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BAZI YENİ 2,4,6–TRİSUBSTİTÜE N,N–DİBENZİLANİLİNLERİN SENTEZ VE KARAKTERİSTİKLERİ

SYNTHESIS AND CHARACTERIZATION OF SOME NEW 2,4,6–TRISUBTITUTED N,N–DIBENZYLANILINES

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SUMMARY

The benzylation of certain ring substituted anilines were carried out in order to produce benzyl derivatives which were required as substrates for drug metabolism studies. The procedure employed gave rise to the desired secondary anilines, but N,N–dibenzyl derivatives were also obtained. Isolation and characterisation of these secondary products were carried out as they may also be used as substrates for future metabolic experiments, on microsomal C– and N–oxidation. This report contains the synthesis, purification and chemical characteristics of such isolated tertiary anilines.

ÖZET

Halkada substitüe olmuş çeşitli anilin türevleri, ilaç metabolizma çalışmalarının substratları olarak gereksinilen benzil türevlerinin sentezi için benzillendi. Yöntem, istenilen sekonder anilinleri verdi, ayrıca N,N–dibenzil türevleri de elde edildi. İlerki mikrozomal C– ve N–oksidasyon tipi metabolizma deneylerinin substratları olarak da kullanılabileceklerinden, bu ikincil bileşikler izole edilerek yapıları aydınlatıldı. Rapor bu şekilde kazanılan tersiyer anilinlerin sentez, saflaştırma ve kimyasal karakteristiklerini içermektedir.

INTRODUCTION

The aliphatic carbon moiety attached to aniline nitrogen is commonly involved in the structures of durgs and other xenobiotics thus creating secondary and tertiary anilines. The formations of chemically

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and pharmacologically active metabolites of these anilines and their intermediates are of particular interest since such species may play an important role in the mechanism of pharmacological and toxicological activities (1).

Oxidative biotransformations of the secondary (2,3,4) and tertiary (5,6,7) anilines may produce N–hydroxylated and N–hydroxylated and N–oxidized metabolites respectively and have been subject to a number of investigations. The oxidative metabolism of secondary and tertiary anilines has two main pathways, N– and C– oxidation. The importance of these two reactions may depend upon the physicochemical characteristics of the corresponding substrate molecule.

In a previous study (2,3,4), N–benzyl–4–substituted anilines were chosen to investigate *in vitro* metabolism of secondary aromatic anilines. Since these compounds have two rings, this allows a number of substituents to be introduced thus altering their physicochemical characteristics. The results from these early studies showed the corresponding amide metabolites, together with a number of other products arising from oxidative N–debenzylation, ring hydroxlation, N–hydroxylation and N–oxidation (2,3,4).

This novel finding of the amide (2,3,4) has led us to investigate the mechanism and chemical process(es) involved in formation of amides. In order to establish a mechanism, a structure–activity relationship on the formation of amides was required. A number of new benzylanilines bearing different substituents on either aromatic ring were synthesised (8) and *in vitro* metabolism studies carried out (9).

The present study shows the isolation and identification of the N,N–dibenzyl–2,4,6–trimethyl–, –2,4,6–tribromo– and – 2,4,6–trifluoro–anilines obtained as secondary products of aniline benzylation. The benzylation of aromatic amines using benzyl halides is a well characterised reaction (10). As an alternative method, a reductive alkylation reaction via an imine (Schiff's base) intermediate has been employed using a primary aniline and benzaldehyde, the benzylidene products are converted into N–benzyl derivatives, by reduction with sodium borohydride (11,12,13). Appropriate secondary amides hav ealso been reduced using alkali metal hydrides to produce secondary aryl/alkyl anilines.

This latter method is not very efficient as the reduction conditions usually lead to cleavage of the amide giving the parent aromatic amine (14).

MATERIALS AND METHODS

Materials

The following substances were purchased from Aldrich Chemical Company, UK. : benzyl bromide, 2,4,6–trimethyl–, 2,4,6–tribromo– and 2,4,6–trifluoro–anilines, potassium iodide, potassium carbonate. All chromatographic solvents were obtained from B.D.H. as S.L.R. grade. Silica gel 60 (70–230 mesh ASTM) and precoated silica gel GF_{254} TLC plates were obtained from Merck company.

Instruments

Mass spectra were determined by direct insertion of samples in methanol on a VG12F mass spectrometer with a 35 and 70 ev ionisation potential, source temperature 200–240°C. NMR Spectra were determined on a Perkin Elmer R32 90 Mz instrument. Deutearted chloroform and TMS were used as sample solvent and internal standard respectively. UV Spectra were obtained on a Kontron–Uvikon 860 UV spectrophotometer, the samples were prepared as 10^{-3} molar solutions in methanol. C, H, N analyses were carried out on a model 240XY Control and 1106 Carlo Erba equipments. Table 2 shows analytical data and table 3 presents mass spectra and nmr data for N,N–dibenzylanilines.

Methods

Into a three necked round bottom flask fitted with a reflux condenser and dropping funnel was placed 0.05 moles of primary aniline, potassium carbonate, and potassium iodine mixture in a minimum amount of acetone. The contents were refluxed while stirring vigorously with a magnetic stirrer/heater. Benzyl bromide (0.075 moles in acetone) were added into the mixture from a separating funnel dropwise over an hour at 90°. Small aliquots of the mixture were periodically removed for

TLC analysis with (95:5) v/v petroleum ether (40–60 C) : acetone solvent system in conjunction with silica gel plates. The reaction was continued until the formation of the tertiary amine became evident from TLC monitoring. The cooled reaction was filtered and the liquid evaporated on a rotary film evaporator. The dry residue, containing the mixture of mono and dibenzyl derivatives, was dissolved in a minimum amount of acetone. Column chromatography was carried out using a 35x2 cm column prepared using the silica gel as slurry in the appropriate mobile phase. Column chromatography allowed easy separation of the mixtures; the tertiary amine being eluted first. Further elution of the mixture gave the N–benzyl compounds in good yields. The solvents used to eluate the N,N–dibenzylanilines were S_1 for N,N–dibenzyl–2,4,6–trimethylaniline and S_2 for N,N–dibenzyl–2,4,6–tribromo– and –2,4,6–trifluoro–anilines (Table 1).

Table – 1 : TLC separations of N,N–dibenzylanilines from N–benzyl & parent anilines

Compound	Rf S_1	100 S_2
2,4,6–trimethylaniline (TMA)	23	7
N–benzyl TMA	56	10
N,N–dibenzyl TMA	83	74
2,4,6–tribromonaniline (TBA)	54	61
N–benzyl TBA	74	53
N,N–dibenzyl TBA	80	79
2,4,6–trifluoroaniline (TFA)	43	31
N–benzyl TFA	54	32
N,N–dibenzyl TFA	69	74

S_1 : Petroleum ether : Acetone (95:5 v/v)

S_2 : Petroleum ether : Chloroform (50:50 v/v)

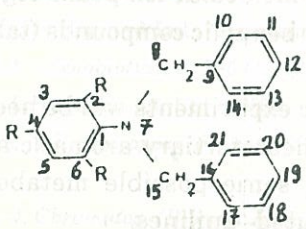
TLC was carried out 20x20 cm plates coated with silica gel GF_{254} 0.25 mm thick. Compounds were visualised by a 254 nm UV lamp. Ehrlich's reagent (10 % p–dimethylaminobenzaldehyde in 5N HCl mixed with acetone 1:4 just before use) gave immediately a yellow colour with primary and secondary anilines; however, tertiary anilines only slowly reacted with this reagent.

Table – 2 : Analytical data for N,N–dibenzylanilines

Compound	Molecular Weight	Molecular Formula	Yield %	Description and m.p.	Elemental Analysis					
					Required			Found		
					C :	H :	N	C :	H :	N
N,N–dibenzyl TMA	315.45	$C_{23}H_{25}N$	50	colourless oil	87.57	7.99	4.44	87.30	7.96	4.42
N,N–dibenzyl TBA	510.05	$C_{20}H_{16}Br_3N$	30	rhomboid crystalls (82°)	47.10	3.16	2.75	47.21	3.13	2.75
N,N–dibenzyl TFA	327.34	$C_{20}H_{16}F_3N$	70	colourless oil	73.38	4.93	4.28	73.39	4.91	4.08

Table – 3 : Mass spectra and NMR data for N,N–dibenzylanilines

Compound	UV DATA Max. Abs.	Major mass spectra fragments m/e (% relative abundapce)		NMR data chemical shift in ppm (type of signal, number of protons, origin of signsl)
	(nm)	35 eV	70 eV	
N,N–dibenzyl–TMA	208 (strong) 260 (weak)	315 (m^+ 44) 224 (100) 91 (47)	315 (m^+ 39) 224 (100) 91 (93)	2.15 (d, 9H, R=CH_3) 4.1 (s, 4H, C_8, C_{15}) 6.8 (s, 2H, C_3, C_5) 7.2 (s, 10H, nonsubstituted pheny protons from C_{10} to C_{21})
N,N–dibenzyl–TBA	210 (strong) 284 (weak)	508 (m^+ –2 18) 419 (29) 91 (100)	508 (m^+ –2 4) 417 (7) 91 (100)	4.3 (s, 4H, C_8, C_{15}) 7.3 (m, 10H, nonsubstituted phenyl protons from C_{10} to C_{21}) 7.6 (s, 2H, C_3, C_5)
N,N–dibenzyl–TFA	208 (strong) 252 weak	327 (m^+ 48) 328 (m+1 11) 236 (30) 91 (100)	327 (m^+ 15) 236 (13.2) 91 (100)	4.2 (s, 4H, C_8, C_{15}) 6.5 (m, 2H, C_3, C_5) 7.3 (m, 10H nonsubstituted phenyl protons from C_{10} to C_{21})



RESULTS

The standard method described by Vogel (10) has been succesfully employed for the preparation of N–benzyl anilines from most primary anilines. However in our cases, with the 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 appropriate anilines did not give the desired N–benzyl product in good yields even though the reation was refluxed for over 48 hours at 140–150°C. Therefore, it was decided to modify Vogel's method. The reaction proceeded much faster when benzyl bromide together with potassium iodide was used as a benzylating agent. It has previously been reported that it was possible to enhance the reaction rate by incorporating potassium iodide into the reaction mixture to generate benzyl iodide (15). This procedure not only gave rise to the desired N–benzyl product (8), but the N,N–dibenzyl product was also obtained from each aniline. 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 separate the N,N–dibenzylanilines from the reaction mixture. It was, in all cases, very much easier to isolate and purify, the N,N–dibenzylanilines than the corresponding N–benzyl derivatives as the tertiary amines were eluted first from the column by the chromatographic solvents utilised. The yield of these secondary products can be improved by increasing the reaction temperature, time and the amount of benzylating agent. The purity of such isolated tertiary anilines was confirmed using TLC (table 1), elemental analysis (table 2) and NMR (table 3) techniques. Mass spectra, in all cases, showed the molecular ion peaks together with characteristic tropylium fragments for benzylic compounds (table 3).

Further metabolic experiments will be needed in order to establish the metabolic fate of these tertiary aromatic amines in biological systems. Figure 1 shows some possible metabolic pathways for N,N–dibenzyl–2,4,6–substituted--anilines.

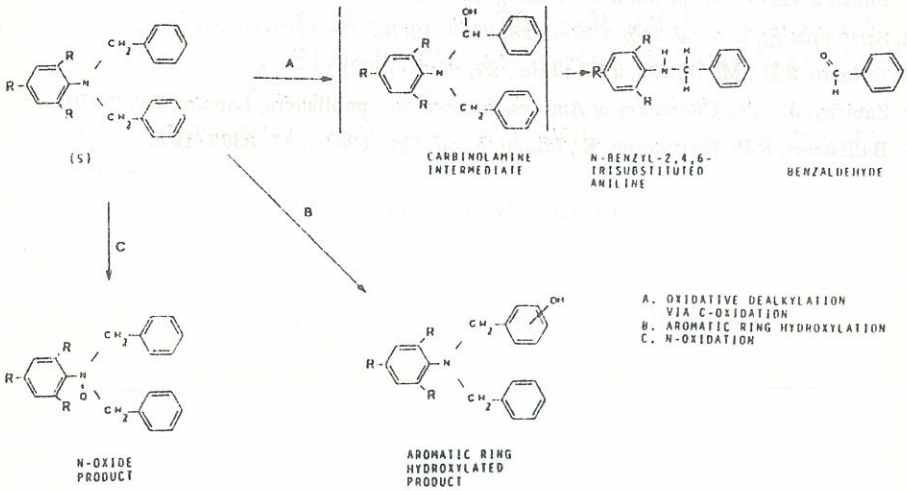


Fig. – 1 : Possible metabolic pathways for N,N–dibenzyl–2,4,6–trisubstituted–anilines (S).

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