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REACTION OF BENZISOXAZOLIUM CATIONS WITH CYCLIC β-DIKETONES

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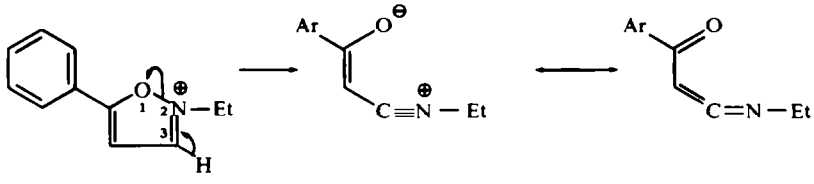
Abstract— Reaction of 2-ethylbenzisoxazolium fluoborate (III) with dimedone, dihydroresorcinol, 2-methyldihydroresorcinol and 2-methylcyclopentane-1,3-dione in the presence of base leads to the formation of amides VIII, XI, X and XIII respectively, *via* the benzoketoketenimine intermediate (IX) and an intramolecular migration. The 7-hydroxy-2-ethylbenzisoxazolium salt (IV) gives the amide (XIV) by double migration. Amides VIII, XI, X and XIII undergo intramolecular Michael reaction to furnish the benzoxazinones (XVI, XVIII, XVII and XXVI). Stereochemistry of this addition is discussed and the conformation in which the —C—N bond at C-1′ is attached equatorially to the cyclohexanone ring is assigned to the spirans (XX, XXX and XXVIII). Effect of acids and bases on the amide (VIII) and the spiran (XVI) is described.

WOODWARD *et al.*[1] have shown that 3-unsubstituted isoxazolium salts (I) can be cleaved under basic conditions to α-ketoketenimines (II) which are subsequently isolated in favourable cases.[2] The ketoketenimine intermediates react with a variety of nucleophiles[1] and the particular reaction with carboxylic acids was exploited for peptide synthesis.[3] Kemp *et al.* have prepared 2-ethylbenzisoxazolium (III) and 2-ethyl-7-hydroxybenzisoxazolium (IV) fluoborates which proved to be superior reagents for the formation of the peptide bond.[4] In the present investigation, we report the reaction of benzisoxazolium cations with acidic 1,3-diketones.



I II

On adding the isoxazolium salt (III) to a two phase system containing an aqueous alkaline solution of dimedone (V) and ethyl acetate, the amide (VIII) was isolated as a solid. The PMR* spectrum of VIII features the vinylic proton at 5·12 δ, the six protons of the gem dimethyl groups at 1·1 δ and the four aromatic protons between 6·83 and 8·0 δ. The formation of the amide (VIII) can be envisaged through the reaction of the β-diketone (V) with the benzoketoketenimine intermediate (IX) followed by an intramolecular migration.[1,4a] By analogy with the previous work,[1,4a] the reaction may be pictured as an electrocyclic Diels–Alder like process involving a

* 100 MHz spectrum.

H-bonding interaction of the enolic β-diketone (rather than the enolate*) and the keto group of the ketenimine (IX) (Chart 1).

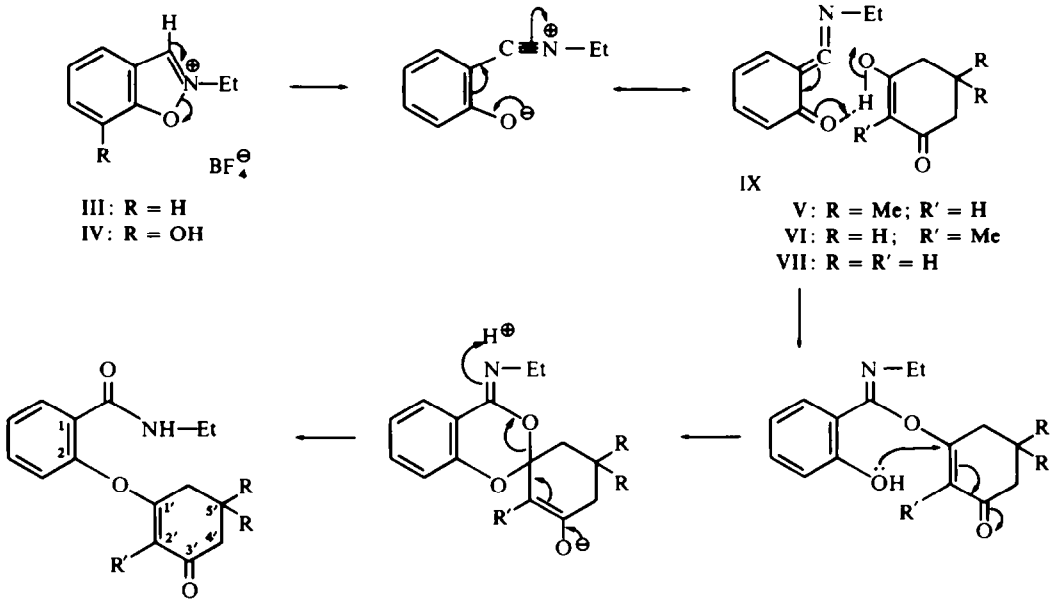
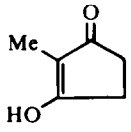
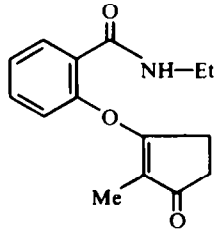


CHART 1

Similar reactions of the isoxazolium salt (III) with 2-methyldihydroresorcinol (VI), dihydroresorcinol (VII) and 2-methylcyclopentane-1,3-dione (XII) furnished the corresponding amides X, XI and XIII respectively. Reaction of 7-hydroxybenzisoxazolium fluoborate (IV) with dimedone (V) afforded the amide (XIV). The UV spectrum



XII



XIII

exhibited maxima at 250 (ε 21,000) and 307 (ε 5387) nm in ethanolic solution. In basic medium, the maxima were shifted to 251 (ε 17,170) and 330 (ε 7180) nm. Comparison

* Woodward[1] and Olofson[2b] showed that during the reactions of isoxazolium salts with carboxylic acids in presence of bases, free acids are involved rather than the carboxylate anions as they observed rapid reactions with carboxylic acids than with the triethylamine salts of the acids.

of these UV spectra with those of the model compounds* suggested that the dimedone moiety was situated at 3-position of the benzene nucleus and the product should be represented by the structure XIV. Obviously, the product (XIV) is formed through a second migration of the initially formed ether XV (Chart 2).

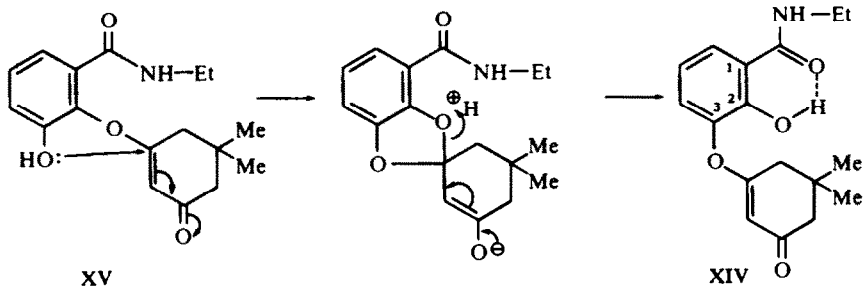
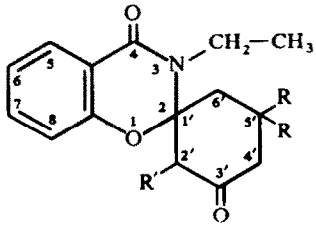


CHART 2

On heating the amide (VIII) with a catalytic amount of *p*-toluenesulphonic acid, the benzoxazinone (XVI) was obtained. The PMR† spectral data (Experimental) are consistent with the assigned structure. A special feature of the spectrum is the appearance of a complex multiplet (more than 10 lines) between 3·17 and 4·05 δ, for the —N—CH_2— protons. This may be due to the proximity of asymmetric center and/or restricted rotation around the N—CH_2 bond. In view of the fact that the



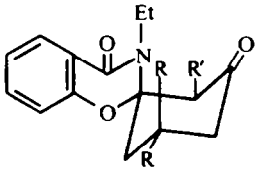
XVI: R = Me; R′ = H
XVII: R = H; R′ = Me
XVIII: R = R′ = H

benzoxazinone (XVIII) (*vide infra*), exhibits a quartet, with some hyperfine splitting, for the —N—CH_2— protons, the magnetic nonequivalence of the —N— methylene protons in XVI may be due to unequal conformer population (restricted rotation), caused presumably by the presence of gem dimethyl groups on the cyclohexanone portion. Although a study of the Dreiding models endorsed this view, further work may be necessary to establish this point. Apparently, the amide adds to the α,β-unsaturated ketone moiety present in VIII in an intramolecular Michael fashion to form the benzoxazinone (XVI).

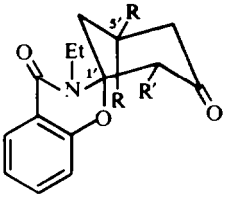
* Kemp and Chien[4c] compared the UV spectra of the phenolic esters, obtained on reacting the 7-hydroxybenzisoxazolium cation with carboxylic acids, and the corresponding anions with that of the 2 and 3-substituted esters and ethers of 2,3-dihydroxybenzamides and placed the carboxylic acid part at 3-position.

† 100 MHz spectrum.

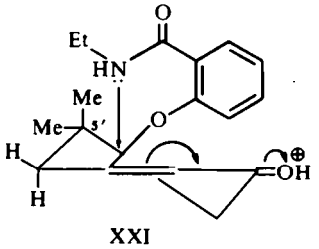
Two conformational isomers are possible for the benzoxazinone (XVI). In one isomer (XIX). the —C—N bond is attached to the cyclohexanone ring axially and in the other (XX). the bonding is equatorial. The approach of the amide group to the terminus of the conjugated system in the amide (VIII) in a perpendicular manner from the top face (antiparallel attack,[5] XXI) is hindered in the chair-like transition state[6] by the developing 1,3-interaction between one of the Me groups at 5′-position and the Michael addend. This attack would lead to the product XIX. In order to



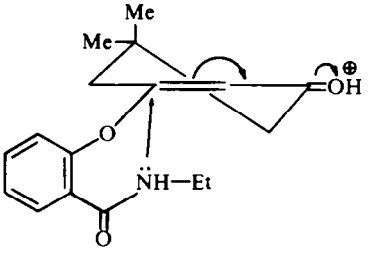
XIX: R = Me; R′ = H
XXVII: R = H; R′ = Me
XXIX: R = R′ = H



XX: R = Me; R′ = H
XXVIII: R = H; R′ = Me
XXX: R = R′ = H

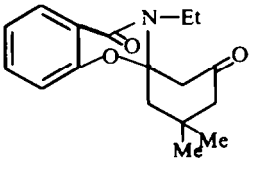


XXI



XXII

relieve this 1,3-interaction, attack of the amide might occur from the bottom side (parallel attack, XXII) through a twist or boat-like transition state and the product (XXIII) may be converted by ring flip to the spiran (XX) with minimum steric encumbrance. During the reactions of enols and enolate anions, in several instances, parallel attack is favoured when antiparallel attack is prohibited due to steric reasons.[7] Of the two spirans (XIX and XX), the latter, in which the more bulky moiety containing the —C—N bond is attached equatorially to the cyclohexanone ring, may be expected to be more stable than the spiran (XIX), in which the —C—O bond at C-1′ is equatorial.* Since the spiran obtained is the product of thermodynamic control, as it



XXIII

* Cf. The conformational energies of OH and NH_2 groups are 0·7 and 1·2 Kcal/mol respectively.[8]

remained unchanged on treatment with *p*-toluenesulphonic acid in benzene for several hours, it may be assigned the conformation XX. Further, the interaction between axial —C—O bond at C-1′ and the axial Me group at C-5′ in XX might be relieved by distortion of the cyclohexanone chair as a result of which the axial hydrogens at C-2′ and C-4′ come closer and the axial groups at C-1′ and C-5′ are kept away from each other (reflex effect[9]).

On treatment with bases, (a) aqueous sodium hydroxide in dioxan, (b) potassium t-butoxide in t-butanol and (c) benzylamine in acetonitrile, the amide (VIII) furnished a mixture of spiran (XVI), dimedone (V) and N-ethylsalicylamide (XXIV) (Chart 3).

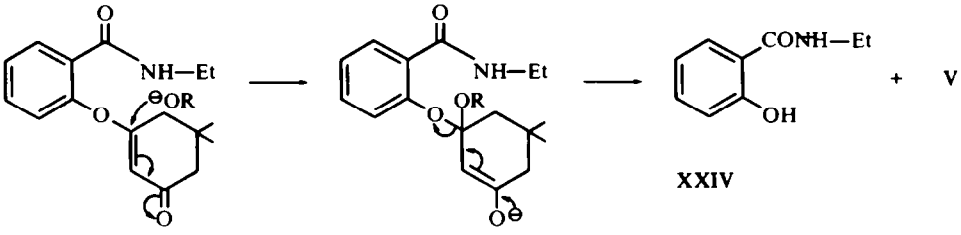
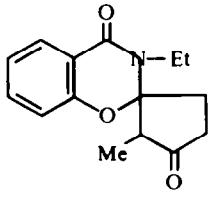


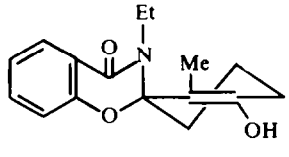
CHART 3

The spiran (XVI) was converted to dimedone (V) and N-ethylsalicylamide (XXIV) in the presence of alkali. Treatment of the amide (VIII) or the spiran (XVI) with 3N HCl in dioxan gave a mixture containing the amide (VIII), spiran (XVI), dimedone (V) and N-ethylsalicylamide (XXIV).

The amides (X, XI and XIII) could be converted to the spirans (XVII, XVIII and XXVI) respectively in the presence of *p*-toluenesulphonic acid. Under the same conditions, the amide (XIV) remained unchanged. On the basis of the arguments advanced earlier, the conformations of the amides could be assigned as follows.

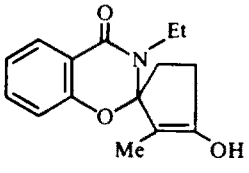


XXVI

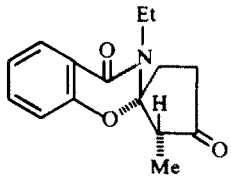


XXXI

During the intramolecular Michael reaction of the amide (XI), antiparallel attack of the amide to the β-position of the cyclohexenone system might lead to the conformer (XXIX) which can flip over to the stable XXX. In the case of X, antiparallel attack of the amide would furnish the enol (XXXI) which on axial protonation gives the spiran (XXVII). Ring flip followed by the equilibration of the C-2′ Me results in the formation of the spiran (XXVIII). Similarly, antiparallel attack of the amide group at the β-position of the cyclopentenone system in XIII might lead to the enol (XXXII)



XXXII



XXXIII

which on protonation furnishes the conformer which has the C-2′ Me group and the C–N bond at C-1′ in a *trans* arrangement with minimum steric congestion.

EXPERIMENTAL

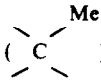
All m.ps are uncorrected. Light petroleum refers to the fraction. b.p. 40–60°. Solvent extracts were dried over Na_2SO_4.

IR spectra were taken on a Perkin–Elmer Infracord model 137B. either as smears (liquids) or Nujol mulls (solids). UV spectra were recorded on a Unicam model 700 Spectrophotometer in 95% EtOH (unless otherwise stated). PMR spectra were scanned on Varian A-60 and HA-100 instruments with TMS as internal standard ($\delta = 0$) in $CDCl_3$. Mass spectra were measured with a CEC-110 mass spectrometer (70 eV) with direct inlet system.

TLC were carried out on silica gel (200 mesh) containing 15% gypsum as binder. Visualization of zones after development was by I_2-vapours. Neutral Alumina (Brockmann-I) was used for column chromatography. Microanalyses were carried out by Messrs. B. R. Seetharamia and H. S. Thyagarajan of this department.

The reactions of isoxazolium salts with acidic 1.3-diketones were carried out in the presence of aqueous NaOH. The procedure (1a) adopted for the reaction of III with V is typical.

N-Ethylcarboxamidophenyl-2-(3′-oxo-5′.5′-dimethylcyclohexenyl)-ether (VIII).

1a. To a stirred solution of V (560 mg. 40 mmoles) in NaOHaq (1N. 4·4 ml) overlayered with EtOAc (15 ml) was added powdered III (940 mg; 40 mmoles) over a period of 5 min. The initial pH of the mixture was between 6–7 which changed to pH 4–5 after the addition of III. Water (30 ml) was added. the layers separated and the aqueous layer extracted with EtOAc (3 × 15 ml). The combined EtOAc extracts were washed with ice-cold NaOHaq (0·4%. 3 × 10 ml). The neutral organic layer was washed with water. brine. and dried. The residue (911 mg). obtained after removal of the solvent. was crystallized from Et_2O–light petroleum to afford VIII (525 mg). m.p. 90–91°; MS: molecular ion M (287) and significant ions at *m/e* 272. 227. 121; λ_{max}^{EtOH} 253 nm (ε 14350); ν_{max}^{Nujol} 3333 (—NH). 1640–1600 (amide-C=O and enone C=O) cm^{-1}; PMR*: δ_{CDCl_3} 1·1 (6H. s). (); 1·2 (3H. t. J = 7·5 Hz). (—N—CH_2—$\underline{CH_3}$); 2·23 (2H. s). (); 2·5 (2H. s). (—C—CH_2—); 3·17–3·65 (2H. quintet. broad). (NH—$\underline{CH_2}$—CH_3); 5·12 (1H. s). (vinyl H); 6·33–6·82 (1H. broad). (—C—$\underline{NH}$—); 6·83–8·0 (4H. m) (aromatic H). (Found: C. 71·06; H. 7·34; N. 5·40. Calc. for $C_{17}H_{21}NO_3$: C. 71·06; H. 7·37; N. 4·89%).

The alkali extract was acidified with 3N HCl and the product taken up in EtOAc (3 × 15 ml). The combined EtOAc extracts were washed with brine and dried. The solvent was removed to give a residue (304 mg) which was found to be a mixture of dimedone and N-ethylsalicylamide. These compounds were separated by TLC and compared with authentic specimens.

1b. To a stirred mixture of dimedone (140 mg) and NEt_3 (100 mg) in MeCN (5 ml). powdered III (235 mg)

* 100 MHz spectrum.

was added over a period of 3 min. Water (20 ml) was added, the two layers separated and the aqueous layer extracted with EtOAc (3 × 10 ml). The mixture was worked up in the usual fashion to furnish VIII (101 mg) in the neutral fraction, and a mixture of dimedone and N-ethylsalicylamide in the alkaline fraction (53 mg).

2-Hydroxy-N-ethylcarboxamidophenyl-3(3'-oxo-5',5'-dimethylcyclohexenyl)-ether (XIV).

A solid (362 mg), obtained in the neutral fraction from the reaction of dimedone (280 mg) with IV (502 mg) was crystallized from EtOAc–light petroleum to furnish XIV (152 mg) as colourless needles, m.p. 180–181°; ν_{max}^{Nujol} 3520 (—NH and OH), 1642–1587 (amide —C═O and enone —C═O); PMR*; δ_{CDCl_3} 1·15 (6H, s), (); 1·23 (3H, t, J = 7·5 Hz) (—N—CH_2—$\underline{CH_3}$); 2·27 (2H, broad s), (); 2·58 (2H, broad s), (—C(═O)—$\underline{CH_2}$); 2·95 (1H, broad s), (—O$\underline{H}$); 3·23–3·67 (2H, quintet, broad) (—NH—$\underline{CH_2}$—CH_3); 5·07 (1H, s), (vinyl H); 6·67–7·5 (4H, m) (aromatic H and —C(═O)—NH). (Found: C, 67·33; H, 6·92; N, 4·94. Calc. for $C_{17}H_{21}NO_4$: C, 67·33; H, 6·93; N, 4·62%).

N-Ethylcarboxamidophenyl-2-(2'-methyl-3'-oxo-cyclohexenyl)-ether (X).

A gummy material (460 mg), obtained in the neutral fraction from the reaction of III (470 mg, 20 mmoles) with 2-methylcyclohexane-1,3-dione (252 mg, 20 mmoles), was purified by TLC over SiO_2 gel with EtOAc as developer to obtain X (250 mg) as a pale yellow oil; UV $\lambda_{max}^{CH_3CN}$ 252 nm (ε 13,650); IR ν_{max}^{smear} cm^{-1} 3425 (NH), 1613–1640 (amide C═O and enone C═O); PMR (100 MHz); ppm 1·22 (3H, t, J = 7·5 Hz), (—N—CH_2—$\underline{CH_3}$); 1·88 (3H, s) (); 1·86–2·6 (6H, m), (protons at C-4', C-5' and C-6'); 3·36–3·68 (2H, m), (HN—$\underline{CH_2}$—CH_3); 6·8–8·18 (5H), (aromatic $\underline{H}$ and —CONH—); (Found: C, 70·12; H, 6·98; N, 5·38. Calc for $C_{16}H_{19}NO_3$: C, 70·31; H, 7·01; N, 5·12%).

N-Ethylcarboxamidophenyl-2-(3'-oxo-cyclohexenyl)-ether (XI)

A gummy material (501 mg) was obtained in the neutral fraction from the reaction of dihydroresorcinol (448 mg) with III (940 mg). This was purified† by TLC over SiO_2 gel with EtOAc as developer to afford XI (202 mg) as a pale yellow oil; UV λ_{max} 252 nm (ε 15,382); IR ν_{max}^{smear} cm^{-1} 3508 (NH), 1600–1640 (amide C═O, enone C═O). (Found: C, 69·60; H, 6·51; N, 5·61. Calc. for $C_{15}H_{17}NO_3$: C, 69·48; H, 6·61; N, 5·40%).

N-Ethylcarboxamidophenyl-2-(2'-methyl-3'-oxo-cyclopentenyl)-ether (XIII)

A waxy solid (825 mg), obtained in the neutral fraction from the reaction of XII (448 mg) with III (940 mg), was crystallized from EtOAc–light petroleum to give XIII (448 mg), m.p. 124–125·5°; UV λ_{max} 275 nm (ε 7902); IR ν_{max}^{Nujol} 3390 (NH), 1600–1639 (amide C═O and enone C═O); PMR (60 MHz): ppm 1·2 (3H, t, J = 7·5 Hz), (—N—CH_2—$\underline{CH_3}$); 1·68 (3H, broad s), (); 2·42 (4H, broad s), () and (); —CO$\underline{CH_2}$); 3·2–3·75 (2H, quintet) (HN—$\underline{CH_2}$—CH_3); 6·5–6·92 (1H, broad), (—CONH—); 7–8·05 (4H, m), (aromatic $\underline{H}$); (Found: C, 69·47; H, 6·73; N, 5·65. Calc. for $C_{15}H_{17}NO_3$: C, 69·48; H, 6·61; N, 5·40%).

The substituted phenyl ethers, described above, on refluxing with catalytic amounts of *p*-toluenesulphonic acid (*p*-TsOH) in benzene furnished the corresponding benzoxazinones. The procedure adopted for the preparation of *spiro*[2H-1,3-*benzoxazine*-2,1'-(3'-*oxo*-5',5'-*dimethylcyclohexan*)]-3-*ethyl*-4-*one* (XVI) is typical.

Spiro[2H-1,3-*benzoxazin*-2,1'-(3'-*oxo*-5',5'-*dimethylcyclohexan*)]-3-*ethyl*-4-*one* (XVI)

A mixture of VIII (100 mg) and *p*-TsOH (5 mg) in benzene (10 ml) was refluxed for 6 hr, the benzene

* 60 MHz spectrum.

† In certain runs small amounts of the benzoxazinone (XXX) could be isolated from the reaction mixture.

soln washed with water, dried and the solvent removed to leave a residue (98 mg) which on crystallization from Et_2O–light petroleum furnished XVI (62 mg). m.p. 103–104°; MS: molecular ion M (287) and significant ions at *m/e* 230, 216, 189, 121, 120, 110; λ_{max}^{EtOH} 298 (ε 2432) nm; ν_{max}^{Nujol} 1720 (6-membered ring C=O); 1667 (amide C=O); PMR*: δ_{CDCl_3} 1·07 (6H, s). (); 1·27 (3H, t, J = 7·5 Hz) (—N—CH_2—$\underline{CH_3}$); 2·02 (1H, s) (axial H at C-6'); 2·23 (1H, s, broad) (equatorial proton at C-6'); 2·35 (2H, s, broad), (protons at C-4'); 2·95 (2H, s, broad), (protons at C-2'); 3·17–4·05 (2H, m) (—N—$\underline{CH_2}$—CH_3); 6·72–8·05 (4H, m) (aromatic H). (Found: C, 70·89; H, 7·44; N, 5·30. Calc. for $C_{17}H_{21}NO_3$: C, 71·06; H, 7·37; N, 4·87%).

Spiro[2H-1,3-*benzoxazine*-2,1'-(3'-*oxo-cyclohexan*)]-3-*ethyl*-4-*one* (XXX)

A sticky solid, obtained from XI (100 mg) and *p*-TsOH (5 mg), was crystallized from Et_2O to afford XXX (71 mg), m.p. 123–124°; UV λ_{max} 296 nm (ε, 1932); IR ν_{max}^{Nujol} cm^{-1} 1721 (6-membered ring C=O), 1653 (amide C=O); PMR (100 MHz) ppm, 1·27 (3H, t, J = 7·5 Hz), (N—CH_2—$\underline{CH_3}$); 1·7–3·15 (8H, m) (protons at C-2', C-4', C-5', C-6'); 3·55–3·77 (2H, quartet) (—N—$\underline{CH_2}$—CH_3); 6·83–8·0 (4H, m), (aromatic $\underline{H}$); MS: molecular ion M (259) and significant ions at *m/e* 258, 216, 202, 121, 120. (Found: C, 69·49; H, 6·61; N, 5·62. Calc. for $C_{15}H_{17}NO_3$: C, 69·48; H, 6·61; N, 5·40%).

Spiro[2H-1,3-*benzoxazine*-2,1'-(2'-*methyl*-3'-*oxo-cyclopentan*)]-3-*ethyl*-4-*one* (XXXIII)

A gummy material, obtained from XIII (300 mg) and *p*-TsOH (15 mg), was chromatographed over neutral Al_2O_3. Elution with light petroleum–benzene (3:1) gave XXXIII (175 mg), m.p. 79–80·5°; UV λ_{max} 294 nm (ε, 3717); IR ν_{max}^{Nujol} cm^{-1} 1748 (5-membered ring C=O), 1665 (amide C=O). (Found: C, 69·26; H, 6·52; N, 5·20. Calc. for $C_{15}H_{17}NO_3$: C, 69·48; H, 6·61; N, 5·40%).

Spiro[2H-1,3-*benzoxazine*-2,1'-(2'-*methyl*-3'-*oxocyclohexan*)]-3-*ethyl*-4-*one* (XXVIII)

A gummy material, obtained from X (200 mg) and *p*-TsOH (10 mg), was chromatographed over neutral Al_2O_3. Elution with light petroleum–benzene (4:1) furnished XXVIII (125 mg), m.p. 127–128°; UV λ_{max} nm 298 (ε, 1980); IR ν_{max}^{Nujol} cm^{-1} 1724 (6-membered ring C=O), 1665 (amide C=O); PMR (60 MHz) ppm, 1·23 (3H, d, J = 7 Hz) (—CH—$\underline{CH_3}$); 1·37 (3H, t, J = 7·2 Hz) (—N—CH_2—$\underline{CH_3}$); 1·6–3·25 (7H), (protons at C-2', C-4', C-5', C-6'); 3·25–4·0 (2H, m) (N—$\underline{CH_2}$—CH_3); 6·7–8·0 (4H), (aromatic $\underline{H}$); (Found: C, 70·17; H, 7·16; N, 5·51. Calc. for $C_{16}H_{19}NO_3$: C, 70·31; H, 7·01; N, 5·12%).

Attempted cyclization of 2-*hydroxy*-N-*ethylcarboxamidophenyl*-3-(3'-*oxo*-5',5'-*dimethylcyclohexenyl*)-*ether* (XIV)

A soln of XIV (50 mg) and *p*-TsOH (10 mg) in benzene (5 ml) was refluxed for 18 hr and then the mixture worked up. The starting material (XIV) was recovered unchanged.

Reaction of N-*ethylcarboxamidophenyl*-2-(3'-*oxo*-5',5'-*dimethylcyclohexenyl*)-*ether* (VIII) *with bases*

(a) *With* NaOH aq. A soln of VIII (50 mg) in dioxan (1 ml) and NaOH aq (1N, 0·25 ml) was heated on a water bath for ½ hr. Water (60 ml) was added and the soln extracted with EtOAc (3 × 10 ml). The neutral organic extract was worked up to give, on crystallization from Et_2O–light petroleum, a product (17 mg) identical with XVI.

The aqueous layer was acidified and the product worked up to give a mixture (24 mg) of dimedone and N-ethylsalicylamide (TLC, IR).

b. *With benzylamine.* A soln of VIII (100 mg) and benzylamine (45 mg) in MeCN (1·5 ml) was heated under N_2 on a water bath for 2 hr. The residue, obtained after removing the solvent and benzylamine *in vacuo* was taken up in EtOAc (30 ml). The EtOAc extract was washed with brine, dried and the solvent removed to give a residue which on crystallization from ether–light petroleum afforded XVI (70 mg).

c. *With potassium t-butoxide.* To a soln of t-BuOK in dry t-BuOH, prepared by dissolving K (27 mg) in dry t-BuOH (3·3 ml), VIII (100 mg) was added and the mixture refluxed for ½ hr under N_2. t-BuOH was removed *in vacuo* at room temp, the residue taken up in water (50 ml) and the soln extracted with EtOAc (3 × 15 ml). The combined EtOAc extracts were washed, dried and the solvent removed. The residue on crystallization from ether–light petroleum gave XVI (35 mg).

The aqueous layer was acidified and the product (38 mg), obtained after usual work up, was found to be a mixture of dimedone and N-ethylsalicylamide.

* 100 MHz spectrum.

Reaction of VIII *with* 3N HCl aq

A soln of VIII (50 mg) in dioxane (1 ml) and 3N HCl aq (0·1 ml) was refluxed for ½ hr and then the mixture was worked up to furnish in the neutral fraction a solid (28 mg). found to be a mixture of XVI and VIII. In the alkaline fraction a mixture of dimedone and N-ethylsalicylamide (23 mg) was obtained.

Reaction of benzoxazinone (XVI) *with* 3N HCl aq

A soln of XVI (50 mg) in dioxan (1 ml) and 3N Hcl (0·1 ml) was refluxed for ½ hr and then the mixture was worked up to furnish a mixture (31 mg) of XVI and VIII in the neutral fraction and a mixture (15 mg) of dimedone and N-ethylsalicylamide in the alkaline fraction.

Reaction of XVI *with* NaOH aq

A soln of XVI (50 mg) in dioxan (1 ml) and NaOH aq (1N. 0·25 ml) was heated on a water bath for 1 hr and then the mixture worked up to furnish a mixture of dimedone and N-ethylsalicylamide (41 mg).

Treatment of XVI *with* p-TsOH

A soln of XVI (50 mg) and *p*-TsOH in benzene (5 ml) was refluxed for 20 hr and then the mixture worked up. The starting XVI was quantitatively recovered unchanged.

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