Benzyl Group Migration in 9-Methyl-10-benzyl-9,10-dihydroacridine

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Abstract □ When 9-methyl-10-benzylacridane was treated with *n*-butyl lithium, its benzyl group was found to migrate to the 9-position. NMR and deuterium oxide-exchange studies suggested that the rearrangement occurred intramolecularly. No rearrangement was noticed when 9-methyl-10-methylacridane was treated similarly. When *N,N*-dimethyl-9-carboxamido-9,10-dimethylacridane was treated with $LiAlH_4$ its carboxamido function was displaced and 9,10-dimethylacridane was produced.

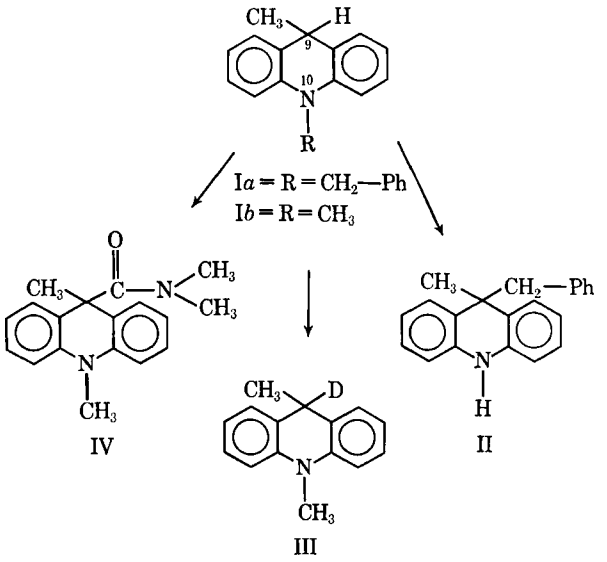
Keyphrases □ 9-Methyl-10-benzyl-9,10-dihydroacridine—benzyl group migration □ *N*-Butyl lithium effect—9-methyl-10-benzylacridine □ UV spectrophotometry—structure, identity □ IR spectrophotometry—structure, identity □ NMR spectroscopy—structure, identity

In the course of synthesizing 9,10-disubstituted dihydroacridines of possible pharmacologic interest, an unusual benzyl group migration was noticed which is described below.

9-Methyl-10-benzylacridane[1,2] (I*a*) was treated with *n*-butyl lithium in tetrahydrofuran at room temperature for 24 hr. in order to form the carbanion (V). Upon subsequent addition of deuterium oxide, undeuterated 9-methyl-9-benzylacridane (II) was isolated after 10 min. in 73% yield.[3,4] This product (II) was characterized by UV and spectra and elemental analysis.

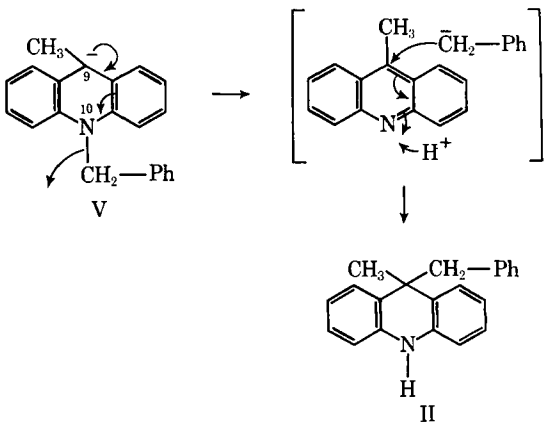
The NMR spectrum showed the following differences between product (II) and starting material (I*a*). The quartet at $\tau = 5.93$, assigned to the proton of the 9-position of the acridane nucleus of Compound I*a*, was absent in the NMR spectrum of II. The doublet at $\tau = 8.63$, assigned to the 9-methyl protons of Compound I*a* also was absent. A singlet appeared at $\tau = 8.22$ which was assigned to the 9-methyl protons of II, and product (II) showed a singlet at $\tau = 4.14$ assigned to the proton on the nitrogen of acridane nucleus (*i.e.*, Position 10). This latter singlet disappeared when deuterium oxide was added to the NMR sample. The rest of the NMR signals are recorded under the *Experimental* section.

It seems probable that at room temperature the anion (V) (Scheme I) is formed, followed by a fast elimination in which the benzyl group migrates from the 10-position to Position 9 of the acridane. One possible reaction mechanism is described in Scheme I.



The mechanism proposed in Scheme I is supported by the work of Semon and Craig (3) who were able to obtain 9,9-dimethylacridane by treating a solution of 9-methylacridine in *n*-butyl ether with methyl magnesium iodide.

When 9,10-dimethylacridane[5] (I*b*) was treated with butyl lithium in tetrahydrofuran it gave a red color which, upon addition of deuterium oxide, disappeared. The NMR spectrum of the product showed that the 9-position of the acridane nucleus of I*b* was deuterated to produce III, as evidenced by the absence of the quartet centered at $\tau = 5.90$ (1H) characteristic of the 9-position proton, and the presence of a singlet at



Scheme I

[1] 9,10-Dihydroacridines will be referred to as derivatives of the acridane nucleus throughout this paper.

[2] Compound I*a* was synthesized by reacting methyl magnesium iodide with *N*-benzylacridinium bromide (1) in dry ether, in 80% yield.

[3] When the procedure was repeated differing only in that (I*a*) was treated for 5 hr. instead of 24 hr. with *n*-butyl lithium, the yield of the undeuterated product (II) was 50% instead of 73%.

[4] NMR and deuterium oxide-exchange studies showed that neither deuteration nor benzyl migration occurred when Compound I*a* was treated in ether at 37° or in tetrahydrofuran at 5° with *n*-butyl lithium and deuterium oxide. Burtner and Cusic (2) were able to introduce a carboxylic acid function at the 9-position of 10-methylacridane by reacting the latter with *n*-butyl lithium and, subsequently, with carbon dioxide. However, all the author's attempts to carbonate Compound I*a* by applying the conditions of Burtner and Cusic (2) resulted in the recovery of starting material only, thereby demonstrating the lack of reactivity of the 9-position proton of the 9-methyl-10-benzylacridane (I*a*) as compared to that of the 10-methylacridane.

[5] 9,10-Dimethylacridane (I*b*) was synthesized according to the procedure of Semon and Craig (3). The NMR spectrum of this compound showed a multiplet centered at $\tau = 2.67$ (8H), assigned to the aromatic protons; a quartet centered at $\tau = 5.90$ (1H) ($J = 7$ c.p.s.), assigned to the proton on the 9-position of the acridane; a singlet at $\tau = 6.53$ (3H) assigned to the methyl protons attached on the nitrogen of the acridane nucleus; and a doublet centered at $\tau = 8.63$ (3H) ($J = 6$ c.p.s.), assigned to the 9-methyl protons.

τ = 8.31 (3H), instead of a doublet centered at τ = 8.63 (3H), of the 9-methyl protons.

That the proton at the 9-position of I*b* could be substituted by a displacement reaction was further substantiated by the preparation of *N,N*-dimethyl-9-carboxamido-9,10-dimethylacridane (IV) in 80% yield by treating 9,10-dimethylacridane (I*b*) with butyl lithium and subsequently adding *N,N*-dimethylcarbamoyl chloride. Lithium aluminum hydride reduction of amide (IV) in ether (under reflux) afforded 9,10-dimethylacridane (I*b*) (in 95.3% yield) instead of the expected amine. When the reduction was repeated at 0° in ether or in tetrahydrofuran, only starting material was isolated.

EXPERIMENTAL[6]

Preparation of 9-Methyl-10-benzylacridane (Ia)[7]—*N*-Benzylacridinium bromide, m.p. 210°, was prepared in 59.3% yield according to the procedure of Krohnke and Honig (1). To 0.22 g. (0.9 mmole) of magnesium turnings in 20 ml. of dry ether contained in a two-neck 100-ml. flask, equipped with a condenser, a nitrogen inlet, and a dropping funnel, was added, with stirring under nitrogen, 5 ml. of a solution containing 1.5 g. (10 mmoles) of freshly distilled methyl iodide in dry ether. When all the magnesium had dissolved and the solution had been cooled in an ice bath, 1.0 g. (2.9 mmoles) of *N*-benzylacridinium bromide was added in small portions, through a powder funnel. The mixture was stirred 5 min., then hydrolyzed by pouring over ice. The resulting material was neutralized with 10% aqueous acetic acid and extracted with ether and chloroform. The combined extracts were dried over anhydrous potassium carbonate and distilled at 25° under reduced pressure to afford a white crystalline residue which after two recrystallizations from ether–chloroform yielded 0.65 g. (80% yield) of 9-methyl-10-benzylacridane (I*a*), m.p. 155–160°.

The NMR spectrum showed a multiplet centered at τ = 3.09 (13H), assigned to the aromatic protons; a singlet at τ = 4.90 (2H), assigned to the *N*-benzyl methylene protons; a quartet centered at τ = 5.93 (1H) (J = 7 c.p.s.), assigned to the proton on the 9-position of acridane; and a doublet centered at τ = 8.63 (3H) (J = 6 c.p.s.) assigned to the 9-methyl protons. The UV spectrum showed $\lambda_{max.}^{MeOH}$ at 288 mμ (1.6×10^4). The IR spectrum showed $\lambda_{max.}^{CHCl_3}$ at 3.30 (m), 3.38 (m), 6.28 (v.s.), 6.78 (v.s), 6.9(v.s.), 7.28(v.s.), 7.6(m), 7.78(s), 7.9(v.s.), 8.10(m) broad, 9.1(m), 9.4(m), 9.6(m), 9.7(m), 9.97(m), 10.85(m), 11.6(v.s.), 14.5(m) μ. Three recrystallizations from ethanol afforded the analytical sample as white plates, m.p. 160°.

Anal.—Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.37; H, 6.70; N, 5.21.

Preparation of 9-Methyl-9-benzylacridane (II)[7]—To a solution of 0.273 g. (0.95 mmole) of 9-methyl-10-benzylacridane (I*a*) in 18 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) contained in a two-neck 100-ml. flask equipped with a condenser, nitrogen inlet, and rubber cap, was added, with stirring under nitrogen at room temperature, 1.5 ml. of a solution of *n*-butyl lithium in hexane (2.0 mmoles, determined by standardization) (4). A deep red color appeared which 7 min. later changed to greenish-brown. The reaction mixture was stirred at room temperature, under nitrogen, for 24 hr. At the end of this time, 2.0 ml. of deuterium oxide[8] was added and the mixture was allowed to stir for 10 min.; the greenish-brown color disappeared. Five milliliters of water was added to create an aqueous layer which was then extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and distilled at 35° under reduced pressure to afford a white crystalline residue which was chromatographed on 12.0 g. of neutral alumina.[9] Ten-milliliter fractions were collected. Elution with 1:9 chloroform–hexane gave 0.20 g. (73.7% yield) of undeuterated 9-methyl-9-benzylacridane,[10] which after one recrystallization from methanol gave 0.160 g. of white needles, m.p. 167–168°. The NMR spectrum showed a multiplet centered at τ = 3.19 (13H), assigned to the aromatic protons; a singlet at τ = 4.14 (1H), assigned to the proton on the secondary amine nitrogen of the acridane nucleus,[11] a singlet at τ = 7.19 (2H) assigned to the methylene protons of the 9-benzyl function; and a singlet at τ = 8.22 (3H) assigned to the 9-methyl protons. The UV spectrum showed $\lambda_{max.}^{MeOH}$ at 287 mμ (1.6×10^4). The IR spectrum showed: $\lambda_{max.}^{CHCl_3}$ at 2.83(m) broad, 3.3(m), 6.23(v.s.), 6.32(s), 6.78(v.s.), 7.15(m), 7.25(m), 7.58(s), 9.70(m), 10.8(m), 14.4(s) μ. Four recrystallizations from methanol afforded the analytical sample as white needles, m.p. 167–168°.

Anal.—Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71: N, 4.91. Found: C, 88.31; H, 6.86; N, 4.88.

C9-H Deuterium Exchange of 9,10-Dimethylacridane (Ib)—9,10-Dimethylacridane (I*b*), m.p. 138–140° was prepared in 64.2% yield according to Semon's procedure (3). To a solution of 0.3 g. (1.4 mmoles) of 9,10-dimethylacridane in 10 ml. of tetrahydrofuran (distilled over lithium aluminum hydride), contained in a two-neck 25-ml. flask fitted with a condenser, a nitrogen inlet, and having a side arm equipped with a rubber cap, was added, by means of a syringe and under nitrogen while stirring, 2.0 ml. of a solution of *n*-butyl lithium in hexane [2.8 mmoles, determined by standardization according to the procedure of Gilman and Haubein (4)]. Immediately upon the addition of the *n*-butyl lithium, a deep red color appeared. The mixture was heated, under reflux and nitrogen with stirring, for 2.5 hr. At this time it was allowed to cool to room temperature, and 0.5 ml. of deuterium oxide was added. The red color disappeared instantly. The reaction mixture was dried over anhydrous sodium sulfate and filtered through a sintered-glass funnel, and there sidue washed with chloroform. The filtrate, together with the washings, was evaporated at 40° under reduced pressure and the residue dried under vacuum for 12 hr. The NMR of a sample taken from the residue showed a multiplet centered at τ = 2.92 (8H), assigned to aromatic protons; a singlet at τ = 6.61 (3H), assigned to the methyl protons attached on the nitrogen of the acridane nucleus (10-methyl); and a singlet at τ = 8.31 (3H) assigned to the 9-methyl protons.

N,N-Dimethyl-9-carboxamido-9,10-dimethylacridane (IV)[7]—To a solution of 0.6 g. (2.8 mmoles) of 9,10-dimethylacridane (I*b*) in 12 ml. of tetrahydrofuran (distilled over lithium aluminum hydride) contained in a two-neck 25-ml. flask, fitted with a condenser, a nitrogen inlet, and a side arm equipped with a rubber cap, was added by means of a syringe, while under nitrogen with stirring, 2.1 ml. of a solution of *n*-butyl lithium in hexane [3.1 mmoles, determined by standardization according to Gilman and Haubein's method (4)]. A deep red color appeared immediately. The mixture was stirred at room temperature for 30 min. At this time 1.5 g. (14.0 mmoles) of freshly distilled, *N,N*-dimethylcarbamoyl chloride[12] was added by means of a syringe. The red color disappeared. The reaction mixture was stirred for 5 min.; a solution of 1.5 g. of sodium bicarbonate in 20 ml. of water was added and stirring was continued for an additional 30 min. The aqueous layer was extracted several times with chloroform. The combined extracts were dried over anhydrous potassium carbonate and distilled at 30° under reduced pressure to afford 0.614 g. (80% yield) of white crystalline compound, m.p. 176–185°. One recrystallization from aqueous ethanol yielded *N,N*-dimethyl-9-carboxamido-9,10-dimethylacridane (IV) as white needles, m.p. 182–185°. The NMR spectrum showed a multiplet centered

[6] All UV spectra were recorded with a Beckman spectrophotometer, model DK-2A. Melting points were uncorrected and taken with a Fisher-Johns melting-point apparatus (hot-block method). All IR spectra were recorded with a Baird spectrophotometer (model B). NMR spectra were measured at 60 Mc. /sec. on a Varian A-60 spectrometer using deuterated chloroform as solvent and tetramethylsilane as internal standard (τ = 10.0 p.p.m.). Sample was 10% in concentration.

[7] A new compound.

[8] The deuterium oxide was added to determine whether or not the carbanion (V) was formed.

[9] Fisher.

[10] It appears that the 10-position of the acridane nucleus of II was not liable to deuteration under the described conditions. However, when Compound II was subjected to deuterium oxide treatment in deuterated chloroform, deuteration at the 10-position did occur (see *Footnote 11*).

[11] To prove the existence of a secondary amine nitrogen at the 10-position of the acridane nucleus, 0.1 ml. of deuterium oxide was added to the NMR probe containing undeuterated (II) and deuterated $CHCl_3$ solvent. After the probe was shaken for 5 min., the NMR spectrum did indeed reveal the disappearance of the singlet at τ = 4.14 assigned to the 10-position proton.

[12] Matheson, Coleman and Bell.

at τ = 2.91 (8H), assigned to the aromatic protons; a singlet at τ = 6.60 (3H), assigned to the methyl protons on the nitrogen of the acridane nucleus (10-methyl); a singlet at τ = 6.95 (3H), assigned to one of the methyl group protons of the amide; a singlet at τ = 7.65 (3H) assigned to the protons of the other methyl group of the amide; and a singlet at τ = 8.40 (3H) assigned to the 9-methyl protons. The UV spectrum showed $\lambda_{max.}^{MeOH}$ at 288 mμ (1.7×10^4). The IR spectrum showed $\lambda_{max.}^{CHCl_3}$ at 3.32(s), 3.41(m), 6.08(v.s.), 6.15(v.s.), 6.3(s), 6.8(v.s.), 6.9(s), 6.95(s), 7.2(s), 7.41(v.s.), 7.85(m), 7.9(s), 8.5(m), 8.7(m), 8.8(s), 9.2(s), 9.6(m), 11.3(m), 11.55(m), 13.8(m)broad μ. Three more recrystallizations from diluted ethanol afforded the analytical sample, white needles, m.p. 183–185°.

Anal.—Calcd. for $C_{18}H_{20}N_2O$: C, 77.11: H, 7.19; N, 9.99. Found: C, 77.19; H, 7.09; N, 9.86.

$LiAlH_4$ Reduction of N,N-Dimethyl-9-carboxamido-9,10-dimethylacridane (IV) to 9,10-Dimethylacridane (Ib)—In a two-neck, 100-ml. flash equipped with a condenser funnel and a nitrogen outlet 0.5 g. (13.0 mmoles) of lithium aluminum hydride in 25 ml. of dry ether was refluxed while stirring under nitrogen for 45 min. At this time, a suspension of 0.3 g. (1.07 mmoles) of *N,N*-dimethyl-9-carboxamido-9,10-dimethylacridane in 10 ml. of ether was introduced. These substances were heated, under reflux while stirring and passing nitrogen, for 12 hr. The excess lithium aluminum hydride was decomposed by adding ethyl acetate while cooling in an ice bath. This was followed by 20 ml. of 40% aqueous sodium potassium tartrate. The mixture was filtered and the ethyl acetate layer separated. The aqueous layer was extracted successively with ethyl acetate and chloroform. The combined organic extracts were distilled at 45° under reduced pressure. The white crystalline residue, m.p. 125–134°, was recrystallized twice from methanol to yield 0.213 g. (95.3% yield), of 9,10-dimethylacridane (*Ib*) as white needles, m.p. 130–134°. Three more recrystallizations from methanol afforded the analytical sample as white needles, m.p. 136–137°, which did not depress the melting point of an authentic sample of 9,10-dimethylacridane [synthesized according to Semon's procedure (3) and recrystallized from methanol], and had identical IR and UV spectra.

Anal.—Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.08; H, 7.19; N, 6.67.

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Insoluble Erythromycin Salts

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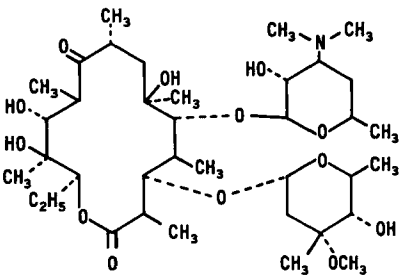
Abstract □ Fifteen salts of erythromycin were prepared and their relative water solubilities and bitterness levels measured. The water solubilities of the salts were found to be related to the size of the alkyl group attached to the acid. The level of bitterness, however, was related not only to the size of the alkyl group but also to the stability of the salt. The stability of the salt was a function of the strength of the acid used to prepare the salt and could be measured by the downfield shift of the *N*-methyl protons in the NMR spectrum of the salt. The stearyl sulfate salt was the least bitter of the salts.

Keyphrases □ Erythromycin salts, insoluble—synthesis □ Solubility, aqueous—alkyl group effect □ Bitterness, erythromycin salts—alkyl group, stability relationship □ Stability, erythromycin salts—acid strength, salt formation □ NMR spectroscopy—identity

Erythromycin, a member of the macrolide family of antibiotics (1) is highly active against a broad spectrum of Gram-positive bacteria. Its structure is shown (2).



ERYTHROMYCIN

Although the antibiotic has been shown to be effective therapeutically, it has an inherently bitter taste which must be masked for oral administration. For adults, the taste problem is overcome by administration of the antibiotic in coated tablets or in capsules. However, in preparations intended for pediatric use, the preferred formulations are chewable tablets and suspensions. The bitterness in these pediatric dosage forms can be minimized by making an insoluble ester derivative of the hydroxyl group on the basic sugar such as the ethyl succinate (3), the ethyl carbonate (4), or the propionate ester (5), or by making an insoluble salt of the amine. Salts of erythromycin can be formed by reaction of the tertiary amine group with acids. This paper describes the authors' studies on the preparation of various salts of erythromycin and their properties.

RESULTS

Two factors were considered in choosing the acids for the preparation of the salts. These were the strength of the acid and the size of the alkyl group attached to the acidic function. Four types of acids with different acid strengths were chosen: carboxylic acids