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SIMPLE AROMATIC AMINES FROM *JUSTICIA GENDARUSSA*. ^{13}C NMR SPECTRA OF THE BASES AND THEIR ANALOGUES†

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Abstract—Four simple o-disubstituted aromatic amines have been isolated from the leaves of *Justicia gendarussa* Burm and characterized as 2-amino benzyl alcohol (**3**), 2-(2'-amino-benzylamino) benzyl alcohol (**4**) and their respective 0-methyl ethers **1** and **2** from ^1H NMR and mass spectral analyses of the bases and their acetates. Structures **3** and **4** have also been confirmed by synthesis. Intramolecular hydrogen bonding (cf. **9**, **13** and **14**) has been envisaged to explain the unexpected shielding of $-CH_2-OH$ carbon signals of **3** and **4** on acetylation and upfield displacement of $-CH_2-N$ signal of **2a** vs **4a** in their ^{13}C NMR spectra in $CDCl_3$ solution. $^1J_{CH}$ values have been found to be useful for the assignment of aromatic methine carbon signals in o-disubstituted compounds.

Justicia gendarussa (Acanthaceae) is known for its medicinal properties[1] in the Indian system of medicine. Apart from topical application in oedema of beriberi and rheumatism, the use of the fresh leaves by the local practitioners in cardiac asthma inspired us to undertake a systematic investigation of this plant from which only β-sitosterol has so far been reported.[2,3] We now report the isolation and characterisation of some basic constituents which, to our knowledge, have not yet been encountered in nature.

Initially, the powdered leaves of *J. gendarussa* were extracted successively with light petrol and methanol. The petrol extract yielded β-sitosterol, lupeol and friedelin. Though the Dragendroff-positive methanol extract was found to contain a considerable amount of a mixture of bases, their separation and purification proved to be extremely difficult owing to their unstable nature in the impure state. Nevertheless, it was still possible to isolate two components as in the sequel.

The concentrated methanolic extract on dilution with water separated a gummy mass. The clear solution upon acid hydrolysis and chromatography of the resulting basic part over silica gel yielded compound **1** as an oil (Dragendroff-negative), $C_8H_{11}NO$, M^+ at *m/z* 137. The gummy mass, on the other hand, on extraction with acid, regeneration of the base followed by repeated column chromatography and plc afforded compound **2** as a viscous oil (Dragendroff-positive), $C_{15}H_{18}N_2O$, M^+ at *m/z* 242.

On acetylation at room temperature, compound **1** furnished a crystalline N-monoacetate (**1a**), mp 80°, M^+ at *m/z* 179 while **2** gave a N,N'-diacetate (**2a**), mp 210°, M^+ at *m/z* 326, as revealed by the IR and mass spectra.

The ^1H NMR spectrum of compound **1** showed a three proton singlet at δ3.29 and a two-proton singlet at δ4.41 respectively assignable to $-O-\underline{CH_3}$ and $Ar-\underline{CH_2}-O-$ groupings, a multiplet between δ6.53 and 7.20 for four aromatic protons and a D_2O exchangeable broad signal centered at δ3.89 for an NH_2 group. That it is a 1,2-disubstituted aromatic compound became evident from the spectrum of its N-acetate (**1a**) which exhibited *inter alia* a down field signal at δ8.30 (J = 8Hz) as a broad doublet assignable to an aromatic proton ortho to an acetamido group.

All the foregoing data are compatible with a 2-amino-0-methyl-benzyl alcohol structure for compound **1**, corroborated by an intense peak at *m/z* 106 (species *a*) in the mass spectra of both **1** and **1a**. Finally, the structure was confirmed by hydrogenolysis of **1a** to yield N-acetyl-o-toluidine.

Compound **2**, like **1**, showed an intense peak at *m/z* 106 in its mass spectrum indicating the presence of an o-amino-benzyl moiety in the molecule. The ^1H NMR spectrum of compound **2** exhibited three singlets at δ3.23(3H), 3.68(2H) and 4.32(2H) respectively assignable to $-O\underline{CH_3}$, $Ar-\underline{CH_2}-N-$ and $Ar-\underline{CH_2}-O-$ groupings, and an exchangeable three proton multiplet at around δ3.57 for an $-N\underline{H_2}$ and an $-N\underline{H}-$ groups. A multiplet between δ6.37 and 7.07 for eight protons was in agreement with two disubstituted benzene rings. The down-field chemical shifts of two aromatic protons of the acetate **2a** resonating as broad doublets at δ7.73 (J = 8Hz) and δ8.09 (J = 8Hz) implies further that the two aromatic nuclei are separately attached to $-NH_2$ and $-NH-$ groups.

All the above observations are consistent with the assignment of structure (2-(2'-amino-benzylamino)-0-methyl-benzyl alcohol for compound **2**. This structure also explains why unlike **1**, compound **2** suffers a primary loss of 32 mass units (corresponding to a molecule of MeOH) followed by loss of a hydrogen atom as a radical.

In order to ascertain whether any or both of the constituents could be artefact(s), the defatted plant material was extracted with chloroform in lieu of methanol. The crude basic fraction, on chromatography over deactivated silica gel and separation by plc, yielded two new compounds, namely, compound **3**, C_7H_9NO, mp 85°, M^+ at *m/z* 123 and compound **4**, $C_{14}H_{16}N_2O$, mp 131°, M^+ at *m/z* 228, the molecular ions in their mass spectra being 14 mass units lower than those of the respective compounds **1** and **2** which they replaced.

On acetylation with Ac_2O-Py, compound **3** formed an N,0-diacetate (**3a**), M^+ at *m/z* 207 and compound **4** gave N, N', 0-triacetate (**4a**), M^+ at *m/z* 354 indicating the

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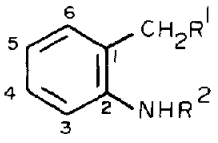
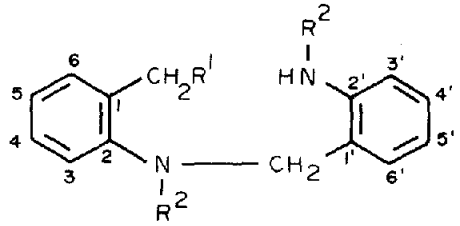
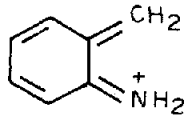


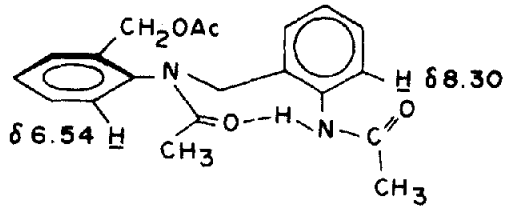


1, R^1 = OMe, R^2 = H
1a, R^1 = OMe, R^2 = Ac
3, R^1 = OH, R^2 = H
3a, R^1 = OAc, R^2 = Ac
5, $R^1 = R^2$ = H
5a, R^1 = H, R^2 = Ac

2, R^1 = OMe, R^2 = H
2a, R^1 = OMe, R^2 = Ac
4, R^1 = OH, R^2 = H
4a, R^1 = OAc, R^2 = Ac



g, m/z 106



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replacement of OMe groups of **1** and **2** by OH functions in these compounds. This conclusion received support from the absence of the $-OCH_3$ signal in the ^1H NMR spectra of **3** and **4** and their acetates (*vide* Experimental) as well as the prominent peaks at *m/z* 106 (species *a*) in their mass spectra. Furthermore, the conversion of compound **3** to **1** by refluxing with methanolic HCl also established their interrelationship.

Finally, the structure of **3** and **4** as 2-amino-benzyl alcohol and 2-(2'-amino-benzylamino)-benzyl alcohol respectively were confirmed by synthesis from o-toluidine as in the Scheme.

2-Phthalimido-toluene (**6**), prepared from o-toluidine and phthalic anhydride, on bromination with NBS in presence of a catalytic amount of AIBN under irradiation yielded the bromo-derivative (**7**) which on saponification in aqueous dioxane[4] gave 2-amino-benzyl alcohol (**3**), characterized as its acetate, identical with the N, 0-diacetate (**3a**) of the natural product.

Compound **3**, obtained from the natural source, was condensed with **7**, in pyridine over a steam-bath to obtain **8**. The latter on refluxing with alcoholic hydrazine hydrate[5] furnished 2-(2'-amino-benzylamino)-benzyl alcohol identical in all respects with the naturally occurring compound **4**.

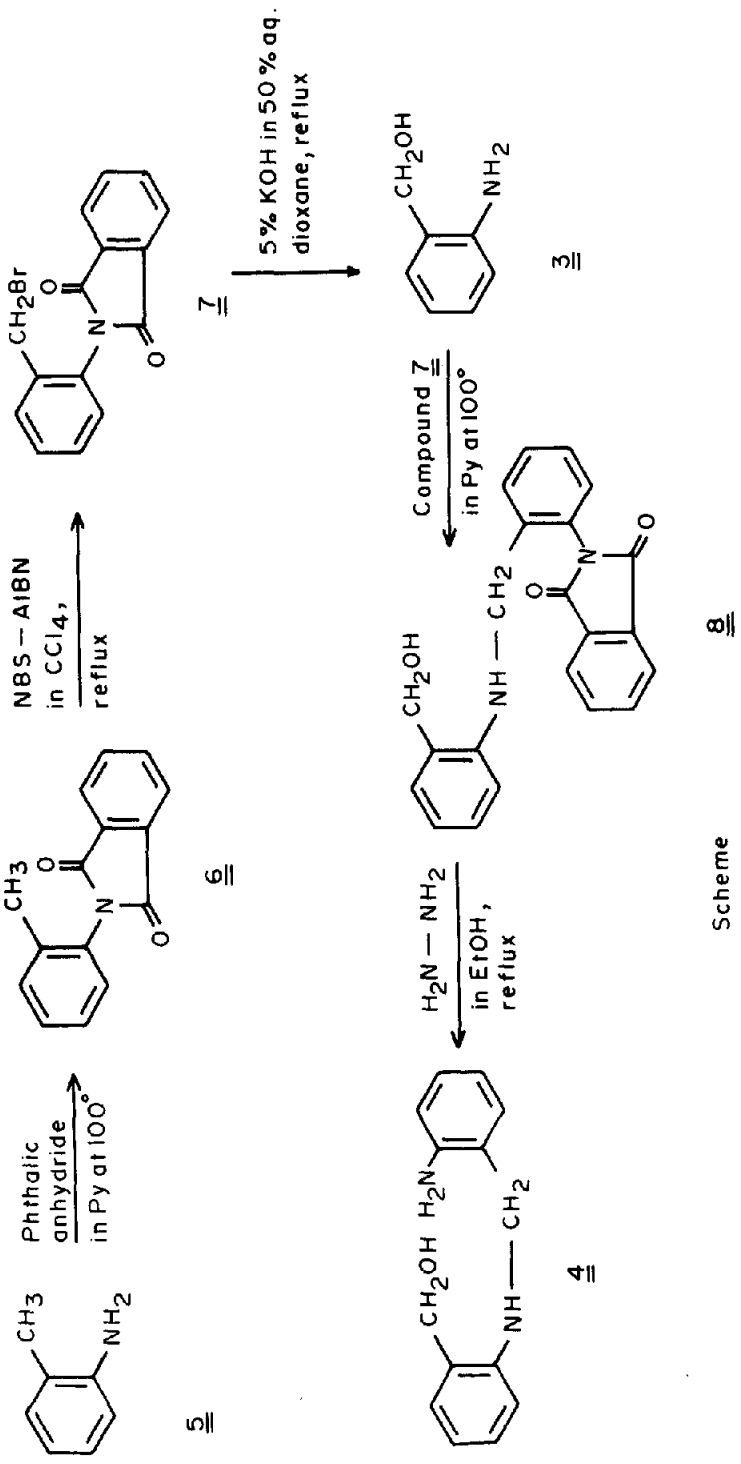
Having had established the structures, the following observations in the ^1H NMR spectrum of **4a** remained to be explained: (i) the magnetic non-equivalence of the methylene protons of both the Ar–CH_2–O– and Ar–CH_2–N– groupings in **4a** while they showed singlets in cases of **2**, **2a** and **4** and (ii) the significant down-field displacement (by ~0.8 ppm) of the resonance frequencies of the protons of Ar–CH_2–N and the up-field shift (by ~1.2 ppm) of one of the aromatic protons (3-H and 3'-H) *ortho* to the acetamido groups in **4a** as against the corresponding ones in **2a**.

While the non-equivalence of Ar–CH_2–O– protons of **4a** could be ascribed to the restricted rotation about Ar–CH_2OAc bond of this highly crowded o-toluidine derivative, the other apparent anomalies mentioned above are compatible with an intramolecular hydrogen bonding in **4a** involving the C=0 and NH respectively of the tertiary and the secondary amides through an eight-membered ring as shown in **9**.

To adduce further evidence to the above contention, the ^{13}C NMR spectra of the bases, their acetates and some allied o-disubstituted aromatic compounds were studied as detailed below.

Both the yield of the compounds and their solubility in $CDCl_3$ being poor, only proton noise decoupled spectra of most of the bases and their acetates could be recorded. In view, however, of the difficulty in assigning the individual chemical shifts to specific carbons in o-disubstituted aromatic compounds,[6] we took o-toluidine, some o-amino-benzamides and their acetates as model compounds for the present study.

For an unambiguous assignment of the aromatic carbons, particularly the more affected ortho and para carbons with respect to the NH_2 and NHAc groups, gated decoupled (with retention of NOE) as well as selective proton decoupled spectra, besides the proton noise decoupled spectra of these compounds were recorded. Since most of the o-amino-benzamides and their acetates exhibited well-resolved signals for aromatic protons in their ^1H NMR spectra, selective proton decoupling experiments enabled us to identify the corresponding ^{13}C


CH3
NH2
5≡
Phthalic anhydride
in Py at 100°
CH3
O
N
O
6≡
NBS – AIBN
in CCl4,
reflux
CH2Br
O
N
O
7≡
5% KOH in 50% aq. dioxane, reflux
CH2OH
NH2
3≡
Compound 7≡
in Py at 100°
CH2OH
NH — CH2
O
N
O
8≡
H2N — NH2
in EtOH,
reflux
CH2OH H2N
NH — CH2
4≡

Scheme

Table 1. ^{13}C Chemical shifts and $^{1}J_{CH}$ values of some o-disubstituted aromatic compounds*

Carbon No.	5	10	11	12	5a	10a	11a	12a
1	122.2	113.7	113.9	114.9	131.1	119.8	135.7	120.7
2	144.5	150.0	150.7	149.4	135.7	139.7	141.2	139.1
3	114.9	116.4	110.5	116.3	124.6	120.2	130.7	120.4
	(155.0)	(158.7)	(160.0)	(158.5)	(160.0)	(164.8)	(162.0)	(164.8)
4	126.8	131.8	132.6	131.4	126.3	132.0	128.8	131.6
	(157.8)	(159.2)	(160.0)	(159.0)	(158.7)	(160.5)	(162.0)	(160.5)
5	118.4	114.4	113.7	114.6	125.5	122.3	127.9	122.4
	(161.0)	(162.9)	(163.0)	(162.0)	(160.5)	(158.1)	(163.5)	(164.2)
6	130.3	128.7	128.9	127.8	130.4	128.5	128.2	127.8
	(156.0)	(155.6)	(156.0)	(155.6)	(156.0)	(156.0)	(160.5)	(160.5)
$\underline{C}H_3$	17.2	—	29.1	25.9	17.7	—	36.5	26.2
$\overline{A}rCONHR$	—	171.2	171.6	169.3	—	170.8	168.9	168.1
$NH\overline{C}OCH_3$	—	—	—	—	169.1	168.1	169.0	168.7
$NHCO\underline{C}H_3$	—	—	—	—	23.6	24.9	22.0	24.8

*Spectra recorded in DMSO-d_6 except those of **5** and **5a** for which $CDCl_3$ was used. The chemical shifts are on δ scale from TMS as internal standard. The figures in parentheses are the $^{1}J_{CH}$ values in Hz.

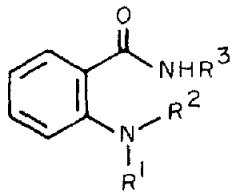
signals. In cases, where proton resonances were ill-resolved, $^{1}J_{CH}$ values (Table 1) were found to be very useful for the correct assignment of the aromatic carbons. Thus, in case of o-amino-benzamides (**10–12**), $^{1}J_{CH}$ value for the signal of the carbon ortho to a substituent was found to be smaller than that for the para carbon viz C-3 *vs* C-5 and C-6 vs C-4. On the other hand, acetylation of 2-NH_2 group enhanced the $^{1}J_{CH}$ values for the ortho carbon (C-3).

Taking the above results into consideration, the ^{13}C chemical shifts for o-toluidine (**5**) and its N-acetate (**5a**) could be assigned with reasonable certainty. Particularly in case of **5**, the assigned (Table 1) and the calculated[7] values (C-3, 115.4; C-4, 126.7; C-5, 118.9 and C-6, 130.4) of the aromatic methine carbons are in excellent agreement.

Now, the Table 1 shows that the replacement of CH_3 by CONHR group more or less affected the chemical shifts of all the aromatic carbons, more markedly in cases of C-4 and C-5 presumably due to change in the electron densities around them consequent on the introduction of the electron-withdrawing group. Furthermore, C-3 and C-4 which were shielded by ~3.5 ppm in relation to C-5 and C-6 in o-toluidine (**5**) were found to be deshielded by ~2.0 and ~3.0 ppm respectively in o-amino-benzamides (**10** and **12**). N-Methylation of 2-NH_2 group (as in **11**), however, caused an up-field shift of the C-3 signal by ~3.0 ppm compared to that of C-5 clearly due to the γ-effect of N-methyl group.

Acetylation of 2-NH_2 group (cf **5a**, **10a** and **12a**), on the other hand, produced the expected[7] significant deshielding effects on C-3 and C-5, the displacement (7–8 ppm) being more or less consistent for C-5. Nevertheless, the effect on C-3 was found to be variable. Thus, it is large (~10 ppm) in N-acetyl-o-toluidine (**5a**) and small (~4 ppm) in o-acetamido-benzamides **10a** and **12a**. The introduction of N-Me group in the latter (cf **11a**) resulted in further down-field shift of C-3 and C-5 by ~10.5 and ~5.5 ppm respectively contrary to what has been observed in case of N-methylation of o-amino-benzamide (**10** vs **11**). This reversal of the effect could plausibly be attributed[8] to redistribution of π electron density due to non-planarity resulting from the repulsive interaction between the bulky substituents.

Based on the above observations, the ^{13}C chemical shifts could be assigned (Table 2) to the aromatic carbons of the naturally occurring bases (**1–4**) and their acetates (**1a–4a**). While the assignments of the other signals are straight forward, the apparently anomalous shielding of the $-CH_2-OH$ carbon signals of **3** and **4** on acetylation and upfield displacement (by ~12 ppm) of the $-CH_2-N-$ carbon signal in **2a** as against **4a** can plausibly be rationalised as follows:



10, $R^1 = R^2 = R^3 = H$

10a, $R^1 = Ac$, $R^2 = R^3 = H$

11, $R^1 = Me$, $R^2 = R^3 = H$

11a, $R^1 = Me$, $R^2 = Ac$, $R^3 = H$

12, $R^1 = R^2 = H$, $R^3 = Me$

12a, $R^1 = Ac$, $R^2 = H$, $R^3 = Me$

It may be seen from Table 2 that the $-CH_2-O-$ carbon of the methyl ether **2a** resonated upfield by 3.5 ppm in DMSO as against $CDCl_3$. This clearly indicated the existence of intramolecular hydrogen bonding[6,9] in the latter solvent. That this bonding involves the lone pair of ether oxygen and NH of the compound (cf **13**) became evident from virtually the same chemical shift for this methylene carbon irrespective of the nature of the nitrogen function, in the same solvent in the methyl ethers **1** and **1a** (cf **14**) also. The pronounced upfield shift of the $-N-CH_2-$ signal in the diacetate **2a** could then be explained envisaging γ-effect of the methyl group of the neighbouring N-acetyl function. On the same premises, the removal of hydrogen bonding of **3** and **4** (cf **14**) consequent on acetylation could lead to the unexpected

Table 2. ^{13}C Chemical shifts of the bases of *J. gendarussa* and their acetates†

Carbon No.	1	3	4	1a	2a	3a	4a
1	122.0	124.9	125.1	126.3	133.6	126.3	133.8
2	146.2	145.9	147.4	137.7	136.7	136.6	140.1
3	115.6	116.0	111.5	122.0	136.0	123.9	131.6
4	129.2	129.1*	129.9*	129.0*	125.8	129.8	129.3*
5	117.8	118.2	117.4	123.8	126.2	124.8	129.7*
6	130.0	129.2*	129.0*	129.3*	128.2*	131.3	130.6
1′	—	—	122.9	—	131.4	—	124.5
2′	—	—	145.6	—	135.1	—	137.4
3′	—	—	116.0	—	124.6	—	122.4
4′	—	—	128.7*	—	127.8*	—	129.3*
5′	—	—	118.5	—	125.2	—	123.1
6′	—	—	129.6*	—	129.8*	—	129.8*
$ArCH_2O$	73.7	64.1	64.4	73.7	70.3 (73.8)	63.3	61.7
$ArCH_2N$	—	—	46.4	—	36.2 (37.9)	—	50.1
OCH_3	57.3	—	—	57.6	57.6 (57.8)	—	—
$NHCOCH_3$	—	—	—	168.3	168.1	168.8	169.3
$NHCOCH_3$	—	—	—	24.7	23.1 (24.0)	24.2	22.3
					23.2 (24.7)		24.5
$OCOCH_3$	—	—	—	—	—	172.1	172.2
$OCOCH_3$	—	—	—	—	—	20.9	20.7

†Spectra recorded in $CDCl_3$. The values for **2a** in DMSO-d_6 due to poor solubility in $CDCl_3$ in which only some up-field signals (in parentheses) are clearly discernible. The chemical shifts are on δ scale from TMS as internal standard.

*Closely lying peaks in each vertical column may be interchanged.

upfield shift of the $-CH_2-O-$ carbon. Furthermore, being relieved of hydrogen bonding with the primary alcohol on acetylation as in the triacetate **4a**, the two newly introduced N-acetyl groups could establish a fresh intramolecular hydrogen bonding as shown in **9** consistent with the structure arrived at on the basis of ^1H NMR spectrum (*vide supra*). The absence of shielding effect on $-N-CH_2-$ carbon in **4a** appears to support the above conclusion.

Now, the possibility of compounds **1** and **2** being artefacts could not rigorously be ruled out even though the isolation of **2** involved no hydrolytic condition.

Biogenetically, compound **3** could be derived from anthranilic acid as the precursor while compound **4** apparently results from self-condensation of **3**.

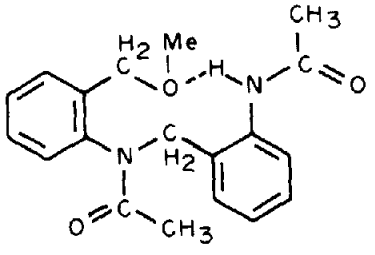
Finally, it is pertinent to point out that although *Justicia* species are known[10–13] to elaborate lignans, no such compound was encountered in this particular specimen despite deliberate search.

EXPERIMENTAL

All mps were taken in open capillaries and are uncorrected. IR spectra were taken on a Perkin-Elmer infrared spectrophotometer (model 177) and mass spectra on a Hitachi RMU-6L instrument. ^1H and ^{13}C NMR spectra were recorded on a Jeol FX-100 FT NMR spectrometer with TMS as an internal standard. The conditions for FT measurements for ^1H were: spectral width, 1 KHz; data points, 8 K; flip angle, 45° and pulse repetition time, 6 sec; and for ^{13}C: spectral width, 6 KHz; data points, 8 K or 16 K; flip angle, 30–45° and pulse repetition time, 1.5 or 2.5 sec.

Extraction of the leaves of Justicia gendarussa

Powdered leaves (1.5 kg) were extracted in a Soxhlet apparatus successively with light petrol and methanol. The petrol extract after removal of solvent and chromatography over silica gel yielded β-sitosterol, mp 136–137°; benzoate, mp 145°; lupeol, mp



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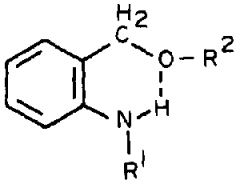

R^1 = H, Ac or
o-$C_6H_4(NH_2)CH_2$-

R^2 = H or Me

14

212–214°; acetate, mp 215–216° and friedelin, mp 251° identified by direct comparison (mp, mmp, TLC, IR) with authentic specimens.

Treatment of the methanol extract and isolation of **1** *and* **2**. The methanol extract was concentrated under reduced pressure to a syrupy mass, diluted with water (750 ml) and stirred. The clear supernatant solution was separated from the deposited gummy mass. To the aqueous solution, conc HCl (75 ml) was added, heated on a steam-bath for 4 h, cooled in ice, basified with NH_3 solution, extracted with chloroform and the extract concentrated to a small volume (50 ml) which was reextracted with 2N HCl (50 ml × 5). The ether soluble fraction (1 g) of the regenerated crude base (3 g) was then chromatographed over silica gel. On elution with 20% $CHCl_3$ in light petrol yielded 2-amino-0-methyl-benzyl alcohol (**1**, 0.3 g) as an oil, *m/z* (rel intensity) 137(M^+, 100), 122(35), 106(90), 105(87), 104(84), 78(60) and 77(52); ∂ 3.29(s, $-OCH_3$), 3.89(br, $-NH_2$), 4.41(s, Ar–CH_2–O–), 6.53–7.20(m, 4 Ar–H).

The deposited gummy mass obtained after dilution of the methanol extract concentrate was dissolved in $CHCl_3$ (50 ml) and repeatedly extracted with 2N HCl (50 ml × 5). The regenerated base was chromatographed over silica gel. Elution with 10% chloroform in light petrol afforded an oil which on purification through PLC gave **2**(25 mg), *m/z* (rel intensity) 242(M^+, 100), 210(67), 209(89), 197(32), 195(50), 194(36), 193(23), 180(21), 137(11), 106(47), 105(28), 104(17) and 77(17); ν_{max}^{film} 3440, 3360, 3225, 1630–1620 and 1585 cm^{-1}; ∂(CCl_4) 3.23(s, $-OCH_3$), 3.57(m, $-NH_2$ and –NH–), 3.68(s, Ar–CH_2–N–), 4.32(s, Ar–CH_2–O–), 6.37–7.07(m, 8 Ar–H).

Isolation of **3** *and* **4**. In a second lot, the defatted leaves (5 kg) were extracted with chloroform in a Soxhlet apparatus for 24 h and the extract was concentrated to 0.5 l. The basic fraction was separated from the concentrate by repeated extraction with 2N HCl(75 ml × 5). The regenerated crude base (0.6 g) was chromatographed over deactivated silica gel. On elution with 10% $CHCl_3$ in light petrol gave a solid (0.14 g) which on repeated crystallisations from light petrol –$CHCl_3$ and benzene yielded **3**(95 mg), mp 85°, *m/z* 123(M^+, 100), 106(30), 105(87), 104(73), 78(39) and 77 (29); ν_{max}^{nujol} 3390, 3300–3100, 1630–1610 and 1590 cm^{-1}; ∂3.40(br, NH_2 and –OH), 4.58(s, Ar–CH_2–OH) and 6.60–7.25(m, 4 Ar–H).

The mother liquor on PLC (C_6H_6: EtOAc, 1 : 1) furnished, besides more (5 mg) of **3**, **4**(20 mg) which crystallised from light petrol –$CHCl_3$ as fine needles, mp 131°, *m/z* (rel intensity) 228(M^+, 73), 210(8), 209(9), 180(6), 123(54), 106(100), 105(30) and 77(19); ∂4.24(s, Ar–CH_2–N–), 4.60(s, Ar–CH_2–OH), 6.60–7.40(m, 8 Ar–H).

Acetates **1a**, **2a**, **3a** *and* **4a**. Acetylation of compounds **1–4** were carried out with Ac_2O-Py at room temperature.

Acetate **1a**, mp 80° (light petrol), *m/z* (rel intensity) 179(M^+, 51), 164(20), 136(36), 122(100), 106(54), 105(42), 104(41), 78(26), 77(21); ν_{max}^{nujol} 3260, 1655–1640, 1588 cm^{-1}; ∂2.19 (s, $-NCOCH_3$), 3.41(s, $-OCH_3$), 4.58(s, Ar–CH_2–O–), 8.30(br d, J = 8 Hz, 3-H), 7.10–7.60 (m, 3 Ar–H).

Acetate **2a**, mp 210°($CHCl_3$–MeOH), *m/z* (rel intensity) 326(M^+, 73), 311(12), 294(100), 283(21), 279(50), 252(43), 251(95), 237(41), 210(28), 209(75), 195(26), 194(31), 193(32), 192(29), 180(22), 148(32), 106(32); ν_{max}^{nujol} 3280, 1658, 1650, 1587 cm^{-1}; ∂1.99 and 2.16 (s, two $NCOCH_3$), 3.34 (s, $-OCH_3$), 3.92 (s, Ar–CH_2–N–), 4.44(s, Ar–CH_2–O–), 7.73(br, d, J = 8 Hz, 3-H), 8.09(br d, J = 8 Hz, 3′-H), 6.80–7.40 (m, 6 Ar–H).

Acetate **3a**, mp 96°(light petrol –$CHCl_3$), *m/z* (rel intensity) 207(M^+, 35), 165(20), 164(33), 147(29), 132(13), 122(80), 106(58), 105(100), 104(57), 78(39), 77(27); ∂2.08(s, $-OCOCH_3$), 2.19(s, $-NCOCH_3$), 5.09(s, Ar–CH_2–O–), 7.91(br d, J = 8 Hz, 3-H), 7.04–7.50(m, 3 Ar–H), 8.76(br, CONH).

Acetate **4a**, mp 116° (light petrol –$CHCl_3$), *m/z* (rel intensity) 354(M^+, 38), 336(3), 311(20), 294(6), 252(22), 251(100), 219(18), 209(55), 194(15), 193(19), 148(23), 146(10), 106(38); ν^{nujol} 3260–3180, 1730, 1680, 1625 cm^{-1}; ∂2.07 (s, $-OCOCH_3$), 1.83 and 2.29 (s, two $-NCOCH_3$), 4.73 and 4.82 (AB doublets, J = 14 Hz, Ar–CH_2–N–), 4.57 and 5.05 (AB doublets, J = 14 Hz, Ar–CH_2–O–), 6.54(dd, J = 8 and 2 Hz, 3-H), 8.30(br d, J = 8 Hz, 3′-H) 6.75–7.60 (m, 6 Ar–H).

N-Acetyl-o-toluidine **5a** *from* **1a**. A solution of compound **1a** (25 mg) in ethanol (5 ml) was stirred with 10% Pd/C (20 mg) in an atmosphere of hydrogen for 4 h yielding **5a** (20 mg), mp 110°, identical (mmp, IR) with an authentic specimen.

2-Phthalimido-toluene **6** *from o-toluidine* **5**. A mixture of **5** (3.5 g), phthalic anhydride (5 g) and pyridine (25 ml) was heated on a steam-bath for 3 h. Work up of the reaction mixture and crystallisation of the product from $CHCl_3$-light petrol yielded **6** (5.2 g), mp 180–181°, *m/z* (rel intensity) 237(M^+, 85), 219(100), 193(45), 104(20).

2-Phthalimidobenzylbromide **7** *from* **6**. A suspension of 2-phthalimido-toluene (**6**, 1.3 g), N-bromosuccinimide (1.2 g) and AIBN (5 mg) in dry CCl_4 (25 ml) was refluxed with stirring under an exposure of a 200 w tungsten lamp for 3 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was washed successively with dil. sodium thiosulphate solution and water, dried and evaporated. The crude product was carefully crystallised from $CHCl_3$-light petrol to get **7** (0.4 g) as shining prisms, mp 179–180°, *m/z* (rel intensity) 315(M^+, 62), 236(100), 235(78), 207(53), 179(31).

2-Aminobenzyl alcohol **3** *from* **7**. Compound **7** (0.3 g) was refluxed with 5% KOH in 50% aqueous dioxane (20 ml) on a steam-bath for 6 h. Water and dioxane were distilled off from the reaction mixture under reduced pressure. The residue on usual work-up afforded a gummy mass, TLC of which showed the presence of **3**. It was purified through acetylation of the crude product and chromatography over silica gel. The solid product (30 mg), mp 96°, was found to be identical (IR) with **3a**.

2-(2′-Phthalimidobenzylamino)-benzyl alcohol **8** *from* **3**. A mixture of **3** (30 mg), **7** (0.1 g) and pyridine (1 ml) was heated on a steam-bath for 3 h and pyridine was removed from the reaction mixture under reduced pressure. The crude product obtained after usual work-up of the residue on chromatography over silica gel yielded **8** (60 mg), mp 178–179°, *m/z* (rel intensity) 358(M^+, 80), 340(70), 338(60), 322(100), 312(34), 269(35), 236(80), 219(45), 208(40), 194(45), 180(40), 105(10), 104(30).

2-(2′-Aminobenzylamino)-benzyl alcohol **4** *from* **8**. A solution of compound **8**(50 mg) in ethanol (2 ml) was treated with a molar solution (0.5 ml) of hydrazine hydrate in ethanol and the mixture was refluxed on a steam-bath for 2 h and solvent was removed under reduced pressure. The crude product on chromatography over silica gel yielded **4** (15 mg), mp 131°, identical (mmp, TLC, IR, MS) with the natural product.

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