

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 4 α -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.

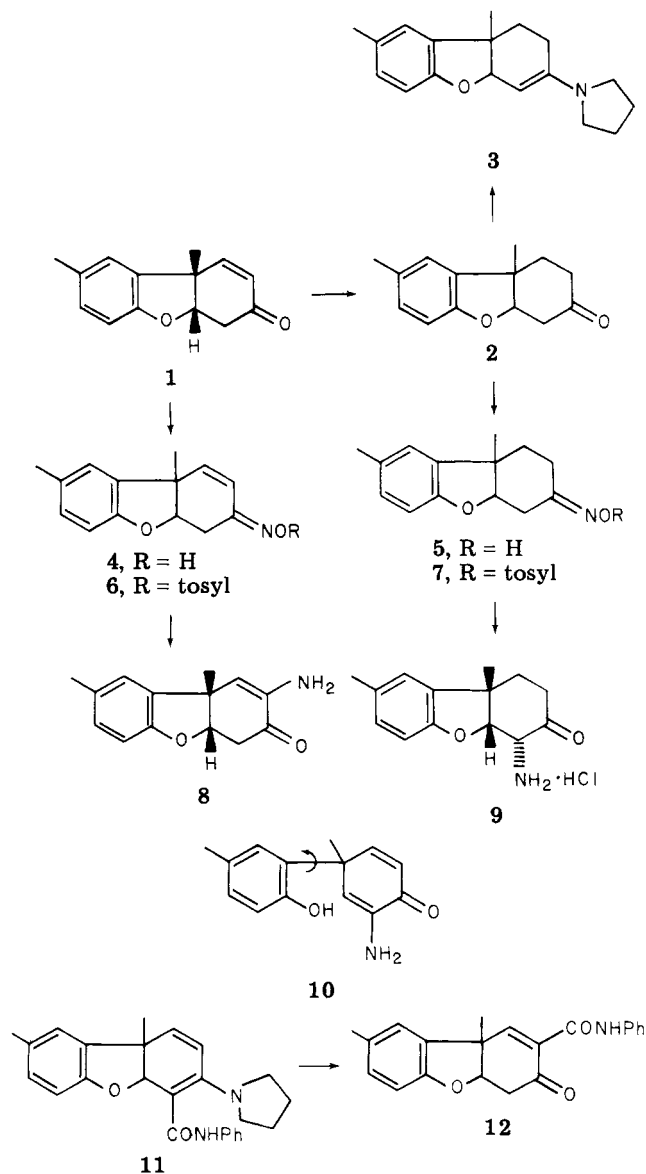
Codeine is an effective analgesic and antitussive agent belonging to the morphine family of narcotic analgesics. In clinical use it manifests the major side effects of sedation, respiratory depression, and constipation.¹ The search for novel analgesics and antitussives incorporating essential features 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 ketone⁵ (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.

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 reported⁸ 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 amino 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 chloroacetyl 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

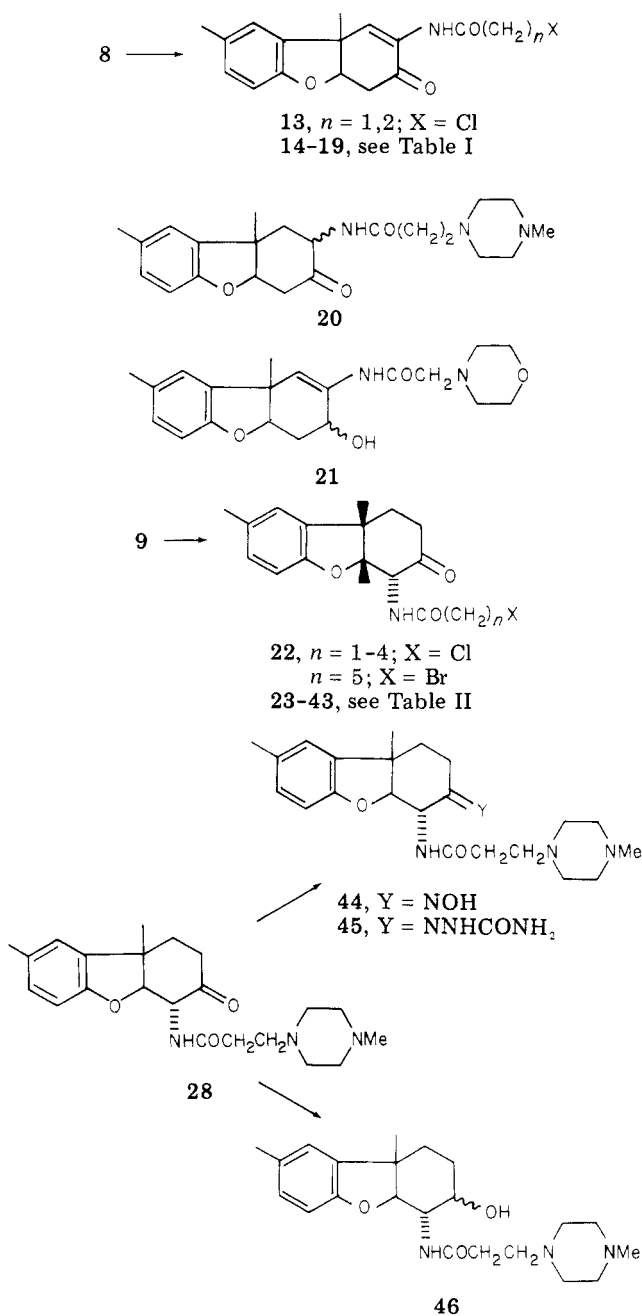
Scheme I



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**.

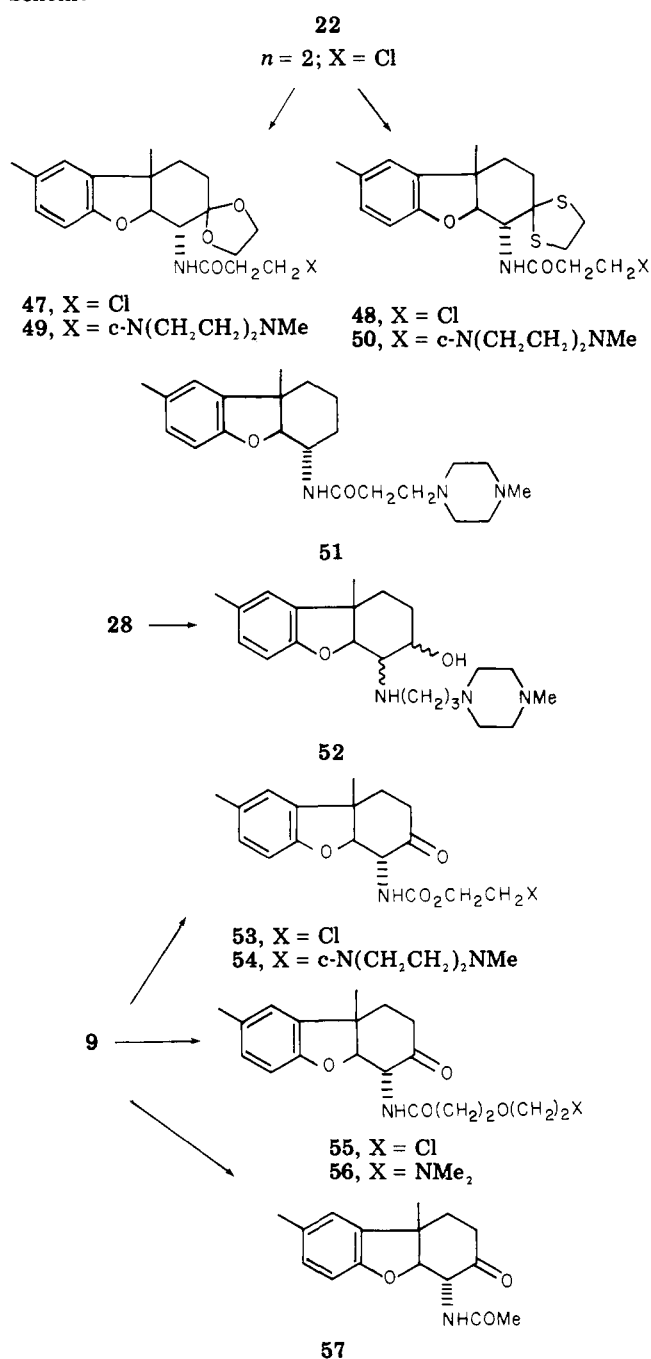
The "reversed" amides of **28** and of its analogue **17** were

Table I. 2-Amino-Substituted Tetrahydrobenzofuranones

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 ₉ ·HCl	O	242-246 dec	EtOH-Et ₂ O	65	C ₂₀ H ₂₂ N ₂ O ₃ Cl	C, H, N, Cl	42
15	-NHCOCH ₂ -c-NC ₄ H ₉ ·HCl	O	234-238 dec	EtOH-Et ₂ O	82	C ₂₁ H ₂₃ N ₂ O ₃ Cl	C, H, N, Cl	17
16	-NHCOCH ₂ -c-NC ₄ H ₉ ·HCl	O	234-236 dec	EtOH-Et ₂ O	70	C ₁₈ H ₂₀ N ₂ O ₃ Cl	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 ₂₆ N ₂ O ₃	C, H, N	25
18	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·HCl	O	220-222 dec	EtOH-Et ₂ O	65	C ₁₀ H ₁₂ N ₂ O ₃ Cl	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 ₂ O 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 ₂ O ₄	C, H, N	29
70	-COHNCH ₂ -c-N(CH ₂ CH ₂) ₂ NMe	O	178-180	EtOAc-Et ₂ O	75	C ₂₂ H ₂₈ N ₂ O 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 ₂₈ N ₂ O ₃ Cl 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 H₂O. ^c Analysis correct for +0.75 mol of H₂O.

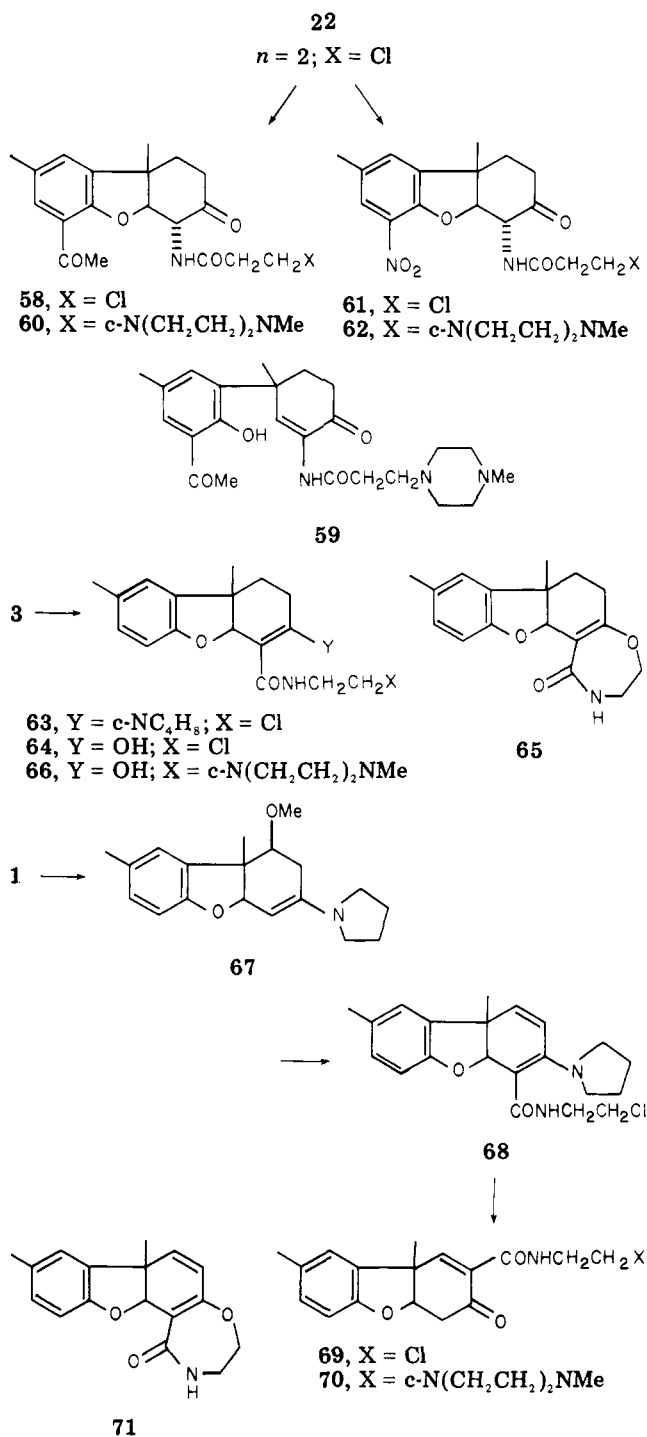
Scheme III



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 amido-dienamine 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

Scheme IV

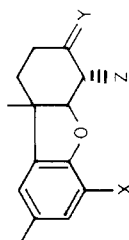


followed by electrical stimulation of cough according to the method of Green and Ward.⁹ All compounds were initially tested at 100 mg/kg po and those compounds exhibiting significant inhibition of cough (>80%) were reexamined at lower dose levels and their ED₅₀'s were determined. Details of the method 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 (ED₅₀ = 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 Hexahydrodibenzofuranones⁷

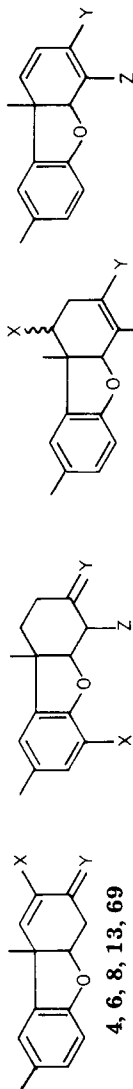
No.	X	Y	Z	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	TEG, ^a % inhibn at 100 mg/kg po
9	H	O	-NH ₂ ·HCl	187-191	EtOH	85	C ₁₄ H ₁₈ N ₂ O ₃ Cl	C, H, N, Cl	33
23	H	O	-NHCOCH ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	155-160	EtOH-Et ₂ O	73	C ₂₁ H ₃₁ N ₃ O ₃ Cl ₂	C, H, N, Cl ^b	43
24	H	O	-NHCOCH ₂ -c-NC ₄ H ₉	88-89	EtOAc	67	C ₂₀ H ₂₆ N ₂ O ₃	C, H, N	17
25	H	O	-NHCOCH ₂ -N(CH ₂ Ph)CH ₂ CH ₃ ·HCl	110-114	EtOH-Et ₂ O	70	C ₂₃ H ₃₁ N ₂ O ₃ Cl	AM ^c	9
26	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ O·HCl	130-135	EtOH-Et ₂ O	83	C ₂₁ H ₂₉ N ₂ O ₄ Cl	C, H, N ^d	39
27	H	O	-NHCO(CH ₂) ₂ NMe ₂ ·HCl	115-120	EtOH-Et ₂ O	58	C ₂₁ H ₂₇ N ₂ O ₃ Cl	C, H, N, Cl	79
28	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	218-221	EtOH-Et ₂ O	73	C ₂₂ H ₃₃ N ₃ O ₃ Cl ₂	C, H, N, Cl ^e	ED ₅₀ 32.5
29	H	O	-NHCO(CH ₂) ₂ -c-NC ₄ H ₉ ·HCl	120-124	EtOH-Et ₂ O	67	C ₂₁ H ₂₉ N ₂ O ₃ Cl	C, H, N, Cl ^f	44
30	H	O	-NHCO(CH ₂) ₂ -c-NC ₄ H ₉ ·HCl	117-120	EtOH-Et ₂ O	71	C ₂₂ H ₃₁ N ₂ O ₃ Cl	C, H, N, Cl ^g	46
31	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NH·2HCl	186-189	EtOH-Et ₂ O	45	C ₂₁ H ₃₁ N ₃ O ₃ Cl ₂	C, H, N, Cl ^h	75
32	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NCO ₂ Et	189-190	EtOAc	67	C ₂₄ H ₃₃ N ₃ O ₅	C, H, N	33
33	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NPh·2HCl	149-152	EtOH-Et ₂ O	58	C ₂₇ H ₃₅ N ₃ O ₃ Cl ₂	AM ^c	54
34	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NCH ₂ CH ₂ OH·2HCl	130-145	EtOH-Et ₂ O	39	C ₂₃ H ₃₅ N ₃ O ₄ Cl ₂	AM ^c	17
35	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NCH ₂ Ph	207-211 ⁱ	EtOAc	73	C ₂₈ H ₃₅ N ₃ O ₃	C, H, N	33
36	H	O	-NHCO(CH ₂) ₂ NMe(CH ₂) ₂ NMe ₂ ·2HCl	135-142	EtOH-Et ₂ O	70	C ₂₂ H ₃₅ N ₃ O ₃ Cl ₂	AM ^c	50
37	H	O	-NHCO(CH ₂) ₂ NEt ₂ ·HCl	57-62	EtOH-Et ₂ O	63	C ₂₁ H ₃₁ N ₂ O ₃ Cl	AM ^c	33
38	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NCOCH ₃ ·HCl	130-135	EtOH-Et ₂ O	75	C ₂₂ H ₃₃ N ₃ O ₄ Cl	C, H, N, Cl	33
39	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NEt ₂ ·2HCl	158-161	EtOH-Et ₂ O	67	C ₂₃ H ₃₅ N ₃ O ₃ Cl ₂	AM ^c	8
40	H	O	-NHCO(CH ₂) ₂ NMe ₂ ·HCl	j	EtOH-Et ₂ O	54	C ₂₀ H ₂₉ N ₂ O ₃ Cl	AM ^c	67
41	H	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	192-196	EtOH-Et ₂ O	61	C ₂₃ H ₃₅ N ₃ O ₃ Cl ₂	C, H, N, Cl ^k	72
42	H	O	-NHCO(CH ₂) ₂ NMe ₂ ·HCl	j	EtOH-Et ₂ O	42	C ₂₁ H ₃₁ N ₂ O ₃ Cl	AM ^c	ED ₅₀ 71
43	H	O	-NHCO(CH ₂) ₂ NMe ₂ ·HCl	j	EtOH-Et ₂ O	36	C ₂₂ H ₃₃ N ₂ O ₃ Cl	AM ^c	25
44	H	NOH	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	168-174	MeOH	85	C ₂₂ H ₃₄ N ₂ O ₃ Cl ₂	C, H, N	55
45	H	NNHCO	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe	209-213 ⁱ	MeOH-H ₂ O	72	C ₂₃ H ₃₄ N ₆ O ₃	C, H, N ^l	25
46	H	H(OH)	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe	168-172 ⁱ	MeOH-Et ₂ O	75	C ₂₂ H ₃₃ N ₃ O ₃	C, H, N	12
49	H	<O>	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	190-196	EtOH-Et ₂ O	55	C ₂₄ H ₃₇ N ₃ O ₄ Cl ₂	AM ^c	11
50	H	<S>	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe	152-153	MeOH	71	C ₂₄ H ₃₅ N ₃ O ₂ S ₂	C, H, N, S	46
51	H	H ₂	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	208-209	EtOH-Et ₂ O	63	C ₂₂ H ₃₅ N ₃ O ₂ Cl ₂	C, H, N, Cl ^m	46
52	H	H(OH)	-NH(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·3HCl	245-249	EtOH	45	C ₂₂ H ₃₈ N ₃ O ₂ Cl ₃	C, H, N, Cl	62
54	H	O	-NHCO ₂ (CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	133-138	EtOH-Et ₂ O	48	C ₂₂ H ₃₃ N ₃ O ₄ Cl ₂	C, H, N, Cl ⁿ	33
56	H	O	-NHCO(CH ₂) ₂ O(CH ₂) ₂ NMe ₂ ·HCl	j	EtOH-Et ₂ O	39	C ₂₂ H ₃₁ N ₂ O ₄ Cl	AM ^c	37
57	H	O	-NHCOCH ₃	168-169	EtOAc	85	C ₁₆ H ₁₉ N ₃ O ₃	C, H, N	25
59			Open-chain analogue of 60·2HCl	178-181	MeOH-Et ₂ O	70	C ₂₄ H ₃₅ N ₃ O ₄ Cl ₂	C, H, N, Cl ^o	22
60	COCH ₃	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	224-226	MeOH-Et ₂ O	85	C ₂₄ H ₃₅ N ₃ O ₄ Cl ₂	C, H, N, Cl	42
62	NO ₂	O	-NHCO(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe	224-227 ⁱ	EtOH-Et ₂ O	65	C ₂₂ H ₃₀ N ₄ O ₅	C, H, N	ED ₅₀ 34
66	H	Enolic OH	-CONH(CH ₂) ₂ -c-N(CH ₂ CH ₂) ₂ NMe·2HCl	220-222	EtOH-Et ₂ O	52	C ₂₂ H ₃₃ N ₃ O ₃ Cl 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 H₂O. ^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 H₂O. ^e Analysis correct for +1 mol of H₂O. 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 H₂O again. ^f Analysis correct for +0.2 mol of H₂O. ^g Analysis correct for +0.5 mol of H₂O. ^h Analysis correct for +1 mol of H₂O. ⁱ Melting point of dihydrochloride salt. ^j These compounds were too hygroscopic to obtain melting points. ^k Analysis correct for +1 mol of H₂O. Accurate mass also obtained. ^l Analysis correct for +0.5 mol of H₂O. ^m Analysis correct for +0.3 mol of H₂O. ⁿ Analysis correct for +0.6 mol of H₂O. ^o Analysis correct for +1 mol of H₂O. ^p Analysis correct for +0.5 mol of H₂O. ^q All compounds given ED₅₀ values (mg/kg) had >80% inhibition at 100 mg/kg po. ^r All amines were checked by TLC on Merck Kieselgel 60 F₂₅₄ and aluminum oxide F₂₅₄ (type E) plates in four solvent systems each and found to be >98% pure.

Table III. Intermediates

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 ₁₁ H ₂₁ NO ₄ S	C, H, N, S
8	NH ₂	O		141-143	Et ₂ O	62	C ₁₄ H ₁₅ NO ₂	C, H, N
13	NHCOCH ₂ CH ₂ Cl	O		142-143	Et ₂ O	93	C ₁₆ H ₁₆ NO ₃ Cl	C, H, N, Cl
69	CONHCH ₂ CH ₂ Cl	O		119-120	Et ₂ O-EtOAc	87	C ₁₆ H ₁₆ NO ₃ Cl	C, H, N, Cl
5	H	O	H	172-173	Et ₂ O	73	C ₁₇ H ₁₈ NO ₃ Cl	C, H, N, Cl
7	H	NOH		160-162	MeOH-EtOAc	99	C ₁₄ H ₁₇ NO ₂	C, H, N
22	H	NOTos		130-132	MeOH	98	C ₁₁ H ₂₃ NO ₄ S	C, H, N, S
	H	O	NHCOCH ₂ Cl	151-153	Et ₂ O	90	C ₁₆ H ₁₈ NO ₃ Cl	C, H, N, Cl
	H	O	NHCO(CH ₂) ₂ Cl	141-143	Et ₂ O-EtOAc	90	C ₁₇ H ₂₀ NO ₃ Cl	C, H, N, Cl
	H	O	NHCO(CH ₂) ₃ Cl	118-119	EtOAc	85	C ₁₈ H ₂₂ NO ₃ Cl	C, H, N, Cl
	H	O	NHCO(CH ₂) ₄ Cl	109-110	Et ₂ O	80	C ₁₉ H ₂₄ NO ₃ Cl	C, H, N, Cl
	H	O	NHCO(CH ₂) ₅ Br	81-83	Et ₂ O	81	C ₂₀ H ₂₆ NO ₃ Br	C, H, N, Br
47	H		NHCO(CH ₂) ₂ Cl	142-144	EtOAc	93	C ₁₉ H ₂₄ NO ₄ Cl	C, H, N, Cl
48	H		NHCO(CH ₂) ₂ Cl	168-169	MeOH-EtOAc	75	C ₁₉ H ₂₄ NO ₄ S ₂ Cl	C, H, N, S, Cl
53	H	O	NHCOCH ₂ CH ₂ Cl	127-128	Et ₂ O	67	C ₁₇ H ₂₀ NO ₄ Cl	C, H, N, Cl
55	H	O	NHCO(CH ₂) ₂ O(CH ₂) ₂ Cl	108-109	Et ₂ O	83	C ₁₉ H ₂₄ NO ₄ Cl	C, H, N, Cl
58	COCH ₃	O	NHCO(CH ₂) ₂ Cl	179-181	EtOAc	82	C ₁₉ H ₂₂ NO ₄ Cl	C, H, N, Cl
61	NO ₂	O	NHCO(CH ₂) ₂ Cl	142-147	EtOAc	52	C ₁₇ H ₁₉ N ₂ O ₅ Cl	C, H, N
3	H	c-NC ₃ H ₈	H	82-83	MeOH	85	C ₁₈ H ₂₃ NO	C, H, N
63	H	c-NC ₃ H ₈	CONHCH ₂ CH ₂ Cl	142-146	Et ₂ O	65	C ₁₈ H ₂₇ N ₂ O ₂ Cl	C, H, N, Cl
64	H	OH	CONHCH ₂ CH ₂ Cl	192-193	EtOAc	70	C ₁₇ H ₂₀ NO ₃ Cl	C, H, N, Cl
65	H		-OCH ₂ CH ₂ NHCO-	178-180	Et ₂ O-EtOAc	20	C ₁₇ H ₁₉ NO ₃	C, H, N
67	OMe	c-NC ₃ H ₈	H	105-108	MeOH	91	C ₁₉ H ₂₅ NO ₂	C, H, N
68		c-NC ₃ H ₈	CONHCH ₂ CH ₂ Cl	128-134	Et ₂ O	80	C ₂₁ H ₂₅ N ₂ O ₂ Cl	C, H, N, Cl
71			-OCH ₂ CH ₂ NHCO-	248-250	Et ₂ O-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 $\pm 0.4\%$ 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-Pummer'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.

4 α -Amino-8,9b β -dimethyl-1,2,3,4,4a β ,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 \times 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 \times 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, $H_{4a} + H_1$), 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}), 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 \times 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_1 , 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 (D₂O) δ 1.60 (s, 3, Me), 1.7–2.8 (m, 4, –CH₂CH₂–), 2.29 (s, 3, aryl Me), 3.14 (t, 2), 3.77 (t, 2, –COCH₂CH₂N<), 3.17 (s, 3, >NMe), 3.86 (br s, 8, piperazine CH₂'s), 4.96 (d, 1), 5.24 (d, 1) (both *J* = 3.5 Hz, H_{4a} + H₄), 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 azeotropic conditions were used for compounds 24, 29, 31–33, and 35. Chromatography was used for purification of 31 (Al₂O₃) and 39, 40, 42, 43, 54, and 56 (SiO₂). 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 (CDCl₃) δ 1.64 (s, 3, Me), 2.33 (s, 3, aryl Me), 2.51 (s, 3, –COCH₃), 1.7–2.6 (m, 4, –CH₂CH₂), 2.82 (t, 2, *J* = 6 Hz), 3.88 (t, 2, *J* = 6 Hz, –CH₂CH₂Cl), 5.0–5.2 (m, 2, H_{4a} + H₄), 6.6–6.8 (m, 1, amide NH, D₂O exchangeable proton), 3.1, 3.56 (2 br s, 2, *J* ~ 2 Hz, C₇, C₉ 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 (CDCl₃) δ 1.63 (s, 3, Me), 2.21, 2.29 (2 s, 2 × 3, aryl Me + COCH₃), 1.8–3.3 (m, ~19 H, includes large br s at 2.56, all CH₂'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 (D₂O) δ 1.68 (s, 3, Me), 2.33 (s, 3, aryl Me), 2.65 (s, 3, –COCH₃), 3.24 (s, 3, >NMe), 3.20 (t, 2, *J* = 7 Hz), 3.80 (t, 2, *J* = 7 Hz, –COCH₂CH₂N<), 3.93 (br s, ~8 H, piperazine CH₂'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 (D₂O) δ 1.62 (s, 3, Me), 2.31 (s, 3, aryl Me), 2.59 (s, 3, –COCH₃), 1.5–2.8 (m, 4, –CH₂CH₂–), 3.13 (t, 2, *J* = 7 Hz), 3.80 (t, 2, *J* = 7 Hz, –COCH₂CH₂N<), 3.19 (s, 3, >NMe), 3.98 (br s, 8, piperazine CH₂'s), 5.03 (d, 1, *J* = 3.5 Hz), 5.31 (d, 1, *J* = 3.5 Hz, H_{4a} + H₄), 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 azeotropic 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 (Na₂CO₃), and extracted well with CHCl₃ (3 × 50 ml). The CHCl₃ 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 semicarbazone 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-(CH₃)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 azeotropic in benzene. The nitro product (61) was recrystallized from ethyl acetate: NMR (CDCl₃) δ 1.57 (s, 3, Me), 2.28 (s, 3, aryl Me), 1.7–2.6 (m, 4, –CH₂CH₂), 2.83 (t, 2, *J* = 6 Hz), 3.8 (t, 2, *J* = 6 Hz, –CH₂CH₂Cl), 4.85 (d, 1, *J* = 3.5 Hz, H_{4a}), 5.05, 5.16 (2 d's, 1, *J* = 3.5 Hz + 8 Hz, H₄, collapses to d, 1, *J* = 3.5 Hz on prolonged D₂O 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 (CDCl₃) δ 1.27 (s, 1, Me),

1.6–2.3 (m, 8, CH₂'s), 2.25 (s, 3, aryl Me), 3–3.3 (m, 4, CH₂'s next to -N<), 4.30 (d, 1, *J* = 5.5 Hz), 4.78 (d, 1, *J* = 5.5 Hz, H_{4a} + H₄), 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)propion-amido]-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)propion-amido]-1,2,3,4,4a,9b-hexahydrodibenzofuran Dihydrochloride (51). The amino thioether **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 (CDCl₃) δ 1.31 (s, 3, Me), 1.6–2.4 (m, 8, CH₂'s), 2.27 (s, 3, aryl Me), 2.8–3.8 (m, 8, CH₂'s next to N and >NCH₂CH₂Cl), 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 (CDCl₃) δ 1.39 (s, 3, Me), 1.5–2.3 (m, 4, CH₂'s), 2.26 (s, 3, aryl Me), 2.85–3.85 (m, 8, CH₂'s next to N and >NCH₂CH₂Cl), 5.16 (br s, 1, H_{4a} long range coupled to H₁), 5.75, 6.17 (AB q, 2, H₁ + H₂ olefinic, H₁ 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-carboxamide (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 (CDCl₃) δ 1.33 (s, 3, Me), 1.5–1.9 (m, 2, CH₂), 2.0–2.4 (m, 2, CH₂), 2.37 (s, 3, aryl Me), 3.66 (br d, 4, >NHCH₂CH₂Cl), 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 (CDCl₃) δ 1.37 (s, 3, Me), 1.7–2.1 (m, 2, CH₂), 2.1–2.4 (m, 2, CH₂), 2.26 (s, 3, aryl Me), 3.79 (t, 2, *J* = 7 Hz, -CH₂- next to O), 4.56 (dt, 2, *J* = 3, 7 Hz, -CONHCH₂-), 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(4H)-oxo-4a,9b-dihydrodibenzofuran-2-carboxamide (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 (CDCl₃) δ 1.60 (s, 3, Me), 2.28 (s, 3, aryl Me), 3.0 (m, d AB q, 2, nonequivalent C₄-CH₂-, *J* ~ 3, 4, 17 Hz), 3.60 (br d, 4, -NHCH₂CH₂Cl), 4.65 (m, 1, H_{4a}, coupled to C₄-CH₂ and long range coupled to H₁), 6.5–7.1 (m, 3, aryl H's), 7.68 (d, 1, *J* = 1.5 Hz, olefinic H₁, 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(2H)-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 (CDCl₃) δ 1.42 (s, 3, Me), 2.25 (s, 3, aryl Me), 3.78 (t, 2, *J* = 8 Hz, CH₂ next to O), 4.54 (dt, 2, *J* = 2–3, 8 Hz, -CONHCH₂-), 5.39 (d, 1, *J* = 1.5 Hz, bridgehead H long range coupled to C₁ olefinic H), 5.85 (d, 1, *J* = 9 Hz, C₂ olefinic H), 6.13 (dd, 1, *J* = 1.5, 9 Hz, C₁ 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.

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