N-SUBSTITUTED TRICYCLIC ISOQUINOLINE HYDANTOINS

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Mannich condensation of the 1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]isoquinoline (*Ia*) and 5-ethoxy-10-bromo-1,3-dioxo-5*H*-imidazo[1,5-*b*]isoquinoline (*IVa*) with secondary amines gave a series of N-2-aminomethyl isoquinoline hydantoins *IIa*—*IIg* and *IVb*, respectively. Alkylation of *Ia* with N,N-dialkylaminoethyl chlorides and ethyl chloroacetate afforded the N-dialkylaminoethyl and N-ethoxycarbonylmethyl derivatives *Va*, *Vb* and *IIh*. The N-2-hydroxymethyl and N-2-amino isoquinoline hydantoins *IIj* and *If* were also prepared.

A number of tricyclic isoquinoline hydantoins *Ia*—*Ie* have been synthesized[1] for pharmacological evaluation and some of these compounds (e.g. *Id*) have been found to exhibit positive inotropic activity[2]. The low solubility of the N-substituted isoquinoline hydantoins *Ib*—*Ie* in aqueous media presents difficulties in their biological evaluation and the introduction of functional groups capable of salt formation at the N-2-position of *Ia* was considered.

RESULTS AND DISCUSSION

The N-3 imide hydrogen of the hydantoin ring is sufficiently acidic to react in the Mannich condensation[3] to give N-aminomethyl derivatives[4]. These products possessed higher water solubilities than the parent compounds and have been proposed as prodrugs of various hydantoins of poor solubility[5].

Mannich condensation of the N-unsubstituted isoquinoline hydantoin *Ia* with a series of secondary amines gave the corresponding 2-aminomethyl derivatives *IIa*—*IIg* in excellent yield. Reaction of *Ia*, in excess, with formaldehyde and piperazine afforded *III*. Accurate mass measurement of the molecular ion at *m/z* 514 gave the appropriate formula. Similar reaction with piperidine of the brominated isoquinoline hydantoin derivative *IVa*, which was obtained by bromination of *Ia* and further work-up with ethanol[6], yielded the corresponding N-Mannich base *IVb*. The product was easily characterised by IR and ^{1}H NMR spectroscopy and the mass spectrum at *m/z* 421/419 (1 : 1) gave the correct formula for *IVb*.

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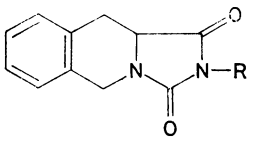
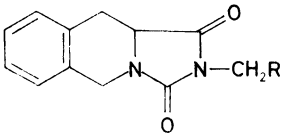
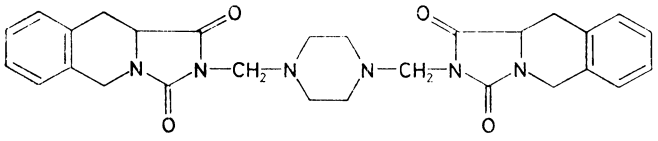


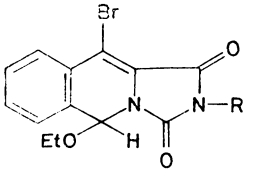
Ia, R = H
Ib, R = Me
Ic, R = Et
Id, R = Pr
Ie, R = Ph
If, R = NH_2



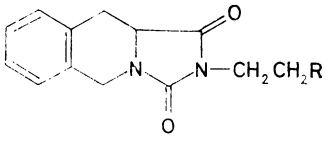
IIa, R = NMe_2
IIb, R = NEt_2
IIc, R = Pyrrolidino
IId, R = Piperidino
IIe, R = Morpholino
IIf, R = N(Me)Bz
IIg, R = N(Et)Bz
IIh, R = CO_2Et
IIi, R = CO_2H
IIj, R = OH



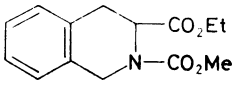
III



IVa, R = H
IVb, R = Piperidinomethyl



Va, R = NMe_2
Vb, R = NEt_2



VI

Hydantoins can easily be alkylated in the N-3 position by treatment with alkyl halides in alkaline solution[7]. Treatment of *Ia* with dialkylaminoethyl chlorides and sodium in ethanol gave the corresponding N-dialkylaminoethyl isoquinoline hydantoins *Va*, *Vb*. Reaction of *Ia* with ethyl chloroacetate under similar conditions afforded the ester *IIh* which was further hydrolysed to the corresponding acid *IIi*.

Treatment of *Ia* with formaldehyde solution[8] gave the N-2-hydroxymethyl isoquinoline hydantoin *IIj*, whereas an attempt to prepare the N-2-amino isoquinoline hydantoin *If* by the reaction of *Ia* with hydrazine hydrate[9] was unsuccessful. The product was prepared by cyclising the N-methoxycarbonyl-3-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (*VI*)[6] with hydrazine hydrate[10].

Treatment of the N-dialkylaminoethyl isoquinoline hydantoins *Va*, *Vb* with ethereal hydrogen chloride afforded the corresponding hydrochloride salts which were stable, on the contrary to the hydrochloride salts of the N-Mannich bases *IIa*–*IIg*, which proved to be unstable.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and IR spectra were recorded on a Perkin–Elmer 197 instrument using KCl pellets. The ^{1}H NMR spectra were obtained with a Perkin–Elmer R32 (90 MHz) spectrometer and chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Mass spectra were run on an AEI 902 double focussing, high resolution spectrometer.

2-Amino-1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]isoquinoline (*If*)

N-Methoxycarbonyl-3-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline *VI* (ref.[6]) (1·32 g, 5 mmol) and hydrazine hydrate (64% N_2H_4, 0·75 g, 15 mmol) in 15 ml of absolute ethanol were refluxed for 20 h. Roto-evaporation to dryness afforded an oil which on standing solidified and after recrystallization from aqueous ethanol gave the product *If* (0·71 g, 65% yield): m.p. 137–138°C. For $C_{11}H_{11}N_3O_2$ (217·2) calculated: 60·82% C, 5·10% H, 19·35% N; found: 60·85% C, 5·25% H, 19·3% N. IR (KCl): 3 340, 3 230, 1 765, 1 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2·68–3·39 dq, 2 H (10-H); 4·09 br, 3 H (10a-H overlapping with N–NH_2; addition of D_2O gave a dd, J = 6 and 13 Hz, 10a-H); 4·30–5·10 ABq, 2 H (J = 17 Hz, 5-H); 7·21 s, 4 H (Ar).

General Procedure for the Preparation of 2-Aminomethyl Isoquinoline Hydantoins (*IIa*–*IIg*)

A suspension of the 2-unsubstituted isoquinoline hydantoin *Ia* (10 mmol) in 20 ml of absolute ethanol was refluxed for 1 h with formaldehyde solution (37–41%, 11 mmol) and the appropriate secondary amine (11 mmol). The hot reaction mixture was filtered, allowed to cool and the precipitate which formed on standing was collected by filtration, washed with ethanol and recrystallized from an appropriate solvent to give the corresponding N-Mannich bases *IIa*–*IIg* (Table I).

2-Ethoxycarbonylmethyl-1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]isoquinoline (*IIh*)

Sodium (0·23 g, 10 mmol), ethyl chloroacetate (1·36 g, 10 mmol) and *Ia* (2·02 g, 10 mmol) were treated as described above to give the product *IIh* (1·2 g, 42% yield): m.p. 130–131°C (from

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TABLE I

Properties and spectral data for compounds *IIa*—*IIg*

Compound Yield, %	M.p., °C (cryst. solv.)	Calculated/Found			^{1}H NMR spectra[a]			
		% C	% H	% N	5-H[b]	10-H[c]	10a-H[d]	NCH_2N
IIa	121—123	64·55	6·35	15·9	4·28—5·10	2·72—3·40	4·10	4·40
75	(ether)	64·85	6·6	16·2				
IIb	107—109	66·7	7·05	14·6	4·28—5·10	2·70—3·38	4·07	4·53
62	(ether)	66·85	7·35	14·6				
IIc	104—106	67·4	6·7	14·45	4·28—5·10	2·69—3·39	4·08	4·55
68	(ether)	67·35	6·7	14·75				
IId	148—150	68·3	6·8	13·95	4·30—5·12	2·72—3·40	4·11	4·48
90	(ethanol)	68·2	7·05	14·05				
IIe	185—186	63·9	6·65	14·25	4·30—5·11	2·73—3·41	4·11	4·48
80	(ethanol)	63·8	6·35	13·95				
IIf	109—110	71·3	6·2	12·85	4·29—5·11	2·65—3·39	4·09	4·58
75	(ether)	71·6	6·3	12·55				
IIg	109·5—110·5	72·55	6·9	12·3	4·32—5·12	2·67—3·35	4·06	4·59
75	(ether)	72·2	6·65	12·05				

[a] The spectra were run in $CDCl_3$; chemical shifts, δ (ppm) from internal standard $SiMe_4$; signals for other protons are not reported; [b] AB quartet ($J = 17$ Hz); [c] doublet of quartets; [d] doublet of doublets.

MeOH). For $C_{15}H_{16}N_2O_4$ (288·3) calculated: 62·49% C, 5·59% H, 9·72% N; found: 62·25% C, 5·4% H, 10·1% N. IR (KCl): 1 780, 1 745, 1 720 cm^{-1}. ^1H NMR ($CDCl_3$): 1·28 s, 3 H (CO_2CH_2**Me**); 2·76—3·41 dq, 2 H (10-H); 4·08—4·29 dd, 5 H (J = 6 and 13 Hz, 10a-H overlapping with a quartet, CO_2**CH_2**Me and a singlet centred at 4·29, N**CH_2CO_2**Et); 4·33—5·16 ABq, 2 H (J = 17 Hz, 5-H); 7·22 s, (Ar).

2-Carboxymethyl-1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]isoquinoline (*IIi*)

The product *IIh* (2·88 g, 10 mmol) was refluxed for 5 h in a mixture of 15% sulphuric acid (60 ml) and glacial acetic acid (8 ml). The clear solution after cooling was extracted with ether (3 × 50 ml) and dried (Na_2SO_4). Evaporation of the solvent gave an oil which on trituration with ether afforded the acid *IIi* (1·82 g, 70% yield): m.p. 202—204°C. For $C_{13}H_{12}N_2O_4$ (260·2) calculated: 60·0% C, 4·65% H, 10·75% N; found: 60·4% C, 4·75% H, 10·7% N. IR (KCl): 2 750—2 550, 1 765, 1 730, 1 690 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): 2·65—3·31 dq, 2 H (10-H); 3·88 s, 2 H (N**CH_2CO_2**H); 4·20—4·98 dd, 3 H (J = 6 and 13 Hz, 10a-H overlapping with an ABq, J = = 17 Hz, 5-H); 7·26 s, 4 H (Ar).

2-Hydroxymethyl-1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]-isoquinoline (*IIj*)

A mixture of *Ia* (2·02 g, 10 mmol), 125 ml water and formaldehyde solution (37—41%, 1·8 ml, 22 mol) was refluxed for 10 min. The precipitate which formed on standing was collected by filtration, washed with 1% formaldehyde solution and dried to give the product *IIj* (1·13 g, 49% yield): m.p. 134—136°C. For $C_{12}H_{12}N_2O_3$ (232·2) calculated: 62·05% C, 5·21% H, 12·05% N; found: 62·35% C, 5·2% H, 12·2% N. IR (KCl): 3 400, 1 760, 1 705 cm^{-1}. ^1H NMR ($CDCl_3$): 2·69—3·35 dq, 2 H (10-H); 4·09 dd, 1 H (J = 6 and 13 Hz, 10a-H); 4·28—5·10 ABq, 2 H (J = 17 Hz, 5-H); 5·16 s, 2 H (N**CH_2**OH); 7·19 s, 4 H (Ar).

N,N-Bis[2-(1,3-dioxo-5*H*-10,10a-dihydroimidazo[1,5-*b*]isoquinolinolyl)methyl]piperazine (*III*)

Formaldehyde solution (37—41%, 1·8 ml, 22 mmol), piperazine (0·86 g, 10 mmol) and *Ia* (4·02 g, 20 mmol) were treated as described in the general method to give the product *III* (4·9 g, 95% yield): m.p. 262—264°C (from DMF). For $C_{28}H_{30}N_6O_4$ (514·6) calculated: 65·35% C, 5·9% H, 16·35% N; found: 65·5% C, 5·95% H, 16·75% N. IR (KCl): 1 760, 1 710 cm^{-1}. ^1H NMR (TFA): 2·80—3·42 m, 4 H (10-H); 3·81—4·17 m, 8 H (methylene protons of piperazine); 4·28—5·22 m, 10 H (10a-H, 5-H, and N**CH_2**N); 7·20 s, 8 H (Ar). MS, m/z: 514·2263 (M^+).

2-Piperidinomethyl-5-ethoxy-10-bromo-1,3-dioxo-5*H*-imidazo[1,5-*b*]isoquinoline (*IVb*)

Piperidine (0·51 g, 6 mmol), *IVa* (ref.[6]) (1·62 g, 5 mmol) and formaldehyde solution (37—41%, 0·5 ml, 6 mmol) were treated as described previously to give the product *IVb* (1·59 g, 75% yield): m.p. 139—140·5°C (from EtOH). For $C_{19}H_{22}BrN_3O_3$ (420·3) calculated: 54·3% C, 5·3% H, 19·0% Br, 10·0% N; found: 54·7% C, 5·3% H, 19·2% Br, 10·15% N. IR (KCl): 1 770, 1 715 and 1 635 cm^{-1}. ^1H NMR ($CDCl_3$): 1·13 t, 3 H (OCH_2Me); 1·37—1·64 m, 6 H (3′,4′ and 5′ methylene protons of piperidine); 2·61 t, 4 H (2′ and 6′ methylene protons of piperidine); 3·69 q, 2 H (**OCH_2**Me); 4·61 s, 2 H (N**CH_2**N); 6·47 s, 1 H (5-H); 7·40—7·59 m, 3 H (Ar); 7·88—7·99 m, 1 H (9-H). MS, m/z: 421·0858 and 419·0831 (1 : 1) (M^+).

2-Aminoethyl Isoquinoline Hydantoins (*Va*, *Vb*)

To a solution of sodium (0·46 g, 20 mmol) in 35 ml of absolute ethanol, *Ia* (2·02 g, 10 mmol) and 2-dimethylaminoethyl chloride hydrochloride (1·44 g, 10 mmol) were added. The reaction mixture

was stirred under reflux for 24 h, filtered while hot and the precipitate which formed on standing was collected by filtration to give the product *Va* (1·39 g, 51% yield): m.p. 65—67°C (from ether). For $C_{15}H_{19}N_3O_2$ (273·3) calculated: 65·9% C, 7·0% H, 15·35% N; found: 65·7% C, 7·1% H, 15·0% N. IR (KCl): 1 765, 1 705 cm^{-1}. ^1H NMR ($CDCl_3$): 2·25 s, 6 H (NMe_2); 2·53 t, 2 H ($NCH_2CH_2NMe_2$); 2·65—3·37 dq, 2 H (10-H); 3·65 t, 2 H ($NCH_2CH_2NMe_2$); 4·06 dd, 1 H (J = 6 and 13 Hz, 10a-H); 4·28—5·10 ABq, 2 H (J = 17 Hz, 5-H); 7·20 s, 4 H, (Ar).

In a similar way treatment of *Ia* (2·02 g, 10 mmol) with 2-diethylaminoethyl chloride hydrochloride (1·72 g, 10 mmol) gave the product *Vb* (1·61 g, 53% yield): m.p. 71—72°C (from ether). For $C_{17}H_{23}N_3O_2$ (301·4) calculated: 67·75% C, 7·7% H, 13·95% N; found: 67·6% C, 7·8% H, 13·8% N. IR (KCl): 1 765, 1 705 cm^{-1}. ^1H NMR ($CDCl_3$): 0·98 t, 6 H ($N(CH_2Me)_2$); 2·41—3·36 two triplets, 8 H ($NCH_2CH_2NEt_2$ and $N(CH_2Me)_2$ overlapping with a multiplet, 10-H); 3·61 t, 2 H ($NCH_2CH_2NE_2$); 4·04 dd, 1 H (J = 6 and 13 Hz, 10a-H); 4·29—5·09 ABq, 2 H (J = 17 Hz, 5-H); 7·19 s, 4 H (Ar).

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