Enamine Chemistry. Part VIII.[1] Reaction of Acryloyl Chloride with Dienamines [2]

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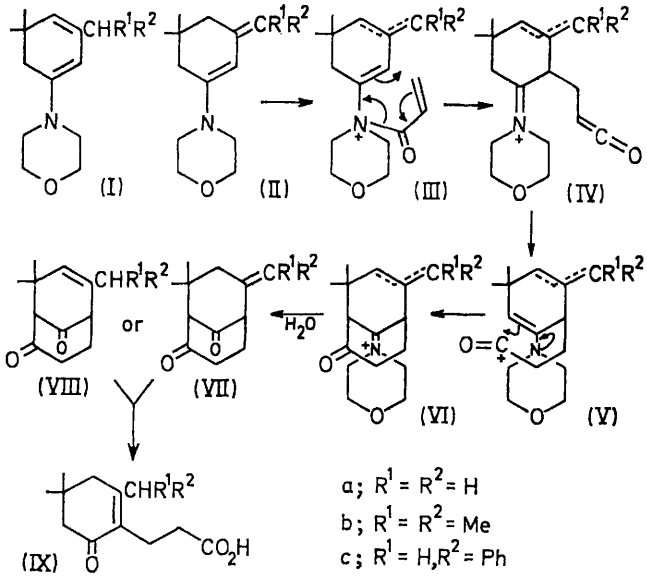
Reaction of acryloyl chloride with dienamines derived from 3-alkyl-5,5-dimethylcyclohex-2-enones gives mainly the corresponding 6-alkyl-8,8-dimethylbicyclo[3,3,1]non-6-ene-2,9-diones formed by initial carbon–carbon bond formation at the β-position (C-2) and cyclisation at C-6. A tricyclic compound formed by reaction at the β- and δ-positions was also isolated in one case, but in very low yield. Reaction of acryloyl chloride with acyclic linear and cross-conjugated dienamines gives mainly the corresponding 2-alkyl-4-alkenyl- and 2-alkenyl-4-alkyl-3-morpholinocyclohex-2-enones respectively.

THE propensity for dienamines to react with electrophilic reagents at the position β to the amino-group is well known; [3] examples of reactions leading to mixtures of β- and δ-substituted products have also been reported.[4] Presumably reaction at the β-position is kinetically favoured, but the more stable δ-substituted product is obtained when conditions are favourable for thermodynamic control. However, studies of the protonation of simple enamines [5] and dienamines [4a] indicate that the most kinetically favoured process involves initial reaction at the nitrogen, and we have also found a similar tendency in the reaction of ketone and aldehyde enamines with αβ-unsaturated acid chlorides.[6] Recently we have shown [7] that dienamines derived from $\Delta^{1,8a}$-2-octalones react with acryloyl chloride preferentially at the β-position to give 1,3- and 1,8-bridged products; the evidence is consistent with the occurrence of a [3,3] sigmatropic rearrangement of the *N*-acyl-dienamine initially formed. Evidence for limited *initial* reaction at the δ-position (C-8 or, less likely, C-4a) was also obtained in that a 4a,8-bridged product was isolated.

We have now extended this investigation to dienamines derived from 3-alkyl-5,5-dimethylcyclohex-2-enones and acyclic αβ-unsaturated ketones. Depending on the substitution pattern the dienamines formed exist predominantly as linear (*s-cis* or *s-trans*) or cross-conjugated diene structures.[1,8] The products obtained by reaction of acryloyl chloride with 3-alkyl-5,5-dimethylcyclohex-2-enone dienamines are summarised in Scheme 1, and their formation can again best be explained in terms of initial *N*-acylation followed by a [3,3] sigmatropic rearrangement, resulting in carbon–carbon bond formation at C-2 [(III) ⟶ (IV)], followed by cyclisation at C-6 [(IV) ⟶ (V) ⟶ (VI)]. The dienamines from 3-benzyl- and 3-isopropyl-5,5-dimethylcyclohex-2-enone both exist completely in the linear *s-trans*-form [1] [(IIc) and (IIb) respectively]. The former (IIc) gave the bicyclic dione (VIIIc) containing an endocyclic double bond, whereas the latter (IIb) gave the dione (VIIb) containing an exocyclic



SCHEME 1

double bond, on mild aqueous hydrolysis of the precipitated iminium salts (VI). The dienamine from isophorone exists as a mixture [9] of linear [(Ia) and (IIa)] and cross-conjugated isomers. Reaction with acryloyl chloride gave a complex mixture from which the dione (VIIIa) was isolated, together with a product formed, in low yield, by reaction with two equivalents of acryloyl chloride. The spectroscopic evidence (Experimental section) is consistent with this latter product being a tautomeric mixture (X).

Alkaline hydrolysis of the bicyclic diones (VIIIa)

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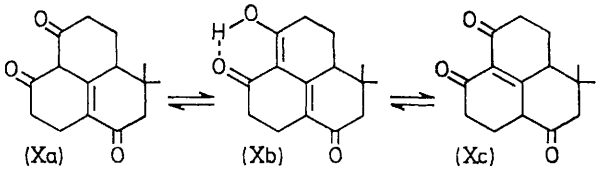
[8] P. W. Hickmott and B. J. Hopkins, *J. Chem. Soc.* (*B*), submitted for publication.

[9] N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (*B*), 1969, 293.

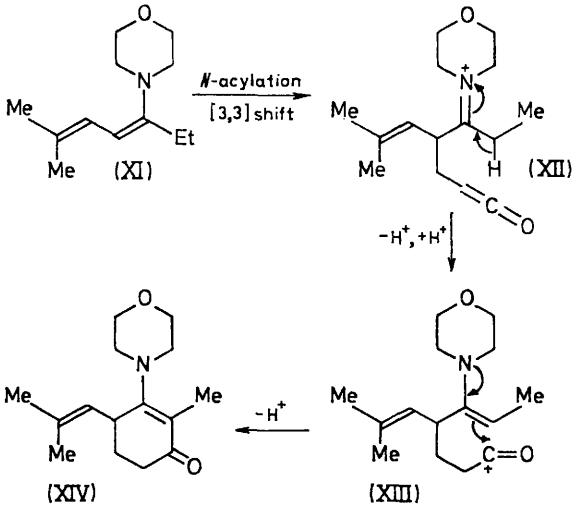
and (VIIb) gave the corresponding acids [(IXa) and (IXb), respectively], in which double bond migration to the αβ-position had taken place. The absence of



olefinic proton signals in the ^{1}H n.m.r. spectrum confirmed the position of the 2-carboxyethyl substituent at C-2, in agreement with the reaction sequence indicated in Scheme 1.

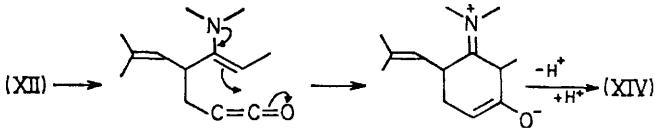
The main products formed by the reaction of acryloyl chloride with linear and cross-conjugated acyclic dienamines in boiling benzene are the enamino-ketones [(XIV) and (XVIII), respectively] Their formation can again be rationalised in terms of an initial *N*-acylation followed by a [3,3] sigmatropic rearrangement. By this process a keten substituent is introduced at the in-chain β-position of the linear dienamine [(XI) ⟶ (XII); Scheme 2], and proton loss from the resulting iminium salt regenerates the enamine system [(XII) ⟶ (XIII)], which collapses to the enamino-ketone (XIV).

For the sake of simplicity the proton lost in regenerating the enamine system is assumed to have been trans-

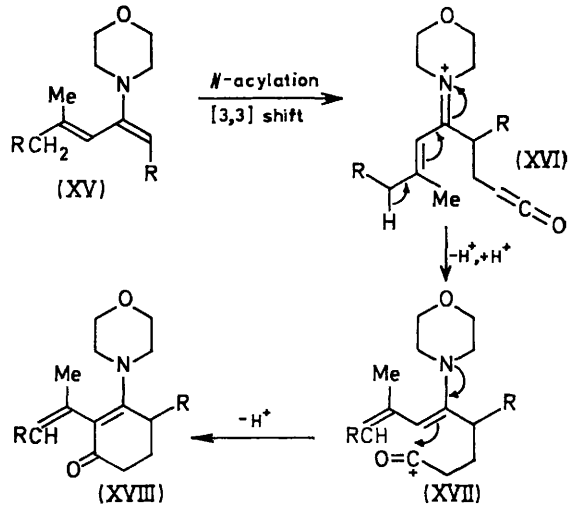


SCHEME 2

ferred to the keten group, to give the acylium ion (XIII). However, it is recognised, in the absence of further evidence, that this could be an intermolecular process in which the proton is accepted by free dienamine and that cyclisation then takes place on to the keten group to give an enolate anion which is subsequently protonated.



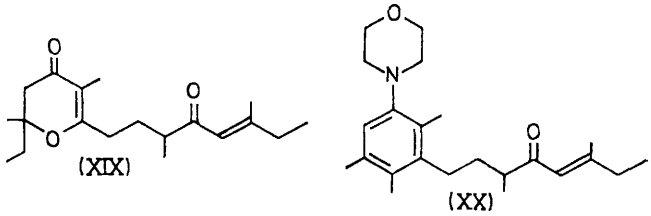
In the case of the cross-conjugated dienamine (XV; R = Me or Et) the same process results in the introduction of the keten substituent at the terminal position [(XV) ⟶ (XVI); Scheme 3]. Regeneration of the enamine system then results in cyclisation on to the in chain position [(XVI) ⟶ (XVII) ⟶ (XVIII)]. *cis-trans*-Isomerism is possible about the unsaturated side-chain of the resulting enamino-ketones (XVIII) and the spectroscopic evidence (Experimental Section) indicates that both stereoisomers are formed, in approximately equal proportions. That the unsaturated side-chain is at C-2 [in (XVIII)] rather than at C-4 [as in (XIV)] is shown by the ^{1}H n.m.r. spectrum of (XVIII; R = Me), which clearly shows the 4-methyl signal for each isomer as a doublet (τ 9·08 and 9·14). The ^{1}H n.m.r. spectrum of (XIV), on the other hand,



SCHEME 3

showed only signals due to three MeC= groups (τ 8·34 and 8·25) proving that the unsaturated side-chain is at C-4 not C-2.

Two other products were isolated, in low yield, from the reaction of acryloyl chloride with 5-methyl-3-morpholinohepta-2,4-diene (XV; R = Me), namely the dihydro-γ-pyrone (XIX) and the pentasubstituted benzene (XX), identified by spectroscopic evidence (Experimental section). Since the carbon–carbon



double bond of the αβ-unsaturated acid chloride is not involved in the cyclisation process leading to these two products [(XIX) and (XX)], but merely serves to react, as an electrophilic olefin, with a second equivalent of the dienamine to form the 3,6-dimethyl-4-oxo-oct-5-enyl side-chain, further investigations into the reactions

of saturated and aromatic acid chlorides with cross-conjugated dienamines are being carried out, to determine whether simple dihydro-γ-pyrones and penta-substituted benzenes can be obtained by this process.

EXPERIMENTAL

U.v. and i.r. spectra were measured with Unicam SP 800 and Perkin-Elmer 221 spectrophotometers respectively. N.m.r. and mass spectra were determined with Varian A60 and AEI MS12 or MS9 instruments respectively. Dienamines were prepared by published methods.

6,8,8-*Trimethylbicyclo*[3,3,1]*non*-6-*ene*-2,9-*dione* (VIIIa).—Acryloyl chloride (4·53 g., 0·05 mole) in dry benzene (30 ml.) was added to the morpholine dienamine of isophorone (10·35 g., 0·05 mole) in boiling dry benzene (70 ml.) during 50 min., and the mixture was heated under reflux for 1 hr. The mixture was cooled and the precipitated iminium salt was collected, washed with dry ether, and hydrolysed with cold water. Extraction with ether gave the crude dione (3·13 g.), a portion (0·36 g.) of which was purified by distillation *in vacuo* and crystallisation (light petroleum) to give 6,8,8-*trimethylbicyclo*[3,3,1]*non*-6-*ene*-2,9-*dione* (0·13 g., 12%), m.p. 76°. A slightly higher yield (15%) was obtained when purification was effected by preparative t.l.c. on silica (10% acetone–benzene) (Found: C, 74·7; H, 8·5%; M^+, 192. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%; M, 192), $\nu_{max.}$ (Nujol) 1725 and 1700 cm.$^{-1}$ (C=O), τ ($CDCl_3$) 8·93 (6H, s, Me_2), 8·22 (3H, d, J 1·5 Hz, Me), 7·1 (1H, m, CH), 6·92 (1H, s, CH), 4·53 (1H, q, J 1·5 Hz, CH=), and *ca.* 7·45br and 8·0br (each m, CH_2).

The same product was obtained in higher yield (25%) by application of the same procedure to the piperidine dienamine.

Evaporation of the original benzene filtrate gave a red-brown oily mixture (1·57 g.). Preparative t.l.c. on silica (10% acetone–benzene) gave a purple band, which was removed and extracted with acetone to give an oil in low yield. The spectral data were consistent with a mixture of structurally isomeric dimethyldecahydrophenalenetriones (X), $\nu_{max.}$ (film) 1727 and 1705 (C=O), and 1660s,br and 1610s,br (enol chelate) cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 320 nm. {ε [corrected for the actual amount of enolic form (Xb) present in the mixture] 19·0 × 10^3}, *m/e* 246 (M^+; required 246), τ ($CDCl_3$) 7·1—9·0 (CH_2 envelope), 8·98, 8·92, 8·78, and 8·72 (singlets of unequal intensity; geminal Me_2 in different structural environments), and −6·13 (H-bonded OH); the integral ratio indicated that *ca.* 30% of the enolic form (Xb) was present.

6-*Isopropylidene*-8,8-*dimethylbicyclo*[3,3,1]*nonane*-2,9-*dione* (VIIb).—Acryloyl chloride (0·36 g., 0·004 mole) in dry benzene (10 ml.) was added to the morpholine dienamine of 3-isopropyl-5,5-dimethylcyclohex-2-enone [1] (0·93 g., 0·004 mole) in boiling dry benzene (15 ml.) during 45 min., and the mixture was heated under reflux for a further 4 hr. It was then cooled, and the precipitated iminium salt was collected and hydrolysed by stirring with cold water for 18 hr. Extraction with ether gave an oil (0·347 g.) which slowly solidified. A portion (0·17 g.) was purified by preparative t.l.c. on silica (10% acetone in benzene) to give 6-isopropylidene-8,8-dimethylbicyclo-[3,3,1]nonane-2,9-dione (0·086 g., 20%), m.p. 77—78°, $\nu_{max.}$ (Nujol) 1725 and 1700 cm.$^{-1}$ (C=O) (Found: M^+, 220·1458. Calc. for $C_{14}H_{20}O_2$: M, 220·1463), τ ($CDCl_3$) 9·08 (3H, s, Me), 8·93 (3H, s, Me), 8·24 (6H, s, $=CMe_2$), 7·03 (1H, s, CH), 6·28 (1H, m, CH), and 7·2—8·3 (CH_2 envelope) (no olefinic signals).

6-*Benzyl*-8,8-*dimethylbicyclo*[3,3,1]*non*-6-*ene*-2,9-*dione* (VIIIc).—Acryloyl chloride (0·14 g., 0·0016 mole) in dry benzene (5 ml.) was added to the morpholine dienamine of 3-benzyl-5,5-dimethylcyclohex-2-enone [1] (0·45 g., 0·0016 mole) in boiling dry benzene (25 ml.) during 30 min. The mixture was heated under reflux for a further 4 hr. and then cooled. The precipitated iminium salt was collected, washed with ether, and hydrolysed by stirring with cold water for 18 hr. Extraction with ether gave an oil (0·1 g.), which solidified on trituration with methanol to give 6-benzyl-8,8-dimethylbicyclo[3,3,1]non-6-ene-2,9-dione (0·051 g., 12%), m.p. 118° (methanol), $\nu_{max.}$ (Nujol) 1728 and 1701 cm.$^{-1}$ (C=O) (Found: M^+, 268·1463. Calc. for $C_{18}H_{20}O_2$: M, 268·1463), τ ($CDCl_3$) 8·93 (6H, s, Me_2), 6·63 (2H, s, $PhCH_2$), 4·51 (1H, s, CH=), 2·73 (5H, s, Ph), and 6·7—8·5 (complex, CH_2 and CH).

2-(2-*Carboxyethyl*)-3,5,5-*trimethylcyclohex*-2-*enone* (IXa).—6,8,8-Trimethylbicyclo[3,3,1]non-6-ene-2,9-dione (0·146 g.) was hydrolysed by boiling with 2N-sodium hydroxide (5 ml.) for a few min. The cooled solution was extracted with ether and acidified; the resulting precipitate was dissolved in ether and the solution was shaken with saturated sodium hydrogen carbonate solution. Acidification of the aqueous layer gave crude material (0·14 g., 88%), which yielded 2-(2-*carboxyethyl*)-3,5,5-*trimethylcyclohex*-2-*enone*, m.p. 74—75° (from light petroleum) (Found: C, 68·9; H, 8·6. $C_{12}H_{18}O_3$ requires C, 68·4; H, 8·6%), $\nu_{max.}$ (Nujol) 3300—2500 (OH), 1700 and 1660 (C=O), and 1630 (C=C) cm.$^{-1}$ *m/e* 210 (M^+; required 210), τ ($CDCl_3$) 8·99 (6H, s, Me_2), 8·02 (3H, s, Me), −1·11 (1H, s, CO_2H), 7·74 (s, ring CH_2), and 7·5 (m, side-chain CH_2).

2-(2-*Carboxyethyl*)-3-*isopropyl*-5,5-*dimethylcyclohex*-2-*enone* (IXb).—6-Isopropylidene-8,8-dimethylbicyclo[3,3,1]-nonane-2,9-dione (0·11 g.) was hydrolysed by boiling with 4N-sodium hydroxide (10 ml.) for 5 min. The procedure used in the preceding example gave 2-(2-carboxyethyl)-3-isopropyl-5,5-dimethylcyclohex-2-enone (0·09 g., 76%) as a low-melting waxy *solid* (Found: C, 70·5; H, 9·3%; M^+, 238. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·25%; M, 238), $\nu_{max.}$ (film) 3500—2500 (OH), 1705 and 1660 (C=O), and 1620 (C=C) cm.$^{-1}$ $\lambda_{max.}$ (hexane) 239 nm. (ε 9·75 × 10^3), τ ($CDCl_3$) 9·0 (6H, s, Me_2), 8·96 (6H, d, $CHMe_2$), 1·35br (1H, s, CO_2H), 7·83 and 7·73 (each s, ring CH_2), and *ca.* 7·5 (m, side-chain CH_2 and CH).

4-*Methyl*-2-(1-*methylprop*-1-*enyl*)-3-*morpholinocyclohex*-2-*en*-1-*one* (XVIII; R = Me).—Acryloyl chloride (1·81) g., 0·02 mole) in dry benzene (20 ml.) was added to 5-methyl-3-morpholinohepta-2,4-diene [8] (3·9 g., 0·02 mole) in boiling dry benzene (30 ml.) during 30 min., and the mixture was heated under reflux for a further 7 hr. and then cooled. The semi-solid precipitate was separated by decantation, dissolved in dilute hydrochloric acid, and shaken with ether. The aqueous layer was basified with 4N-sodium hydroxide and extracted with ether. Evaporation of the dried extract gave an oil, which was separated by preparative t.l.c. on silica (10% acetone–benzene) into three distinct bands, which were extracted with acetone.

The third band (from the solvent front) gave an oil (1·66 g.) which was further purified by preparative t.l.c. on silica [acetone–triethylamine–benzene (10 : 2 : 88)] to give 4-methyl-2-(1-methylprop-1-enyl)-3-morpholinocyclohex-2-en-1-one (1·0 g., 20%) as a mixture of stereoisomers in approximately equal proportions (Found: N, 5·4.

Calc. for $C_{15}H_{23}NO_2$: N, 5·6%), $\nu_{max.}$ (film) 1626 (C=O), and 1540 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 318·5 nm. (ε 26·0 × 10^3), *m/e* 249 (M^+; required 249), τ (C_6D_6) 9·08 and 9·14 (each d, *J* 7·0 Hz, 4-Me of two isomers), 8·6 and 8·63 (each d, *J* 6·75 Hz Me_a of *cis*- and *trans*-CMe_b=$CHMe_a$, broadened by long-range coupling with Me_b), 7·9 and 8·0 (each m, Me_b of *cis*- and *trans*-CMe_b=$CHMe_a$, weakly coupled with the olefinic and Me_a protons), 7·67 and 8·05 (each m, ring CH_2), 7·1 (CH_2·N·CH_2), 6·64 (CH_2·O·CH_2), and 4·55 (complex, *cis*- and *trans*-CMe=C*H*Me). The second band gave an oil, identified as 2-(3,6-dimethyl-4-oxo-oct-5-enyl)-6-ethyl-5,6-dihydro-3,6-dimethyl-γ-pyrone (XIX) (0·25 g., 8% based on dienamine), on the basis of spectral evidence [$\nu_{max.}$ (film) 1685 and 1665 (C=O), 1615 (C=C), and 1160, 1120, and 1055 (C–O–C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 241 and 279 nm., *m/e* 306 (M^+; required 306), τ 8·95 (9H, complex d + 2t, 3 × Me), 8·7 (3H, s, Me), 8·37 (3H, s, Me), 7·87 (3H, s, Me), and 3·95br (1H, s, CH=)].

The first band gave an oil identified as 3-(3,6-dimethyl-4-oxo-oct-5-enyl)-2,4,5-trimethyl-1-morpholino benzene (XX) (0·45 g., 13% based on dienamine) on the basis of the spectral evidence [$\nu_{max.}$ (film) 1680 (C=O) and 1620 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 214·5 and 239 nm., *m/e* 357 (M^+; required 357), τ (CCl_4) 8·90 (3H, t, Me), 8·89 (3H, d, Me), 7·87 (6H, s, Me_2) 7·80 (6H, s, Me_2), 7·26 (4H, m, CH_2·N·CH_2), 6·26 (4H, m, CH_2·O·CH_2), 3·93br (1H, s, CH=), 3·38sharp (1H, s, aromatic), and 8·5—7·5 (CH_2 envelope)].

4-Ethyl-2-(1-methylbut-1-enyl)-3-morpholinocyclohex-2-en-1-one (XVIII; R = Et).—Acryloyl chloride (2·26 g., 0·025 mole) in dry benzene (25 ml.) was added to 6-methyl-4-morpholinonona-3,5-diene [8] (5·5 g. 0·025 mole) in boiling dry benzene (150 ml.) during 1 hr., and the mixture was heated under reflux for a further 18 hr. The solution was cooled, filtered from precipitated salts and evaporated to give an oil (6·43 g.), a portion (0·25 g.) of which was purified by preparative t.l.c. on silica (10% ethanol–benzene) and crystallised from light petroleum to give the *enamino-ketone* (XVIII; R = Et) (0·115 g., 42%), m.p. 76° (Found: C, 73·6; H, 9·8; N, 5·5. $C_{17}H_{27}NO_2$ requires C, 73·6; H, 9·7; N, 5·05%), $\nu_{max.}$ (film) 1620 (C=O) and 1530 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 319·5 nm. (ε 21·5 × 10^3), τ (CCl_4) 8·97 (6H, t, Me_2), 8·28 (3H, s, Me), 6·76 (4H, m, CH_2·N·CH_2), 6·40 (4H, m, CH_2·O·CH_2), 5·05 and 4·73 (total 1H, each t, *cis*- and *trans*-CMe=C*H*Et), and 8·7—7·2 (9H, CH_2 envelope).

2-Methyl-4-(2-methylprop-1-enyl)-3-morpholinocyclohex-2-en-1-one (XIV).—Acryloyl chloride (0·36 g., 0·004 mole) in dry benzene (10 ml.) was added to 2-methyl-5-morpholinohepta-2,4-diene [8] (0·77 g., 0·004 mole) in boiling dry benzene (20 ml.) during 30 min. The mixture was heated under reflux for a further 4 hr. and cooled, and the benzene solution was decanted from a small amount of oil and evaporated. The residue (0·83 g.) was purified by preparative t.l.c. on silica (10% acetone–benzene) to give the *enamino-ketone* (XIV) (0·48 g., 48%) (Found: N, 5·4. $C_{15}H_{23}NO_2$ requires N, 5·6%), $\nu_{max.}$ (film) 1640 (C=O) and 1570 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 318 nm. (ε 21·0 × 10^3), *m/e* 249 (M^+) τ (CCl_4) 8·34 (3H, s, Me), 8·25br (6H, s, Me_2), 7·8 (4H, m, CH_2·CH_2), 6·95 (4H, m, CH_2·N·CH_2), 6·40 (4H, m, CH_2·O·CH_2), 4·75 (1H, dm, *J* 10 Hz CH=), and 7·9 (m, remaining ring protons).

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