Reissert Compound Chemistry. XXVI. The Syntheses of Bis-benzylisoquinolines.

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The condensation of the anion of isoquinoline Reissert compounds with diaryl ethers is reported. These condensation products are converted into analogues of bis-benzylisoquinoline alkaloids.

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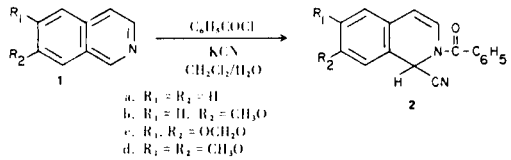
While the synthetic utility of Reissert compounds in the benzylisoquinoline and aporphine alkaloid systems is well known (2), their application to the bis-benzylisoquinoline alkaloid system has been limited. In a further development of the general Reissert compound scheme, as applied to alkaloid synthesis, we have prepared a series of bis-benzylisoquinoline alkaloid models (**11, 14, 17**) for biological testing in hopes that this may shed additional light on the structural requirements for antineoplastic activity in this alkaloid system (3).

Isoquinoline (**1b**) was prepared by the Pomerantz-Fritsch reaction of *m*-methoxybenzaldehyde in 76% sulfuric acid (4). Isoquinolines **1c** and **1d** were prepared from piperonal and 3,4-dimethoxybenzaldehyde, respectively, by the Birch *et al.*, addition (5) to Bobbitt's modification (6) of the Pomerantz-Fritsch isoquinoline synthesis (7). These isoquinolines, **1**a-d, were converted (8) to the corresponding benzoyl Reissert compounds (**2**a-d) (9).



1

a. $R_1 = R_2 = H$
b. $R_1 = H$, $R_2 = CH_3O$
c. $R_1, R_2 = OCH_2O$
d. $R_1 = R_2 = CH_3O$

2

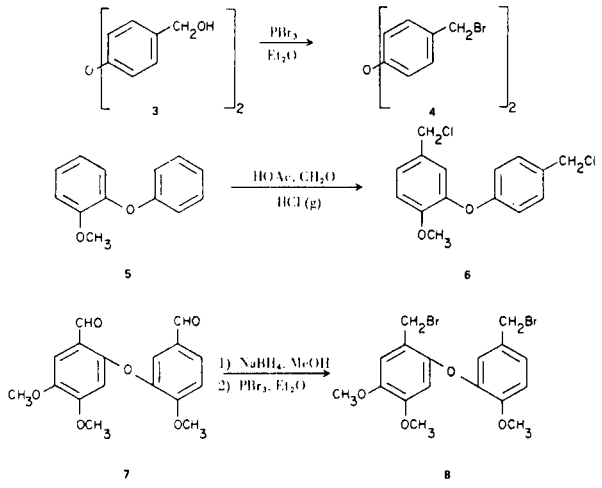
Phosphorus tribromide bromination of diaryl ether **3** (available commercially) gave 4,4′-oxydibenzyl bromide (**4**) (10). Chloromethylation (11) of diaryl ether **5** (12) gave 4′,5-dichloromethyl-2-methoxydiphenyl ether (**6**). Sodium borohydride reduction of diaryl ether **7** (13) followed by treatment with phosphorus tribromide gave

Table I

α,α′-Bis-1-(2-benzoyl-1-cyano-1,2-dihydro-substituted-isoquinolyl) Dimethyl-Diaryl (**9**a,b,d, **12**a-c, **15**a-d)

Compound No.	% Yield (a)	M.p. °C (b)	Formula	% C	% H	%N	% C	% H	% N
9a (c)	88	123-127 (d)	$C_{48}H_{34}N_4O_3$	80.65	4.79	7.84	80.75	4.93	7.94
9b (e)	82 (f)	122-127 (d)	$C_{50}H_{38}N_4O_5$	77.50	4.94	7.23	77.64	5.01	7.16
9d	100	130.5-133 (d)	$C_{52}H_{42}N_4O_7$	74.80	5.07	6.71	74.84	5.11	6.57
12a	97	136-139 (g)	$C_{49}H_{36}N_4O_4$	79.01	4.87	7.52	78.80	4.93	7.57
12b	96	129-133 (g)	$C_{51}H_{40}N_4O_6$	76.10	5.01	6.96	75.68	4.88	6.74
12c	100	137-140 (g)	$C_{51}H_{36}N_4O_8$	73.55	4.36	6.73	73.47	4.28	6.69
15a	75	134-136.5 (h)	$C_{51}H_{40}N_4O_6$	76.10	5.01	6.96	75.94	5.18	6.86
15b	100	130-133 (h)	$C_{53}H_{44}N_4O_8$	73.60	5.13	6.48	73.39	5.23	6.17
15c (i)	95	134.5-136 (h)	$C_{53}H_{40}N_4O_{10}$	71.29	4.52	6.28	71.21	4.58	5.52
15d (i)	98	134.5-136 (h)	$C_{55}H_{48}N_4O_{10}$	71.42	5.23	6.06	70.66	5.06	5.45

(a) Crude yield unless otherwise noted. (b) Analytical sample recrystallized from ethanol. (c) Pmr: 6.60-7.85 (M, 26H, Ar-H); 5.68, 6.48 (AB quartet, 4H, vinyl-H); 3.65 (d, 4H, Ar-CH_2-). (d) Over 1 hour. (e) Pmr: 6.60-8.00 (M, 24H, Ar-H); 5.75, 6.45 (AB quartet, 4H, vinyl-H); 3.80 (broad s, 10H, Ar-CH_2- + -OCH_3). (f) After stirring with ethanol. (g) Over 40 minutes. (h) Over 30 minutes. (i) Apparently impure but used to prepare a compound giving correct analytical data (see Tables II and III).



the third diaryl ether, **8** (10).

Condensation (14) of Reissert compounds **2**a,b,d and diaryl ether **4** gave the dialkylated products **9**a,b,d (Table I), which were hydrolyzed to bis-isoquinolydimethyldiphenyl ethers **10**a,b,d (pmr data collected into Table II), characterized as the dimethiodide salts (Table III). Sodium borohydride reduction of these dimethiodide salts gave the bis-benzylisoquinoline alkaloid analogues **11**a,b,d (pmr data collected in Table IV), characterized as the dimethiodide salts (Table V).

Treatment of diaryl ether **6** with Reissert compounds **2**a-c gave intermediates **12**a-c (Table I) and **13**a-c (pmr data collected in Table II), characterized as the dimethiodide salts (Table III). Sodium borohydride reduction of these dimethiodide salts gave *o*-methyldauricine (**14**d)

Table II

Pmr Data (a,b) of α,α′-Bis-1-(substituted-isoquinolyl) Dimethyl-Diaryl Ethers (**10**a,b,d, **13**a-c, **16**a-d)

Compound No.	3-Protons (c)	Ar-H	Ar-CH_2-Ar	OCH_3
10a	8.60 (d, 2)	6.8 -8.4 (m, 18)	4.65 (d, 4)	
10b	8.55 (d, 2)	6.8 -8.0 (m, 16)	4.65 (d, 4)	3.90 (s, 3)
10d	8.30 (d, 2)	6.55-7.45 (m, 14)	4.50 (s, 4)	3.90, 3.80 (2s, 6)
13a	8.45 (t, 2)	6.45-8.30 (m, 17)	4.55 (d, 4)	3.65 (s, 3)
13b	8.30 (t, 2)	6.55-7.75 (m, 15)	4.45 (d, 4)	3.75 (s, 3); 3.65 (s, 6)
13c	8.30 (t, 2)	6.60-7.75 (m, 13)	4.40 (d, 4)	6.00 (s, 4-OCH_2-); 3.70 (s, 3)
16a (d)	8.50 (d, 2)	6.40-7.90 (m, 15)	4.55 (s, 4)	3.80 (s, 3); 3.65 (s, 3); 3.55 (s, 3)
16b	8.35 (d, 2)	6.30-7.80 (m, 13)	4.45 (s, 4)	3.40-3.90 (m, 23) (e)
16c	8.50 (d, 2)	6.50-7.88 (m, 11)	4.52 (s, 4)	6.15 (3, 4-OCH_2O-); 3.95 (s, 3); 3.76 (s, 3); 3.65 (s, 3)
16d	8.42 (d, 2)	6.50-7.90 (m, 11)	4.32 (d, 4)	3.54, 3.62 (2s, 6); 3.75 (s, 6); 3.90 (s, 9)

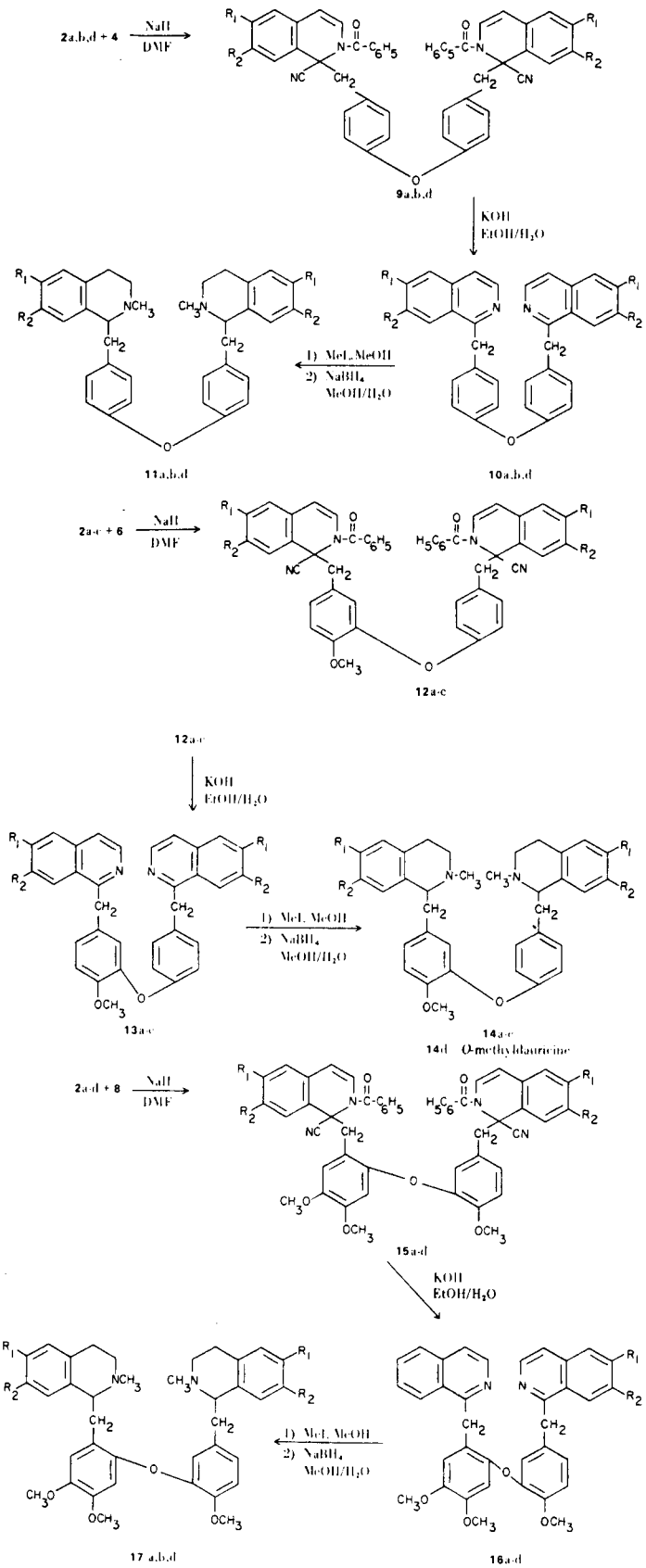
(a) Appearance, integration in ( ). (b) Chromatographed materials. (c) Downfield half of AB quartet. (d) Microtube. (e) Apparently impure but used to prepare a compound giving correct analytical data (see Tables IV, V).

Table III

Dimethiodide Derivatives of α,α′-Bis-1-(substituted-isoquinolyl) Dimethyl-Diaryl Ethers (**10**a,b,d, **13**a-c, **16**a-d)

Compound No.	% Yield (a)	M.p. °C (b)	Formula	Analysis Calculated % C	% H	% N	% I	Found % C	% H	% N	% I
10a	80	257-260	$C_{34}H_{30}N_2O_2I_2$	55.45	4.11	3.80	34.47	55.20	4.21	3.73	34.58
10b	67	234-237 (c)	$C_{36}H_{34}N_2O_3I_2$	54.29	4.30	3.52	31.87	54.20	4.41	3.46	31.88
10d (d)			$C_{38}H_{38}N_2O_5I_2$								
13a	60	161-164 (e)	$C_{35}H_{32}N_2O_2I_2$	54.85	4.21	3.66		54.60	4.26	3.46	
13b	40	168-171	$C_{37}H_{36}N_2O_4I_2$	53.77	4.39	3.39		53.65	4.47	3.46	
13c (f)	50	221-224	$C_{37}H_{32}N_2O_6I_2$	52.01	3.77	3.28	29.70	50.81	3.76	3.22	30.45
16a (d)			$C_{37}H_{36}N_2O_4I_2$								
16b (f)	5 (b)	201-204	$C_{39}H_{40}N_2O_6I_2$	52.84	4.55	3.16	28.63	54.18	4.76	2.80	26.30
16c	49	227-230	$C_{39}H_{36}N_2O_8I_2$	51.22	3.87	3.06	27.75	50.96	4.02	3.04	27.79
16d	32	211-214	$C_{41}H_{52}N_2O_{12}I_2$ (g)	48,34	5,15	2,75	24,92	48,82	5.02	2.70	25.31

(a) Includes hydrolysis and extensive chromatography of the free bases unless otherwise noted, not optimized. (b) Analytical sample filtered from reaction vessel unless otherwise noted. (c) Recrystallized from methanol/ethyl acetate. (d) No physical data obtained, but used to prepare a compound giving correct analytical data (see Tables III, IV). (e) Over 1 hour. (f) Apparently impure but used to prepare a compound giving correct analytical data (see Table IV). (g) $C_{41}H_{44}N_2O_8I_2 \cdot 4H_2O$.



analogues **14**a-c (pmr data collected in Table IV) which were characterized as the dimethiodide salts (Table V).

Similarly, diaryl ether **8** gave intermediates **15**a-d (Table I) and **16**a-d (pmr data in Table II), which were characterized as the dimethiodide salts (Table III). Reduction gave alkaloid analogues **17**a,b,d (pmr data, Table IV) characterized as the dimethiodide salts (Table II).

Acknowledgment.

This work was supported in part by a grant from the National Cancer Institute (CA 10965).

EXPERIMENTAL

Apparatus.

Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. All ^{1}H nmr spectra were recorded on a Varian Associates Model A60-A Spectrometer, in deuteriochloroform, chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane.

α,α′-Bis-1-(2-benzoyl-1-cyano-1,2-dihydro-substituted-isoquinolyl) Dimethyl-Diaryl Ether (**9**a,b,c, **12**a-c, **15**a-d).

To an ice cold solution of Reissert compounds (**2**a-d) (0.030 mole) and the dihalomethyl diaryl ethers (**4**, **6**, and **8**) (0.015 mole) in 50 ml. of anhydrous DMF under a nitrogen atmosphere was added sodium hydride (1.65 g., 0.036 mole, 52% oil dispersion). Stirring was continued for 1 hour in ice and 2½ hours at room temperature, after which the nitrogen flow was stopped and the solution poured into 1 l. of ice. The products were filtered and recrystallized from ethanol. Compounds prepared in this manner (**9**a,b,d, **12**a-c, and **15**a-d) are collected into Table I. The yields reported are crude unless otherwise noted.

α, α′-Bis-1-(Substituted-isoquinolyl) Dimethyl-Diaryl Ethers (**10**a,b, d, **13**a-c, **16**a-d).

To n g. of the above alkylated Reissert compounds (**9**a,b,d, **12**a-c, and **15**a-d) and (30-35) n ml. of hot ethanol (either in solution or as a suspension) was added 10n g. of potassium hydroxide in (30-35)n ml. of water and the resulting mixture refluxed with mechanical stirring for 3 to 6 hours after which most of the ethanol was distilled and (30-35)n ml. of water added. The chloroform extract was washed with water, dried (magnesium sulfate) and evaporated *in vacuo*. The gum obtained was purified by chromatography over alumina with chloroform. Pmr data for compounds prepared in this manner (**10**a,b,d, **13**a-c and **15**a-d) are collected into Table II.

The dimethiodide derivatives were prepared by refluxing the ether for 3 hours with 20-30 times its weight of iodomethane and enough methanol to cause initial solution. Compounds prepared in this manner are collected in Table III and were filtered from the reaction mixture and washed with ether unless otherwise noted.

α,α′-Bis-1-(*N*-methyl-substituted-1,2,3,4-tetrahydroisoquinolyl) Dimethyl-Diaryl Ethers (**11**a,b,d, **14**a-c, **17**a,b,d).

To a solution, or suspension, of n g. of the isoquinoline (**1**a,b,d, **13**a-c, **16**a,b,d) dimethiodides in 150n ml. of methanol and 30n ml. of water was added sodium borohydride (3.2n g.) and the solution refluxed for 3-5 hours after which most of the methanol was distilled off and 150n ml. of water added. The chloroform

Table IV

Pmr Data (a,b) of α,α′-Bis-1-(2-methyl-substituted-isoquinolyl) Dimethyl-Diaryl Ethers (**11**a,b,d, **14**a-c, **17**a,b,d)

Compound No.	Ar-H	OCH_3	1-Protons	Ar-CH_2-+2-+3-protons	N-CH_3
11a	6.6 -7.14 (m, 16)		3.78 (t, 2)	3.0 (d, 4); 2.6-2.95 (m, 8)	2.45 (s, 6)
11b	6.20-7.25 (m, 14)	3.65 (s, 6)	3.7-3.95 (unsym. t, 2)	2.55-3.45 (m, 12)	2.50 (s, 6)
11d	6.0 -7.15 (m, 12)	3.80 (s, 6); 3.65 (broad s, 8)(c)		2.55-3.40 (m, 12)	2.50 (s, 6)
14a	6.40-7.20 (m, 15)	3.80 (s, 6)		2.60-3.75 (m, 14)(c)	2.50 (d, 6)
14b	6.15-7.20 (m, 13)	3.75 (s, 3); 3.60 (s, 6)		2.50-3.40 (m, 14)(c)	2.45 (d, 6)
14c	6.20-7.00 (m, 11)	5.80 (s, 4, -OCH_2-); 3.80 (s, 3)		2.50-3.75 (m, 14)(c)	2.45 (d, 6)
17a	6.35-7.30 (m, 13)	3.45-4.45 (m, 11)(c)		2.45-3.15 (m, 12)	2.40 (d, 6)
17b	6.20-7.20 (m, 11)	3.55-4.00 (m, 17)(c)		2.45-3.45 (m, 12)	2.40 (s, 6)
17d	6.05-6.95 (m, 9)	3.55-4.15 (m, 23)(c)		2.45-3.35 (m, 12)	2.35 (s, 6)

(a) Appearance, integration in ( ). (b). Chromatographed materials. (c) +1 Protons.

Table V

Dimethiodide Derivatives of α,α′-Bis-1-(2-methyl-substituted-1,2,3,4-tetrahydroisoquinolyl) Dimethyl-Diaryl Ethers (**11**a,b,d, **14**a,b, **17**a,b,d)

				Analysis							
Compound				Calculated				Found			
No.	% Yield (a)	M.p. °C (b)	Formula	% C	% H	% N	% I	% C	% H	% N	% I
11a	71	154-160 (c)	$C_{36}H_{42}N_2OI_2$	55.97	5.48	3.63		55.83	5.46	3.58	
11b	55	150-170 (d)	$C_{38}H_{46}N_2O_3I_2$	54.82	5.57	3.36		54.83	5.58	3.37	
11d	48	245-246	$C_{40}H_{50}N_2O_5I_2$	53.82	5.65	3.14		53.65	5.50	3.16	
14a	47	190-230 (a)	$C_{37}H_{44}N_2O_2I_2$	55.37	5.53	3.49		55.50	5.44	3.47	
14b	62	167-175	$C_{39}H_{48}N_2O_4I_2$	54.30	5.61	3.25		54.27	5.66	3.27	
17a	73	136-147 (e)	$C_{39}H_{48}N_2O_4I_2$	54.30	5.61	3.25	29.42	53.88	5.67	3.21	29.08
17b	60	185-190 (d)	$C_{41}H_{52}N_2O_6I_2$			3.04				2.77	
17d	51	160-175 (d)	$C_{43}H_{56}N_2O_8I_2$	52.55	5.74	2.85		52.55	5.66	2.85	

(a) Includes reduction and extensive chromatography of the free bases, not optimized. (b) Analytical sample filtered from reaction vessel unless otherwise noted. (c) Over 1 hour. (d) Reaction poured into ether and filtered. (e) Over 40 minutes.

extract was washed with water, dried (magnesium sulfate) and evaporated *in vacuo*. The gum obtained was purified by chromatography over alumina with chloroform. Pmr data for compounds prepared in this manner (**11**a,b,d, **14**a-c, **17**a,b,d) are collected in Table IV.

The dimethiodide derivatives were prepared as above and are collected into Table V.

REFERENCES AND NOTES

(1a) Taken in part from the Ph.D. Thesis of D.S.S., CCT, 1975; (1b) To whom inquiries should be addressed at Department of Chemistry, University of Missouri-Kansas City, Kansas City, Missouri 64110.

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