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# SYNTHESIS, ISOLATION AND CHARACTERISATION OF SOME SUBSTITUTED N-BENZYL AND N-BENZOYL ANILINES

**M. ULGEN*, J.W. GORROD****

## SUMMARY

The benzylation and benzoylation of certain ring substituted anilines were performed to produce benzyl and benzoyl derivatives which were required as substrates and potential metabolites for drug metabolism studies. The methods employed yielded the desired secondary anilines together with corresponding amides. The structures and purity of these products were confirmed using spectroscopic methods and their separations from both starting materials and corresponding primary anilines were achieved by use of column and thin-layer chromatography. Although some of these products are known compounds, this present work decribes a useful separation technique and detailed spectroscopic and chromatographic data for the related required compounds under study.

**Key Words:** Substituted N-benzyl and N-benzoyl anilines, Column chromatography.

(*) University of Marmara, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 81010 Haydarpaşa, Istanbul, Turkey.
(**) Chelsea Department of Pharmacy, King's College London, University of London, Manresa Road. London, SW3 6LX, UK

## ÖZET

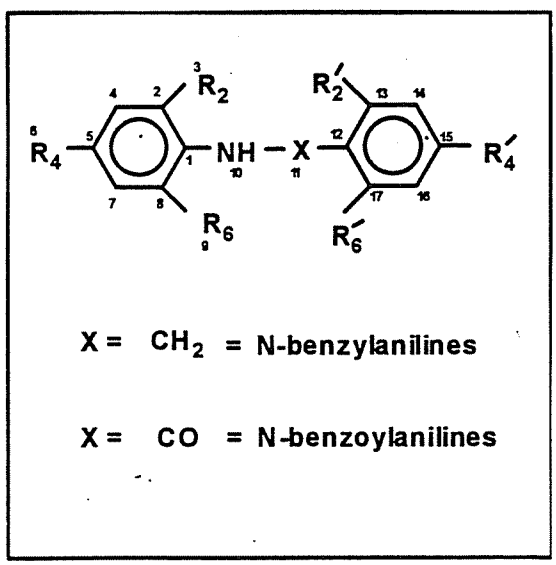
Halkada sübstitüe olmuş çeşitli anilinlerin benzillenme ve benzoillenmeleri ilaç metabolizma çalışmalarının substratları ve muhtemel metabolitleri olarak gereksinilen benzil ve benzoil türevlerini elde etmek için yapıldı. Uygulanan yöntem ilgili amidlerle beraber arzu edilen sekonder anilinleri (ve bazı durumlarda tersiyer aminleri) verdi. Bu maddelerin yapıları ve saflıkları spektroskopik metodlarla onaylandı. Maddelerin başlangıç maddeleri ve karşılıkları olan primer anilinlerden ayrılmaları ince tabaka kromatografisi ve kolon kromatografisi ile sağlandı. Bu ürünlerin bazıları bilinen bileşikler olmalarına rağmen, bu çalışmada hedeflenen ürünlerin elde edilmesinde kullanılabilecek bir ayırma tekniği ile detaylı spektroskopik ve kromatografik bulgular verilmektedir.

## INTRODUCTION

Work on the microsomal metabolism of N-benzyl substituted anilines required the synthesis, preparation and characterization of related substrates and potential amide metabolites (see Table 1. for abbreviations and structures). The usual method for the preparation of N-benzylanilines is benzylation of the appropriate aniline using benzylhalide (1, 2). However, unless the reaction is carefully controlled or one of the protons on the aniline is protected, mixtures of mono- and di-substituted products are often obtained. The reaction of an approprate aniline and aldehyde to give a Schiff base followed by its reduction with sodium borohydride is an alternative two step preparative method for mono or unsubstituted N-benzylanilines (3, 4). Another method of synthesis of N-alkylanilines is reduction of the corresponding secondary amides using an alkali metal hydride (5). However this latter method is not very efficient and can lead to cleavage of the anilide giving the primary amine. Reaction with a benzoyl halide has been used to prepare the benzoyl derivative of primary aromatic amines (1). Whilst most of the anilides ie NBZTMA, NBZTBA and NBZTCA are known compounds and have been used to characterise primary anilines, their spectroscopic and chromatographic characteristics are not extensively available in the literature (6).

**Table 1:** The structures and abbreviations of N-benzylanilines and corresponding N-benzoyl analogues prepared

| Compound | Abbreviations | $R_2$ | $R_4$ | $R_6$ | $R_2'$ | $R_4'$ | $R_6'$ |
|---|---|---|---|---|---|---|---|
| N-benzyl-2, 4, 6-trimethylaniline | NBTMA | $CH_3$ | $CH_3$ | $CH_3$ | – | – | – |
| N-benzoyl-2, 4, 6-trimethylaniline | NBZTMA | $CH_3$ | $CH_3$ | $CH_3$ | – | – | – |
| N-benzyl-2, 4, 6-tribromaniline | NBTBA | Br | Br | Br | – | – | – |
| N-benzoyl-2, 4, 6-tribromaniline | NBZTBA | Br | Br | Br | – | – | – |
| N-benzyl-2, 4, 6-trichloraniline | NBTCA | Cl | Cl | Cl | – | – | – |
| N-benzoyl-2, 4, 6-trichloraniline | NBZTCA | Cl | Cl | Cl | – | – | – |
| N-benzyl-2, 4, 6-trifloraniline | NBTFA | F | F | F | – | – | – |
| N-benzoyl-2, 4, 6-trifloraniline | NBZTFA | F | F | F | – | – | – |
| N-(2, 4-dichlorobenzyl)aniline | N24DCBA | – | – | – | Cl | Cl | – |
| N-(2, 4-dichlorobenzoyl)aniline | N24DCBZA | – | – | – | Cl | Cl | – |
| N-(2, 6-dichlorobenzyl)aniline | N26DCBA | – | – | – | Cl | – | Cl |
| N-(2, 6-dichlorobenzoyl)aniline | N26DCBZA | – | – | – | Cl | – | Cl |

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# EXPERIMENTAL

## Materials

All the parent amines, appropriate benzyl and benzoyl halides, potassium carbonate, potassium iodide and sodium hydroxide were purchased from Aldrich Chemical Company, UK. All the chromatographic solvents were obtained from British Drug Houses, Poole, Dorset as S.L.R. grade. Silica gel 60; particle size 0.063 - 0.200 mm (70-230 mesh ASTM) for column chromatography and plastic-backed TLC plates precoated with silica gel $60F_{254}$ were obtained from E. Merck, Darmstadt, Germany.

## Instrumentation

UV spectra were recorded on a KONTRON UVIKON 860 UV spectrophotometer. IR spectra were determined on a Perkin Elmer IR spectrophotometer as Nujol mulls for solid compounds. Mass spectra were determined by direct insertion of samples on a VG12F mass spectrometer with a 70 eV ionisation potentials, source temperature 200-240°C. $^1H$ NMR spectra were determined on a Perkin Elmer R32 90MHz NMR spectrometer. Deuterated chloroform and tetramethylsilane were used as sample solvent and internal standard respectively. Elemental C, H, N analyses were carried out on a model 24 0XY Control and 1106 Carlo Erba equipment by Medac, Brunel University, Uxbridge, UK.

## Synthesis of N-benzylanilines:

The appropriate aniline was dissolved in acetone and potassium iodide and potassium carbonate added. The contents were refluxed while stirring vigorously. When the temperature rose to 90°C, benzylbromide was added to the mixture dropwise over half an hour. The reaction was carried out using the appropriate substituted benzyl chlorides when 2, 6- and 2, 4-dichlorobenzylanilines were synthesised. The reaction was monitored by thin layer chromatography until a second product became evident. The cooled reaction mixture was filtered and the acetone evaporated to give an oil. The required compound was isolated by use of column chromatography using a 35x2 cm glass column filled wuith silica gel 60 as a slurry in a suitable solvent or column chromatography followed by preparative thick layer chromatography on Silica Gel $GF_{254}$ 0.5

mm plates. Yield, description of product and purification solvents are given in tables 2 and 3 respectively.

**Preparation of N-benzoylanilines:**

These anilides were rapidly prepared in a pure state using the Schotten-Baumann reaction (1). Essentially, the primary amines were treated with sodium hydroxide (2N) and the appropriate acid chloride added; the mixture was shaken until the temperature returned to about 25°C. The solid which formed was collected, washed with water and recrystallised from ethanol. Most of these compounds ie NBZTCA, NBZTMA and NBZTBA were known and their m.p.s., which were uncorrected, were recorded in the literature (6). Table 2 shows the yield, description, analytical and spectral data of the prepared anilides.

## RESULTS AND DISCUSSION

The present method employed for the benzylation of certain ring substituted anilines was a modification of Vogel's method (1) and usually gave rise to the desired secondary anilines. In some cases N, N-dibenzyl derivatives were also obtained and characterised (7), although their separation is not described herein; however in the case of parent amines bearing strong electron withdrawing substituents; or methyl groups on the phenyl ring which can sterically hinder the amino group, the reaction using benzyl chloride and the appropriate anilines did not give the desired N-benzyl product in good yields, even though the reaction was allowed to proceed under reflux for over 48 hours at 140-150°C. Therefore, it was decided to modify Vogel's method. These "lethargic" reactions proceeded much faster when benzyl bromide together with potassium iodide was used as a benzylating agent. It has previously been reported that it is possible to enhance the benzylation rate by incorporating potassium iodide into the reaction mixture to generate benzyl iodide *in situ* (2). This procedure not only gave rise to the desired N-benzyl product, but the N, N-dibenzyl product was also obtained from each aniline (7). In some cases, the tertiary amine was isolated together with a small amount of unreacted primary amine and benzylating agent. Isolation and characterisation of these N, N- dibenzyl-2, 4, 6-trisubstituted anilines as well as the desired secondary anilines was carried out. Column chromatography was used to isolate the required N-benzylanilines from the reaction mixture.

**Table 2:** Analytical and spectral data of N-benzylanilines and corresponding N-benzoyl analogues

| Compound | M.W. | Molecular Formula | Elemental Analysis % Calculated (Found) C | H | N | m.p. and description | Yield % | UV max. (nm) (in MeOH) | m/e (% relative abundance) 70 ev |
|---|---|---|---|---|---|---|---|---|---|
| NBTCA | 286 | $C_{13}H_{10}C_{13}N$ | 54.48 (54.47 | 3.52 3.53 | 4.89 4.85) | oil | 40 | 211.256 | 91 (100), 285 (7.59) 286 (1.51), 287 (7.04) 289 (1.92) |
| NBTMA (HCl) | 225 (261.8) | $C_{16}H_{20}ClN$ | 73.41 (73.69 | 7.70 7.81 | 5.35 5.24) | 198 (HCl) white powder | 50 | 241 | 91 (52.07), 134 (100) 225 (42.64), 226 56.93) |
| NBTFA (HCl) | 237 (273.7) | $C_{13}H_{11}ClF_3N$ | 57.05 (56.85 | 4.05 3.80 | 5.12 5.16) | 135 (HCl) white powder | 50 | 210,235 | 91 (100), 236 (1.75), 237 (22.70). 238 (3.40) |
| NBTBA (HCl) | 419.9 (456.4) | $C_{13}H_{11}ClBr_3N$ | 34.21 (34.70 | 2.43 2.31 | 3.07 3.04) | 124 (HCl) white powder | 40 | 220,255 | 91 (100), 418 (13.20), 421 (12.12) |
| N24DCBA | 252.2 | $C_{13}H_{11}Cl_2N$ | 61.93 (62.04 | 4.40 4.39 | 5.56 5.56) | oil | 55 | 206,250 | 159 (100),161 (68), 163 (11.67), 251 (59.16) 252 (16.23), 253 (37.7) 254 (7.03, 255 (6.36) |
| N26DCBA (HCl) | 252.2 | $C_{13}H_{11}Cl_2N$ | 61.93 (61.80 | 4.40 4.40 | 5.56 5.49) | oil | 55 | 206,244 | 251 (95.33), 253 (60.20), 254 (11.43). 255 (10.45) |
| NBZTCA | 300.7 | $C_{13}H_8Cl_3NO$ | 51.95 (51.96 | 2.68 2.72 | 4.66 4.57) | 174 white crystals | 70 | 205 | 77 (52.04), 105 (100), 264 (9.83), 266 (6.37) |
| NBZTMA | 239.3 | $C_{16}H_{17}NO$ | 80.30 (80.01 | 7.16 7.18 | 5.85 5.77) | 204 white crystals | 80 | 207,221 | 77 (52.04), 105 (100), 134 (17.13), 239 (26.21) 240 (4.79) |
| NBZTBA | 433 | $C_{13}H_8Br_3NO$ | 35.98 (36.85 | 1.86 2.04 | 3.23 3.30) | 197 pale yellow powder | 40 | 215,226 | 77 (42.21), 105 (100), 352 (9.65). 354 (18.92), 356 (9.35), 357 (1.42) |
| NBZTFA | 251 | $C_{13}H_8F_3NO$ | 62.16 (62.10 | 3.21 3.16 | 5.58 5.53) | 161 white crystals | 90 | 206,231 | 77 (49.86), 105 (100), 251 (6.51) |
| N24DCBZA | 266.2 | $C_{13}H_9Cl_2NO$ | 58.67 (58.65 | 3.41 3.35 | 5.26 5.42) | 144 white crystals | 80 | 206,250 | 173 (100), 175 (58.52). 176 (4.71), 177 (9.69), 265 (11.06), 266 (1.74), 267 (7.05), 268 (100) |
| N26DCBZA | 266.2 | $C_{13}H_9Cl_2NO$ | 58.67 (58.70 | 3.41 3.40 | 5.26 5.24) | 174 white crystals | 85 | 206,244 | 173 (100), 175 (63.16). 177 (11.50), 265 (308.05), 265 (38.05, 266 (5.64). 267 (24.66), 268 (3.53) |

**Table 3:** Chromatographic method and solvent system used to isolate N-benzylanilines from reaction mixtures

| Compound | Separation Method and Solvent System Utilised |
|---|---|
| NBTCA* | CC using petroleum ether : acetone (95:5, v/v) followed by Prep. TLC using petroleum ether : chloroform (75:25, v/v) |
| NBTMA | CC using petroleum ether : acetone (95:5, v/v) |
| NBTBA | CC using petroleum ether : chloroform (50:50, v/v) followed by Prep. TLC using petroleum ether : acetone (95:5, v/v) |
| NBTFA | CC using petroleum ether : chloroform (50:50, v/v) |
| N26DCBA | CC using petroleum ether : chloroform (50:50, v/v) |
| N24DCBA | CC using petroleum ether : chloroform (50:50, v/v) |

(Petroleum ether : b.p. 40-60°C)
* for abbreviations see code in table 1.
CC : column chromatography

**Table 4:** Thin layer chromatographic properties (Rfx100) of N-benzyl and N-benzoylsubtituted anilines

| Compound | S1 | S2 | S3 | S4 | S5 |
|---|---|---|---|---|---|
| TMA | ND | 55 | 29 | 45 | ND |
| NBTMA | ND | 74 | 57 | 65 | ND |
| NBZTMA | ND | 47 | 24 | 53 | ND |
| TCA | ND | 66 | ND | 66 | ND |
| NBTCA | ND | 72 | ND | 72 | ND |
| NBZTCA | ND | 54 | ND | 62 | ND |
| TBA | ND | 67 | 66 | 77 | ND |
| NBTBA | ND | 75 | 77 | 83 | ND |
| NBZTBA | ND | 50 | 44 | 72 | ND |
| TFA | ND | ND | 58 | 72 | ND |
| NBTFA | ND | ND | 69 | 79 | ND |
| NBZTFA | ND | ND | 35 | 65 | ND |
| A | 14 | ND | ND | 58 | ND |
| N24DCBA | 35 | 81 | ND | 85 | 93 |
| N24DCBZA | 17 | 63 | ND | 81 | 57 |
| N26DCBA | 37 | 41 | ND | 85 | 92 |
| N26DCBZA | 9 | 54 | ND | 75 | 48 |

see table 1 for abbreviations; ND: not determined
S1; petroleum ether*: acetone (90:10, v/v)
S2; petroleum ether*: acetone (70:30, v/v)
S3; petroleum ether: ethylacetate (80:20, v/v)
S4; benzene: ethylacetate: acetone (80:10:10, v/v)
S4; benzene: chloroform (50:50, v/v)

The purity of such isolated secondary anilines was confirmed using TLC (see table 4) and elemental analysis (Table 2). NMR spectroscopy confirmed the assigned structures. NBTMA 1H-NMR (MHz, CDC13); δ 2.23 (9H, s, H-3, H-6 and H-9), 4.05 (2H, s, H-11), 6.84 (2H, s, H-4 and H-7), 7.34 (5H, m, H-13, 14, 15, 16 and 17, NBTCA 3.7 (1H, s, H-10), 4.46 (2H, s, H-11), 7.20-7.33 (7H, m, H-4, 7, 13, 14, 15, 16 and 17), N26DCBA 4.6 (2H, s, H-11), 6.71-7.50 (7H, m, H-2, 4, 5, 7, 8, 14, 15, 16), 6.71-7.50 (7H, m, H2, 4, 5, 7, 8, 14, 15 and 16) (see table 1).

Mass spectral analysis, in all cases, showed molecular ion peaks ($M^+$) together with characteristic tropylium fragments (a peak at m/e 91) for benzylic compounds (Table 2). The IR spectrum showed an absorption band at 3350 $cm^{-1}$ and 1580 $cm^{-1}$ corresponding to N-H stretch of secondary aromatic amines and C=C stretch of the phenyl ring. The UV maximum absorption of N-benzylanilines are presented in Table 2.

Authentic samples of benzoyl derivatives were also required to compare with metabolites of secondary anilines thought to be amides. The corresponding amides were therefore prepared by direct benzoylation of the parent amine using benzoyl halide (1). TLC analysis showed only one product. Elemental analysis was consistent with the required structure (Table 2). NMR spectroscopy confirmed the structure. NBZTMA $^1$H-NMR (MHz, CDC13); δ 2.22 (6H, s, H-3 and H-9), 2.30 (3H, s, H-6), 6.95 (2H, s, H-4 and H-7), 7.30-7.61 (3H, m, H-14, 15 and 16), 7. (2H, m, H-13 and H-17). N26DCBZA 7.21-7.50 (5H, m, H-2, 4, 5, 7 and 8), 7.51-7.82 (3H, m, H-14, 15 and 16) (Table 1).

The IR spectrum of the amides showed a band at 1640 $cm^{-1}$ which corresponded to the C=0 stretch band vibration of secondary amides. NMR analysis showed that the unsubstituted phenyl protons gave a peak at 7.58 ppm. The substituted aniline ring protons gave a peak at 8 ppm; due to its lability no amide proton was observed. Mass spectral data of the prepared anilides are shown in Table 2. The correct molecular ions and a base peak at m/e 105 were observed. Phenyl radicals, m/e 77 were also observed as a secondary abundant peak for compounds containing a nonsubstituted benzoyl ring, as a result of carbon monoxide loss from the m/e 105 fragment. The UV maximum absorptions of N-benzylic amines are presented in Table 2.

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