ANALOGUES OF 9-AMINO-1,2,3,4-TETRAHYDROACRIDINE

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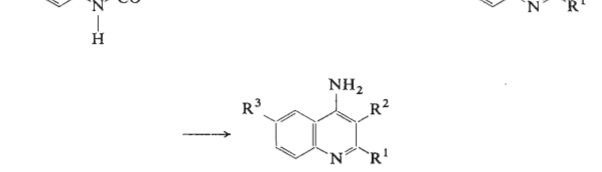
The title compounds have been prepared by Hofmann degradation of amides resulting from condensation of the corresponding derivatives of isatin, ketone and ammonia. Further derivatives substituted at the amino group were obtained from 9-chloro-1,2,3,4-tetrahydroacridine. The ultraviolet and fluorescence spectra of 11 compounds thus synthesized are reported in relation to the protonation of the molecule and the ionization constants for the first protonation have been determined.

9-Amino-1,2,3,4-tetrahydroacridine (*I*, tacrine) is known to be an efficient antidote counteracting the poisoning by cholinergic psychomimetics. Due to this ability and also to remarkable pharmacologic properties (the antagonist of morphine, an analeptic, an inhibitor of cholinesterase) tacrine and the structurally related compounds have been intensively investigated. Tacrine was prepared by various processes from 9-chloro-1,2,3,4-tetrahydroacridine[1,2], 1,2,3,4-tetrahydroacridine-9-carboxamide[3], anthranylamide or 2-aminobenzonitrile[4] and 9-nitro-1,2,3,4-tetrahydroacridine N-oxide[5]. This paper deals with alternative preparation of those compounds and some their physico-chemical properties.

A survey of final products is given in Table I. Substances *I* – *VII* were synthesized according to Scheme (*A*) by Hofmann degradation of the corresponding amides easily accesible by condensation of the respective derivatives of isatins, ketones and



(*A*)

ammonia[12]. (The amides thus synthesized are surveyed in Table II). This method is advantageous for the preparation of tacrine in particular, since it starts from available chemicals (isatin and cyclohexanone), has only two steps and offers a virtually pure product. The degradation of 1,2,3,4-tetrahydroacridine-9-carboxamide through uretane, as described by Ettel and Neumann[3], did not perfectly proceed due to a high stability of urethane towards acid hydrolysis.

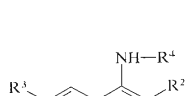
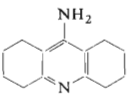


TABLE I
Compounds of General Formula

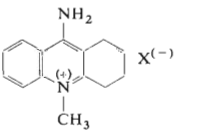
Compound	R^1	R^2	R^3	R^4	M.p., °C	Yield %	Hydrochloride m.p., °C	IR (in $CHCl_3$) cm^{-1}
I	$-(CH_2)_4-$		H	H	181–183[a]	65	284–287[b]	1 625; 3 430; 3 520
II	$-(CH_2)_4-$		CH_3	H	231–233[c]	81	270–277[d]	1 630; 3 430; 3 520
III	$-(CH_2)_4-$		CH_3O	H	210–214[e]	75	263–268[f]	1 635; 3 440; 3 535
IV	$-(CH_2)_4-$		Br	H	251–255[g]	72	295–303[h]	1 630; 3 430; 3 520
V	C_2H_5	CH_3	H	H	144–146[i]	81	287–291[j]	1 630; 3 430; 3 520
VI	C_6H_5	H	H	H	162–166[k]	60	272–277[l]	1 630; 3 430; 3 530
VII	4-Py[m]	H	H	H	223–230[n]	89	250–260[o]	1 630; 3 425; 3 520
VIII	$-(CH_2)_4$		H	C_2H_5	—	55	206–212[p]	1 620; 3 440
IX	$-(CH_2)_4-$		H	NH_2	—	78	260–261[q]	1 620; 3 400
X[r]	—	—	—	—	220–224[s]	57	245–248[t]	1 630; 3 430; 3 525
XIa[u]	—	—	—	—	241–244[v]	65	—	—
XIb[w]	—	—	—	—	306–310[x]	87	—	1 665; 3 190; 3 360[y]

[a] Ref.[1] 179–180°C; [b] monohydrate, ref.[6] 283–284°C; [c] ref.[7] 222–224°C; [d] monohydrate; calculated: 13·28% Cl; found: 13·56% Cl; calculated: 6·75% H_2O found: 6·60% H_2O; lactate m.p. 211–214°C; calculated: 67·53% C, 7·33% H, 9·26% N; found: 67·33% C, 7·18% H, 9·12% N; [e] ref.[7] 212–213°C; [f] monohydrate; calculated: 12·54% Cl; found: 12·32% Cl; calculated: 6·37% H_2O; found: 6·59% H_2O; sulphate 289–303°C; lactate 196–201°C; calculated: 8·80% N; found: 8·59% N; [g] calculated: 10·11% N; found: 9·98% N; [h] calculated: 11·30% Cl; found: 11·19% Cl; [i] calculated: 15·04% N; found: 14·90% N; [j] calculated: 15·92% Cl; found: 16·00% Cl; [k] ref.[8] 165°C, ref.[9] 168°C; [l] dihydrate, ref.[9] 272°C; [m] 4-pyridyl; [n] calculated: 18·99% N; found: 18·73% N; [o] monohydrate; calculated: 12·86% Cl; found: 13·05% Cl; calculated: 6·53% H_2O; found: 6·46% H_2O; dihydrochloride monohydrate 255–265°C; calculated: 22·71% Cl; found: 22·90% Cl; calculated: 5·77% H_2O; found: 5·50% H_2O; [p] calculated: 10·66% N; found: 10·48% N; calculated: 13·49% Cl; found: 13·45% Cl; [q] calculated: 62·52% C, 5·46% H, 16·82% N, 14·20% Cl; found: 62·79% C, 6·69% H, 17·14% N, 14·24% Cl; [r] 9-amino-1,2,3,4,5,6,7,8-octahydroacridine; [s] ref.[10] 218–219°C; [t] ref.[10] 239·5–240·5°C; [u] 9-amino-10-methyl-1,2,3,4-tetrahydroacridinium *p*-toluenesulphonate; [v] ref.[11] 245–247°C; [w] 9-amino-10-methyl-1,2,3,4-tetrahydroacridinium chloride; [x] calculated: 11·26% N; found: 11·21% N; calculated: 14·25% Cl; found: 14·17% Cl; [y] in KBr.

Compounds *VIII* and *X* were obtained according to procedures already reported[10,14]. The derivative of hydrazine was synthesized from 9-chloro-1,2,3,4-tetrahydroacridine analogously as with substance *VIII* replacing ethylamine by hydrazine. The relatively little soluble hydrochloride (18·5 g/l at 25°C) precipitated from the aqueous solution of the base with hydrochloric acid. The quaternization of substance *I* with methyl iodide in acetone solution did not lead to an individual product and therefore, the quaternary compound was obtained *via* methyl *p*-toluenesulphonate and subsequent anion exchange over Amberlite IRA 402.



X



XIa, X = $CH_3C_6H_4SO_3$
XIb, X = Cl

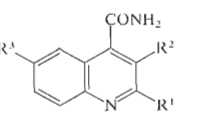
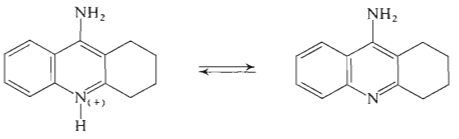


TABLE II
Amides of General Formula

Compound	R^1	R^2	R^3	M.p., °C	Yield %	Calc./Found % N	UV (EtOH) λ_{max}, nm/(ε)	IR (in KBr) cm^{-1}
XII	$-(CH_2)_4-$		H	260–264[a]	85	—	323 (6 300)	1 652; 3 160; 3 410
XIII	$-(CH_2)_4-$		CH_3	253–257	84	11·66 11·74	328 (6 300)	1 665; 3 080; 3 340
XIV	$-(CH_2)_4-$		CH_3O	247–250	70	10·93 10·85	340 (6 300)	1 675; 3 100; 3 330
XV	$-(CH_2)_4-$		Br	267–268	78	9·18 8·95	329 (6 600)	1 662; 3 180; 3 320
XVI	C_2H_5	CH_3	H	204–206	84	13·07 12·80	320 (4 800)	1 680; 3 180; 3 390
XVII	C_6H_5	H	H	199–200[b]	36	—	326 (7 600)	1 660; 3 200; 3 390
XVIII	4-Py[c]	H	H	262–264	41	16·86 16·59	320 (8 300)	1 696; 3 150; 3 290

[a] Ref.[12] 265°C; [b] ref.[13] 199°C; [c] 4-pyridyl.

Hydrochlorides of 7-substituted derivatives of tacrine showed a substantially lower solubility in water than the parent bases: *I* 292, *II* 5·3, *III* 3·05, *IV* 3·95 g/l at 25°C. On the other hand their salts with organic acids (lactic, acetic) are well soluble.



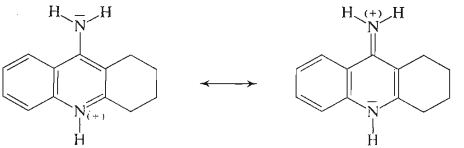
(*B*)

TABLE III

The pK'_a Values of the First Protonation and UV Maxima (λ_{max}, nm) of Compounds *I*—*XIb*

Compound	pK'_a	Base[a] $\lambda_{max}(\varepsilon)$	Monocation[b] $\lambda_{max}(\varepsilon)$	Dication[c] $\lambda_{max}(\varepsilon)$
I	9·85[d]	312 (6 900) 317 (6 900)	323 (10 700) 335 (9 800)	330 (11 500)
II	9·86[e]	313 (7 350)	328 (10 100) 339 (8 750)	336 (11 500)
III	9·58	305 (6 300) 335 (4 700)	335 (8 300) 346 (7 800)	328 (6 800) 356 (6 350)
IV	9·26	320 (5 900)	332 (9 250) 344 (8 100)	336 (10 650)
V	9·59	310 (7 100)	323 (12 150) 334 (11 050)	328 (10 450)
VI	8·38	314 (9 500)	327 (14 250)	360 (21 500)
VII[f]	7·43	316 (6 800) 330 (6 200)	338 (9 250)	335 (9 400)[g]
VIII	9·50	309 (7 050) 321 (7 400)	336 (14 100) 348 (14 000)	332 (11 700)
IX	9·50	322 (5 000)	335—347 (12 100)	323 (10 650)
X	10·76[h]	247 (7 400)	268 (15 500)	290 (10 800)
XIb	—		332 (11 600) 344 (11 000)	334 (10 400)

[a] In 0·05M-NaOH; [b] at pH 5·5; [c] in 87% H_2SO_4; [d] ref.[15] 9·85; [e] ref.[15] 9·92; [f] pK'_{a2} 3·20; dication in 0·5M-HCl 318 (6 050), 353 (6 800); [g] trication; [h] ref.[15] 11·0.



(C)

TABLE IV

Wave Lengths of the Activation and Emission Maxima of the Fluorescence Spectra *I*—*XIb* (in nm), $c = 0{\cdot}5-2$ mg/l.

Compound	Base[a]		Monocation[b]		Dication[c]	
	λ_{act}	λ_{em}	λ_{act}	λ_{em}	λ_{act}	λ_{em}
I	243 317	380	243 324	358	245 331	412
II	245 316	380	247 329	365	250 337	417
III	248 309	384	249 343	389	257 357	440
IV		—[d]	254 324 346	366		—[d]
V	*244* 315	380	244 330	356	245 328	408
VI	268 320	390	266 330	380	260 286 361	410
VII[e]	274 330	440[d]	262 342	405	259 360	441[f]
VIII		—[d]		—[d]	246 334	412
IX	246 322	390	239 328	375	248 336	416
X		—[d]		—[d]	298	348
XIb		—	248 344	373	246 366	408

[a] In 0·05M-NaOH; [b] in water; [c] in 87% H_2SO_4; [d] very weak or no fluorescence; [e] dication in 0·5M-HCl λ_{act} 278, 322, 358 — λ_{em} 494 nm; [f] trication.

The UV spectra and ionization constants for the first protonation (*B*) of substances surveyed in Table I are listed in Table III. The existence of a resonance (*C*), described particularly with the monocation of 4-aminopyridine and analogous derivatives of quinoline and acridine, notably influences also the properties of tacrine and its analogues. The great stability of the monocation is evidenced by the fact that its second protonation occurs only in concentrated sulphuric acid, whereas the base is freed in a considerably alkaline medium. A specially high pK_a value is encountered with substance *X*; lower values were found with compounds *VI* and *VII*. The correlation between σ_m and pK_a of the first protonation (*1*) was calculated for 7-substituted 9-amino-1,2,3,4-tetrahydroacridines.

$$pK_a = -1{\cdot}38\sigma_m + 9{\cdot}79 \qquad (1)$$

The similarity of tacrine with a strong fluorescing 9-aminoacridine stimulated the recording of fluorescence spectra (Table IV). The group of substituents under study consists of relatively strong fluorescing substances changing their fluorescence properties in relation to the protonation of the molecule. Their activation spectrum revealed two maxima above 200 nm corresponding to the absorption maxima in the UV spectrum. One main emission maximum, belonging to all maxima of the activation spectrum, is in some cases accompanied with fluorescence within 700–800 nm, which has not been studied in detail. The most fluorescent substance is *X* as a base, *III* as a monocation, *VI* as a dication and *VII* as a trication. Compound *VII* as dication displays a remarkable bathochromic shift of the emission maximum when compared with the mono- or trication. The hydrochloride of *X* phosphoresces after irradiation with UV-light.

EXPERIMENTAL

The melting points are uncorrected. The water content was determined with Fischer reagent. Measurements were done with following apparatuses: Unicam SP 200 (UV spectra), Carl Zeiss VSU 1 and pH-meter Radiometer model 26 (spectrophotometric determination of pK_a), Unicam SP 1000 (IR spectra) and spectrofluorimeter Aminco-Bowman equipped with a photomultiplier 1P21 (fluorescence spectra). The pK_a values are corrected for alkaline error of sodium ions of the glass electrode 202 C. The fluorescence data are uncorrected.

9-Amino-7-bromo-1,2,3,4-tetrahydroacridine (*IV*)

Amide *XV* (18 g) was dissolved under stirring in a solution obtained from bromine (3 ml) and 5% potassium hydroxide (100 ml) at 5–10°C. The unreacted amine (2·5 g) was filtered off after 2 h, the filtrate heated at 50°C, the precipitated substance removed by filtration and the filtrate heated at 60–70°C for 2 h. The precipitate was crystallized from 2-propanol. Yield 10·2 g.

9-Hydrazino-1,2,3,4-tetrahydroacridinium Chloride (*IX*.HCl)

9-Chloro-1,2,3,4-tetrahydroacridine[16] (10·9 g), phenol (60 ml) and 85% hydrazine hydrate were refluxed for 8 h and after addition of the same amount of hydrazine hydrate for additional 5 h. The mixture was diluted with water (50 ml), phenol steam-distilled and the residue neutralized with hydrochloric acid to afford a crude product, which was crystallized from ethanol–water. Yield 9·8 g.

9-Amino-10-methyl-1,2,3,4-tetrahydroacridinium *p*-Toluenesulphonate (*XIa*)

Methyl *p*-toluenesulphonate (6·6 g) in methanol (5 ml) was added to a solution of *I* (7·1 g) in acetone (30 ml) and methanol (5 ml). The product, separated after a 7-day standing, was crystallized from ethanol. Yield 9·0 g.

9-Amino-10-methyl-1,2,3,4-tetrahydroacridinium Chloride (*XIb*)

A solution of *XIa* (7·4 g) in water (600 ml) was passed through a column of Amberlite IRA 402 (100 ml) in Cl^- form and evaporated. The residue was crystallized from ethanol. Yield 4·2 g.

7-Methyl-1,2,3,4-tetrahydroacridine-9-carboximide (*XIII*)

5-Methylisatin (24·3 g), cyclohexanone (45 ml) and conc. aqueous ammonia (135 ml) were heated in an autoclave at 150°C for 2 h. The crude product was filtered after being cooled, washed with acetone–water 1 : 1 and crystallized from ethanol. Yield 30·4 g.

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