at 90—100 °C. The mixture was heated for 1 h at 120 °C, and stored at room temperature overnight. The solvent was removed by steam distillation and the residue was triturated with acetone. The solid obtained was recrystallised from ethanol to afford the *product*, m.p. 235° (17.9 g, 47%) (Found: C, 80.8; H, 6.4; N, 5.8. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.9%).

6,11-*Dihydro*-10,11-*dimethyl*-5H-*dibenz*[b,e]*azepine*. A suspension of 10,11-dimethylmorphanthridinone (27 g) in dioxan (200 ml) was added to lithium aluminium hydride (20 g) in dioxan (300 ml), and the mixture was boiled under reflux for 12 h. The excess of lithium aluminium hydride was decomposed with wet dioxan, and the solution was filtered. The filtrate was concentrated and the residue was recrystallised from methanol to afford the *product*, m.p. 80—82° (17 g, 68%) (Found: C, 86.2; H, 7.5; N, 5.9. $C_{16}H_{17}N$ requires C, 86.0; H, 7.7; N, 6.3%).

10,11-*Dimethyldibenz*[b,e]*azepine* (29). The above dihydro-derivative (10 g) and sulphur (1.52 g) were heated under nitrogen at 130—140 °C for 10 h. The mixture was distilled (b.p. 112—114° at 0.04 mmHg) and the distillate recrystallised from ethanol to afford the *product*, m.p. 75° (5 g, 49%).

Procedure E. 1,4-*Dimethyldibenz*[b,e]*azepine* (27).—2-(2,5-*Dimethylbenzoyl*)*benzoic acid*.[16] Powdered aluminium chloride (180 g) was added in portions to a stirred solution of phthalic anhydride (90 g) in *p*-xylene (150 ml) and dry methylene chloride (250 ml). The mixture was stored overnight at room temperature, and water and hydrochloric acid were added. The solvent was removed by steam distillation, the solid residue was filtered off and dissolved in aqueous sodium carbonate, and the alkaline solution was filtered. The filtrate was acidified with concentrated hydrochloric acid and the white precipitate filtered off and dried to afford the product, m.p. 140—142° (133 g, 86%).

1,4-*Dimethylanthraquinone*. A stirred solution of 2-(2,5-dimethylbenzoyl)benzoic acid (187 g) in concentrated sulphuric acid was heated on a steam-bath for 2 h. The solution was poured into water and the solid filtered off, dried, and recrystallised from acetic acid (charcoal) to afford buff needles, m.p. 143° (87 g, 50%).

1,4-*Dimethylmorphanthridinone*. Sodium azide (102 g) was added in portions to a suspension of 1,4-dimethylanthraquinone (68 g) in concentrated sulphuric acid (680 ml), the temperature being maintained at 20—25 °C. The mixture was stored at room temperature for 40 h, then poured into iced water, and the precipitate was filtered off and washed with water, aqueous sodium hydrogen carbonate, and water and dried. Recrystallisation of the solid from pyridine afforded the *product*, m.p. 225—226° (70 g, 97%) (Found: C, 76.7; H, 5.3; N, 5.9. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2; N, 5.6%), δ_H [$(CD_3)_2SO$] 2.34 (Me), 2.43 (Me), and doublets centred at 7.05 and 7.27 (2 H and 3 H).

The structure of 1,4-dimethylmorphanthridinone was established by alkaline hydrolysis to the amino-acid, m.p. 175—176°, followed by diazotisation and hydrolysis to afford 2-(2,5-dimethylbenzoyl)benzoic acid.

6,11-*Dihydro*-1,4-*dimethyl*-5H-*dibenz*[b,e]*azepine* (1,4-*Dimethylmorphanthridine*). A suspension of 1,4-dimethylmorphanthridinone (26 g) in dioxan (170 ml) was added slowly to lithium aluminium hydride (20 g) in dioxan (660 ml) and the mixture was boiled under reflux for 7 h. The excess of lithium aluminium hydride was decomposed with water, the mixture was filtered, the residue was washed with hot dioxan, and the combined filtrate and washings were concentrated. The residue was recrystallised from ethanol to afford the product, m.p. 64—65° (20 g, 76%).

1,4-*Dimethyldibenz*[b,e]*azepine* (27). An intimate mixture of the above dihydro-compound (8 g) and sulphur (1.3 g) was heated under nitrogen at 135—140 °C for 7 h. The mixture was distilled (b.p. 108° at 0.025 mmHg) and the distillate, which solidified on cooling, was recrystallised from ethanol to afford the *product*, m.p. 79—80° (4 g, 50%).

Dibenz[b,e]*azepine* (22) was similarly prepared from anthraquinone.

Procedure F. 11-*Methyl*-11H-*dibenz*[b,e]*azepine* (26).—The Grignard reagent prepared from magnesium (32 g) and methyl iodide (189 g) in ether (600 ml) was added to a stirred suspension of 5*H*-dibenz[*b*,*e*]azepine-6,11-dione (morphanthridine-6,11-dione) (102 g) in toluene (1 500 ml), and the mixture was boiled under reflux for 5 h, then poured into aqueous ammonium chloride (4 500 ml). The resulting mixture was filtered to give a white solid (100 g), m.p. 170°. This solid (60 g) was dried, suspended in dry dioxan, and added to a suspension of lithium aluminium hydride (40 g) in dry dioxan (1 500 ml). The mixture was boiled under reflux for 8 h, the excess of lithium aluminium hydride was decomposed with water, the mixture was filtered, and the filtrate was concentrated. The residue was recrystallised from ethanol to give 6,11-*dihydro*-11-*methyl*-5H-*dibenz*[b,e]*azepine* (48 g, 91%), m.p. 80° (Found: C, 85.9; H, 7.5; N, 6.9. $C_{15}H_{15}N$ requires C, 86.1; H, 7.2; N, 6.7%). An intimate mixture of the dihydro-compound (69 g) and flowers of sulphur (12 g) was heated at 140 °C under nitrogen for 7 h and the product was distilled at 130° and 0.1 mmHg. The distillate was recrystallised from light petroleum (b.p. 40—60°) to afford 11-*methyl*-11H-*dibenz*[b,e]*azepine* (26) (54 g, 79%), m.p. 68—69° (Found: C, 86.9; H, 6.6; N, 6.7. $C_{15}H_{13}N$ requires C, 86.9; H, 6.3; N, 6.8%).

1,4,11-*Trimethyl*-11H-*dibenz*[b,e]*azepine* (30) was prepared in a similar manner from 1,4-dimethylmorphanthridine-6,11-dione.

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