Synthesis of an *s*-Butyldibenz[*a,h*]acridine. Alkyl Migration in the Bernthsen Reaction

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The Bernthsen reaction between *N*-1-naphthyl-2-naphthylamine and 2-methylbutanoic acid and its anhydride at 200-230° for seven hours gives a low yield of 12- or 13-*s*-butyldibenz[*a,h*]acridine, instead of the expected 14-isomer. The parent molecule dibenz[*a,h*]acridine results from the same reaction conducted at 270° for thirteen hours. It is suggested that alkyl migration may have occurred in some other cases where the Bernthsen reaction was reported to yield 14-alkyldibenz[*a,h*]acridines.

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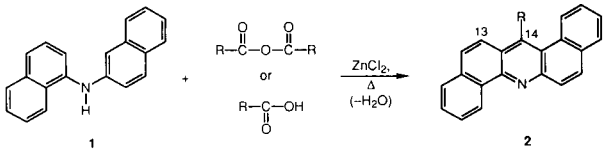
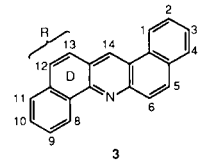
The Bernthsen reaction has been used extensively for the synthesis of acridines, benzacridines, and dibenzacridines bearing a substituent in the position *gamma* to the heterocyclic nitrogen atom of the product [2-7]. It involves heating a diarylamine with a carboxylic acid or its anhydride in the presence of a Lewis acidic dehydrating agent such as anhydrous zinc chloride or polyphosphoric acid [8]. The present paper concerns our effort to employ the Bernthsen reaction to synthesize the target molecule 14-*s*-butyldibenz[*a,h*]acridine (**2e**), according to Scheme 1, where R is the *s*-butyl group. It is the crux of this paper that 12- or 13-*s*-butyldibenz[*a,h*]acridine (**3b**) and parent molecule dibenz[*a,h*]acridine (**3a**) were obtained, instead of **2e**, albeit in very low yields.

Scheme 1



1 2

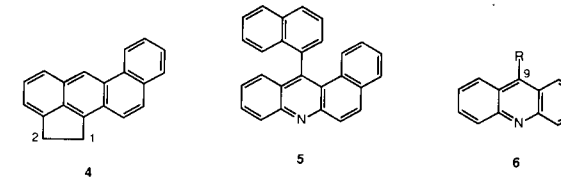
a, R = Me d, R = *i*-Bu
b, R = *n*-alkyl e, R = *s*-Bu
c, R = *n*-Bu f, R = Et



3

a, R = H
b, R = *s*-Bu
c, R = alkyl

We initiated our synthetic studies in 1957 with the hope of preparing enantiomeric forms of **2e** and having them tested separately for carcinogenic activity. There was some reasonable chance that **2e** would be carcinogenic, inasmuch as the parent molecule **3a** and compound "**2c**" were reported to have notable activities, although "**2d**" was inactive [3]. An early theory for the mechanism of carcinogenicity assumed that the process is initiated by flatwise adsorption of a selected planar condensed polycyclic aromatic compound onto a biological cell site with which it forms a molecular complex [9]. In fact, in 1935 Fieser and Seligman suggested that if one could introduce a chiral center into a planar carcinogen one might observe different degrees of activity of the enantiomers and, thereby, help to elucidate aspects of the stereochemical relationships involved in the complexation [10]. These authors called attention to the cholanthrene system **4**, where one might introduce chirality at C-1 and/or C-2, but where (particularly for introduction of methyl substituents) one



4 5 6

a, R = Me

would be unable to effect optical resolution without use of a molecular complexing agent [10,11]. Buu-Hoï in 1949 reported the synthesis of **5**, a substance which would deviate markedly from coplanarity but which should be susceptible to optical resolution by salt formation with a chiral acid [4]. At least in 1957 compound **2e** seemed to be a better target molecule than **4** or **5** for testing the Fieser and Seligman concept. However, our project was discontinued after a few months, with only tentative identification (by melting point and elemental analysis) of two Bernthsen products, **3a** and its butyl derivative [12]. Recently these products have been characterized further by chromatography and spectra and the overall results are reported here.

Our procedure was modified from that of Buu-Hoï and co-workers for the syntheses of various 9-alkylacridines **6** [6,13]. Initially a mixture of amine **1**, 2-methylbutanoic acid, 2-methylbutanoic anhydride, and anhydrous zinc chloride (molar ratios 1:1.16:2.36:2.6) was heated at 200-230° for 7 hours to yield a fluorescent product [14] of mp 167-168° (<2% yield), identified as a butyldibenzacridine by means of elemental analysis (C, H, N) and mass

spectrometry (molecular ion at m/z 335). The ^{1}H nmr spectrum of this product clearly establishes the alkyl substituent as *s*-butyl, and this is corroborated by the fact that the most abundant mass spectral fragment occurs at m/z 306 for loss of an ethyl group. The downfield portion of the ^{1}H nmr spectrum of the 168° product is consistent with its structural assignment of either 12- or 13-*s*-butyldibenz[*a,h*]acridine (**3b**), and not with that of the expected 14-*s*-butyldibenz[*a,h*]acridine (**2e**). First, the parent structure of the 168° product was identified as dibenz[*a,h*]acridine (**3a**), rather than that due to some rearrangement of amine **1** during the reaction [15], by comparison of its spectrum with data for **3a** from the literature [17] and from both proton 1D and COSY spectra of our own sample of **3a** (Figure 1). Second, the location of the *s*-butyl group at

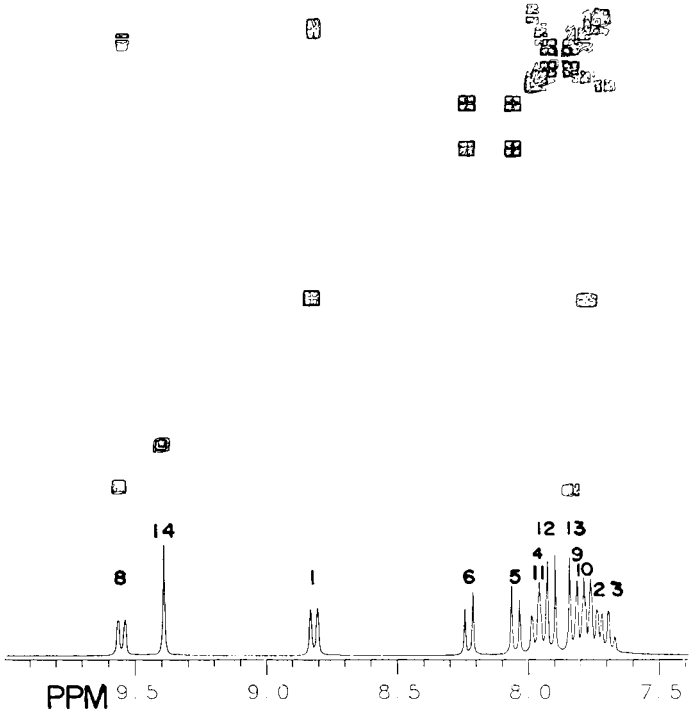


Figure 1. COSY spectrum of dibenz[*a,h*]acridine (**3a**) obtained in deuteriochloroform at a frequency of 300.15 MHz. The numbers on the 1D spectrum shown give the structural assignments for the various signals.

position 14 was precluded by the presence of two singlets for one proton each in the spectrum of the 168° product. Compound **2e** should be devoid of singlets. Specifically, the 168° product shows a series of five nmr signals, for one proton each in the region $\delta > 8$, as follow: a doublet at 9.57 for H-8, a singlet at 9.38 for H-14, a doublet at 8.90 for H-1, a partially split doublet at 8.29 (J = 7.6 Hz, plus long range splitting by H-14) for H-6, and a singlet at 8.17 for H-12 or H-13. In addition, there are two overlapping doublets at 7.97 and 7.93 for H-5 and H-4 or H-11, as well as a multiplet for the five other aromatic protons at 7.7-7.9. Analogously, the ^{1}H nmr spectrum of dibenz[*a,h*]acridine shows corresponding signals at 9.55 (H-8), 9.39 (H-14), 8.81 (H-1), 8.13 (AB system for H-5 and H-6), 7.96 (overlapping doublets for H-4 and H-11), 7.87 (AB system for H-12 and H-13), and a multiplet for four aromatic protons at 7.65-7.78 [18]. While these spectra do not permit specific location of the *s*-butyl group on C-12 or C-13 they do establish that it is substituted at one of these two positions.

In a subsequent experiment we attempted to increase the yield of **3b** by conducting the Bernthsen reaction at 270° for 13 hours. Instead of isolating **3b**, however, we obtained only a minimal yield of dibenz[*a,h*]acridine itself as the fluorescent product, identified by melting point, mass spectra (molecular ion at m/z 279), elemental analysis, plus the ^{1}H and COSY nmr spectra noted before.

A search of the literature showed that Jacquignon *et al.* reported use of the Bernthsen reaction to synthesize a series of fourteen different 14-*n*-alkyldibenz[*a,h*]acridines (**2b**) of possible value as fluorescent probes for plasmic membranes [7]. Used in their reactions were amine **1** [19], a carboxylic acid, and zinc chloride in molar ratios of 1:2:3 for a period of only three hours at 220°. While yields were not given, they reported acceptable elemental analyses and expected ^{1}H nmr spectra, but without experimental data. Through the courtesy of Jacquignon [20] we were sent copies of the 60 MHz ^{1}H nmr spectra of twelve of these compounds in deuteriochloroform. The aromatic regions of all of them are remarkably similar and consist of a multiplet for one proton (H-8) at about δ 9.39, a multiplet for one proton (H-1) at *ca.* 8.46, and a complex multiplet for ten other protons at 7.3-7.9. No singlet for H-14 is observed between the signals for H-1 and H-8 [21]. Thus, it is apparent that the structures of the Jacquignon products were correctly assigned. However, two of the products, namely the methyl derivative "**2a**" [22] and *n*-butyl derivative "**2c**" [5], were reported by Buu-Hoï previously and with markedly higher melting points, 222° *versus* 173° and 223° *versus* 129°, respectively, than found by Jacquignon. *Prima facie* it appears that Buu-Hoï's products may have undergone alkyl migration analogous to ours over the long reaction time [13] to give sterically less hindered (and, hence, higher melting) isomers **3c**.

It is proposed that in our reactions some of the desired compound **2e** probably forms initially, but that the extended reaction time and/or elevated temperature, acting in conjunction with zinc chloride as a Lewis acid, causes labilization of the 14-alkyl group, which either migrates to ring D to give **3b** or escapes from the molecule to form **3a**. In fact, it has been reported that use of trimethylacetic acid in the Bernthsen reaction under refluxing conditions for 20 hours gives cyclization to the parent benzacridine or dibenzacridine with loss of the *t*-butyl group [23]. When, however, a *t*-butyl-2-naphthol was used along with

1-naphthylamine in the Ullmann-Fettvadjian reaction the *t*-butyl group was ostensibly retained (but not at position 14) in the resultant dibenz[*a,h*]acridine [3,5].

EXPERIMENTAL [24]

N-1-Naphthyl-2-naphthylamine (**1**), prepared from 1-naphthylamine and 2-naphthol by the procedure of Benz [25], was distilled, bp 208-217° (2 mm), and crystallized by trituration with 95% ethanol, mp 104-106° (lit 104° crude [19], 110-111° pure [25]). 2-Methylbutanoic acid [26] was converted to its anhydride, bp 100-105° (15-20 mm) (lit 103-104° at 17 mm [27]), through interaction of its anhydrous sodium salt and its acid chloride [28].

12- or 13-*s*-Butyldibenz[*a,h*]acridine (**3b**).

A mixture of 57 g (0.212 mole) of amine **1**, 93 g (0.5 mole) of 2-methylbutanoic anhydride, 25 g (0.245 mole) of 2-methylbutanoic acid, and 75 g (0.55 mole) of freshly fused zinc chloride was heated in a 500 ml steel bomb at 200-230° for 7 hours. To the cooled reaction mixture were added 300 ml of 10% aqueous sodium hydroxide solution plus sufficient ether to remove the contents of the bomb. The aqueous layer, containing suspended solid, was separated and extracted repeatedly with ether. Combined ether layers (4 ℓ total) were filtered, washed with water, and evaporated to leave a dark brown, syrupy residue. The residue was triturated with a small amount of ether [29] and the resultant solid was sublimed at 150-180° (0.03 mm) to yield *ca.* 10 g of tan product, R_f's 0 (brown, non-fluorescent) and 0.74 (bright blue fluorescence). The fluorescent component (10% by weight) was isolated by thick layer chromatography (under the preceding conditions) from a bright yellow, fast-moving zone to give **3b**, mp 158-163° (overall yield 1-2%), readily soluble in acetone. Trituration of this product with methanol plus recrystallization from absolute ethanol or benzene produced fine, faintly yellow needles, mp 167-168°; ^{1}H nmr (deuteriochloroform): δ 9.57 (d, $J_{8,9}$ = 8 Hz, 1H, H-8), 9.38 (s, 1H, H-14), 8.90 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1), 8.29 (partially split doublet, $J_{5,6}$ = 7.6 Hz, $J_{6,14} \cong$ 1 Hz, 1H, H-6), 8.17 (s, 1H, H-12 or H-13), 7.97 (d, H-5) which overlaps 7.93 (d, J = 9.8 Hz, 2H total, H-4 or H-11), 7.88-7.70 (m, 5H), 3.61 (sextet, J = 6.8 Hz, 1H, methinyl group), 2.11 and 1.88 (d of septets, J = 7.2 Hz, 2H, methylene group), 1.57 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.09 (t, J = 7.2 Hz, 3H, $CHCH_2CH_3$); ms: m/z 336 (20), 335 (M^+, 64), 307 (33), 306 ($M^+ - C_2H_5$, 100), 304 (36), 279 (306^+ -HCN, 29), 152 ($C_{12}H_8^+$, 20).

Anal. Calcd. for $C_{25}H_{21}N$: C, 89.51; H, 6.31; N, 4.17. Found: C, 89.50; H, 6.32; N, 4.32.

Dibenz[*a,h*]acridine (**3a**) [30].

The preceding reaction was repeated except that the bomb was heated at 270° for 13 hours to yield 8.8 g of crude tan solid. Part of this was recrystallized from benzene repeatedly to yield yellow leaflets, mp 220.5-221.5° (lit 221° [17b], 228° [17a]), with blue-green fluorescence [31], R_f 0.71; ^{1}H nmr (deuteriochloroform): δ 9.55 (d, $J_{8,9}$ = 7.8 Hz, 1H, H-8), 9.39 (s, 1H, H-14), 8.81 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1), 8.13 (AB system, $J_{5,6}$ = 9.3 Hz, Δδ = 52.6 Hz, 2H, H-6 and H-5), 7.96 (2 overlapping d, 2H, H-4 and H-11), 7.87 (AB system, $J_{12,13}$ = 8.8 Hz, Δδ = 23.8 Hz, 2H, H-12 and H-13), 7.76 (2 overlapping dd, 2H, H-9 and H-10), *ca.* 7.72 (2 overlapping dd, 2H, H-2 and H-3); ms: m/z 280 (31), 279 (M^+, 100), 278 (24), 140 (20), 139 ($[M - H]^{++}$, 26).

Anal. Calcd. for $C_{21}H_{13}N$: C, 90.29; H, 4.69; N, 5.01. Found: C, 90.20; H, 4.78; N, 4.95.

The COSY spectrum of **3a** (deuteriochloroform) was obtained with the pulse sequence supplied as part of the spectrometer software [32]. Operating characteristics were the following: 300.15 MHz, 12.77 μs for 90° pulse width, relaxation delay 2.5 s, acquisition time 300 ms for 1024 data points in t_2 and 75 ms for 256 increments in t_1. During data processing t_1 was zero-filled to 1024 points to give a resolution of 3.3 Hz in both directions. The spectrum is shown as Figure 1. In a separate COSY plot (not shown) a blob for long-range interaction between H-6 and H-14 was also readily observed.

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[12] The low yields and lack of success in obtaining funding for this project led us to pursue more promising research.

[13] Buu-Hoï and Lecocq [6] used these conditions: molar ratios of diphenylamine:free carboxylic acid:catalyst of 1:1.3 ± 0.4:2.1 ± 0.2, 200-230°, and 8 hours for reaction time. Purified products were characterized by elemental analysis for nitrogen and by melting point. Only crude yields (all low) were reported. Reaction conditions for their syntheses of alkyl derivatives of **3a** were not specifically stated but may have been as long as 24 hours [5].

[14] Non-fluorescent products were discarded.

[15] We considered the possibilities that amine **1** (a) may cyclize to a dibenz[*b,h*]acridine directly or (b) rearrange first to 1,1'-dinaphthylamine or 2,2'-dinaphthylamine before cyclization. However, none of the possible resultant alkyl-substituted dibenzacridines [16] should give a ^{1}H nmr spectrum consistent with that of the 168° product.

[16] For structures of all six of the possible dibenzacridines which might form see Ring Systems Handbook, Chemical Abstracts Service, Columbus, Ohio, File 3, RF numbers 58894-58899 (1988).

[17] Many chemical shifts are reported by B. Clin and B. Lemanceau, *C. R. Hebd. Seances Acad. Sci.*, **271**, *ser.* **D**, 788 (1970). More limited data are given by others, but structural assignments of the signals are not always consistent with ours. See (a) J. Andre, P. Jacquignon, F. Perin and N. P. Buu-Hoï, *Bull. Soc. Chim. France*, 389 (1970); (b) V. N. Gogte, G. B. Mullick and B. D. Tilak, *Indian J. Chem.*, **12**, 1227 (1974); (c) N. P. Buu-Hoï, M. Dufour, P. Jacquignon, M. Renson, G. Marechal and A. Ruwet, *J. Chem. Soc. (C)*, 2308 (1971).

[18] Our assignments are consistent with those reported by E. Vander

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[20] Present address: Chargé de Mission, Ministere de L'environment, 14, Boulevard du Général Leclerc, 92524 Neuilly-sur-Seine Cedex, France.

[21] For the especially clean spectrum of 14-ethyldibenz[*a,h*]acridine (**2f**) the methylene quartet falls at 3.66 and the methyl triplet at 1.72 ppm.

[22] N. P. Buu-Hoï and P. Cagniant, *Revue Sci.*, **81**, 503 (1943) synthesized "**2a**" by the Ullmann-Fettvadjian reaction [3] between 1-naphthylamine, 2-naphthol, and paraldehyde at a temperature up to 250° (although for a short time). The resultant "7,14-dihydro-**2a**" was aromatized by treatment with bromine in boiling benzene. The strongly fluorescent product gave a suitable analysis for nitrogen but failed to react with 4-nitroso-*N,N*-dimethylaniline in the manner found with 9-methylacridine (**6a**).

[23] N. P. Buu-Hoï, P. Jacquignon, M. Dufour and M. Mangane, *J. Chem. Soc. (C)*, 1792 (1966).

[24] The ^{1}H and COSY nmr spectra were determined on a General Electric QE-300 instrument. Electron-impact mass spectra were obtained at 70 eV by Dr. Richard Wielesek of this laboratory on a VG 12-250 instrument. Thin and thick layer chromatography were conducted with non-fluorescent silica gel/toluene. Fluorescent products were examined in ultraviolet light of 254 nm. Elemental analyses were obtained by Micro-Tech Laboratories, Skokie, Illinois.

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[29] Unfortunately, the ether triturate was discarded without further investigation.

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