# Phase Transfer Catalysis in *N*-Alkylations of the Pharmaceutical Intermediates 5*H*-Dibenz[*b*,*f*]azepine and 5*H*-10,11-Dihydrodibenz[*b*,*f*]azepine



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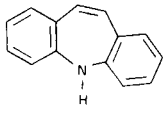
Received May 17, 1982

The two title compounds were alkylated under very mild phase-transfer-catalysis conditions. Differences in reactivities of the two heterocyclic nucleophiles, and in the reactivities of various alkyl halides are discussed.

*J. Heterocyclic Chem.*, **19**, 1569 (1982).

The heterocyclic ring systems 5*H*-dibenz[*b*,*f*]azepine (**1**) and 5*H*-10,11-dihydrodibenz[*b*,*f*]azepine (**2**) are common pharmaceutical intermediates in the syntheses of a number of drugs, *e.g.*, the widely used antidepressant, imipramine (**3**) (1). The syntheses of these drugs usually involve an *N*-alkylation step on the central azepine ring. Since the acidity of the N-H bonds, and the nucleophilicities of the corresponding anions in **1** and **2** are low, drastic conditions are necessary in order to carry out the *N*-alkylation: high temperatures (*e.g.*, refluxing toluene) and very strong bases (Na, K, $KNH_2$, $LiNH_2$, NaH, PhNa, *n*-BuLI, PhLi, TlOEt) have been required in these reactions (2,3). It would therefore be desirable that these processes, which are energy-consuming and hazardous, be replaced by simple and safe methods.



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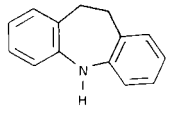

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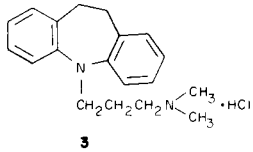

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Phase-transfer-catalysis (PTC) techniques proved in many cases to offer mild conditions for nucleophilic substitution reactions, by virtue of the increase in reactivity of the anion formed under these reaction conditions (4). The use of PTC methods in nucleophilic reactions has indeed expanded very rapidly in recent years (4,5). Of special interest is the use of PTC methods with heterocyclic *N*-nucleophiles, in which the nitrogen is incorporated in a ring system (6). This interest is due, in part, to the fact that such heterocyclic moieties are found in a vast number of drugs (1,6,7). Previous attempts, however, to reduce reaction temperatures in alkylations of **1** and **2** utilizing PTC techniques have failed (8).

We wish to report that **1** and **2** can be alkylated with a variety of alkyl halides, under mild conditions, *i.e.*, room temperature and aqueous sodium hydroxide as the base, in a two phase system. Two phase transfer catalysts were used: tetra-*n*-butylammonium hydrogen sulfate (TBAH) and the less common *n*-butyltriethylammonium bromide (BTEB). Typical experiments and results are presented in the Table.

The following observations and conclusions can be drawn based on the data indicated. (a) The two heterocyclic nucleophiles, **1**, **2** differ significantly in reactivity (*c.f.*, *e.g.*, experiments 6 and 8). Such differences in reactivity have been observed previously (9), and are attributed to the increase in steric hindrance of the nitrogen in **2** as compared to **1** (3,10). The reactivity of the nitrogen center of **2** is affected by the saturated $C_{10}$-$C_{11}$ bridge because of easier ring puckering. However, the unsaturated $C_{10}$-$C_{11}$ bridge in **1**, does not permit such easy puckering. (b) Similar steric effects are probably the reason for the decreased yields observed in the alkyl iodide series, with increasing alkyl chain lengths (*c.f.*, *e.g.*, experiments 11, 15, 19, 20). This trend was also observed in *N*-alkylation of **1** with alkyl iodides, and with thallium ethoxide as catalyst (3). (c) There are some indications pointing to the possibility that the alkylating methanism is $S_N2$, type I (12) (nucleophile$^-$ + RX → nucleophile-R + $X^-$). First, reactivity order of alkyl halides emerges from the table, which is typical for $S_N2$ reactions: Ph-$CH_2Br$ > $CH_2$ = $CHCH_2Br$ ~ $CH_3I$ > $CH_3CH_2I$ > $CH_3CH_2CH_2CH_2I$ (13). (Notice the high yields for benzyl bromide, allyl bromide and methyl iodide.) Second, when methylene chloride (dielectric constant 8.93) was replaced with methyl isobutyl ketone (MIK, dielectric constant 30.10) in alkylations with benzyl and allyl bromide (experiments 4, 5 and 8, 9), the yields dropped sharply. This observation not only excluded an $S_N1$ mechanism but is typical of type I $S_N2$ reactions

Table

PTC *N*-Alkylations of **1** and **2**

| Experiment No. | Alkylating Agent | Equimolars of alkylating agent (a) | Nucleophile | Solvent/ base (b) | Catalyst (c) (equimolars (a)) | Reaction Time (hours) | Coversion to product % (d) |
|---|---|---|---|---|---|---|---|
| 1 | $Ph\text{-}CH_2Br$ | 1.5 | **1** | A/C | TBAH (0.1) | 48 | 100 (e) |
| 2 | | 1.5 | **1** | A/C | BTEB (0.1) | 48 | 100 |
| 3 | | 1.0 | **1** | A/C | TBAH (0.1) | 48 | 83 |
| 4 | | 3.0 | **2** | A/C | TBAH (0.1) | 72 | 33 |
| 5 | | 3.0 | **2** | B/C | TBAH (0.1) | 72 | <5 |
| 6 | $CH_2=CHCH_2Br$ | 3.0 | **1** | A/C | TBAH (0.1) | 48 | 100 |
| 7 | | 3.0 | **1** | A/C | BTEB (0.1) | 48 | 100 |
| 8 | | 3.0 | **2** | A/C | TBAH (0.1) | 72 | 14 |
| 9 | | 3.0 | **2** | B/C | TBAH (0.1) | 73 | <5 |
| 10 | $ClCH_2CH_2CH_2Br$ | 3.0 | **1** | A/D | BTEB (0.1) | 60 | 55 (f) |
| 11 | $CH_3I$ | 6.0 | **1** | A/C | BTEB (1.0) | 23 | 91 |
| 12 | | 6.0 | **1** | A + B/C | TBAH (1.0) | 23 | 91 |
| 13 | | 1.0 | **1** | A/C | TBAH (1.0) | 48 | 22 |
| 14 | | 6.0 | **2** | A/C | TBAH (1.0) | 72 | 19 |
| 15 | $CH_3CH_2I$ | 6.0 | **1** | A/C | TBAH (1.0) | 47 | 57 |
| 16 | | 1.0 | **1** | A/C | TBAH (1.0) | 48 | 5 |
| 17 | | 6.0 | **1** | A/D | TBAH (1.0) | 47 | 60 |
| 18 | $CH_3CH_3CH_2I$ | 6.0 | **1** | A/C | TBAH (1.0) | 24 | 21 |
| 19 | $CH_3CH_2CH_2CH_2I$ | 6.0 | **1** | A/C | TBAH (1.0) | 47 | 40 |
| 20 | | 1.0 | **1** | A/C | TBAH (1.0) | 24 | 0 |
| 21 | | 6.0 | **1** | A/D | TBAH (1.0) | 47 | 21 |

(a) Relative to **1** or **2**. (b) A: Methylene chloride; B: Methyl isobutylketone; C: 50% aqueous sodium hydroxide; D: solid potassium hydroxide. (c) TBAH: tetrabutylammonium hydrogen sulfate; BTEB: Butyl triethyl ammonium bromide. (d) There are no significant side reactions of **1** and **2**, other than the desired alkylation. The unreacted nucleophile may be isolated by column chromatography. Yields based on recovered **1** and **2**, were usually close to 100%. Except *N*-benzyl-**11** (e), all other products are known, and were characterized by mp and nmr. (e) New compound. Fully characterized (see experimental). (f) Two products: 10% of the *N*-propyl chloride derivative and 45% of the de-hydrohalogenation product, the *N*-allyl derivative. Chlorobutane did not alkylate **1** under these conditions.

(14). Third, the difference in reactivities of **1** and **2** is indicative of an $S_N2$ mechanism. Rates of $S_N1$ reactions are usually independent of the nature of the nucleophile (15). Fourth, within the alkyl iodides series, the trend described under (b) is, again, typical of $S_N2$ reactions (16). (d) The mild conditions under which our *N*-alkylations were performed were probably possible by increase in anion-nakedness (17). Acceleration of reactions under PTC conditions is indeed partially attributed to such an effect (4).

Further synthetic and mechanistic studies on the applications of PTC methods in *N*-alkylations of pharmaceutical intermediates are in progress.

## EXPERIMENTAL

*N*-Benzyl-5*H*-dibenz[*b*,*f*]azepine.

The following alkylation of **1** with benzyl bromide, illustrates a typical procedure.

A solution of 0.50 g (2.6 mmoles) of **1**, 0.888 g (0.26 mole) of tetrabutylammonium hydrogen sulfate, and 0.46 ml (4.0 mmoles) of benzyl bromide in 15 ml of methylene chloride, was stirred vigorously with 10 ml of 50% aqueous sodium hydroxide for 48 hours. Progress of the reaction was followed by tlc (silica gel, methylene chloride: petrol-ether 40°-60° = 3:7). The mixture was then diluted with 50 ml of water and 10 ml of dichloromethane. The organic layer was separated, and the aqueous layer washed with methylene chloride. The combined organic extracts were washed twice with water, dried over magnesium sulfate, and the solvent removed under vacuum. The oily residue was purified by flash-chromatography (18) (silica gel, methylene chloride: petrol-ether 40°-60° = 3:7), to yield 0.74 g (2.6 mmoles) of the pure *N*-benzylated product, mp 74-76°; ir was free of N-H stretching; nmr (deuteriochloroform): δ 4.85 (s, $Ph\text{-}CH_2\text{-}$, 2H), (s, CH=CH, 2H), 6.8-7.6 (m, aromatic, 13H); ms: 283 ($M^+$, $PhCH_2$, 100), 91 ($C_7H_7^+$, 34).

*Anal.* Calcd. for $C_{21}H_{17}N$: C, 89.0; H, 6.1; N, 4.9. Found: C, 89.1; H, 6.2; N, 4.8.

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