Preparation of Some New N-Substituted 9,10-Dihydroacridine Derivatives

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Some new 9,10-dihydroacridines were prepared owing to the well-known central nervous system activity of the structurally related tricyclic molecules. These compounds were easily obtained from 9(10*H*)-acridinones.

From a biological point of view, acridine derivatives act as intercalating agents (*1*). Due to that, these compounds are known as anticancer drugs, like amsacrine (*2*) or ledakrin (*3*) as well as antimicrobial drugs (*4*, *5*). As intercalation directly proceeds from molecular planarity (*6*), any change in the molecular shape must induce the lack of the properties mentioned above, while some new properties could probably be detected because the folded acridines closely resemble the antipsychotic tricyclic drugs. With reference to this, the 9,10-dihydroacridine series was studied. Some new compounds were prepared from their 9(10*H*)-acridinone homologues by reduction with sodium in pentanol (*7*). The starting 9-oxo derivatives (**2**) were prepared in a very good yield by phase-transfer catalysis under refluxing conditions according to the method of Nishi et al. (*8*). However, compound **2e** was only obtained by using the method of Galy et al. (*9*). In the latter, which was successfully used in similar cases (*10-12*), toluene is used as solvent instead of butanone and the mixture is refluxed 5 days instead of about 2 h. On the other hand, alkylation of the 9,10-dihydroacridine (**4**) by phase-transfer catalysis never succeeded, whatever the previously quoted methods used were.

The synthetic pathways are portrayed in Scheme I.

Results regarding the 9(10*H*)-acridinone compounds are gathered in Table I, while those regarding the 9,10-dihydroacridine derivatives are collected in Table II.

In conclusion, it must be emphasized that, despite the fact that the methods used are very convenient for preparing 9,10-dihydroacridines, the latter are not useful compounds.

Table I. 9(10*H*)-Acridinones 2

compd	R	yield, %	mp, °C	mol formula	^{1}H NMR ($CDCl_3$/Me_4Si_{int})[a] δ, ppm
2a	CH_3	98	201 (9)	$C_{14}H_{11}NO$ (209.25)	8.5 (m, 2 H), 7.65 (m, 2 H), 7.25 (m, 4 H), 3.8 (s, 3 H)
2b	CH_2-CH_2-CH_3	80	130 (9)	$C_{16}H_{15}NO$ (237.30)	8.5 (m, 2 H), 7.55 (m, 2 H), 7.2 (m, 4 H), 4.1 (t, 2 H), 1.8 (m, 2 H), 1.05 (t, 3 H)
2c	CH_2-CH_2-N-$(C_2H_5)_2$	86	111 (9)	$C_{19}H_{22}N_2O$ (294.40)	8.6 (m, 2 H), 7.8 (m, 2 H), 7.6 (m, 2 H), 7.3 (m, 2 H), 4.5 (t, 2 H), 2.9 (t, 2 H), 2.75 (q, 4 H), 1.1 (t, 6 H)
2d	CH_2-CH_2-N-$(CH_3)_2$	84	136 (13)	$C_{17}H_{18}N_2O$ (266.35)	8.35 (d, 2 H), 7.9-7.75 (m, 4 H), 7.35 (m, 2 H), 4.6 (t, 2 H), 2.7 (t, 2 H), 2.3 (s, 6 H)
2e	CH_2-$CH(CH_3)$-CH_2-N-$(CH_3)_2$	90	92	$C_{19}H_{22}N_2O$ (294.40)	8.6 (m, 2 H), 7.7 (m, 4 H), 7.25 (m, 2 H), 4.6 (m, 1 H), 4.3 (m, 1 H), 2.3 (m, 9 H), 0.85 (d, 3 H)
2f	$C_7H_{14}N$	97	160	$C_{20}H_{22}N_2O$ (306.41)	8.5 (m, 2 H), 7.75 (m, 2 H), 7.5 (m, 2 H), 7.25 (m, 2 H), 4.5 (t, 2 H), 2.8 (t, 2 H), 2.55 (m, 4 H), 1.65 (m, 4 H), 1.5 (m, 2 H)
2g	$C_6H_{12}N$	90	138	$C_{19}H_{20}N_2O$ (292.38)	8.5 (m, 2 H), 7.75 (m, 2 H), 7.55 (m, 2 H), 7.3 (m, 2 H), 4.55 (t, 2 H), 2.95 (t, 2 H), 2.7 (m, 4 H), 1.9 (m, 4 H)
2h	$C_6H_{12}NO$	82	202	$C_{19}H_{20}N_2O_2$ (308.38)	8.5 (m, 2 H), 7.65 (m, 2 H), 7.4 (m, 2 H), 7.2 (m, 2 H), 4.45 (t, 2 H), 3.8 (m, 4 H), 2.8 (t, 2 H), 2.6 (m, 4 H)

[a] Recorded with a Bruker AM 200 spectrometer.

Table II. 9,10-Dihydroacridines 3 and 4

compd	R	yield, %	mp, °C	mol formula	^{1}H NMR ($CDCl_3$/Me_4Si_{int})[a] δ, ppm
4	H	72	172 (7)	$C_{13}H_{11}N$ (181.24)	7.1 (m, 4 H), 6.9 (m, 2 H), 6.65 (m, 2 H), 4.1 (s, 2 H)
3a	CH_3	66	96 (14)	$C_{14}H_{13}N$ (195.27)	7.15 (m, 4 H), 6.9 (m, 4 H), 3.85 (s, 2 H), 3.35 (s, 3 H)
3b	CH_2-CH_2-CH_3	74	68	$C_{16}H_{17}N$ (223.50)	7.15 (m, 4 H), 6.9 (m, 4 H), 4.0 (s, 2 H), 3.80 (t, 2 H), 1.85 (m, 2 H), 1.05 (t, 3 H)
3c	CH_2-CH_2-N-$(C_2H_5)_2$	71	52	$C_{19}H_{24}N_2$ (280.41)	7.1 (m, 4 H), 6.9 (m, 4 H), 4.0 (t, 2 H), 3.95 (s, 2 H), 2.8 (t, 2 H), 2.65 (q, 4 H), 1.1 (t, 6 H)
3d	CH_2-CH_2-N-$(CH_3)_2$	67	48 (15)	$C_{17}H_{20}N_2$ (252.36)	7.15 (m, 4 H), 6.95 (m, 4 H), 4.05 (t, 2 H), 3.95 (s, 2 H), 2.70 (t, 2 H), 2.15 (s, 6 H)
3e	CH_2-$CH(CH_3)$-CH_2-N-$(CH_3)_2$		*b*	$C_{19}H_{24}N_2$ (280.41)	7.5 (m, 4 H), 6.9 (m, 4 H), 4.0 (m, 1 H), 3.8 (s, 2 H), 3.65 (m, 1 H), 2.2 (m, 9 H), 0.9 (d, 3 H)
3f	$C_7H_{14}N$	90	68	$C_{20}H_{24}N_2$ (292.43)	7.2 (m, 4 H), 7.0 (m, 4 H), 4.15 (t, 2 H), 4.0 (s, 2 H), 2.75 (t, 2 H), 2.55 (m, 4 H), 1.7 (m, 4 H), 1.5 (m, 2 H)
3g	$C_6H_{12}N$		*b*	$C_{19}H_{22}N_2$ (278.40)	7.1 (m, 4 H), 6.9 (m, 4 H), 4.1 (t, 2 H), 4.0 (s, 2 H), 2.95 (t, 2 H), 2.7 (m, 4 H), 1.9 (m, 4 H)
3h	$C_6H_{12}NO$	86	105	$C_{19}H_{22}N_2O$ (294.40)	7.15 (m, 4 H), 6.9 (m, 4 H), 4.1 (t, 2 H), 3.95 (s, 2 H), 3.75 (m, 4 H), 2.75 (t, 2 H), 2.6 (m, 4 H)

[a] Recorded with a Bruker AM 200 spectrometer. [b] Pasty at room temperature.

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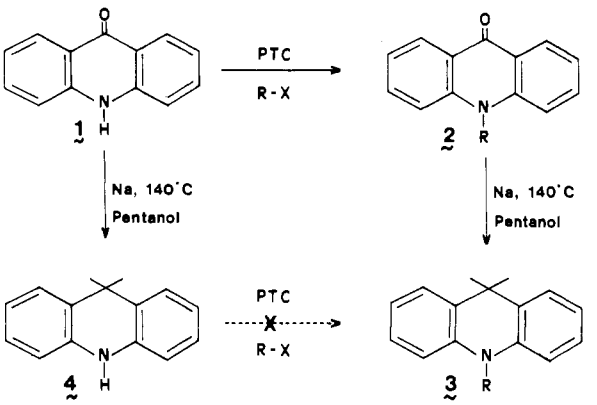
Scheme I



Indeed, they lead back to the 9-oxo homologues within a few weeks even if they are bottled in brown flasks, safe from air. This has been proved by TLC.

Experimental Section

Alkylation of 9(10H)-Acridinones 2: General Procedures. A stirred mixture of 9(10*H*)-acridinones **2** (10 mmol), alkylating agents (15 mmol), triethylbenzylammonium chloride (0.3 mmol), aqueous 50% sodium hydroxide (10 mL), and butanone (20 mL) is refluxed for about 2 h at 80 °C. The reaction mixture is poured into hot water and left overnight at room temperature. The precipitated solid is collected, washed with water, and dried before recrystallization from ethanol or ethanol–water mixture.

Alkylation of 2e. A stirred mixture of 9(10*H*)-acridinones **2** (15 mmol), alkylating agents (37.5 mmol), triethylbenzylammonium chloride (7.5 mmol), aqueous 50% potassium hydroxide (75 mL), and toluene (150 mL) is refluxed for 5 days. The toluene layer is separated, washed three times with water (50 mL each time), dried with sodium sulfate, and evaporated in vacuo. The residual oil is recrystallized from light petroleum and provides a microcrystalline yellow powder.

Preparation of 9,10-Dihydroacridines 3: General Procedure. 9(10*H*)-Acridinone (10 mmol) is refluxed with pentanol (150 mL) and treated with sodium (7.5 g) added in small amounts until the sodium has dissolved and the greenish fluorescence has vanished. After cooling and cautiously diluting with water (150 mL), pentanol was distilled off in a current of steam. The residue of 9,10-dihydroacridine was filtered off, washed with water, dried, and recrystallized from ethanol.

Thin-Layer Chromatography. Thin-layer chromatography was carried out on silica gel plates (20 × 20 cm). Experiments were performed in Desaga tanks, with the following system: chloroform; ethanol; dioxane (93–5–2 v/v). Plates were examined under an ultraviolet lamp (366 nm) yielding fluorescent spots (R_f values of **2** are about 0.60; R_f values of **3** are about 0.78).

Registry No. **2**, 578-95-0; **2a**, 719-54-0; **2b**, 60536-17-6; **2c**, 60536-22-3; **2d**, 13396-07-1; **2e**, 117121-15-0; **3a**, 4217-54-3; **3b**, 18448-45-8; **3c**, 102008-08-2; **3d**, 78305-11-0; **3e**, 94436-61-0; **4**, 92-81-9.

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Synthesis and Properties of Substituted Dicinnamylidene Cycloketones

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Different substituted dicinnamylidene cycloketones were synthesized via base-catalyzed condensations of substituted cinnamaldehydes and different cycloketones. The reaction products were identified on the basis of their infrared, proton and carbon-13 nuclear magnetic resonance, and ultraviolet spectral data as well as elemental analysis. Some of the synthesized compounds show fluorescence properties in solution.

Introduction

In the course of our study on the condensation of α,β-unsaturated Michael acceptors with compounds having active

Table I. Results for Substituted Dicinnamylidene Cycloketones (IIIa–k)

compd	mol formula	reaction time, min	crystn solvent	mp, °C	yield,[a] %
IIIa	$C_{23}H_{20}O$	20	C_2H_5OH	209–210	84
IIIb	$C_{25}H_{24}O_3$	30	CH_3COOH	204–205	77
IIIc	$C_{24}H_{22}O$	50	C_2H_5OH	185–186	85
IIId	$C_{24}H_{20}N_2O_5$	20	CH_3COOH	220–221	91
IIIe	$C_{26}H_{26}O_3$	60	C_2H_5OH	203–205	78
IIIf	$C_{25}H_{24}O$	30	C_2H_5OH	164–166	84
IIIg	$C_{25}H_{22}N_2O_5$	20	CH_3COOH	215–216	85
IIIh	$C_{27}H_{28}O_3$	20	C_2H_5OH	141–142	73
IIIi	$C_{25}H_{24}O$	60	C_2H_5OH	212–214	65
IIIj	$C_{27}H_{28}O_3$	50	C_2H_5OH	110–112	68
IIIk	$C_{28}H_{30}O_3$	20	C_2H_5OH	193–194	75

[a] These reported yield values are for crude products.

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