

¹H NMR SPECTRA OF SOME JUVABIONE ANALOGUES*

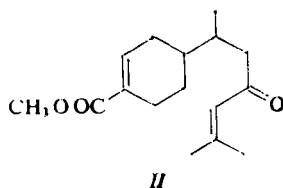
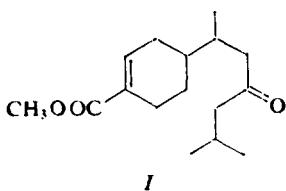
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A number of aromatic aza-analogues of juvabione and dehydrojuvabione have been synthesized by treatment of substituted benzylamine with 3-methylbutanoyl chloride and 3-methyl-2-butenoyl chloride. Reaction of substituted phenoxyacetyl chlorides with isopropylamine and 2-propanol gives other series of aromatic juvabione analogues. The ¹H NMR spectra of some analogues are discussed.

Juvenile hormones (JH), the potential third generation pesticides are most important of the three insect hormones which control the postembryonic development of insects. Their synthetic analogues (JHA) are often considered to be pesticides¹⁻³. Juvabione (I) and dehydrojuvabione (II) were the first cyclic JHA which were detected and isolated in Balsam fir^{4,5}. These were found to be selectively biologically active on hemipterans of the *Pyrrhocoridae* family⁶. Since then a considerable amount of work has been reported on the synthesis and biological activities of juvabione, dehydrojuvabione and many of their synthetic variations⁷. In this direction a programme on the synthesis of JH like substances has been undertaken in our laboratory also^{8,9} and now a series of juvabione and dehydrojuvabione analogues have been synthesized¹⁰. The ¹H NMR spectra of these compounds have been recorded and the salient features are discussed in this communication.

**EXPERIMENTAL**

¹H NMR spectra were recorded for solutions in ²CHCl₃ at 90 MHz on an EM-390 spectrometer with tetramethylsilane as internal standard. The chemical shifts are expressed in δ values and coupling constant in Hz. Melting points and boiling points reported are uncorrected.

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Synthesis of IVa–IVc and Va–Vc: Amine *IIIa–IIIc* was taken in benzene and pyridine was added. The mixture was cooled in ice bath and 3-methylbutanoyl chloride or 3-methyl-2-butanoyl chloride was added dropwise with stirring. The mixture was then stirred at room temperature for 5 h. Water was added and the organic layer was separated. The aqueous layer was extracted once with benzene. The solvent was distilled off from the combined extracts to leave a residue which gave a solid on addition of a little ether. The solid was filtered and recrystallised from aqueous methanol to give the products (*IVa–IVc* and *Va–Vc*; Table I) as crystalline solid in 60 to 70% yields.

Synthesis of VIIa–VIIc: A solution of phenoxyacetyl chloride *VIa–VIc* in benzene was added dropwise to the solution of isopropylamine in benzene and a little pyridine at 0–5°C under stirring. The mixture was stirred at 0°C for 2 h and then at room temperature for 2 h, poured into water and extracted with ether. The extract was dried over anhydrous Na₂SO₄ and the solvent was evaporated to leave a solid. Crystallisation from light petroleum (60–80°C) gave crystalline products (*VIIa–VIIc*; Table II) in 50–60% yields.

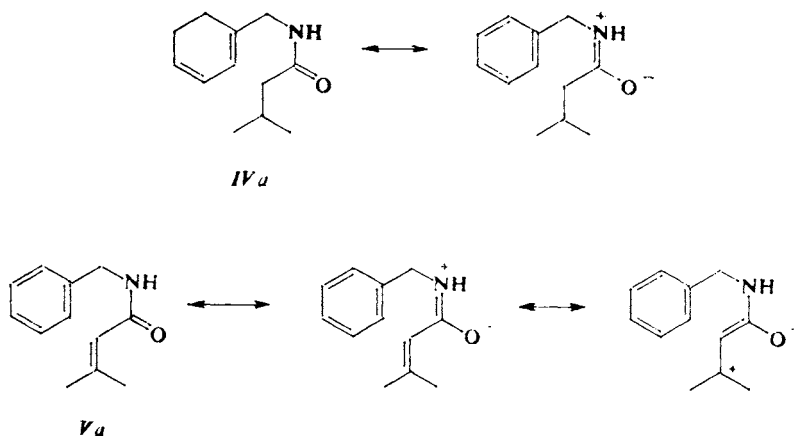
Synthesis of VIIIa–VIIIc: 2-Propanol (1.25 equivalent) was added to phenoxyacetyl chloride *VIa–VIc* and the mixture was refluxed in an oil bath (110–120°C) for 1 h. After allowing it to stand at room temperature overnight, the excess of 2-propanol was removed under vacuum to leave the respective products. Liquid products were distilled and solids crystallised from aqueous methanol to give the products *VIIIa–VIIIc* (Table II).

TABLE I
¹H NMR Spectra of *IVa–IVc* and *Va–Vc*

Compound	M.p., °C	Data
<i>IVa</i>	58–60	7.6 (5 H, aromatic); 4.57 (d, 2 H, $J = 5.5$, benzylic); 2.25 (2 H, –CO–CH ₂); 1.66 (m, 1 H); –CH(CH ₃) ₂); 1.17 (d, 6 H, $J = 6$, CH ₃).
<i>IVb</i>	64–65	7.4 (5 H, aromatic); 5.85 (1 H, NH); 5.23 (m, 1 H, benzylic); 2.1 (2 H, –CO–CH ₂ –); 1.8 (m, 1 H); 1.5 (d, 3 H, $J = 7$ Hz, >CH–CH ₃); 0.97 (d, 6 H, $J = 6$, CH(CH ₃) ₂ –CH(CH ₃) ₂).
<i>IVc</i>	67–68	7.43 (4 H, aromatic); 5.9 (1 H, NH); 5.2 (m, 1 H, benzylic); 2.08 (2 H, –CO–CH ₂); 1.8 (m, 1 H, –CH(CH ₃) ₂); 1.48 (d, 3 H, $J = 7$, CH–CH ₃); 0.97 (d, 6 H, $J = 6$).
<i>Va</i>	55–57	7.45 (5 H, aromatic); 6.1 (1 H, NH); 5.7 (1 H, olefinic); 4.5 (d, 2 H, $J = 5.5$, benzylic); 2.2 (3 H, <i>cis</i> -CH ₃); 1.87 (3 H, <i>trans</i> -CH ₃).
<i>Vb</i>	82–84	7.4 (5 H, aromatic); 5.97 (1 H, NH); 5.67 (1 H, olefinic); 5.2 (m, 1 H, $J = 7$, benzylic); 2.2 (3 H, <i>cis</i> -CH ₃); 1.87 (3 H, <i>trans</i> -CH ₃); 1.52 (d, 3 H, $J = 7$, >CH–CH ₃).
<i>Vc</i>	94–96	7.4 (4 H, aromatic); 5.53 (1 H, olef.); 5.15 (m, 1 H, benzylic); 2.2 (3 H, <i>cis</i> -CH ₃); 1.87 (3 H, <i>trans</i> -CH ₃); 1.51 (d, 3 H, $J = 7$, >CH–CH ₃).

RESULTS AND DISCUSSION

Considerable amount of work has been reported on the effect of substituents on the chemical shift of aromatic protons in benzene derivatives¹¹. Introduction of various substituents into the benzene nucleus results in characteristic chemical shifts at the *ortho*, *meta* and *para* positions and the magnitude of the latter two is related approximately to Hammett's substituent constants¹²⁻¹⁶. In *meta* and *para* disubstituted benzene the substituent effects are approximately additive¹⁷. In the spectra



SCHEME 1

of *IVa* and *Va* the aromatic protons appear at δ 7.6 and 7.45 respectively. The reported chemical shift of aromatic protons in benzylamine is δ 7.27. The lower field values in *IVa* and *Va* are caused by lower basicity of nitrogen here because of the presence of carbonyl group attached to it. Further, comparing *IVa* and *Va*, the nitrogen in *Va* is slightly more basic than *IVa* because the positive charge in its resonance forms is dispersed between nitrogen and carbon, as shown in Scheme 1.

Thus the lower-field shift in *IVa* is larger than in *Va*. Similarly, the same argument explains the little difference in the benzylic protons of *IVa* and *Va* (4.57 and 4.50, respectively). The aromatic protons in compounds *IVb*, *IVc*, *Vb*, *Vc* resonate between 7.40–7.43.

The benzylic protons which generally resonate between 2.3–2.9 are shifted considerably downfield due to the presence of the —NH—C(=O)—R group. The benzylic methylene protons in *IVa* and *Va* show approximately a downfield shift of 1.9–2.0 while the benzylic methine protons in *IVb*, *IVc*, *Vb* and *Vc*, which show a multiplet

between 5.15 and 5.23, are shifted downfield by 2.25 to 2.35. Generally the —NH—

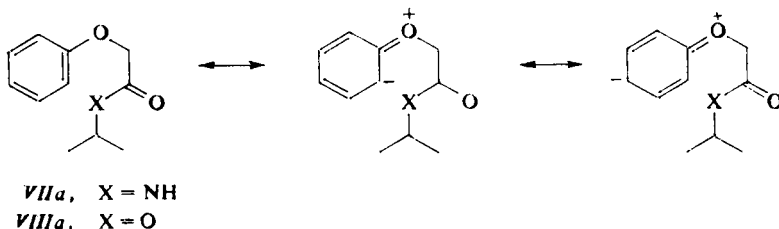
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{R} \end{array}$
 should lower the absorption by about 3.0. It, therefore, appears that the amide group exerts some positive shielding of benzylic methine protons¹⁸. The benzylic methylene protons in (*IVa*) and (*Va*) are coupled with N—H and show $J_{\text{H-C-N-H}} = 5.5$ Hz. In *IVb*, *IVc*, *Vb*, *Vc* the benzylic methine is split up into a complex multiplet because of additional coupling with C₍₁₎-methyl group ($J = 7$ Hz), and the C₍₁₁₎-methyl group in all these compounds appears around δ 1.5 as a doublet ($J = 7$ Hz). The CO—CH₂ protons appear between δ 2.1–2.25 in all these compounds as expected. The NH proton appears as a very broad signal at δ 5.85–6.1 in *IVb*, *IVc*, *Va* and *Vb* while it is not clearly observable in *IVa* and *Vc*. The terminal geminal dimethyl group in *IVa–IVc* appear at δ 0.97–1.17 as a six protons doublet ($J = 6$ Hz), while in *Va–Vc* the two methyl groups appear as separate sharp singlets due to their different configuration on double bond with respect to the carbonyl group. The *cis*-methyl group appears at a lower field at δ 2.2 and the *trans*- at δ 1.87.

TABLE II
¹H NMR Spectra of *VIIa–VIIc* and *VIIIa–VIIIc*

Compound	M.p., °C	Data
<i>VIIa</i>	63–65	7.05 (3 H, aromatic); 7.35 (2 H, aromatic); 6.25 (1 H, NH); 4.40 (2 H, O—CH ₂); 4.15 (m, 1 H, —N—CH(CH ₃) ₂), 1.27 (d, 6 H, $J = 6.5$ -CH(CH ₃) ₂)
<i>VIIb</i>	83–85	7.05 (2 H, aromatic); 7.45 (2 H, aromatic); 6.40 (1 H, NH); 4.5 (2 H, O—CH ₂); 4.20 (m, 1 H, —N—CH(CH ₃) ₂); 1.25 (d, 6 H, $J = 6.5$ -CH(CH ₃) ₂)
<i>VIIc</i>	116	7.10 (2 H, aromatic); 8.40 (2 H, aromatic); 6.35 (1 H, NH); 4.60 (2 H, O—CH ₂); 4.20 (m, 1 H, —N—CH(CH ₃) ₂); 1.25 (d, 6 H, $J = 6.5$, —CH(CH ₃) ₂)
<i>VIIIa</i>	125–130/1.3 kPa (B.p.)	6.8 (3 H, aromatic); 7.17 (2 H, aromatic); 4.97 (s, 1 H, $J = 6.5$, O—CH(CH ₃) ₂); 4.40 (2 H, —OCH ₂); 1.15 (d, 6 H, $J = 6.5$, —CH(CH ₃) ₂)
<i>VIIIb</i>	51–53	6.85 (2 H, aromatic); 7.27 (2 H, aromatic); 4.55 (2 H, O—CH ₂); 5.12 (s, 1 H, $J = 6.5$, O—CH(CH ₃) ₂); 1.25 (d (6 H, $J = 6.5$, —CH(CH ₃) ₂)
<i>VIIIc</i>	72–74	7.02 (2 H, aromatic); 8.30 (2 H, aromatic); 4.73 (2 H, O—CH ₂); 5.18 (s, 1 H, $J = 6.5$, —O—CH(CH ₃) ₂); 1.3 (d, 6 H, $J = 6.5$, —CH(CH ₃) ₂)

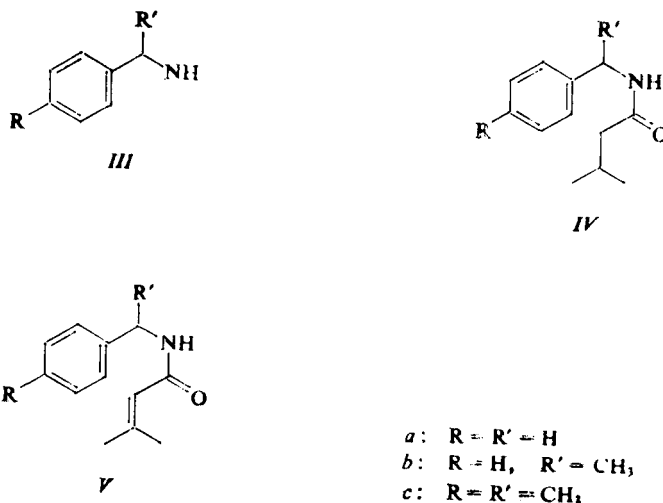
Nearly same values are observed for *cis*- and *trans*- methyl groups in ketones¹⁹.

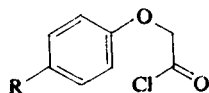
In the ¹H NMR spectra of *VIIa* and *VIIIa* the 5 aromatic protons are divided into two complex signals, one appearing at slightly higher field (δ 7.05 (3 H) in *VIIa* and δ 6.8 (3 H) in *VIIIa*, and the other at approximately normal values at δ 7.35 (2 H) and δ 7.17 (2 H) in *VIIa* and *VIIIa*. The higher field signal is due to the two *ortho* and one *para* protons while the normal signal is due to the two *meta* protons. The contributions due to the following type of structures can explain the above difference in *ortho-para* and *meta* protons (Scheme 2).



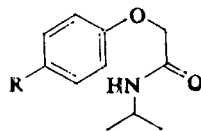
SCHEME 2

On introduction of a *p*-chloro substituent in the benzene nucleus, the compounds *VIIb* and *VIIIb* showed only a marginal shift (0.05–0.1 ppm;) lowerfield to *VIIa* and *VIIIa*. However, introduction of a nitro group at the *para* position (*VIIc* and *VIIIc*) showed an expected significant shift of *ortho* protons (with respect to nitro group, 8.40 and 8.30 in *VIIc* and *VIIIc*) and the *meta* protons (7.10 and 7.02 in *VIIc* and *VIIIc*). This is attributed to the strong inductive effect of the nitro group.

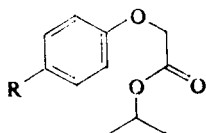




VI



VII



VIII

- a: R = H
 b: R = Cl
 c: R = NO₂

The signal due to the protons $\text{—O—CH}_2\text{—CO—}$ in *VIIa*, *VIIIa*, *VIIb* and *VIIIb* appears between 4.40 and 4.55, while in *nitro* compounds *VIIc* and *VIIIc* these protons appear at 4.60 and 4.73, respectively. The value of such protons can be predicted by Shoolery's rules²⁰. The calculations show that these values should be approximately 5.05 for amides (*VII*) and 5.01 for ester (*VIII*). The effect of *p*-nitro and *p*-chloro groups, if any, should be to shift these calculated values further low-field. The upfield values observed in our compounds indicate the positive shielding influence of carbonyl group in the methylene protons.

The NH proton in *VII* appears as a wide signal at 6.25–6.40 (slightly lowerfield than in *IV* and *V*). The terminal geminal dimethyl group in both *VII* and *VIII* appears as doublet ($J = 6\text{--}6.5$) at 1.15–1.30 which is slightly lowerfield than expected due to the inductive effect of oxygen and nitrogen atoms present at β -position. The methine protons next to nitrogen show a septet at 4.25–4.20 in *VII* while it appears downfield at 4.97–5.18 in *VIII*, where it is present next to the more electronegative oxygen atom.

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