Synthesis and Antitussive Activity of Aminotetra- (and -hexa-) hydrodibenzofurans

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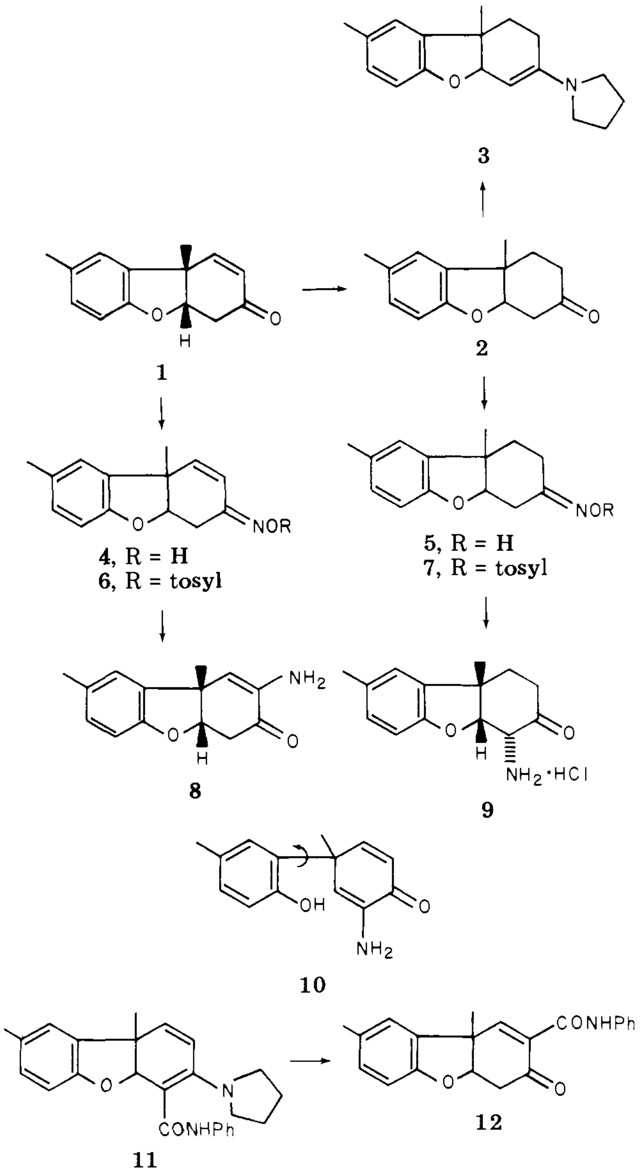
The synthesis of a novel series of antitussive agents is described. Two series of amino-substituted tetra- and hexahydrodibenzofurans were prepared and examined for antitussive activity in the guinea pig after cough elicited by electrical stimulation of the vagus nerve. A significant level of activity, comparable with that of codeine, was found in the 4α-amino series. The 4-methylpiperazin-1-ylpropionamide (**28**) was found to be the most active of the compounds synthesized and was equipotent with codeine. The effects of structural modification upon antitussive activity were investigated in numerous analogues but no enhancement of activity was achieved over that of **28**.

Codeine is an effective analgesic and antitussive agent belonging to the morphine family of narcotic analgesics. In clinical use it manifests the major side effects of sedation, respiratory depression, and constipation.[1] The search for novel analgesics and antitussives incorporating essential features of the codeine series had led to the evaluation of many related ring systems.[2-4] As part of our investigation of the synthesis of less complex analogues of codeine, the readily accessible dibenzofuranone, Pummerer's ketone[5] (**1**), has been used as a "pharmacophoric synthon". This molecule contains a reactive enone system which, it was felt, could be used to elaborate several related series of novel aminodibenzofurans with potential biological activity.

This paper reports the preparation of compounds in two series derived from Pummerer's ketone containing the classical analgesic pharmacophore. In particular, a significant level of antitussive activity was discovered in the 4-aminodibenzofuranone derivatives and this paper reports the investigation of the novel series. The 4-methylpiperazin-1-ylpropionamide (**28**), which exhibits antitussive activity comparable with that of codeine but without its marked effects upon the CNS, CVS, and GI tract, is currently being evaluated in man.

Scheme I

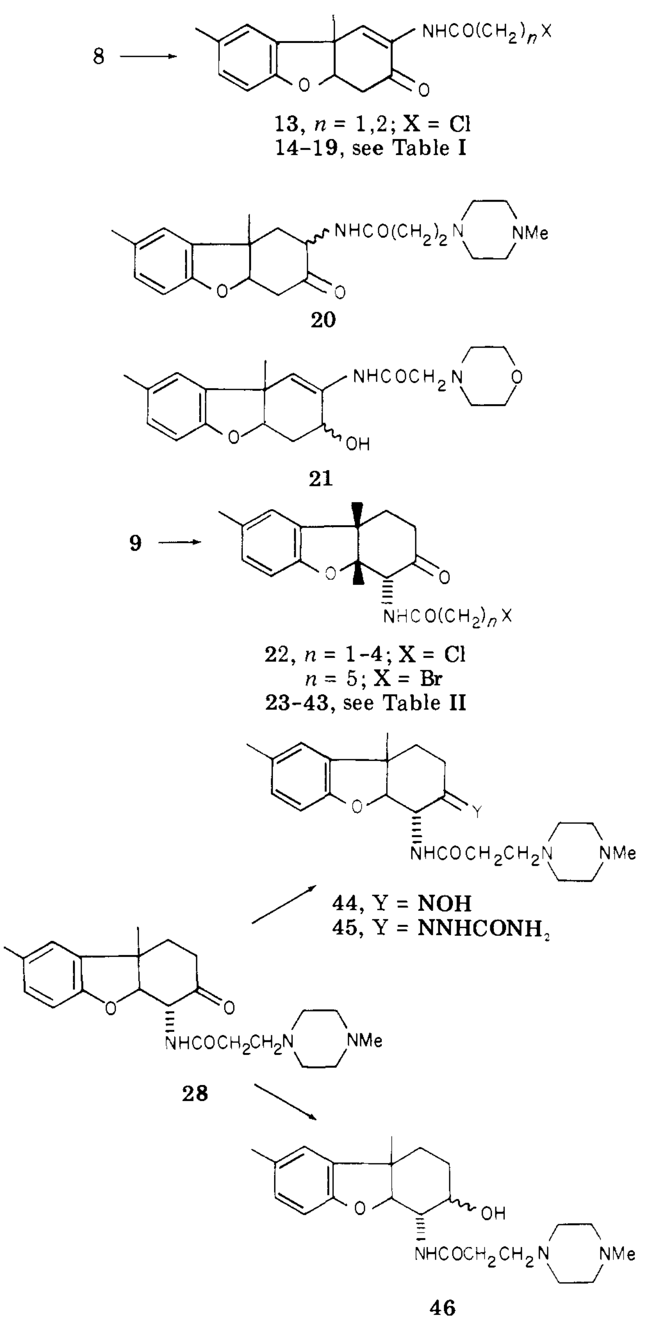


Chemistry. The synthesis of the compounds described in Tables I-III is outlined in Schemes I-IV. Pummerer's ketone (**1**) was obtained from p-cresol by oxidative coupling according to the method of Bacon.[6] Hydrogenation over palladium on carbon gave the dihydro ketone **2**. The ketone **2** readily formed enamines, e.g., the pyrrolidine-enamine **3**, in which the $\Delta^{3,4}$ double bond isomer was formed exclusively. The selectivity of enamine formation suggested that it might be possible to control the direction of the Neber rearrangement,[7] the intended route to the intermediate α-amino ketones for the two series. Thus ketones **1** and **2** were converted via the oximes **4** and **5** to their respective oxime tosylates **6** and **7**. From these oxime tosylates two unrelated α-amino ketone products were obtained using the standard Neber rearrangement conditions. The unsaturated oxime tosylate **6** gave the 2-amino ketone **8** in good yield, stable as its free base, presumably via rearrangement of a ring-open intermediate **10**. A similar rearrangement has been reported[8] in which the analogous enaminoamide **11** gave the amide **12** on acid hydrolysis. The oxime tosylate **7** gave a high yield of the anticipated 4-amino ketone **9**, since a dienone intermediate was not possible in this case. The stereochemistry of the amine group in **9** was assigned "equatorial-α" on the basis of the NMR evidence.

The two series described in Tables I and II were elaborated from the key intermediate α-amino ketones **8** and **9** according to the following procedures. The amine **8** was treated with chloroacyl halides in the presence of sodium carbonate to give the intermediate chloroamides **13** (n = 1, 2) which were subsequently converted to the amides **14-19** using an excess of the appropriate amines in benzene. Hydrogenation of the amide **17** in the presence of palladium on carbon gave the dihydro product **20**, while reduction of **19** with sodium borohydride gave the carbinol **21**. Similarly, reaction of the amino ketone **9** gave the series of haloamides **22** (n = 1-5) from which the amides (**23-43**) were obtained by heating under reflux with excess of the appropriate amine in benzene or toluene.

To investigate the effect of the substituent at C-3 on activity, compound **28** was converted to its oxime **44** and semicarbazone **45** under standard conditions and to the carbinol **46** by sodium borohydride reduction. The intermediate chloropropionamide **22** (n = 2; X = Cl) was converted via the ethylene ketal **47** and thioketal **48** to the amino ketal **49** and the amino thioketal **50**, respectively.

Scheme II



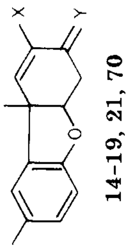
Raney nickel desulfurization of **50** gave the deoxy compound **51**. Lithium aluminum hydride reduction of **28** gave the amino alcohol **52**.

The carbamate analogue (**54**) of **28** was prepared via the chloro intermediate (**53**). Two further amides were also prepared to complete the series, namely the long chain ether **56** which was obtained from intermediate **55** and the *N*-acetyl compound **57**.

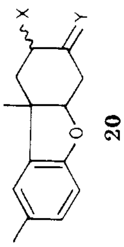
The effect of aromatic substitution on antitussive activity was investigated by means of acetylation and nitration of the chloropropionamide intermediate **22** ($n = 2$; X = Cl). The acetylated derivative **58** gave two products on treatment with *N*-methylpiperazine, the ring-opened enone phenol **59** being the initially formed product. The phenol was readily converted to **60** on recrystallization from methanol saturated with hydrogen chloride. Nitration also took place ortho to the oxygen bridge giving **61**, the intermediate used to obtain the nitro analogue (**62**) of **28**.

The "reversed" amides of **28** and of its analogue **17** were

Table I. 2-Amino-Substituted Tetrahydrodibenzofuranones



14-19, 21, 70



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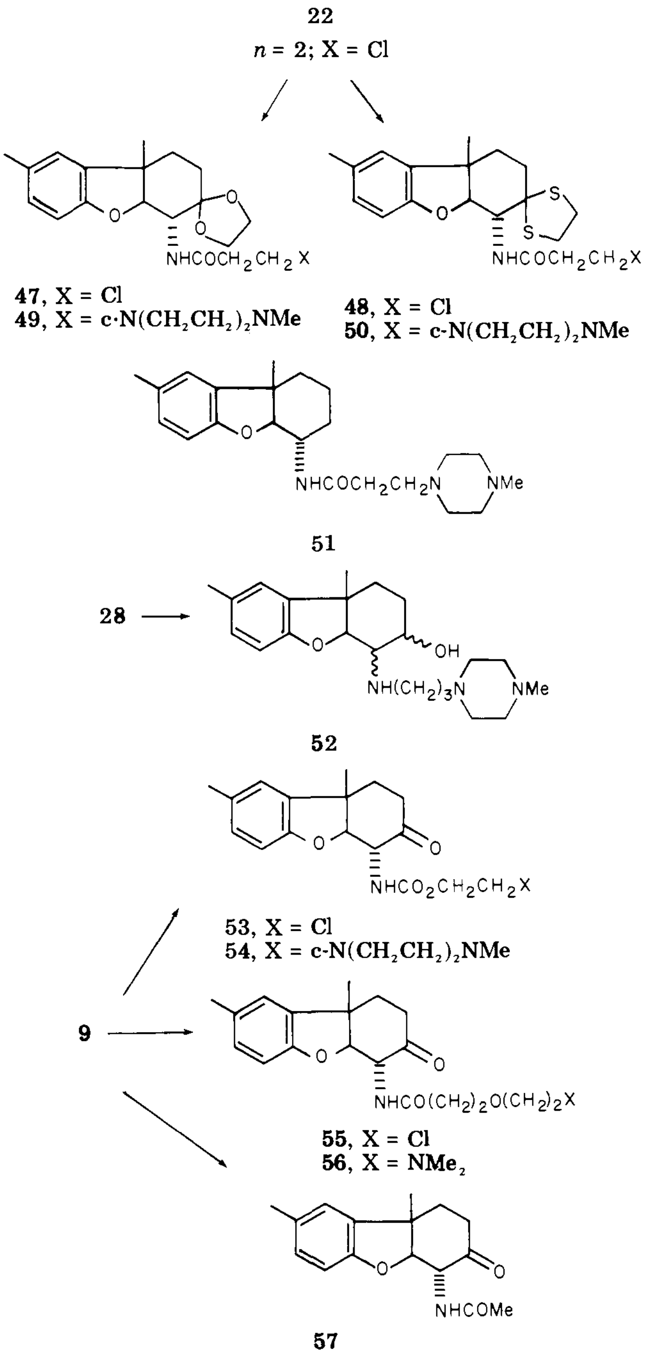
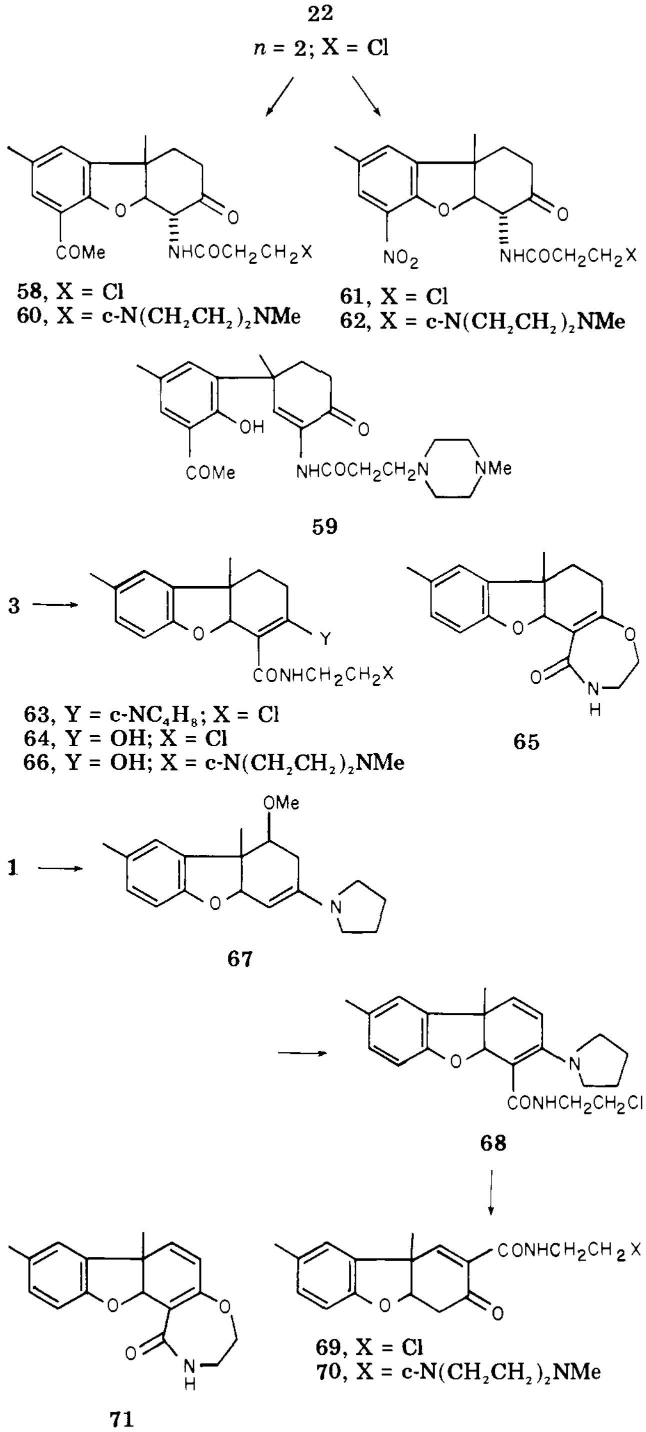
No.	X	Y	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	TEG,[a] % inhibn at 100 mg/kg po
14	-NHCOCH$_2$-c-NC$_4$H$_8$·HCl	O	242-246 dec	EtOH-Et$_2$O	65	$C_{20}H_{25}N_2O_3Cl$	C, H, N, Cl	42
15	-NHCOCH$_2$-c-NC$_5$H$_{10}$·HCl	O	234-238 dec	EtOH-Et$_2$O	82	$C_{21}H_{27}N_2O_3Cl$	C, H, N, Cl	17
16	-NHCOCH$_2$NMe$_2$·HCl	O	234-236 dec	EtOH-Et$_2$O	70	$C_{18}H_{23}N_2O_3Cl$	C, H, N, Cl[b]	33
17	-NHCO(CH$_2$)$_2$-c-N(CH$_2$CH$_2$)$_2$NMe	O	137-139	EtOAc	80	$C_{22}H_{29}N_3O_3$	C, H, N	25
18	-NHCO(CH$_2$)$_2$NMe$_2$·HCl	O	220-222 dec	EtOH-Et$_2$O	65	$C_{19}H_{25}N_2O_3Cl$	C, H, N, Cl	58
19	-NHCOCH$_2$-c-N(CH$_2$CH$_2$)$_2$O	O	213-214	EtOAc-Et$_2$O	86	$C_{20}H_{24}N_2O_4$	C, H, N	31
21	-NHCOCH$_2$-c-N(CH$_2$CH$_2$)$_2$O	H(OH)	194-195	EtOAc-Et$_2$O	67	$C_{20}H_{26}N_2O_4$	C, H, N	29
70	-COHNCH$_2$CH$_2$-c-N(CH$_2$CH$_2$)$_2$NMe	O	178-180	EtOAc-Et$_2$O	75	$C_{22}H_{29}N_3O_3$	C, H, N	62.5
20	-NHCO(CH$_2$)$_2$-c-N(CH$_2$CH$_2$)$_2$NMe·2HCl	O	258-260 dec	EtOH-Et$_2$O	63	$C_{22}H_{33}N_3O_3Cl_2$	C, H, N, Cl[c]	12.5

[a] TEG = cough induced by electrical stimulation of the vagus nerve in the guinea pig. Inhibition of greater than 35% considered statistically significant by Student's *t* test ($p < 0.05$). [b] Analysis correct for +0.5 mol of H_2O. [c] Analysis correct for +0.75 mol of H_2O.

Scheme III



Scheme IV

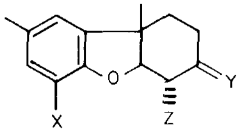


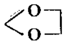
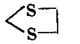
also prepared for comparison. Reaction of the pyrrolidineenamine 3 and 2-chloroethyl isocyanate gave the enaminoamide 63, which on hydrolysis gave the required amido ketone, isolated in the enolic form (64), together with some of the cyclized product (65). Treatment of the enol 64 with *N*-methylpiperazine gave the amine 66, the "reversed" amide analogue of 28. Reaction of Pummerer's ketone (1) and pyrrolidine in methanol gave the enamine 67, which on treatment with 2-chloroethyl isocyanate and concomitant elimination of methanol gave the amidodienamine 68, an analogue of 11. Acid hydrolysis of 68 caused the expected rearrangement to the amido enone 69, from which the "reversed" amide analogue (70) of 17 was obtained on treatment with *N*-methylpiperazine. Treatment of the amido enone 69 with ammonia caused a further rearrangement to the cyclic amide 71.

Biological Results and Discussion. For primary evaluation of the series, antitussive activity was determined in the guinea pig after oral administration of the compound followed by electrical stimulation of cough according to the method of Green and Ward.[9] All compounds were initially tested at 100 mg/kg po and those compounds exhibiting significant inhibition of cough (>80%) were reexamined at lower dose levels and their ED$_{50}$'s were determined. Details of the method are described in the Experimental Section and the results are summarized in Tables I and II.

In Table II the results illustrate the structural requirements within the series for maximum antitussive activity. The 4-methylpiperazin-1-ylpropionamide (28) was clearly the optimum compound in the series (ED$_{50}$ = 32.5 mg/kg po). Variation of chain length led to maximum antitussive activity when $n = 2$ (compare 23, 28, and 41) whereas replacement of the piperazine moiety by other cyclic amines resulted in decreased activity (26, 29, and

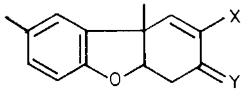
Table II. 4-Amino-Substituted Hexahydrodibenzofuranones[r]



No.	X	Y	Z	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	TEG,[a] % inhibn at 100 mg/kg po
9	H	O	$-NH_2\cdot HCl$	187-191	EtOH	85	$C_{14}H_{18}NO_2Cl$	C, H, N, Cl	33
23	H	O	$-NHCOCH_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	155-160	EtOH-Et_2O	73	$C_{21}H_{31}N_3O_3Cl_2$	C, H, N, Cl[b]	43
24	H	O	$-NHCOCH_2$-c-NC_4H_8	88-89	EtOAc	67	$C_{20}H_{26}N_2O_3$	C, H, N	17
25	H	O	$-NHCOCH_2N(CH_2Ph)CH_2CH_3\cdot HCl$	110-114	EtOH-Et_2O	70	$C_{25}H_{31}N_2O_3Cl$	AM[c]	9
26	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2O\cdot HCl$	130-135	EtOH-Et_2O	83	$C_{21}H_{29}N_2O_4Cl$	C, H, N[d]	39
27	H	O	$-NHCO(CH_2)_2NMe_2\cdot HCl$	115-120	EtOH-Et_2O	58	$C_{19}H_{27}N_2O_3Cl$	C, H, N, Cl	79
28	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	218-221	EtOH-Et_2O	73	$C_{22}H_{33}N_3O_3Cl_2$	C, H, N, Cl[e]	ED_{50} 32.5
29	H	O	$-NHCO(CH_2)_2$-c-$NC_4H_8\cdot HCl$	120-124	EtOH-Et_2O	67	$C_{21}H_{29}N_2O_3Cl$	C, H, N, Cl[f]	44
30	H	O	$-NHCO(CH_2)_2$-c-$NC_5H_{10}\cdot HCl$	117-120	EtOH-Et_2O	71	$C_{22}H_{31}N_2O_3Cl$	C, H, N, Cl[g]	46
31	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NH\cdot 2HCl$	186-189	EtOH-Et_2O	45	$C_{21}H_{31}N_3O_3Cl_2$	C, H, N, Cl[h]	75
32	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NCO_2Et$	189-190	EtOAc	67	$C_{24}H_{33}N_3O_5$	C, H, N	33
33	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NPh$ 2HCl	149-152	EtOH-Et_2O	58	$C_{27}H_{35}N_3O_3Cl_2$	AM[c]	54
34	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NCH_2CH_2$-$OH\cdot 2HCl$	130-145	EtOH-Et_2O	39	$C_{23}H_{35}N_3O_4Cl_2$	AM[c]	17
35	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NCH_2Ph$	207-211[i]	EtOAc	73	$C_{28}H_{35}N_3O_3$	C, H, N	33
36	H	O	$-NHCO(CH_2)_2NMe(CH_2)_2NMe_2\cdot 2HCl$	135-142	EtOH-Et_2O	70	$C_{22}H_{35}N_3O_3Cl_2$	AM[c]	50
37	H	O	$-NHCO(CH_2)_2NEt_2\cdot HCl$	57-62	EtOH-Et_2O	63	$C_{21}H_{31}N_2O_3Cl$	AM[c]	33
38	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NCOCH_3\cdot HCl$	130-135	EtOH-Et_2O	75	$C_{22}H_{32}N_3O_4Cl$	C, H, N, Cl	33
39	H	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NEt\cdot 2HCl$	158-161	EtOH-Et_2O	67	$C_{23}H_{35}N_3O_3Cl_2$	AM[c]	8
40	H	O	$-NHCO(CH_2)_3NMe_2\cdot HCl$	*j*	EtOH-Et_2O	54	$C_{20}H_{29}N_2O_3Cl$	AM[c]	67
41	H	O	$-NHCO(CH_2)_3$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	192-196	EtOH-Et_2O	61	$C_{23}H_{35}N_3O_3Cl_2$	C, H, N, Cl[k]	72
42	H	O	$-NHCO(CH_2)_4NMe_2\cdot HCl$	*j*	EtOH-Et_2O	42	$C_{21}H_{31}N_2O_3Cl$	AM[c]	ED_{50} 71
43	H	O	$-NHCO(CH_2)_5NMe_2\cdot HCl$	*j*	EtOH-Et_2O	36	$C_{22}H_{33}N_2O_3Cl$	AM[c]	25
44	H	NOH	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	168-174	MeOH	85	$C_{22}H_{34}N_4O_3Cl_2$	C, H, N	55
45	H	NNHCO NH_2	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe$	209-213[i]	MeOH-H_2O	72	$C_{23}H_{34}N_6O_3$	C, H, N[l]	25
46	H	H(OH)	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe$	168-172[i]	MeOH-Et_2O	75	$C_{22}H_{33}N_3O_3$	C, H, N	12
49	H		$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	190-196	EtOH-Et_2O	55	$C_{24}H_{37}N_3O_4Cl_2$	AM[c]	11
50	H		$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe$	152-153	MeOH	71	$C_{24}H_{35}N_3O_2S_2$	C, H, N, S	46
51	H	H_2	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	208-209	EtOH-Et_2O	63	$C_{22}H_{35}N_3O_2Cl_2$	C, H, N, Cl[m]	46
52	H	H(OH)	$-NH(CH_2)_3$-c-$N(CH_2CH_2)$ $NMe\cdot 3HCl$	245-249	EtOH	45	$C_{22}H_{38}N_3O_2Cl_3$	C, H, N, Cl	62
54	H	O	$-NHCO_2(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	133-138	EtOH-Et_2O	48	$C_{22}H_{33}N_3O_4Cl_2$	C, H, N, Cl[n]	33
56	H	O	$-NHCO(CH_2)_2O(CH_2)_2NMe_2\cdot HCl$	*j*	EtOH-Et_2O	39	$C_{21}H_{31}N_2O_4Cl$	AM[c]	37
57	H	O	$-NHCOCH_3$	168-169	EtOAc	85	$C_{16}H_{19}NO_3$	C, H, N	25
59			Open-chain analogue of $60\cdot 2HCl$	178-181	MeOH-Et_2O	70	$C_{24}H_{35}N_3O_4Cl_2$	C, H, N, Cl[o]	22
60	$COCH_3$	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	224-226	MeOH-Et_2O	85	$C_{24}H_{35}N_3O_4Cl_2$	C, H, N, Cl	42
62	NO_2	O	$-NHCO(CH_2)_2$-c-$N(CH_2CH_2)_2NMe$	224-227[i]	EtOH-Et_2O	65	$C_{22}H_{30}N_4O_5$	C, H, N	ED_{50} 34
66	H	Enolic OH	$-CONH(CH_2)_2$-c-$N(CH_2CH_2)_2NMe\cdot 2HCl$	220-222	EtOH-Et_2O	52	$C_{22}H_{33}N_3O_3Cl_2$	C, H, N, Cl[p]	61
Codeine									ED_{50} 38.5[q]

[a] Inhibition of greater than 35% considered statistically significant by Student's *t* test ($p < 0.05$). [b] Analysis correct for +1 mol of H_2O. [c] Due to the extreme hygroscopic nature of this series of amine mono- and dihydrochlorides, it was not possible in these cases to recrystallize the precipitated salts. Accurate mass values (AM) for the M^+ ion were determined to confirm the free base molecular structures. For the same reason, melting points for these compounds are not accurate. [d] Analysis correct for +1.2 mol of H_2O. [e] Analysis correct for +1 mol of H_2O. A sample dried at 105 °C for 48 h had C, H, and N values as calculated, but exposure to air led to the immediate taking up of +1 mol of H_2O again. [f] Analysis correct for +0.2 mol of H_2O. [g] Analysis correct for +0.5 mol of H_2O. [h] Analysis correct for +1 mol of H_2O. [i] Melting point of dihydrochloride salt. [j] These compounds were too hygroscopic to obtain melting points. [k] Analysis correct for +1 mol of H_2O. Accurate mass also obtained. [l] Analysis correct for +0.5 mol of H_2O. [m] Analysis correct for +0.3 mol of H_2O. [n] Analysis correct for +0.6 mol of H_2O. [o] Analysis correct for +1 mol of H_2O. [p] Analysis correct for +0.5 mol of H_2O. [q] All compounds given ED_{50} values (mg/kg) had >80% inhibition at 100 mg/kg po. [r] All amines were checked by TLC on Merck Kieselgel 60 F_{254} and aluminum oxide F_{254} (type E) plates in four solvent systems each and found to be >98% pure.

Table III. Intermediates



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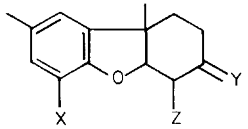
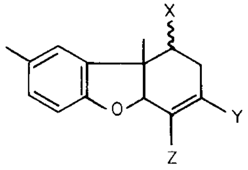
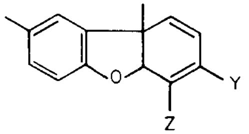


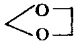
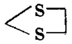
5, 7, 22, 47, 48, 53, 55, 58, 61



3, 63-65, 67



68, 71

No.	X	Y	Z	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
4	H	NOH		209-211	MeOH	95	$C_{14}H_{15}NO_2$	C, H, N
6	H	NOTos		190-194	MeOH	98	$C_{21}H_{21}NO_4S$	C, H, N, S
8	NH_2	O		141-143	Et_2O	62	$C_{14}H_{15}NO_2$	C, H, N
13	$NHCOCH_2Cl$	O		142-143	Et_2O	93	$C_{16}H_{16}NO_3Cl$	C, H, N, Cl
	$NHCOCH_2CH_2Cl$	O		119-120	Et_2O-EtOAc	87	$C_{17}H_{18}NO_3Cl$	C, H, N, Cl
69	$CONHCH_2CH_2Cl$	O		172-173	Et_2O	73	$C_{17}H_{18}NO_3Cl$	C, H, N, Cl
5	H	NOH	H	160-162	MeOH-EtOAc	99	$C_{14}H_{17}NO_2$	C, H, N
7	H	NOTos	H	130-132	MeOH	98	$C_{21}H_{23}NO_4S$	C, H, N, S
22	H	O	$NHCOCH_2Cl$	151-153	Et_2O	90	$C_{16}H_{18}NO_3Cl$	C, H, N, Cl
	H	O	$NHCO(CH_2)_2Cl$	141-143	Et_2O-EtOAc	90	$C_{17}H_{20}NO_3Cl$	C, H, N, Cl
	H	O	$NHCO(CH_2)_3Cl$	118-119	EtOAc	85	$C_{18}H_{22}NO_3Cl$	C, H, N, Cl
	H	O	$NHCO(CH_2)_4Cl$	109-110	Et_2O	80	$C_{19}H_{24}NO_3Cl$	C, H, N
	H	O	$NHCO(CH_2)_5Br$	81-83	Et_2O	81	$C_{20}H_{26}NO_3Br$	C, H, N, Br
47	H	 O O	$NHCO(CH_2)_2Cl$	142-144	EtOAc	93	$C_{19}H_{24}NO_4Cl$	C, H, N, Cl
48	H	 S S	$NHCO(CH_2)_2Cl$	168-169	MeOH-EtOAc	75	$C_{19}H_{24}NO_2S_2Cl$	C, H, N, S, Cl
53	H	O	$NHCO_2CH_2CH_2Cl$	127-128	Et_2O	67	$C_{17}H_{20}NO_4Cl$	C, H, N, Cl
55	H	O	$NHCO(CH_2)_2O(CH_2)_2Cl$	108-109	Et_2O	83	$C_{19}H_{24}NO_4Cl$	C, H, N, Cl
58	$COCH_3$	O	$NHCO(CH_2)_2Cl$	179-181	EtOAc	82	$C_{19}H_{22}NO_4Cl$	C, H, N, Cl
61	NO_2	O	$NHCO(CH_2)_2Cl$	142-147	EtOAc	52	$C_{17}H_{19}N_2O_5Cl$	C, H, N
3	H	c-NC_4H_8	H	82-83	MeOH	85	$C_{18}H_{23}NO$	C, H, N
63	H	c-NC_4H_8	$CONHCH_2CH_2Cl$	142-146	Et_2O	65	$C_{21}H_{27}N_2O_2Cl$	C, H, N, Cl
64	H	OH	$CONHCH_2CH_2Cl$	192-193	EtOAc	70	$C_{17}H_{20}NO_3Cl$	C, H, N, Cl
65	H		$-OCH_2CH_2NHCO-$	178-180	Et_2O-EtOAc	20	$C_{17}H_{19}NO_3$	C, H, N
67	OMe	c-NC_4H_8	H	105-108	MeOH	91	$C_{19}H_{25}NO_2$	C, H, N
68		c-NC_4H_8	$CONHCH_2CH_2Cl$	128-134	Et_2O	80	$C_{21}H_{25}N_2O_2Cl$	C, H, N, Cl
71			$-OCH_2CH_2NHCO-$	248-250	Et_2O-EtOAc	65	$C_{17}H_{17}NO_3$	C, H, N

30). Changes of substituent on the 4-piperazine nitrogen also resulted in decreased antitussive activity (**31**–**35**, **38**, and **39**) as did cleavage of the piperazine ring in **36**. However, the activity of the alkylamino analogues (n = 1–5) was maximized with the C_4 side chain (compare **25**, **27**, **37**, **40**, **42**, and **43**) with the dimethylamino group being the preferred substituent. In particular, the amine **42** (n = 4; R = NMe_2) possessed about one-half the antitussive activity of **28** and was more active than the cleaved piperazine compound **36** and its oxygen analogue **56**. It is possible that the *N*-methyl group in **42** is in a similar position to that in the *N*-methylpiperazine compound **28**.

The amide analogue **17**, the "reversed" amides **66** and **70**, and the carbamate analogue **54** were significantly less active than **28**. Any change of substituent from carbonyl at C_3 in **28** inevitably resulted in a significant loss of antitussive activity (**44**–**46** and **49**–**52**). Nitration in the aromatic ring resulted in little change of activity (**62**, ED_{50} = 34 mg/kg po) although the compound was markedly more toxic. Acetylation in the same position in the aromatic ring led to a reduction in activity (**59** and **60**).

In the series of Table I, only compounds **18** and **70** showed any significant antitussive activity and for **18** this was less than that of its analogue **27**.

Conclusion

This work describes the syntheses and evaluation of a series of aminohexahydrodibenzofurans with antitussive activity. Compound **28** was clearly the most potent of this novel class of antitussive agents and has activity comparable with that of codeine (Table II). The compound has a significantly improved therapeutic index over that of codeine and manifests no CNS, CVS, or GI effects. The detailed pharmacological evaluation of the product will be described elsewhere.

Experimental Section

Melting points were determined on a Townson and Mercer open-ended capillary melting point apparatus and are uncorrected. Solvents were removed in vacuo on a Büchi Rotavapor R. Magnesium sulfate (dried) was used for the drying of all organic solutions. Infrared spectra (IR) were recorded on a Unicam SP 1000 infrared spectrophotometer. ^1H NMR spectra were recorded on a Perkin-Elmer R12A spectrometer using Me_4Si as internal standard except in those spectra taken in D_2O where DSS was used. Microanalyses were carried out by CHN Analysis Ltd., Leicester, England. Analyses are indicated by symbols of the elements and the analytical values were within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F_{254} plates (using ethyl acetate–petroleum ether as eluent for intermediates and methanol as eluent for amine products) and chromatography on Merck Kieselgel 60 or BDH neutral aluminum oxide. Mass spectra were recorded on a CEC 110/CE5 by direct inlet at 180–240 °C and 70 eV. All compounds had IR, NMR, and mass spectra that were fully in accord with their proposed structures. The procedures presented below are representative of all the syntheses used. IR and NMR spectra are shown only when representative of series, key intermediates, or rearrangements.

Biological Test Procedure. Primary screening for antitussive activity was determined in the guinea pig after oral administration of the compound followed by electrical stimulation of the vagus nerve to induce cough. Male guinea pigs (Dunkin–Hartley guinea pigs of 350–450-g body weight supplied by Charles River, Manston, Kent) were randomly allocated into groups of six animals and starved overnight. Anesthesia was induced by using a 25% w/v solution of urethane and distilled water in a value of 5 ml/kg of body weight (ip). The trachea was cannulated, the vagus nerve exposed, and cough was elicited by electrical stimulation of the vagus nerve in a manner similar to that described by Green and Ward,[9] stimulation taking place at 20 and 40 min after oral drug treatment. Compounds were tested as the hydrochloride or dihydrochloride salts dissolved in water.

Methods of Synthesis. 8,9b-Dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuranone 3-Oxime (5). Dihydro-Pummerer's ketone (**2**) (150 g, 0.69 mol) was dissolved in hot ethanol (375 ml) and hydroxylamine hydrochloride solution (60 g, 0.85 mol in H_2O, 225 ml) and sodium acetate (75 g, 0.915 mol) were added with swirling. The solution was heated on a water bath for 2 h. TLC then indicated no starting material remaining. Water (100 ml) was added and the flask was cooled in an ice bath. After filtering off and washing well with water (0.75–1 l.), the crystalline oxime **5** was dried under vacuum over P_2O_5. The unsaturated oxime **4** was prepared in a similar manner.

8,9b-Dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuranone 3-Oxime Tosylate (7). *p*-Toluenesulfonyl chloride (160 g, 0.84 mol) was dissolved in dry pyridine (300 ml) and the solution was stirred and cooled to <0 °C in an ice–salt bath. A solution of the oxime **5** (97 g, 0.42 mol) in dry pyridine (300 ml) was then added at such a rate that the temperature of the reaction mixture remained below 10 °C. After 2 h, TLC indicated no starting material remaining, so the mixture was poured onto iced water (4 l.). The precipitated product (**7**) was filtered off, washed well with water (1+ l.) and cold methanol (0.5 l.), and was then dried under vacuum over P_2O_5. The unsaturated oxime tosylate **6** was prepared similarly.

4α-Amino-8,9bβ-dimethyl-1,2,3,4,4aβ,9b-hexahydrodibenzofuran-3-one Hydrochloride (9). Sodium metal (14.7 g, 0.63 mol) was dissolved in dry ethanol (from Mg) (1 l.) and the solution obtained was cooled in an ice bath. The oxime tosylate **7** (230 g, 0.61 mol) was added with vigorous mechanical stirring. After 4 h of stirring at ice bath temperatures, the mixture stood overnight at room temperature. The mixture was then filtered and the residue washed with dry ether (2 × 200 ml). The filtrate was concentrated to 250 ml and was then poured onto cold 10% HCl (500 ml) in a separating funnel along with ether (750 ml). The aqueous acid layer was removed and the ether layer further extracted with 10% HCl (2 × 125 ml). The combined acid extract was washed once with ether (200 ml) and was then reduced in volume at 50 °C on a rotary evaporator until crystallization commenced. The mixture was cooled and filtered, the filtrate being further reduced in volume to obtain second and third crops. The amine hydrochloride **9**, colorless needles, was washed with a little acetone and was dried over P_2O_5: NMR (Me_2SO–d_6) δ 1.59 (s, 3, Me), 1.5–2.5 (m, 4, $-CH_2CH_2-$), 2.31 (s, 3, aryl Me), 4.94, 5.13 (2 d's, 2, J = 4 Hz, H_{4a} + H_4), 6.71, 7.05 (AB q, 2, J = 8 Hz), and 7.13 (br s, 1) (aryl H's), 8.8–9.2 (br s, 3+, amine H's exchangeable with D_2O); IR (KBr disk) 1738 cm^{-1} (carbonyl).

The analogue **8** was prepared from **6** under similar conditions except that in the work-up the 10% HCl solution was basified (Na_2CO_3) and extracted well with ether. Removal of the ether caused crystallization of **8**, stable as its free base: brownish needles; NMR ($CDCl_3$) δ 1.49 (s, 3, Me), 2.28 (s, 3, aryl Me), 2.90 (d AB q, 2, J = 3, 4, 13 Hz, nonequivalent $-CH_2-$), 4.52 (m, 1, H_{4a}), 5.30 (d, 1, J = 1.5 Hz, H_1, long range coupled to H_{4a}),[10] 6.5–7.05 (m, 3, aryl H's); IR (KBr disk) 1630, 1679, 3335, 3435 cm^{-1}.

4-(3-Chloropropionamido)-8,9b-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one (22) (n = 2; X = Cl). The amine hydrochloride **9** (53.5 g, 0.20 mol) was suspended in benzene–chloroform (1:2, 1 l.) and 3-chloropropionyl chloride (50.8 g, 0.40 mol) and anhydrous sodium carbonate (100 g, 0.94 mol) were added. The mixture was stirred and heated under reflux for 4–6 h, after which TLC indicated that the reaction was complete. After pouring onto water (1 l.), the organic layer was separated and the aqueous layer further extracted with chloroform (2 × 200 ml). The combined organic layer was washed thoroughly with water and was then dried. After filtering and removal of solvent, the oil obtained was triturated with ether to give **22** as colorless needles: NMR ($CDCl_3$) δ 1.57 (s, 3, Me), 1.7–2.6 (m, 4, $-CH_2CH_2-$), 2.26 (s, 3, aryl Me), 2.79 (t, 2, J = 6.5 Hz), 3.81 (t, 2, J = 6.5 Hz, $-CH_2CH_2Cl$), 4.85 (d, 1, J = 3.5 Hz, H_{4a}), 5.0, 5.11 (2 d's, 1, J = 3.5, 8 Hz, H_4, collapses to d, 1, J = 3.5 Hz on prolonged D_2O shake), 6.6–7.05 (m, 4, 3 aryl H's + amide NH); IR (KBr disk) 1641, 1731, 3275 cm^{-1}.

Similarly prepared were compounds **22** (n = 1, 3, 4; X = Cl), **22** (n = 5; X = Br), **53**, **55**, 13 (n = 1, 2; X = Cl), and **57**.

8,9b-Dimethyl-4-[3-(4-methylpiperazin-1-yl)propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one Dihydrochloride (28). The chloropropionamide **22** (n = 2; X =

Cl) (40.0 g, 0,125 mol) and *N*-methylpiperazine (31 g, 0.31 mol) were heated under reflux overnight in dry benzene (700 ml). The mixture was cooled and poured onto water (500 ml) and the organic layer separated. The aqueous layer was further extracted with ether (2 × 250 ml) and the combined organic layer was washed well with water and dried. After filtering, the solvent was removed under reduced pressure to give a yellow oil from which low R_f material was removed using a short column of silica with 5% methanol–chloroform as eluent. The dihydrochloride salt was prepared by adding excess ethereal HCl to the oil in methanol. Recrystallization was from methanol: colorless needles; NMR on salt (D_2O) δ 1.60 (s, 3, Me), 1.7–2.8 (m, 4, $-CH_2CH_2-$), 2.29 (s, 3, aryl Me), 3.14 (t, 2), 3.77 (t, 2, $-COCH_2CH_2N<$), 3.17 (s, 3, $>$NMe), 3.86 (br s, 8, piperazine CH_2's), 4.96 (d, 1), 5.24 (d, 1) (both J = 3.5 Hz, $H_{4a} + H_4$), 6.6–7.2 (m, 3, aryl H's); IR (KBr disk) 1650, 1743 cm^{-1}.

Similarly prepared were the amines **14–19**, **23–43**, **49**, **50**, **54**, **56**, **62**, **66**, and **70** except that compounds **32–35**, **40–42**, and **56** were prepared in toluene rather than benzene and azeotroping conditions were used for compounds **24**, **29**, **31–33**, and **35**. Chromatography was used for purification of **31** (Al_2O_3) and **39**, **40**, **42**, **43**, **54**, and **56** (SiO_2). Salts were prepared using ethereal HCl or methanolic HCl added to ether or methanol solutions of the products.

6-Acetyl-4-(3-chloropropionamido)-8,9b-dimethyl-1,2,3,-4,4a,9b-hexahydrodibenzofuran-3-one (58). Compound **22** (n = 2; X = Cl) (9.65 g, 0.03 mol) was dissolved in tetrachloroethane (200 ml) and acetyl chloride (3.1 g, 0.04 mol) and aluminum chloride (powdered, 13.2 g, 0.10 mol) were added. The mixture was stirred at room temperature for 3 days and water (300 ml) then added. The mixture was extracted with chloroform (3 × 100 ml); the combined chloroform solution was dried and filtered and the chloroform removed on a rotary evaporator. Addition of ether gave the acetyl compound **58** as colorless needles: NMR ($CDCl_3$) δ 1.64 (s, 3, Me), 2.33 (s, 3, aryl Me), 2.51 (s, 3, $-COCH_3$), 1.7–2.6 (m, 4, $-CH_2CH_2$), 2.82 (t, 2, J = 6 Hz), 3.88 (t, 2, J = 6 Hz, $-CH_2CH_2Cl$), 5.0–5.2 (m, 2, $H_{4a} + H_4$), 6.6–6.8 (m, 1, amide NH, D_2O exchangeable proton), 3.1, 3.56 (2 br s, 2, $J \sim 2$ Hz, C_7, C_9 aromatic protons); IR (KBr disk) 1198, 1650, 1681, 1729, 3275 cm^{-1}.

4-(3-Acetyl-2-hydroxy-5-methylphenyl)-4-methyl-2-[3-(methylpiperazin-1-yl)propionamido]cyclohex-2-en-1-one Dihydrochloride (59). The acetylated chloropropionamide **58** (2.9 g, 8 mmol) was dissolved in dry benzene (50 ml) and *N*-methylpiperazine (2.0 g, 20 mmol) was added. The mixture was heated under reflux overnight. Work-up as for **28** gave an oil which crystallized on trituration with ether, colorless needles, and was recrystallized from ethyl acetate: 2.0 g; 85% yield; mp 181–183 °C; NMR ($CDCl_3$) δ 1.63 (s, 3, Me), 2.21, 2.29 (2 s, 2 × 3, aryl Me + $COCH_3$), 1.8–3.3 (m, ~19 H, includes large br s at 2.56, all CH_2's + NMe), 7.27, 7.39 (2 d's, 2, J = ~2 Hz, aryl H's), 7.90 (s, 1, olefinic H), –0.4 to –0.6 (br s, 1, amide NH), –2.97 (s, 1, hydrogen bonded phenolic –OH); IR (KBr disk) 1631, 1671 cm^{-1}.

The product was dissolved in methanol and methanolic HCl was added followed immediately by ether. The precipitated product **59** was collected, washed with ether, and dried: NMR (D_2O) δ 1.68 (s, 3, Me), 2.33 (s, 3, aryl Me), 2.65 (s, 3, $-COCH_3$), 3.24 (s, 3, $>$NMe), 3.20 (t, 2, J = 7 Hz), 3.80 (t, 2, J = 7 Hz, $-COCH_2CH_2N<$), 3.93 (br s, ~8 H, piperazine CH_2's), 7.48 (d, 1, J = 2 Hz), 7.66 (d, 1, J = 2 Hz, aryl H's), 7.79 (s, 1, olefinic H); IR (KBr disk) 1635, 1679 cm^{-1}.

6-Acetyl-8,9b-dimethyl-4-[3-(4-methylpiperazin-1-yl)-propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one Dihydrochloride (60). The amine dihydrochloride **59** was dissolved in hot methanolic HCl and stood overnight. The crystalline cyclized product **60** was collected and dried: NMR (D_2O) δ 1.62 (s, 3, Me), 2.31 (s, 3, aryl Me), 2.59 (s, 3, $-COCH_3$), 1.5–2.8 (m, 4, $-CH_2CH_2-$), 3.13 (t, 2, J = 7 Hz), 3.80 (t, 2, J = 7 Hz, $-COCH_2CH_2N<$), 3.19 (s, 3, $>$NMe), 3.98 (br s, 8, piperazine CH_2's), 5.03 (d, 1, J = 3.5 Hz), 5.31 (d, 1, J = 3.5 Hz, $H_{4a} + H_4$), 7.39, 7.48 (2 br s, 2, aryl H's); IR (KBr disk) 1680, 1723 cm^{-1}.

4-(3-Chloropropionamido)-8,9b-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one Ethylene Acetal (47). The chloropropionamide **22** (n = 2; X = Cl) (10 g, 0.031 mol) was heated under azeotroping conditions in benzene (200 ml) with *p*-toluenesulfonic acid (250 mg) and ethylene glycol (6 g, 0.10 mol). After 10 h, the mixture was cooled, water (200 ml) and ether (150 ml) were added, and the organic layer was separated. The aqueous layer was further extracted with ether (2 × 100 ml). The combined ethereal layer was dried, filtered, and evaporated to dryness. Trituration with ether gave the crystalline product **47**: IR (KBr disk) 1650, 3310 cm^{-1}.

8,9b-Dimethyl-4-[3-(4-methylpiperazin-1-yl)propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuranone 3-Oxime Dihydrochloride (44). Compound **28** (2.3 g, 5 mmol) was dissolved in water–methanol (1:1, 20 ml) and hydroxylamine hydrochloride (0.55 g, 8 mmol) and sodium acetate (1.1 g, 13.5 mmol) were added. The mixture was heated under reflux for 3 h. TLC then indicated no **28** remaining, so the mixture was cooled, basified to pH 9 (Na_2CO_3), and extracted well with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ solution was dried, filtered, and evaporated to dryness. The oil obtained was dissolved in methanol and ethereal HCl added. A crystalline precipitate of **44** formed which was collected and dried: IR (KBr disk) 1630 cm^{-1}.

8,9b-Dimethyl-4-[3-(4-methylpiperazin-1-yl)propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuranone 3-Semicarbazone (45). Compound **28** (2.3 g, 5 mmol) was dissolved in water–methanol (1:1, 20 ml) and semicarbazole hydrochloride (0.9 g, 8 mmol) and sodium acetate (1.1 g, 13.5 mmol) were added. The mixture was heated under reflux for 5 h. Work-up was as for **44** except that trituration of the oil with ether gave the semicarbazone **45** as the crystalline free base, which was recrystallized from methanol–water.

8,9b-Dimethyl-3-hydroxy-4-[3-(4-methylpiperazin-1-yl)-propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuran (46). Compound **28** (2.3 g, 5 mmol) was suspended in ethanol (50 ml) and sodium borohydride (0.57 g, 15 mmol) was added. The mixture was stirred at room temperature for 5 h, and then water (100 ml) and ether (100 ml) were added. The ether layer was separated and the aqueous layer further extracted with ether. The combined ether layer was dried, filtered, and evaporated to dryness. The residual oil was dissolved in methanol and ether was added. The product (**46**) crystallized and was collected. Compound **21** was prepared in a similar manner.

8,9b-Dimethyl-3-hydroxy-4-[3-(4-methylpiperazin-1-yl)-propylamino]-1,2,3,4,4a,9b-hexahydrodibenzofuran Trihydrochloride (52). Compound **28** (4.58 g, 10 mmol) was suspended in dry THF (150 ml) and lithium aluminum hydride (1.9 g, 50 mmol) was added slowly. The mixture was heated under reflux for 3 h. After cooling in an ice bath, ethyl acetate followed by water was slowly added. The white precipitate was removed by filtering through Celite and the organic layer was separated. The aqueous layer was extracted twice with ether. The combined ether layer was washed once with water, dried, filtered, and evaporated to dryness. The yellowish oil was dissolved in dry ether and ethereal HCl was added. The white solid was collected and recrystallized from EtOH–$(CH_3)_2CO$ giving the trihydrochloride **52**: IR (KBr disk) no carbonyls.

4-(3-Chloropropionamido)-8,9b-dimethyl-6-nitro-1,2,3,4,-4a,9b-hexahydrodibenzofuran-3-one (61). The chloropropionamide **22** (n = 2; X = Cl) (20 g, 0.064 mol) was suspended in acetic anhydride (50 ml) and the stirred solution was cooled to 5 °C. A mixture of fuming nitric acid (4 ml)–glacial acetic acid (40 ml) was slowly added at such a rate that the temperature remained below 10 °C. After 1 h the starting material had all dissolved and after 5 h TLC indicated no **22** remaining. The yellow solution was poured onto iced water (1 l.). The yellow solid formed was collected and dried by azeotroping in benzene. The nitro product (**61**) was recrystallized from ethyl acetate: NMR ($CDCl_3$) δ 1.57 (s, 3, Me), 2.28 (s, 3, aryl Me), 1.7–2.6 (m, 4, $-CH_2CH_2$), 2.83 (t, 2, J = 6 Hz), 3.8 (t, 2, J = 6 Hz, $-CH_2CH_2Cl$), 4.85 (d, 1, J = 3.5 Hz, H_{4a}), 5.05 5.16 (2 d's, 1, J = 3.5 Hz + 8 Hz, H_4, collapses to d, 1, J = 3.5 Hz on prolonged D_2O shake), 6.7–7.0 (br d, 1, J = 8 Hz, amide –NH), 7.16, 7.69 (v br s, 2 × 1, aryl H's); IR (KBr disk) 1352, 1532, 1641, 1730 cm^{-1}.

8,9b-Dimethyl-3-(pyrrolidin-1-yl)-1,2,4a,9b-tetrahydrodibenzofuran (3). Dihydro-Pummerer's ketone (**2**) (21.6 g, 0.10 mol) was dissolved in hot methanol (50 ml) and pyrrolidine (13.6 g, 0.2 mol) was slowly added. The product crystallized out almost immediately. The mixture was cooled in an ice bath and then filtered. The product (**3**) was washed with a little cold methanol and recrystallized from methanol: NMR ($CDCl_3$) δ 1.27 (s, 1, Me), 1.6–2.3 (m, 8, CH_2's), 2.25 (s, 3, aryl Me), 3–3.3 (m, 4, CH_2's next to –N<), 4.30 (d, 1, J = 5.5 Hz), 4.78 (d, 1, J = 5.5 Hz, $H_{4a} + H_4$), 6.5–7.0 (m, 3, aryl H's); IR (KBr disk) 1616 cm^{-1}.

The methoxyenamine **67** was prepared in a similar manner.

8,9b-Dimethyl-2-[3-(4-methylpiperazin-1-yl)propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one Dihydrochloride (20). The amino enone 17 (2.1 g, 5.5 mmol), dissolved in ethanol (150 ml) with 5% palladium on carbon (50 mg) present, was hydrogenated at 4 atm of pressure for 2 h. The catalyst was then filtered off and the filtrate was evaporated to dryness. The oil obtained was dissolved in ether and ethereal HCl was added. The precipitated product **20** was collected and recrystallized from ethanol–ether: IR (KBr disk) 1650, 1738 cm^{-1}.

4-(3-Chloropropionamido)-8,9b-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one Ethylene Thioacetal (48). The chloropropionamide **22** (n = 2; X = Cl) (10.0 g, 0.032 mol) was dissolved in glacial acetic acid (40 ml) and boron trifluoride etherate (4 ml) and 1,2-ethanedithiol (5.6 g, 0.06 mol) were added with warming. After 2 h at room temperature, TLC indicated no starting material remaining. Water (200 ml) and sodium carbonate (to pH 9) were added. The mixture was extracted well with ether. The ether extracts were dried, filtered, and evaporated to dryness. Trituration with ether gave the product as colorless needles which was recrystallized from methanol–ethyl acetate: IR (KBr disk) 1654, 3300 cm^{-1}.

8,9b-Dimethyl-4-[3-(4-methylpiperazin-1-yl)propionamido]-1,2,3,4,4a,9b-hexahydrodibenzofuran Dihydrochloride (51). The amino thioketal **50** (3.0 g, 6.5 mmol) in ethanol (50 ml) was heated under reflux with W2 Raney nickel (ca. 15 g) for about 4 h. After this time TLC indicated completion of reaction. The Raney nickel was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in methanol and ethereal HCl was added. The precipitated dihydrochloride was collected and recrystallized from ethanol–ether: IR (KBr disk) 1665 cm^{-1}.

***N*-(2-Chloroethyl)-8,9b-dimethyl-3-(pyrrolidin-1-yl)-1,2,4a,9b-tetrahydrodibenzofuran-4-carboxamide (63).** The enamine **3** (2.69 g, 10 mmol) was dissolved in dry ether (50 ml) and 2-chloroethyl isocyanate (1.6 g, 15 mmol) was added. The mixture was heated under reflux for 1 h and then cooled in an ice bath. The product crystallized and was filtered off, washed with a little ether, and dried: 2.36 g; 65% yield; mp 128–134 °C; NMR ($CDCl_3$) δ 1.31 (s, 3, Me), 1.6–2.4 (m, 8, CH_2's), 2.27 (s, 3, aryl Me), 2.8–3.8 (m, 8, CH_2's next to N and $>NCH_2CH_2Cl$), 4.5–4.8 (br s, 1, amide NH), 5.18 (s, 1, H_{4a}), 6.5–7.0 (m, 3, aryl H's); IR (KBr disk) 1490, 1590, 1618, 3200, 3435 cm^{-1}.

The corresponding unsaturated analogue **68** was prepared in a similar manner from the enamine **67**: 80% yield; 3.7 g; mp 142–146 °C; NMR ($CDCl_3$) δ 1.39 (s, 3, Me), 1.5–2.3 (m, 4, CH_2's), 2.26 (s, 3, aryl Me), 2.85–3.85 (m, 8, CH_2's next to N and $> NCH_2CH_2Cl$), 5.16 (br s, 1, H_{4a} long range coupled to H_1), 5.75, 6.17 (AB q, 2, $H_1 + H_2$ olefinic, H_1 long range coupling to H_{4a}), 6.3–7.05 (m, 4, 3 aryl H's + amide NH); IR (KBr disk) 1618, 1653, 3315 cm^{-1}.

***N*-(2-Chloroethyl)-3-hydroxy-8,9b-dimethyl-1,2,4a,9b-tetrahydrodibenzofuran-4-carboxyamide (64).** The enamine **63** (3.6 g, 10 mmol) was added to a mixture of methanol (20 ml)–10% HCl (20 ml). The solution was heated under reflux for 2 h, then cooled, and extracted well with ethyl acetate (3 × 150 ml). The ethyl acetate layer was dried, filtered, and evaporated to dryness. Trituration with ether gave the product as colorless needles which was recrystallized from ethyl acetate: NMR ($CDCl_3$) δ 1.33 (s, 3, Me), 1.5–1.9 (m, 2, CH_2), 2.0–2.4 (m, 2, CH_2), 2.37 (s, 3, aryl Me), 3.66 (br d, 4, $>NHCH_2CH_2Cl$), 4.78 (s, 1, H_{4a}), 6.5–7.0 (m, 4, 3 aryl H's + amide NH), –0.5 to –0.15 (v br s, 1, enolic –OH); IR (KBr disk) 1640 (br), 3420 cm^{-1}(s).

From the mother liquors, a second compound was isolated and recrystallized from ether–ethyl acetate: 20% yield. This was the cyclized enol ether **65**: NMR ($CDCl_3$) δ 1.37 (s, 3, Me), 1.7–2.1 (m, 2, CH_2), 2.1–2.4 (m, 2, CH_2), 2.26 (s, 3, aryl Me), 3.79 (t, 2, J = 7 Hz, $-CH_2-$ next to O), 4.56 (dt, 2, J = 3, 7 Hz, $-CONHCH_2-$), 5.29 (s, 1, bridgehead H), 6.5–7.0 (m, 3, aryl H's), –0.1 to –0.5 (v br m, 1, amide NH); IR (KBr disk) 1451, 1486, 1631, 1650, 1752, 3235 cm^{-1}.

***N*-(2-Chloroethyl)-8,9b-dimethyl-3(4*H*)-oxo-4a,9b-dihydrodibenzofuran-2-carboxyamide (69).** The enamine **68** (2.6 g, 7 mmol) was dissolved in ethanolic HCl as in **64** and was heated under reflux for 3 h. Work-up as in **64** gave the rearranged chloroethylcarboxamide **69**: NMR ($CDCl_3$) δ 1.60 (s, 3, Me), 2.28 (s, 3, aryl Me), 3.0 (m, d AB q, 2, nonequivalent C_4-CH_2–, $J \sim$ 3, 4, 17 Hz), 3.60 (br d, 4, $-NHCH_2CH_2Cl$), 4.65 (m, 1, H_{4a}, coupled to C_4-CH_2 and long range coupled to H_1), 6.5–7.1 (m, 3, aryl H's), 7.68 (d, 1, J = 1.5 Hz, olefinic H_1, long range coupled to H_{4a}), 8.7–9.1 (br m, 1, amide NH); IR (KBr disk) 1605, 1648, 1691, 3310 cm^{-1}.

7a,9-Dimethyl-3,4,7a,12a-tetrahydrobenzofuro[2,3-*g*]-[1,4]benzoxazepin-1(2*H*)-one (71). The chloroethylcarboxamide **69** (1.0 g, 3.1 mmol) was dissolved in chloroform (20 ml) and concentrated ammonia (10 ml) was added. The mixture was stirred vigorously overnight, then poured onto water (100 ml), and extracted with chloroform (3 × 20 ml). The chloroform extract was dried, filtered, and evaporated to dryness. Trituration with ether gave the product (**71**) in good yield, which was recrystallized from ether–ethyl acetate: NMR ($CDCl_3$) δ 1.42 (s, 3, Me), 2.25 (s, 3, aryl Me), 3.78 (t, 2, J = 8 Hz, CH_2 next to O), 4.54 (dt, 2, J = 2–3, 8 Hz, $-CONHCH_2-$), 5.39 (d, 1, J = 1.5 Hz, bridgehead H long range coupled to C_1 olefinic H), 5.85 (d, 1, J = 9 Hz, C_2 olefinic H), 6.13 (dd, 1, J = 1.5, 9 Hz, C_1 olefinic H), 6.55–7.1 (m, 3, aryl H's), 0.1 to –0.4 (br m, 1, amide NH); IR (KBr disk) 1490, 1555, 1630, 1655, 3250 cm^{-1}.

References and Notes

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