HYDROACRIDINES AND RELATED COMPOUNDS

IX.* STEPWISE ALKYLATION OF 1,2,3,4-TETRAHYDROACRIDINE AND sym-OCTAHYDROACRIDINE THROUGH THEIR LITHIUM DERIVATIVES

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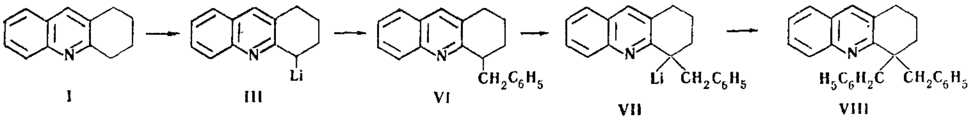
One hydrogen atom is replaced by lithium in the reaction of 1,2,3,4-tetrahydroacridine and sym-octahydroacridine with phenyllithium; effective replacement of a second hydrogen atom by lithium becomes possible after replacement of the first lithium by an alkyl group. This makes it possible to achieve stepwise alkylation.

The metallation of 2,6-lutidine [2] gives the monolithio derivative; only very small amounts of the dilithio derivatives are formed.

Only the monolithio derivatives (III and IV, respectively) are also formed by the action of 2 mole of phenyllithium on 1,2,3,4-tetrahydroacridine (I) or sym-octahydroacridine (II) in ether at room temperature. Treatment of the reaction mixture with benzyl chloride gives almost exclusively the monobenzylhydroacridine (V or VI), and only traces of the dibenzyl derivative are formed.

The hindrance to further substitution of hydrogen by lithium in III or IV is, in our opinion, associated with the strong positive inductive effect of lithium. An increase in the electron density in the aromatic rings of III and IV as compared with I and II leads to a decrease in the lability of the hydrogen in the 4 position in III or in the 4 and 5 positions in IV. This hinders the introduction of a second lithium atom.

Replacement of lithium by a less electron-donor alkyl group again opens up the possibility for the introduction of lithium. In this case, 4-alkyltetrahydroacridines are metallated by phenyllithium in the 4 position, while 4-alkyloctahydroacridines are metallated in the 5 position. Thus treatment of 4-benzyltetrahydroacridine (VI) with phenyllithium gives 4-lithio-4-benzyltetrahydroacridine (VII), which reacts with benzyl chloride to give 4,4-dibenzyltetrahydroacridine (VIII).



The structure of VIII was confirmed by the PMR spectrum, in which the signals of nonaromatic methylidyne protons are absent, while the signals of the protons of the methylene groups of the benzyl radicals appear as two doublets at 3.66 and 3.73 ppm and 2.77 and 2.90 ppm.

The reaction of 4-benzyloctahydroacridine (V) with phenyllithium leads to 5-lithio-4-benzyloctahydroacridine (IX). The latter reacts with benzyl chloride to give approximately equal amounts of the two stereoisomeric 4,5-dibenzyloctahydroacridines (X and XI). Both of these stereoisomers are also obtained

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[*] See [1] for communication VIII.

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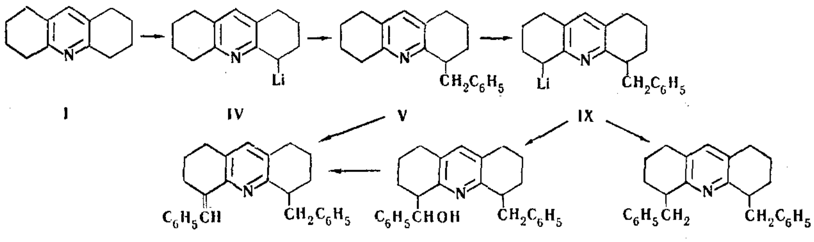
TABLE 1. Alkylhydroacridines

Compound	Mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
VI[a]	—	$C_{20}H_{19}N$	87,9	7,1	87,8	7,0	66
VIII	153—154 (alcohol)	$C_{27}H_{25}N$	89,7	7,1	89,2	6,9	39
X[b]	99—101 (alcohol)	$C_{27}H_{29}N$	88,2	8,0	88,2	8,0	31
XI[c]	79—81 (petroleum ether)	$C_{27}H_{29}N$	88,0	8,1	88,2	8,0	31
XII	157 (petroleum ether)	$C_{27}H_{29}NO$	84,5	7,6	84,5	7,6	42
XVI	27—28 (petroleum ether)	$C_{14}H_{18}DN$	83,2	10,1[d]	83,1	10,0^{r}	89

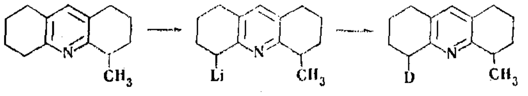
[a]The hydrochloride had mp 205-207° (from water). Found: Cl 11.2%. $C_{20}H_{19}N \cdot HCl$. Calculated: Cl 11.4%. [b]The picrate had mp 201-202° (from dioxane). Found: N 9.2%. $C_{27}H_{29}N \cdot C_6H_3N_3O_7$. Calculated: N 9.4%. [c]The picrate had mp 182-184° (from dioxane). Found: N 9.0%. $C_{27}H_{29}N \cdot C_6H_3N_3O_7$. Calculated: N 9.4%. [d]H+D.

in the catalytic hydrogenation of 4,5-dibenzaloctahydroacridine, by which their structures are confirmed. Treatment of IX with benzaldehyde gives 5-hydroxybenzyl-4-benzyloctahydroacridine (XII), which is readily dehydrated in acetic anhydride to 5-benzylidene-4-benzyloctahydroacridine (XIII). Compound XIII is also obtained by alternative synthesis by direct condensation of V with benzaldehyde.



I IV V IX XIII XII X, XI

4-Methyl-sym-octahydroacridine (XIV) is also metallated by phenyllithium in the 5 position. Treatment of the resulting lithio derivative (XV) with heavy water gives 5-deutero-4-methyloctahydroacridine (XVI).



XIV XV XVI

The structure of XVI was confirmed by the PMR spectrum, in which the protons of the methyl group appear as a doublet at 1.11 and 1.23 ppm. A singlet from the methyl protons would have been observed for 4-deutero-4-methyloctahydroacridine.

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EXPERIMENTAL

We have previously described the synthesis of 4-alkyloctahydroacridines V and XIV [3, 4].

General Method for the Synthesis of VIII, X, XI, XII, and XVI. An equivalent amount of an ether solution of phenyllithium was added under argon in the course of 1 h to a solution of 0.01 mole of the 4-alkylhydroacridine in 50 ml of absolute ether, and the mixture was allowed to stand at room temperature for 12 h. A 0.01 mole sample of benzyl chloride (for the synthesis of VIII, X, and XI), benzaldehyde (for the synthesis of XII), or heavy water (for the synthesis of XVI) in ether solution was then added carefully, and the mixture was allowed to stand for 4 h, after which it was treated with 50 ml of 20% hydrochloric acid. The hydrochloric acid extract was washed with ether and made alkaline. The precipitated product was filtered off and crystallized. Stereoisomeric X and XI were separated by preparative thin-layer chromatography on activity II Al_2O_3 with elution with petroleum ether–carbon tetrachloride (2 : 1).

In order to determine the degree of metallation of I and II, 0.02 mole of phenyllithium in ether solution was added under argon to a solution of 0.01 mole of the hydroacridine in 50 ml of absolute ether, and after 12 h the resulting suspension was poured with vigorous stirring into an ether solution of 0.02 mole of benzyl chloride. The reaction mixture was separated as indicated above, and the mixture of reaction products was chromatographed on activity II Al_2O_3 with elution with petroleum ether–carbon tetrachloride. Compound I yielded 66% VI with bp 180-185° (0.1 mm) and ~0.3% VIII. The properties of VI are described in Table 1. Compound II yielded 78% V and ~0.8% of a mixture of X and XI.

5-Benzylidene-4-benzyl-sym-octahydroacridine (XIII). A. A 0.5 g sample of XII was refluxed with 5 ml of acetic anhydride for 3 h. When the mixture was cooled, 0.32 g (87%) of XIII with mp 110-111° (from alcohol) crystallized out. Found: C 88.84; H 7.49%. $C_{27}H_{27}N$. Calculated: C 88.70; H 7.46%.

B. A solution of 0.6 g (0.002 mole) of V and 1.06 g (0.01 mole) of benzaldehyde in 8 ml of acetic anhydride was refluxed for 8 h and cooled. Alcohol (8 ml) was added, and 0.63 g (80%) of XIII was removed by filtration. The identical character of the preparations obtained by the two methods was confirmed by mixed-melting-point determination.

4,5-Dibenzyl-sym-octahydroacridines (X, XI). A 3.0 g (0.0082 mole) sample of 4,5-dibenzaloctahydroacridine [5] was hydrogenated in a mixture of 60 ml of dioxane and 15 ml of acetic acid over 0.5 g of platinum dioxide. A total of 322 ml of hydrogen was absorbed (the calculated value is 370 ml). Dioxane (50 ml) was added, and the mixture was heated to the boiling point and filtered. The filtrate was made alkaline with 200 ml of 10% KOH, and the precipitated solid mass was removed by filtration, dried, and chromatographed on activity II Al_2O_3 with elution with petroleum ether–benzene with variation of the components from 30 : 1 to 1 : 1 to give 0.07 g (2.3%) of XI and 1.9 g (63%) of X. The identification of this product with the samples obtained by organometallic synthesis was accomplished by determining the melting point of a mixed sample of the picrates.

The PMR spectra of carbon tetrachloride solutions of the compounds were obtained with a ZKR-60 spectrometer with tetramethylsilane as the internal standard. The chemical shifts are given on the δ scale.

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