METHYLATION OF 1, 2, 3, 4-TETRAHYDROACRIDINE BY BUTYLLITHIUM, AND THE PREPARATION OF TETRAHYDROACRIDYL ARYL CARBINOLS

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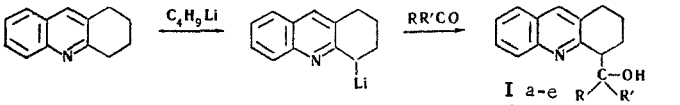
A number of aryl 4-(1, 2, 3, 4-tetrahydroacridyl) carbinols have been synthesized via the 4-lithio derivative of 1, 2, 3, 4-tetrahydroacridine. Some of them have been dehydrated to the corresponding arylidines.

We have previously synthesized the cis and trans isomers of 10-dimethylaminopropyl-1,2,3,4,4a, 9, 9a, 10-octahydroacridine, and the corresponding trans-desmethyl derivative [1]. It was shown that these compounds are active on the central nervous system, causing a variety of pharmacological effects characteristic of Imizine (Imipramine) and other tricyclic antidepressants [2].

The present paper is devoted to the preparation of lithio derivatives of 1, 2, 3, 4-tetrahydroacridine, and to a study of their reactions with carbonyl compounds.

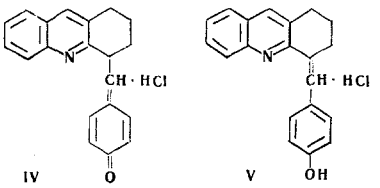
It might be expected that, by analogy with quinaldines [3], 1, 2, 3, 4- tetrahydroacridine would metallate readily at the active methylene group in the 4-position. In fact, treatment of 1, 2, 3, 4-tetrahydroacridine with an ether solution of butyllithium [4] at –45 to –50° caused the lithio derivative to separate as a dark orange precipitate, which was allowed to react without isolation with benzaldehyde, anisaldehyde, cuminic aldehyde, p-nitrobenzaldehyde, and benzophenone. The resulting aryltetrahydroacridylcarbinols (Ia-e) were obtained either as the free bases or as the hydrochlorides, in 66-72% yields.



I a $R=H, R'=C_6H_5$; b $4\text{-}CH_3OC_6H_4$; c $4\text{-}(CH_3)_2CHC_6H_4$, d $4\text{-}NO_2C_6H_4$; e $R=R'=C_6H_5$

In order to confirm that reaction occurred at the 4-position of the tetrahydroacridine nucleus, phenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ia) was dehydrated with concentrated sulfuric acid, giving 4-benzylidene-(1, 2, 3, 4-tetrahydroacridine) (II), which was identical with the benzylidene derivative obtained by reaction of 1,2, 3, 4-tetrahydroacridine with benzaldehyde in presence of anhydrous zinc chloride [5]. It was therefore proved that metallation of 1, 2, 3, 4-tetrahydroacridine occurs at the 4-position.

Dehydration of diphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ie) occurred with similar ease to give α-phenyl-4-benzylidene-(1, 2, 3, 4-tetrahydroacridine)(III). On heating the colorless Ib hydrochloride above its mp, or on recrystallization from concentrated hydrochloric acid, a bright orange compound was



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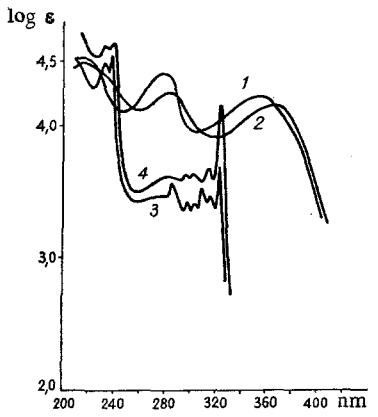

Fig. 1. UV absorption spectra. 1) 4-Benzylidene-1, 2, 3, 4-tetrahydroacridine (II), 2) 4-p-hydroxybenzylidene-1, 2, 3, 4-tetrahydroacridine (V), 3) phenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ia), 4) p-methoxyphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ib).

obtained which differed in its analytical data from the starting material by one molecule of methanol. This compound could have the quinonoid structure IV, but, on the basis of comparison of its UV spectrum with those of Ia, Ib, and II (see Fig. 1), it was assigned structure V. The IR spectrum of this compound did not contain absorption bands characteristic of the quinonoid structure.

Attempts to introduce a carboxyl group into the 4-position of 1, 2, 3, 4-tetrahydroacridine by carbonation of the lithio derivative were unsuccessful, starting material being isolated from the reaction mixture.

EXPERIMENTAL

Phenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ia). To an ether solution of butyllithium containing 0.09 mole of butyllithium was added slowly with cooling at –45° 12.82 g (0.07 mole) of 1, 2, 3, 4,-tetrahydroacridine in 70 ml of dry ether. The mixture was stirred at this temperature for 45 min, and a solution of 12.00 g (0.113 mole) of benzaldehyde in ether was added dropwise. The mixture was stirred for a further 2 h at –45°, and 80 ml of dilute (1:4) hydrochloric acid was added to precipitate 16.45 g (72.5%) of Ia hydrochloride Colorless crystals, mp 198-200° (from methanol). Found: C 73.90; H 6.42; N 4.38; Cl 10.94%. $C_{20}H_{19}NO \cdot HCl$. Calculated: C 73.72; H 6.19; N 4.30; Cl 10.38%.

Trituration with ammonia gave the free base as colorless crystals, mp 140-141° (from methanol). Found: C 82.63; H 6.91; N 4.75%. $C_{20}H_{19}NO$. Calculated: C 83.01; H 6.62; N 4.84%.

p-Methoxyphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ib) was obtained as for Ia. The yield of Ib hydrochloride was 70.3%, colorless crystals, mp about 150° (from absolute ethanol). On heating above 150° it turned orange, resolidified, and melted again at about 200°. Found: C 71.16; H 6.24; N 3.79; Cl 10.00%. $C_{21}H_{21}NO_2 \cdot HCl$. Calculated: C 70.87; H 6.23; N 3.94; Cl 9.96%. The free base was obtained in the usual way by trituration with ammonia, as colorless crystals, mp 161-163° (from absolute ethanol). Found: C 78.80; H 6.45; N 4.34%. $C_{21}H_{21}NO_2$. Calculated: C 78.97; H 6.62; N 4.38%.

p-Isopropylphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ic) was obtained as above. Yield of hydrochloride 68% calculated on cuminic aldehyde. Colorless needles, mp 134-135° (from methanol). Found: C 74.90; H 6.84; N 3.69; Cl 9.55%. $C_{23}H_{25}NO \cdot HCl$. Calculated: C 75.09; H 7.12; N 3.81; Cl 9.64%. Free base, colorless crystals, mp 118-120.5° (from 50% ethanol). Found: C 83.43; H 7.34; N 4.46%. $C_{23}H_{25}NO$. Calculated: C 83.34; H 7.60; N 4.22%.

p-Nitrophenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Id) was obtained as for Ia, from 14 g of 1, 2, 3, 4-tetrahydroacridine and 11.3 g of p-nitrobenzaldehyde. The reaction mixture was treated with 80 ml of dilute (1:4) hydrochloric acid, and unreacted p-nitrobenzaldehyde (5 g) was filtered off. The acid filtrate was neutralized with alkali, with cooling, and extracted with ether. The extract was dried over calcined magnesium sulfate and evaporated, and the residual oil was treated with an ethereal solution of HCl to give about 10 g of the dark brown hydrochloride, which was filtered off. Part of the precipitate was reprecipitated from dimethylformamide with water, filtered off, resuspended in water and neutralized with aqueous ammonia. The pale cream precipitate was recrystallized twice from absolute ethanol, mp 137-138.5°. Found: C 71.78; H 5.58; N 8.03%. $C_{20}H_{18}N_2O_3$. Calculated: C 71.84; H 5.42; N 8.38%.

Diphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol (Ie). To 47 ml of an ethereal solution of butyllithium containing 4.86 g (0.076 mole) of butyllithium cooled at –45° was added gradually a solution of 10.7 g (0.0584 mole) of 1, 2, 3, 4-tetrahydroacridine in 60 ml of dry ether. The orange-colored reaction mixture was stirred at this temperature for 50 min, and an ethereal solution of 10.5 g (0.0576 mole) of benzophenone was added. After keeping the temperature at –40° to –50° for 2 h, the reaction mixture was treated with 70 ml of dilute (1:4) hydrochloric acid, and the sparingly-soluble hydrochloride was filtered off to give 15.5 g (66.3%) of

product (the decomposition was better carried out by adding a saturated solution of NH_4Cl). Part of the precipitate was suspended in water and triturated with aqueous ammonia to give colorless crystals, mp 130-131° (from absolute alcohol). Found: C 85.33; H 6.42; N 4.05%. $C_{26}H_{26}NO$. Calculated: C 85.44; H 6.34; N 3.85%.

4-Benzylidene-(1, 2, 3, 4-tetrahydroacridine) (II). To a solution of 4 g of phenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol in 40 ml of glacial acetic acid was added 6 ml of concentrated sulfuric acid, and the mixture was boiled for 5 min, then poured into 100 ml of cold water. The solution was basified with ammonia, extracted with ether, and the ether solution was dried over calcined magnesium sulfate and the ether removed, giving 3 g of colorless crystals, mp 103.5-105.5° (from absolute alcohol). It gave no depression of mp on admixture with 4-benzylidene-(1, 2, 3, 4-tetrahydroacridine) obtained by method [5]. Found: C 88.31; H 6.38; N 5.11%. $C_{20}H_{17}N$. Calculated: C 88.52; H 6.31; N 5.16%.

4-α-Phenylbenzylidene-(1, 2, 3, 4-tetrahydroacridine) (III). To a warm solution of 2 g of diphenyl-tetrahydroacridylcarbinol in 20 ml of glacial acetic acid was added carefully 5 ml of concentrated sulfuric acid. The mixture was boiled for 3-5 min, then poured into 50 ml of water. After neutralization with ammonia, there was obtained 1.35 g of colorless crystals, mp 146-147° (from 96% alcohol). Found: C 89.45; H 6.13; N 3.86%. $C_{26}H_{21}N$. Calculated: C 89.89; H 6.09; N 4.03%.

4-p-Hydroxybenzylidene-(1, 2, 3, 4-tetrahydroacridine) (V). p-Methoxyphenyl-(1, 2, 3, 4-tetrahydro-4-acridyl)carbinol hydrochloride (3.8 g) was boiled with 10 ml of concentrated hydrochloric acid until it had dissolved completely (5-10 min). On cooling, 2.8 g of 4-p-hydroxybenzylidine-(1,2, 3, 4-tetrahydroacridine) hydrochloride separated as brick red-orange crystals, mp 205-207° (from 96% alcohol). Found: C 74.83; H 5.60; N 4.11; Cl 10.69%. $C_{20}H_{17}NO \cdot HCl$. Calculated: C 74.16; H 5.60; N 4.32; Cl 10.95%. The free base was obtained in the usual way as colorless crystals, mp 110-110.5° (from 96% alcohol). Found: C 83.26; H 6.13; N 4.69%. $C_{20}H_{17}NO$. Calculated: C 83.60; H 5.96; N 4.87%.

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