173. *Carcinogenic Nitrogen Compounds. Part VI. Derivatives of* 1 : 2- *and* 3 : 4-*Benzophenarsazines.*

By Ng. Ph. Buu-Hoï and René Royer.

In continuation of earlier research, a series of new 10-chloro-, 10-alkyl-, and 10-aryl-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines has been prepared by known methods for biological testing as potential carcinogens, fungicides, and chemotherapeutic agents. During this study, several new diarylamines were prepared.

Of the cancers produced by definite chemical substances, those evoked by arsenic compounds have been the most often studied, except for those produced by polycyclic hydrocarbons, amines, and azo-dyes. However, the carcinogenic properties of arsenic have so far been demonstrated only for its inorganic derivatives such as arsenic trioxide, arsenious acid, and arsenites (see Lacassagne, " Les cancers produits par des substances chimiques exogènes," 1946, Paris, p. 5). Very few organic arsenicals have as yet been tested. Hval (quoted by Hartwell, " Survey of Compounds which have been tested for Carcinogenic Activity," 1941, Washington, p. 310) used neoarsphenamine in subcutaneous injections, with negative results; Visser and ten Seldam (*Geneesk. tijdschr. Nederl.-Indië*, 1938, **78**, 3280) obtained no cancers from 10-chloro-5 : 10-dihydrophenarsazine, diphenylchloroarsine, and diphenylcyanoarsine in skin-painting tests, but some papillomas with the last two compounds.

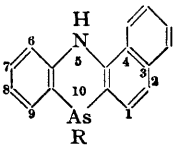
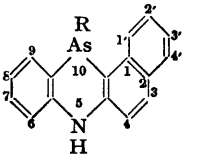
However, in these researches the short duration of the experiments (140 days in the case of Hval and 5 months in that of Visser and ten Seldam) is likely to invalidate any conclusion

concerning inactivity. Furthermore, the high degree of structural specificity in neighbouring groups of carcinogenic hydrocarbons, amines, and azo-dyes suggests that large series of organic arsenicals should be tested before any definite conclusions are elaborated.

This paper deals with the synthesis of a wide series of derivatives of 5 : 10-dihydro-3 : 4- (I) and -1 : 2-benzophenarsazines (II), and is part of a broad investigation of organic arsenicals. Renewed incentive for such research has been offered by Ludford's work (*Arch. exp. Zellforsch.*, 1936, **18**, 411) on cacodylic acid, and that of King and Ludford (*J.*, 1950, 2086) on various

Substituent.	Decomp. above :	M. p.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.
10-*Chloro*-5 : 10-*dihydro*-3 : 4-*benzophenarsazines* (I ; R = Cl).							
7 : 9-Dimethyl	275°	312—314°	$C_{18}H_{15}NClAs$	60·9	4·0		
6 : 9-Dimethyl	206	217	$C_{18}H_{15}NClAs$	60·5	4·5		
6 : 8-Dimethyl	215	244	$C_{18}H_{15}NClAs$	60·8	4·4	60·7	4·2
7 : 8-Dimethyl	253	280	$C_{18}H_{15}NClAs$	61·0	4·2		
6 : 7-Dimethyl	230—235	260	$C_{18}H_{15}NClAs$	61·0	4·0		
6-Methyl-9-*iso*propyl	208	230	$C_{20}H_{19}NClAs$	62·3	5·0	62·5	4·9
7-Chloro-6-methyl	240	275—280	$C_{17}H_{12}NCl_2As$	54·0	3·2	54·2	3·2
8-Chloro	206	221—222	$C_{16}H_{10}NCl_2As$	53·2	3·0	53·0	2·7
8-1′-Methyl-*n*-butyl	160	165	$C_{21}H_{21}NClAs$	63·2	5·6	63·4	5·3
8-(1 : 1-Dimethyl-*n*-propyl)	190	199	$C_{21}H_{21}NClAs$	63·1	5·2	,,	,,
8-Phenyl	255	275	$C_{24}H_{15}NClAs$	65·0	3·6	65·4	3·7
6-Phenyl	181	195	$C_{22}H_{15}NClAs$	65·1	3·8	,,	,,
8-Methoxy	220	242	$C_{17}H_{13}ONClAs$	57·2	3·3	57·0	3·6
6-Methoxy	215	239	$C_{17}H_{13}ONClAs$	57·1	3·5	,,	,,
6-Ethoxy	190	204	$C_{18}H_{15}ONClAs$	58·3	4·1	58·1	4·0
10-*Chloro*-5 : 10-*dihydro*-1 : 2-*benzophenarsazines* (II ; R = Cl).							
7 : 9-Dimethyl	275	314	$C_{18}H_{15}NClAs$	60·4	4·0		
6 : 9-Dimethyl	220	250	$C_{18}H_{15}NClAs$	60·6	4·2	60·7	4·2
6 : 7-Dimethyl	235	249	$C_{18}H_{15}NClAs$	60·4	4·4		
7 : 8-Dimethyl	250	285	$C_{18}H_{15}NClAs$	60·8	4·0		
6-Methyl-9-*iso*propyl	220	265	$C_{20}H_{19}NClAs$	62·6	5·2	62·5	4·9
8-Chloro	240	262	$C_{16}H_{10}NCl_2As$	53·3	2·9	53·0	2·7
7-Chloro-6-methyl	270	290	$C_{17}H_{12}NCl_2As$	53·9	3·0	54·2	3·2
8-1′-Methyl-*n*-butyl	165	174	$C_{21}H_{21}NClAs$	63·0	5·5	63·4	5·3
8-(1 : 1-Dimethyl-*n*-propyl)	210	228	$C_{21}H_{21}NClAs$	63·2	5·5	,,	,,
8-Phenyl	245	260—265	$C_{22}H_{15}NClAs$	65·2	3·5	65·4	3·7
6-Phenyl	215	242	$C_{22}H_{15}NClAs$	65·1	3·8	,,	,,
8-Methoxy	233—235	245	$C_{17}H_{13}ONClAs$	56·5	3·8	57·0	3·6
6-Ethoxy	170	192	$C_{18}H_{15}ONClAs$	57·7	4·1	58·1	4·0
3′-*tert.*-Butyl-8-methyl	268	271	$C_{21}H_{21}NClAs$	63·0	5·4	63·4	5·3
5 : 10-*Dihydro*-3 : 4-*benzophenarsazines* (I).							
7 : 9 : 10-Trimethyl		121	$C_{19}H_{18}NAs$	68·0	5·6		
6 : 9 : 10-Trimethyl		110	$C_{19}H_{18}NAs$	67·8	5·2		
6 : 7 : 10-Trimethyl		130	$C_{19}H_{18}NAs$	67·7	5·5	68·0	5·4
6 : 8 : 10-Trimethyl		92	$C_{19}H_{18}NAs$	68·2	5·6		
7 : 8 : 10-Trimethyl		171	$C_{19}H_{18}NAs$	68·3	5·1		
8-Chloro-10-methyl		123	$C_{17}H_{13}NClAs$	59·4	3·7	59·7	3·8
8-Chloro-10-ethyl		81	$C_{18}H_{15}NClAs$	60·5	4·4	60·7	4·2
10-Ethyl-6 : 9-dimethyl		109	$C_{20}H_{20}NAs$	68·8	5·9	68·7	5·7
10-Benzyl-6 : 9-dimethyl		174	$C_{25}H_{22}NAs$	72·4	5·1	72·9	5·0
5 : 10-*Dihydro*-1 : 2-*benzophenarsazines* (II).							
7 : 8 : 10-Trimethyl		142	$C_{19}H_{18}NAs$	68·2	5·5		
6 : 9 : 10-Trimethyl		138	$C_{19}H_{18}NAs$	68·4	5·4	68·0	5·4
6 : 7 : 10-Trimethyl		137	$C_{19}H_{18}NAs$	68·2	5·2		
10-Ethyl-7 : 9-dimethyl		104	$C_{20}H_{20}NAs$	68·4	5·8	68·7	5·7
10-Ethyl-6 : 7-dimethyl		128	$C_{20}H_{20}NAs$	68·6	5·6	,,	,,
7 : 8-Dimethyl-10-*iso*propyl		dec. >180	$C_{21}H_{22}NAs$	69·3	5·7	69·4	6·0
7-Chloro-6 : 10-dimethyl		143	$C_{18}H_{15}NClAs$	60·9	4·0	60·7	4·2
7-Chloro-10-ethyl-6-methyl		110	$C_{19}H_{17}NClAs$	61·4	4·8	61·6	4·6
10-*n*-Butyl-7-chloro-6-methyl		105	$C_{21}H_{21}NClAs$	63·5	5·4	63·3	5·3
10-Methyl-8-1′-methyl-*n*-butyl		101	$C_{22}H_{24}NAs$	69·7	6·5	70·0	6·3
10-Methyl-8-(1 : 1-dimethyl-*n*-propyl)		151	$C_{22}H_{24}NAs$	70·3	6·1	,,	,,
8-Methoxy-10-methyl		158	$C_{18}H_{16}ONAs$	64·3	4·6	64·0	4·7
10-Methyl-8-phenyl		189	$C_{23}H_{18}NAs$	72·4	4·4	72·0	4·7
10-Methyl-6-phenyl		135	$C_{23}H_{18}NAs$	72·0	4·8	,,	,,
10-Ethyl-6-phenyl		116	$C_{24}H_{20}NAs$	72·3	5·2	72·5	5·0
6 : 10-Diphenyl		162	$C_{28}H_{20}NAs$	75·8	4·5	75·5	4·5

alkyl- and aryl-arsonic acids and 3-(1-phenylethylamino)propylarsine dichloride as potent mitotic poisons.

(I.)  (II.) 

The angular benzophenarsazines were chosen because of their molecular kinship with 1 : 2- and 3 : 4-benzacridines and 1 : 2- and 3 : 4-benzocarbazoles, in which groups several carcinogens have already been detected (Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Lacassagne, Buu-Hoï, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635). The Wieland–Rheinheimer reaction of arsenic trichloride with secondary diarylamines (*Annalen*, 1921, **423**, 1) has already been used for the preparation of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazine (Lewis and Hamilton, *J. Amer. Chem. Soc.*, 1921, **43**, 2219; Burton and Gibson, *J.*, 1926, 2243), and of several of their functional derivatives (Buu-Hoï, Hiong-Ki-Weï, and Royer, *Compt. rend.*, 1945, **220**, 50; *Rev. scientif.*, 1944, **82**, 453; 1945, **83**, 41). A number of new 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines bearing alkyl, alkyloxy-, and halogen substituents in various positions have now been similarly synthesised (see Table). Several new *N*-arylnaphthylamines used were prepared by the Knoevenagel reaction (*J. pr. Chem.*, 1914, **89**, 17); however, an attempt to prepare *N*-*p*-bromophenyl-α-naphthylamine from *p*-bromoaniline and α-naphthylamine by this reaction resulted in a complete removal of the nuclear halogen at relatively low temperature; this is similar to Knoevenagel's observation (*loc. cit.*) that *N*-*p*-chlorophenyl-α-naphthylamine could not be prepared from α-naphthol and *p*-chloroaniline.

The 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines were yellow to orange substances with high melting points, which did not lend themselves to *N*-nitrosation, a peculiarity that had previously been observed in the case of 10-chloro-5 : 10-dihydrophenarsazine (Rasuwajew and Godina, *Ber.*, 1932, **65**, 666).

The action of alkyl- or aryl-magnesium halides on 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines readily replaced the 10-chlorine atom by alkyl or aryl (cf. Seide and Gorski, *Ber.*, 1929, **62**, 2186; Buu-Hoï and Royer, *loc. cit.*). The new 10-alkyl- and 10-aryl-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines thus obtained are listed in the Table.

The tests for carcinogenicity of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines (performed in this Institute by Dr. G. Rudali under Professor A. Lacassagne) are not yet complete and will be reported later. The widespread epilation and papillomas obtained so far in painting tests suggest activity in a few of these compounds; no such reactions are to be observed with the corresponding 10-alkyl compounds. Similarly, tests for fungicidal properties showed notable activity against *Fusarium graminearum* in the group of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines, but none in that of 10-alkyl compounds. On the other hand, several of the latter inhibit the growth of *Staphylococcus aureus* at a concentration of $\sim 10^{-5}$. Details will be published elsewhere.

Experimental.

[With J. F. Miquel and M. Hubert-Habart.]

N-(3 : 5-*Dimethylphenyl*)-α-*naphthylamine*.—A mixture of *s*-*m*-xylidine (10 g.), α-naphthol (12 g.), and iodine (0·2 g.) was heated under reflux for 20 hours, water being copiously evolved. The dark oil obtained was dissolved in toluene, washed with aqueous sodium hydroxide, and dried (Na_2SO_4); after removal of the solvent, the residue was vacuum-distilled, giving N-(3 : 5-*dimethylphenyl*)-α-*naphthylamine*, b. p. 255—257°/16 mm. (8 g.), crystallising from ligroin in shiny colourless needles, m. p. 52° (Found : N, 5·7. $C_{18}H_{17}N$ requires N, 5·6%). The use of α-naphthylamine in place of α-naphthol (cf. Knoevenagel, *loc. cit.*) for the preparation of this amine is not advisable, since it gave a product containing much di-α-naphthylamine.

N-(2-*Methyl*-5-iso*propylphenyl*)-α-*naphthylamine*, similarly obtained from 2-aminocymene (8 g.), α-naphthol (12 g.), and iodine (0·2 g.) (yield, 8 g.), was a viscous pale yellow oil, b. p. 258—260°/20 mm. (Found : N, 5·0. $C_{20}H_{21}N$ requires N, 5·1%).

N-(*p*-1-*Methylbutylphenyl*)-α-*naphthylamine* was obtained from *p*-1-methylbutylaniline (10 g.), α-naphthol (10 g.), and iodine (0·2 g.) as a pale yellow viscous oil (10 g.), b. p. 270—275°/20 mm. (Found : N, 4·8. $C_{21}H_{23}N$ requires N, 4·8%).

N-2-*Diphenylyl*-α-*naphthylamine*, from 2-aminodiphenyl (20 g.), α-naphthol (23 g.), and iodine (0·3 g.), formed, from ethanol, silky colourless needles (8 g.), m. p. 127°, b. p. 295—298°/28 mm. (Found : N, 4·5. $C_{22}H_{17}N$ requires N, 4·7%).

N-o-*Ethoxyphenyl-α-naphthylamine*, from *o*-phenetidine (15 g.), α-naphthol (20 g.), and iodine (0·2 g.), was a pale yellow viscous oil, b. p. 257—260°/21 mm. (Found: N, 5·0. $C_{18}H_{17}ON$ requires N, 5·3%). The isomeric N-o-*ethoxyphenyl-β-naphthylamine* obtained from *o*-phenetidine and β-naphthol crystallised from ligroin or methanol in fine shiny colourless needles, m. p. 82—83° (Found: N, 5·2. $C_{18}H_{17}ON$ requires N, 5·3%).

N-p-*Tolyl*-6-tert.-*butyl*-2-*naphthylamine*, from *p*-toluidine (10 g.), 6-*tert.*-butyl-2-naphthol (Buu-Hoï, Le Bihan, Binon, and Rayet, *J. Org. Chem.*, 1950, **15**, 1060) (15 g.), and iodine (0·2 g.), formed, from methanol, shiny colourless prisms, m. p. 99° (Found: N, 4·6. $C_{21}H_{23}N$ requires N, 4·8%).

Condensation of Arsenic Trichloride with Diarylamines.—A solution of the appropriate diarylamine (1 mol.) and arsenic trichloride (1 mol.) in *o*-dichlorobenzene (5—6 times the weight of amine) was gently refluxed for 6—8 hours. The reaction could be perceived by the gradual change of colour to yellow. After cooling, the chloroarsine generally crystallised, and was collected, washed with benzene, and recrystallised from an appropriate solvent (chlorobenzene or *o*-dichlorobenzene). In some cases (*e.g.*, the amyl derivatives) concentration of the reaction mixture was necessary in order to bring about crystallisation; light solvents (benzene, toluene) were then used for purification. The 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines thus obtained were well-formed greenish to orange-yellow needles, giving orange to red colours with sulphuric acid. They were best characterised by a point of commencing decomposition as well as by the real m. p.

Action of Grignard Reagents on 10-*Chloro*-5 : 10-*dihydro*-1 : 2- *and* -3 : 4-*benzophenarsazines.*—The finely powdered and well-dried chloroarsine (1 mol.) was cautiously added, in small portions, to an ethereal solution of the appropriate alkyl- or aryl-magnesium compound (2·5 mols.), with frequent shaking. A lively reaction generally set in, with gradual disappearance of the insoluble chloroarsine; after 15 minutes' refluxing on a water-bath, the mixture was decomposed with ice-cooled aqueous ammonium chloride, the ether allowed to evaporate, and the residue recrystallised from ethanol, ligroin, or acetone. All the arsines thus obtained were colourless or faintly yellow needles, giving with sulphuric acid yellow, orange, or brown-red halochromic colours.

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