Synthesis of Some Amino-4,5-dihydropyrazolo[3,4-a]acridines as Potential Cholinesterase Inhibitors

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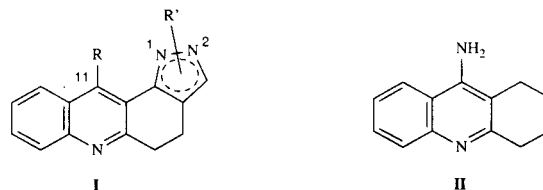Hoechst-Roussel Pharmaceuticals Inc.,
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A synthesis of the 4,5-dihydro derivatives of the previously known pyrazolo[3,4-a]acridine ring system is described. The reaction of a 3,4-dihydroacridin-1(2H)-one with N,N-dimethylformamide dimethyl acetal gave a reactive enamino ketone, which yielded the desired heterocycle upon reaction with hydrazine. Using this chemistry, 11-amino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine (3) and a number of its 2-substituted derivatives 4a-k were synthesized and evaluated as acetylcholinesterase inhibitors, based on their relationship to 1,2,3,4-tetrahydro-9-acridinamine (THA). 1-Amino-4,5-dihydro-1H-pyrazolo[3,4-a]acridine (11a) and 2-amino-4,5-dihydro-1H-pyrazolo[3,4-a]acridine (11b) were also synthesized and investigated as potential cholinesterase inhibitors.
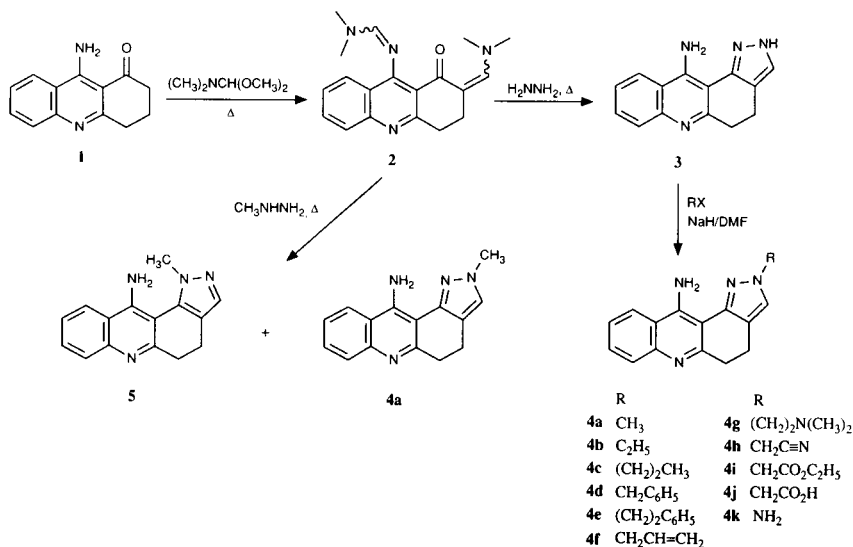
As part of our continuing interest in 1,2,3,4-tetrahydro-9-acridinamines as reversible, centrally acting cholinesterase inhibitors [1], we have synthesized a number of 4,5-dihydropyrazolo[3,4-a]acridines **I** and have tested them as acetylcholinesterase inhibitors [2]. It has been suggested that the 9-amino group of 1,2,3,4-tetrahydro-9-acridinamine (THA, **II**) forms a hydrogen bond near the catalytic site of the cholinesterase enzyme, a fact which may account for the unusually high activity of **II** [3]. Thus, while we viewed the 11-amino-3,4-dihydropyrazolo[3,4-a]acridines (**I**, R = NH₂) as direct analogs of **II**, we were particularly interested in 1-amino derivatives of **I** (R = H, R' = 1-NH₂), in which the amino group would occupy approximately the same spatial orientation as in **II**.

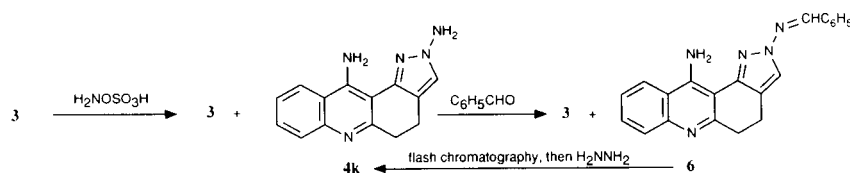The synthesis of these compounds is described in Schemes 1-3. It has been shown that N,N-dimethylforma-

mide dimethyl acetal reacts with activated methylene groups to give enamines [4]. Thus, 3,4-dihydroacridin-1(2H)-one (**1**, Scheme 1) reacted with N,N-dimethylformamide dimethyl acetal to give the enamino ketone **2**, in which the 9-amino group was simultaneously protected as the amidine. This somewhat unstable compound was reacted with hydrazine to give 11-amino-4,5-dihydro-1H-pyrazolo[3,4-a]acridine (**3**) in good yield.

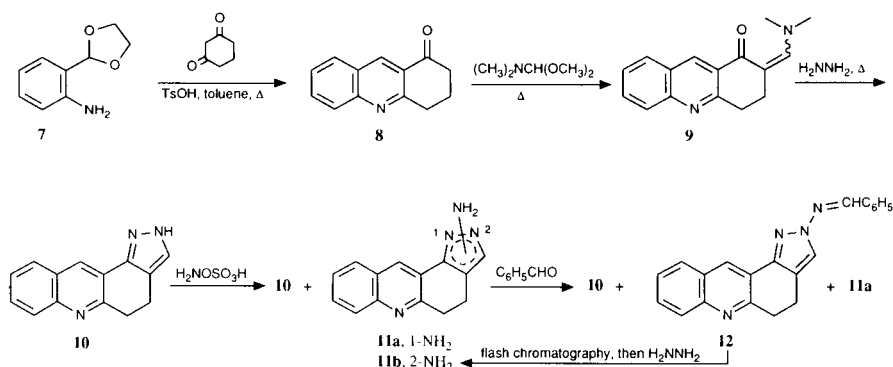## Scheme 1

	R		R
4a	CH₃	4g	(CH₂)₂N(CH₃)₂
4b	C₂H₅	4h	CH₂C≡N
4c	(CH₂)₂CH₃	4i	CH₂CO₂C₂H₅
4d	CH₂C₆H₅	4j	CH₂CO₂H
4e	(CH₂)₂C₆H₅	4k	NH₂
4f	CH₂CH=CH₂		

Scheme 2

Scheme 3

The position of the double bonds in the pyrazole portion of **3** was determined by ^{13}C nmr. The 1- and 2-methyl-4,5,6,7-tetrahydroindazoles have been studied by ^{13}C nmr [5] and this study showed that the ^{13}C chemical shifts of the carbons in positions 3 and 7a were highly indicative of each respective substitution pattern and, thus, could be used to determine the position of the double bonds. In the 1-methyl derivative (N-2/C-3 double bond) the shifts of these two carbons were closely spaced around 137 ppm. In the 2-methyl derivative (N-2/C-3 single bond), however, the shifts of these carbons were widely spaced: C-3 was at 127 ppm and C-7a was at 148 ppm. It was on this basis that the unsubstituted derivative was assigned as the 1-H tautomer (see Table I). The same relationships held among the present pyrazolo[3,4-*a*]acridines: the two isomeric methyl derivatives, **4a** and **5**, obtained from the reaction of **3** with methylhydrazine (Scheme 1), gave ^{13}C shifts for C-3 and C-11b (corresponding to C-3 and C-7a of the tetrahydroindazoles) of 128.5 and 146.8 ppm, respectively, for isomer **4a**, while the corresponding shifts for isomer **5** were 135.4 and 138.7 ppm, respectively. On this basis, **4a** was assigned as the 2-methyl isomer (N-2/C-3 single bond) and **5** was assigned as the 1-methyl isomer (N-2/C-3 double bond). It was also on this basis that **3** was assigned as the 2-H tautomer (see Table I; C-3: 128.8 ppm; C-11b: 145.6 ppm; N-2/C-3 single bond).

A number of substituted derivatives of **3** were synthesized by alkylation of the parent heterocycle with sodium hydride and the appropriate alkyl halide. When methyl iodide was used, a single product was obtained that was identical in every respect to **4a**. Thus, all the other

substituted derivatives **4b-4i** (Table II) were assigned as the 2-substituted isomers. The acetic acid derivative, **4j**, was obtained by the aqueous basic hydrolysis of the ester, **4i**, and the 2-amino analog, **4k**, was obtained by the amination of **3** with hydroxylamine-*O*-sulfonic acid (Scheme 2), conditions that have been employed in the literature for the amination of pyrazoles [6] (see Experimental). These conditions gave the desired **4k** in the presence of unreacted **3**, which could not be separated from **4k** by chromatography. Rather, the purification of **4k** was ac-

Table I

Characteristic ^{13}C NMR Chemical Shifts for Some
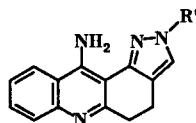3,4-Dihydro-1*H*- and 2*H*-pyrazolo[3,4-*a*]acridines

Compound	R	R'	C-3	C-11b	Compound	R	R'	C-3	C-11b
5	NH₂	CH₃	135.4	138.7	**3**	NH₂	H	128.8	145.6 [a]
11a	H	NH₂	132.1	132.6	**4a**	NH₂	CH₃	128.5	146.8
					4k	NH₂	NH₂	129.8	144.4
					11b	H	NH₂	128.7	142.0
					10	H	H	129.5	146.4

R	C-3	C-7a
CH₃	136.2	138.1 [b]
H	131.7	143.2 [b]

C-3	C-7a
127.0	148.4 [b]

[a] These values were determined on the free base. [b] J. de Mendoza, P. Prados, and J. Elguero, *Heterocycles*, **23**, 2629 (1985).

Table II

4,5-Dihydro-2H-pyrazolo[3,4-a]acridines

Compound	R	Mp°C [a]	Yield [b] %	Molecular Formula	Analysis % Calcd./Found		
					C	H	N
4b	C_2H_5	240-242	67 [c]	$C_{16}H_{16}N_4$	72.70	6.10	21.20
					72.28	5.98	20.97
4c	$(CH_2)_2CH_3$	225-226	64 [c]	$C_{17}H_{18}N_4$	73.35	6.52	20.13
					73.09	6.52	19.96
4d	$CH_2C_6H_5$	206-207	72 [c]	$C_{21}H_{18}N_4$	77.27	5.56	17.17
					77.01	5.58	17.22
4e	$(CH_2)_2C_6H_5$	238-239	32 [c]	$C_{22}H_{20}N_4$	77.62	5.92	16.46
					77.51	5.95	16.51
4f	$CH_2CH=CH_2$	226-227	79 [c]	$C_{17}H_{16}N_4$	73.89	5.84	20.27
					73.66	5.77	20.19
4g	$(CH_2)_2N(CH_3)_2$	177-178	43 [c]	$C_{18}H_{21}N_5$	70.33	6.89	22.78
					70.31	6.86	22.92
4h	$CH_2C\equiv N$	250 dec	17 [d]	$C_{16}H_{13}N_5$	69.80	4.76	25.44
					69.76	4.74	25.31
4i	$CH_2CO_2C_2H_5$	250 dec	92 [e]	$C_{18}H_{18}N_4O_2$	67.07	5.63	17.38
					67.21	5.54	17.35

[a] Melting points are uncorrected. [b] Yields were not optimized. [c] Recrystallized from ethyl acetate. [d] Recrystallized from methanol. [e] Recrystallized from ethanol.

complished through its benzylidene derivative 6, which was synthesized by reacting 4k with benzaldehyde at room temperature and separated from unreacted 3 by chromatography. Treatment of the pure 6 obtained in this way with hydrazine gave pure 4k (see Table I for the ^{13}C nmr verification of the position of amination).

As stated above, we were interested in a derivative with an amino group in the 1-position of the new heterocycle, because of hypotheses about the role of the 9-amino group of II in binding to acetylcholinesterase. In order to obtain the required acridinone starting material, the ethylene ketal of o-aminobenzaldehyde (7) and cyclohexane-1,3-dione were reacted in the presence of p-toluenesulfonic acid to yield the ketone 8 (Scheme 3). Treatment of 8 with N,N-dimethylformamide dimethyl acetal as with 1 above gave the enamino ketone 9 which, when treated with hydrazine, gave 4,5-dihydro-2H-pyrazolo[3,4-a]acridine (10, cf. Table I).

Amination of 10 with hydroxylamine-O-sulfonic acid as before gave a mixture of 1-amino derivative 11a, 2-amino derivative 11b, and unreacted 10. As in the purification of 4k above, this mixture was reacted with benzaldehyde, giving 12 as the only benzylidene derivative. Flash chromatography readily purified 12 and 11a, and 11b was ob-

tained by hydrazinolysis of 12 as above. Table I contains the relevant ^{13}C nmr data for 11a and 11b. The structural assignments were also confirmed by ^1H nmr: the proton in the 11-position of the 1-amino derivative, 11a, was shifted dramatically downfield compared to the analogous proton in 11b (9.18 ppm as compared to 8.20 ppm, see Experimental section) due to the influence of the proximal amino group.

All the compounds synthesized in this work were tested in an in vitro cholinesterase assay [7], but they were all relatively weak, with IC_{50}'s greater than $20\mu M$.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 547 and nuclear magnetic resonance spectra were taken on a Varian XL-200. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra data were determined by direct insertion at 70 eV with a Finnigan 4000 GC-MS equipped with a INCOS data system. E. Merck 230-400 mesh silica gel was used for flash chromatography. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY.

3,4-Dihydro-2-[(dimethylamino)methylene]-9-{[(dimethylamino)-methylene]amino}acridin-1(2H)-one (2).

3,4-Dihydroacridin-1(2H)-one hydrochloride (1) [1] (50.0 g, 0.198 mole) was refluxed in 188 ml of N,N-dimethylformamide dimethyl acetal (1.4 moles) for 55 hours and then the volatiles were removed under reduced pressure. The remaining residue was triturated twice with diethyl ether and then the resulting product was filtered off and washed with a little diethyl ether to give 60.28 g (94%) of 2. Attempts to further purify the crude 2 by either recrystallization or chromatography resulted in extensive decomposition; therefore the 2 thus obtained was used without further purification; ^{1}H nmr (DMSO-d$_6$): δ 2.91 (s, 2H, CH$_2$), 3.05 (s, 2H, CH$_2$), 3.09 (s, 6H, N(CH$_3$)$_2$), 3.12 (s, 6H, N(CH$_3$)$_2$), 7.40 (t, 1H, Ar-H), 7.44 (s, 1H, =CH), 7.49 (s, 1H, =CH), 7.63 (t, 1H, Ar-H), 7.73 (d, 1H, H-5), 8.25 (d, 1H, H-8) [8].

11-Amino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine Hydrochloride (3).

Compound 2 (3.0 g, 9.31 mmoles) was refluxed for 30 minutes in 50 ml of ethanol containing 2.0 g of anhydrous hydrazine (62.4 mmoles). At the end of this time the solvent was evaporated under reduced pressure and then the residue was dissolved in methanol and adhered to silica gel. Purification by flash chromatography (methanol:ethyl acetate, 1:19) gave material which was converted to the hydrochloride in aqueous 5% hydrochloride acid. Recrystallization from methanol/diethyl ether gave 1.72 g of 3 (67%), mp 360° dec; ^{1}H nmr (DMSO-d$_6$): δ 2.97 (t, 2H, CH$_2$), 3.41 (t, 2H, CH$_2$), 7.66 (t, 1H, Ar-H), 7.80 (s, 1H, H-3), 7.92 (t, 1H, Ar-H), 8.18 (d, 1H, H-7), 8.63 (d, 1H, H-10), 9.2 (broad s, 1H, exchanges with deuterium oxide, NH$_2$), 9.6 (broad s, 1H, exchanges with deuterium oxide, NH$_2$), 13.30 (s, 1H, pyrazole NH), 14.9 (broad s, 1H, exchanges with deuterium oxide, pyridinium NH); ms: m/z 236 (M$^+$).

Anal. Calcd. for C$_{14}$H$_{12}$N$_4$·HCl·0.25H$_2$O: C, 60.65; H, 4.74; N, 20.21. Found: C, 60.77; H, 4.74; N, 20.24.

11-Amino-4,5-dihydro-2-methyl-2H-pyrazolo[3,4-a]acridine (4a) and 11-Amino-4,5-dihydro-1-methyl-1H-pyrazolo[3,4-a]acridine (5).

Compound 2 (12.0 g, 0.037 mole) was refluxed for 60 minutes in 150 ml of ethanol containing 8.0 g of methylhydrazine (0.174 mole). At the end of this time the solvent was evaporated under reduced pressure and then the residue was dissolved in methanol and adhered to silica gel. Purification by flash chromatography (toluene:methanol:triethylamine, 18:1:1) and evaporation of the respective product-containing fractions gave 4.93 g of 4a (42%) and 1.71 g of 5 (18%). Analytically pure 4a was obtained by recrystallization from methanol, mp 280° dec; ^{1}H nmr (DMSO-d$_6$): δ 2.83 (t, 2H, CH$_2$), 3.05 (t, 2H, CH$_2$), 3.94 (s, 3H, CH$_3$), 7.41 (t, 1H, Ar-H), 7.48 (m, 4H, Ar-H, H-3 and NH$_2$), 7.76 (d, 1H, H-7), 8.22 (d, 1H, H-10); ms: m/z 250 (M$^+$).

Anal. Calcd. for C$_{15}$H$_{14}$N$_4$: C, 71.98; H, 5.63; N, 22.39. Found: C, 71.89; H, 5.75; N, 22.39.

Recrystallization from toluene gave analytically pure 5, mp 240° dec; ^{1}H nmr (DMSO-d$_6$): δ 2.62 (m, 2H, CH$_2$), 2.88 (m, 2H, CH$_2$), 3.91 (s, 3H, CH$_3$), 6.78 (broad s, 2H, exchanges with deuterium oxide, NH$_2$), 7.40 (m, 2H, Ar-H and H-3), 7.60 (t, 1H, Ar-H), 7.76 (d, 1H, H-7), 8.28 (d, 1H, H-10); ms: m/z 250 (M$^+$).

Anal. Calcd. for C$_{15}$H$_{14}$N$_4$: C, 71.98; H, 5.63; N, 22.39. Found: C, 71.95; H, 5.63; N, 22.09.

Synthesis of 4a from 3.

Compound 3 (1.18 g, 5.0 mmoles) was dissolved in 30 ml of N,N-dimethylformamide to which sodium hydride was then added (0.25 g of 60% oil dispersion, 6.25 mmoles) and then the reaction mixture was stirred for 15 minutes. At the end of this time, methyl iodide was added (0.91 g, 6.40 mmoles) and stirring was continued for an additional 15 minutes. The reaction mixture was then poured into water and the product was filtered off and dried. In this manner, 1.08 g (86%) of 4a was isolated, mp 280° dec. It was identical in every respect to the 4a isolated above from the reaction of methylhydrazine with 2. Thin layer chromatography of the isolated product and the residual filtrate detected no 5.

Compounds 4b-i were synthesized in an analogous manner by using the appropriate alkyl halide. The physical properties and analytical data for 4b-i are compiled in Table II.

11-Amino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine-2-acetic Acid Hydrochloride (4j).

Compound 4i (7.78 g, 0.024 mole) was added to a solution of potassium hydroxide (6.73 g, 0.12 mole) in 200 ml of methanol and then the reaction mixture was stirred at room temperature for 1.5 hours and subsequently heated at 60° for 2 hours until a homogeneous solution was obtained. At the end of this time, the solution was cooled and concentrated under reduced pressure. The resulting solid was stirred in 5% aqueous hydrochloric acid for 30 minutes and then the solid which was obtained was filtered off, washed with water, and air dried. Recrystallization from methanol yielded 5.0 g (61%) of 4j, mp 194° dec; ^{1}H nmr (DMSO-d$_6$): δ 2.96 (t, 2H, CH$_2$), 3.37 (t, 2H, CH$_2$), 5.10 (s, 2H, CH$_2$COOH), 7.68 (t, 1H, Ar-H), 7.75 (s, 1H, H-3), 7.89 (t, 1H, Ar-H), 8.11 (d, 1H, H-7), 8.63 (d, 1H, H-10), 9.0 (broad s, 1H, exchanges with deuterium oxide, NH$_2$), 9.4 (broad s, 1H, exchanges with deuterium oxide, NH$_2$), 14.0 (broad s, 2H, exchanges with deuterium oxide, COOH and HCl); cims: m/z 295 (MH$^+$).

Anal. Calcd. for C$_{16}$H$_{14}$N$_4$O$_2$·HCl·0.5H$_2$O: C, 56.55; H, 4.75; N, 16.50. Found: C, 56.66; H, 4.85; N, 16.43.

2,11-Diamino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine (4k).

Ethanol (1550 ml) was added to a suspension of 3 (40.0 g, 0.169 mole) in a solution of sodium hydroxide (37.1 g, 0.928 mole) in water (560 ml) at 50°. The resulting solution was maintained at 55° as solid hydroxylamine-O-sulfonic acid (51.6 g, 0.456 mole) was added in portions over 15 minutes. The reaction was stirred for 30 minutes without heat and then the resulting solid was filtered off, washed with water, and boiled in methanol (1500 ml) and filtered hot to remove inorganics. Concentration and trituration of the resulting residue with diethyl ether yielded 5.79 g of 4k containing approximately 20% of 3 (analyzed by ^{1}H nmr) which was inseparable by chromatography.

This mixture was stirred in excess benzaldehyde (170 g, 1.6 moles) at room temperature for three hours and then the reaction mixture was diluted with pentane (700 ml) and stirred mechanically for an additional three hours. The resulting solid was filtered off and triturated with pentane to yield 11.5 g of crude 6. This mixture was adhered to silica gel and flash chromatographed two times (ethyl acetate, then triethylamine:toluene, 1:19) to yield 4.3 g of pure 6, which was refluxed overnight in 1-butanol (100 ml) containing hydrazine monohydrate (13.2 g, 0.26 mole). The reaction mixture was cooled to room temperature and diluted with diethyl ether (100 ml), after which the precipitate was filtered off and washed with diethyl ether to yield 2.3 g

(5.4%) of yellow crystalline **4k**, mp 298° dec; ¹H nmr (DMSO-d₆): δ 2.81 (t, 2H, CH₂), 3.02 (t, 2H, CH₂), 6.53 (broad s, 2H, exchanges with deuterium oxide, NH₂), 7.40 (t, 1H, Ar–H), 7.42 (s, 1H, H-3), 7.50 (broad s, 2H, exchanges with deuterium oxide, NH₂), 7.53 (t, 1H, Ar–H), 7.73 (d, 1H, H-7), 8.22 (d, 1H, H-10); ms: m/z 251 (M⁺).

Anal. Calcd. for C₁₄H₁₃N₅: C, 66.92; H, 5.21; N, 27.87. Found: C, 66.70; H, 5.18; N, 27.79.

3,4-Dihydroacridin-1(2H)-one (8).

2-Aminobenzaldehyde ethylene ketal [9] (7, 30.3 g, 0.184 mole), cyclohexane-1,3-dione (20.6 g, 0.184 mole), and *p*-toluenesulfonic acid (3.0 g, 0.018 mole) were refluxed for 2 hours in 900 ml of toluene with the separation of water in a Dean-Stark trap. At the end of this time, the reaction mixture was evaporated and the residue distributed between ethyl acetate (700 ml) and saturated aqueous potassium carbonate (500 ml). The organic phase was washed with brine solution, dried, concentrated, and purified by flash chromatography (30-50% ethyl acetate/hexane). The product-containing fractions were concentrated and the product obtained in this manner was triturated with diethyl ether and then diethyl ether/pentane to yield 20.7 g of **8** (57%) as a pale yellow solid, mp 107-109°; ¹H nmr (DMSO-d₆): δ 2.19 (m, 2H, 3-CH₂), 2.78 (t, 2H, 2-CH₂), 3.21 (t, 2H, 4-CH₂), 7.60 (t, 1H, Ar–H), 7.87 (t, 1H, Ar–H), 8.00 (d, 1H, Ar–H), 8.18 (d, 1H, Ar–H), 8.87 (s, 1H, H-9) [8]; ms: m/z 197 (M⁺).

Anal. Calcd. for C₁₃H₁₁NO: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.75; H, 5.67; N, 7.04.

2-(Dimethylaminomethylene)-3,4-dihydroacridin-1(2H)-one (9).

Ketone **8** (19.43 g, 0.099 mole) was refluxed in *N,N*-dimethylformamide dimethyl acetal (50 ml) and triethylamine (10.1 g, 0.10 mole) for 10 hours. The reaction was concentrated, triturated first with diethyl ether/pentane and then diethyl ether to yield 22.43 g (90%) of **9**. Attempts to further purify the crude **9** by either recrystallization or chromatography resulted in extensive decomposition; therefore the **9** thus obtained was used without further purification; ¹H nmr (DMSO-d₆): δ 3.08 (m, 4H, (CH₂)₂), 3.20 (s, 6H, N(CH₃)₂), 7.78 (t, 1H, Ar–H), 7.76 (s, 1H, =CH), 7.80 (t, 1H, Ar–H), 7.98 (d, 1H, Ar–H), 8.12 (d, 1H, Ar–H), 8.77 (s, 1H, H-9) [8]; ms: m/z 252 (M⁺).

4,5-Dihydro-2H-pyrazolo[3,4-a]acridine (10).

Compound **9** (23.50 g, 0.093 mole) was refluxed in hydrazine (12.7 ml, 0.40 mole) and ethanol (370 ml) for 2.5 hours. The reaction was cooled, concentrated, triturated with diethyl ether, and recrystallized from methanol to yield 9.45 g (46%) of **10** as an off white crystalline solid, mp 248-248.5°; ¹H nmr (DSMSO-d₆): δ 2.91 (t, 2H, CH₂), 3.20 (t, 2H, CH₂), 7.5-7.7 (m, 3H, H-3, 8, 9), 7.9-8.1 (m, 2H, H-7, 10), 8.52 (s, 1H, H-11), 13.0 (broad s, 1H, NH); ms: m/z 221 (M⁺).

Anal. Calcd. for C₁₄H₁₁N₃: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.12; H, 4.99; N, 19.02.

1-Amino-4,5-dihydro-1H-pyrazolo[3,4-a]acridine (11a) and 2-Amino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine (11b).

Ethanol (200 ml) was added to a suspension of **10** (12.60 g, 0.057 mole) at 50° in 190 ml of water containing sodium hydroxide (12.52 g, 0.313 moles). The resulting solution was heated to

60° and solid hydroxylamine-*O*-sulfonic acid (17.72 g, 0.152 mole) was added in portions over 15 minutes. The reaction was stirred for 45 minutes without heat, diluted with water (500 ml), stirred for 30 minutes and then filtered. The filter cake was washed with water and air dried to yield 12.28 g of an inseparable mixture of **11a, 11b**, and **10**. This mixture was stirred in benzaldehyde (168 g, 1.6 moles) and triethylamine (10.1 g, 0.10 mole) at room temperature overnight and flash chromatographed (hexane, then increasing percentages of ethyl acetate:hexane up to 3:7) to yield 8.7 g of the benzylidene derivative **12** and 0.22 g of **11a**. The **12** obtained in this way was refluxed in hydrazine (24 ml) and 1-butanol (120 ml) for 6.5 hours, concentrated, adhered to silica gel and flash chromatographed (hexane, then increasing percentages of ethyl acetate:hexane up to 6:4, and then finally triethylamine:hexane:ethyl acetate, 1:39:60) to yield 2.6 g of **11b** after evaporation of the fractions that contained only **11b**. This was recrystallized from methanol to yield 2.3 g (17%) of **11b**, mp 184-185°; ¹H nmr (DMSO-d₆): δ 2.83 (t, 2H, CH₂), 3.21 (t, 2H, CH₂), 6.58 (broad s, 2H, exchanges with deuterium oxide, NH₂), 7.42 (s, 1H, H-3), 7.50 (t, 1H, Ar–H), 7.64 (t, 1H, Ar–H), 7.90 (d, 1H, H-7), 7.98 (d, 1H, H-10), 8.20 (s, 1H, H-11); ms: m/z 236 (M⁺).

Anal. Calcd. for C₁₄H₁₂N₄: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.07; H, 5.12; N, 23.61.

The mixed fractions were concentrated and flash chromatographed (ethyl acetate:hexane, increased from 1:4 to 3:2, then triethylamine:hexane:ethyl acetate, 1:39:60) to yield an additional 0.397 g of **11a**. This was combined with the **11a** isolated above and recrystallized from ethanol (Darco) to yield 0.33 g (2.45%) of **11a**, mp 235° dec; ¹H nmr (DMSO-d₆): δ 2.82 (t, 2H, CH₂), 3.18 (t, 2H, CH₂), 6.67 (broad s, 2H, exchanges with deuterium oxide, NH₂), 7.25 (s, 1H, H-3), 7.54 (t, 1H, Ar–H), 7.70 (t, 1H, Ar–H), 7.91 (d, 1H, H-7), 7.98 (d, 1H, H-10), 9.18 (s, 1H, H-11); ms: m/z 236 (M⁺).

Anal. Calcd. for C₁₄H₁₂N₄: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.89; H, 4.96; N, 23.57.

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[2] To our knowledge, this is the first synthesis of the 4,5-dihydro derivatives of the previously known ring system. The synthesis of some pyrazolo[3,4-a]acridin-9(10H)-ones has been described by G. Boyer, J.-P. Galy, R. Faure, J. Elguero and J. Barbe, *J. Chem. Res. (S)*, 350 (1990).

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[7] Details of the cholinesterase inhibition assay are contained in reference 1.

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