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Some Reactions of Enamines. Part II.[1] Some Alkylation Reactions of the Pyrrolidine Enamines of 3,4-Dihydronaphthalen-1(2*H*)-one and 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-one

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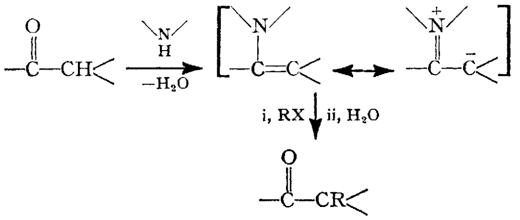
The pyrrolidine enamines (III) and (IV) of 3,4-dihydronaphthalen-1(2*H*)-one (I) and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (II), respectively, were prepared. Alkylation of (III) and (IV) with methyl iodide and with methyl vinyl ketone yielded the α-methyl and the α-(3-oxobutyl) ketones of (I) and (II). Conformations for the tricyclic products formed in the intramolecular aldol condensations of the α-(3-oxobutyl) ketones of (I) and (II) are proposed.

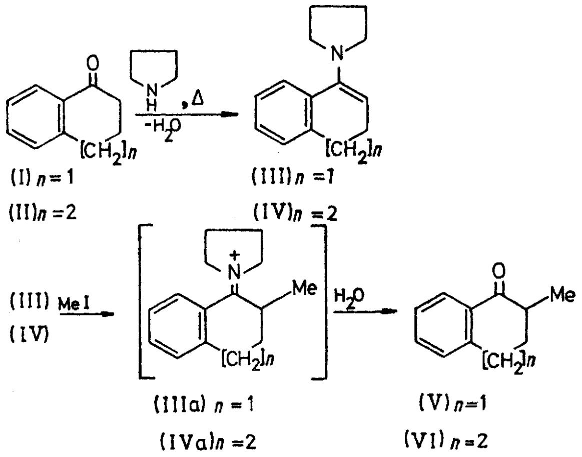
STORK and his co-workers[2] have described the preparation of α-substituted carbonyl compounds by the reaction of electrophilic reagents with enamines derived from the α-unsubstituted compounds[3] (Scheme 1). We describe here the preparation of some enamines derived from 3,4-dihydronaphthalen-1(2*H*)-one (I) and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (II), and some of their alkylation reactions.



SCHEME 1

The pyrrolidine enamines (III) † and (IV) of (I) and (II), respectively, and the morpholine enamine (XI) ‡ of (II) were prepared (76—88%)[3b,5] from the appropriate ketone and an excess of secondary amine in the presence of a trace of toluene-*p*-sulphonic acid. Their i.r. and u.v. spectra showed the absorptions expected for an α-phenyl enamine;[6,7] however, the n.m.r. spectra of (III) and (XI) exhibited vinyl hydrogen absorption τ *ca.* 5·0, at lower field than the more usual value (5·6) because of the anisotropy of the aromatic ring.

Methylation.—Except in the case of strongly electrophilic halides, alkylations of enamines with alkyl halides have usually given only small yields of α-alkyl ketones.[3] Typically, reaction of (IV) with methyl iodide[3b,8] gave the α-methyl ketone (VI) (34%); the yield was raised to 43% when an extra equivalent of methyl iodide was added. However, (III) was far less reactive toward methyl iodide. In our hands, use of a 1 : 1 molar ratio of methyl iodide to (III)[8] gave only starting ketone (I) (94%) after hydrolysis. Only when the molar ratio was raised to 4—5·5 : 1 was any α-methyl ketone (V) obtained (11—14%).



SCHEME 2

Dreiding models suggest that *C*-alkylation is more difficult in (III) than in (IV) because of steric inhibition of resonance in the enamine system of (III) caused by interaction between the α-hydrogens of the pyrrolidine ring and the benzene hydrogen *ortho* to the enamine function [at maximum *p*-orbital overlap in the enamine, this distance is 1·36 Å in (III) and 2·00 Å in (IV)]. A second factor that may contribute is that steric effects may make the rate of formation of the α-methylated immonium salt (IIIa) slower than in the case of (IVa). On the assumption of stereoelectronic control,[9] Dreiding models indicate minimal relief of steric interactions in the

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† Since the completion of this work, (III) has been reported[4] without elemental analysis but with spectral data similar to ours.

‡ M. Muehlstaedt and J. Reimer, *Z. Chem.*, 1964, **4**, 70, reported the preparation of (presumably) (XI) but no experimental details or physical properties were given.

[1] (*a*) Part I, L. H. Hellberg and M. F. Stough, *Acta Chem. Scand.*, 1967, **21**, 1368; (*b*) presented in part at the Western Regional Meeting of the American Chemical Society, Los Angeles, California, November 1965.

[2] (*a*) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029; (*b*) G. Stork and H. Landesman, *ibid.*, 1956, **78**, 5128.

[3] Reviews include: (*a*) J. Szmuszkovicz, *Adv. Org. Chem.*, 1963, **4**, 1; (*b*) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207; (*c*) J. A. West, *J. Chem. Educ.*, 1963, **40**, 194; (*d*) P. A. Smith, 'Open-Chain Nitrogen Compounds,' vol. 1, Benjamin, New York, 1965, pp. 313—322.

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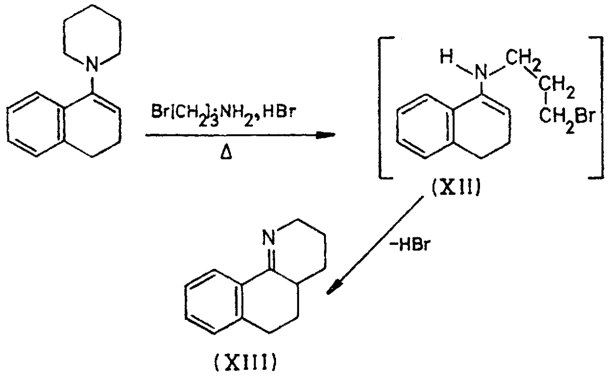
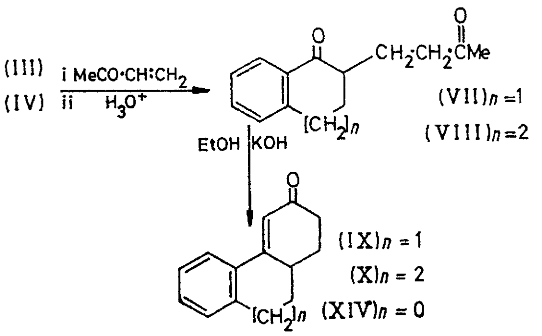
formation of (IIIa), regardless of whether *C*-methylation takes place in the anti-parallel or the parallel sense.[10] In contrast, any steric interaction in (IV) disappears upon formation of (IVa). Moreover, when the factors just described were apparently absent [in the enamine (XII)] the yield of *C*-alkylation was 84%.[11]



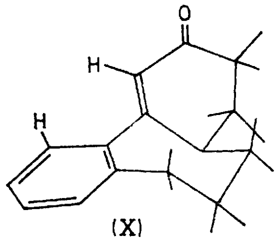
SCHEME 3

Oxobutylation.—The reactions of (III) and (IV) with methyl vinyl ketone were investigated. Unlike the reaction with methyl iodide, alkylation with αβ-unsaturated ketones is reversible.[3b] Thus, the yield of (VII) from the reaction of (III) at 25° was 38%, along with 29% recovered [hydrolysed to (I)] starting material. The δ-diketone (VIII) from the reaction of (IV) at 80° was obtained in at least 65% yield but only in crude form, identified by its n.m.r. spectrum and by formation of its bis-2,4-dinitrophenylhydrazone. In neither reaction mixture was there evidence of the expected[3b] cyclisation to (IX) or (X); the n.m.r. spectra showed no trace of the vinyl hydrogen absorption. Several δ-diketones (experimental conditions unspecified;[12] one reaction at 25°[3b]) as well as δ-keto-aldehydes and δ-dialdehydes have been prepared under milder conditions (−60° to 25°).[13]*

Compounds (VII) and (VIII) were readily cyclised to (IX) and (X) by heating in alcoholic potassium hydroxide. N.m.r. spectra showed the vinyl proton of (IX) at lower field (τ 3·54) than the equivalent proton in (X) (τ 4·08), and the aromatic proton absorption region of (IX) only was split into two multiplets (1 : 3 ratio). The olefin bond in (IX), being more or less coplanar with the benzene ring (Dreiding model), leads to an aromatic ring current deshielding, and perhaps steric deshielding [in (IX), *ortho*-H-vinyl H distance (*d*) *ca.* 1·8 Å][14] of the vinyl proton, as well as to the olefin bond deshielding the *ortho*-proton of the benzene ring. However, such deshieldings cannot occur if (X) possesses the conformation shown, for the vinyl proton is outside the ring current region (calculated[15] shielding contribution from model +0·04 p.p.m.), *d ca.* 3·0 Å, and the olefin bond is not coplanar with the benzene ring. In (XIV), the vinyl proton (τ 3·87) and benzene ring are coplanar *d ca.* 2·3 Å.[16]



SCHEME 4



EXPERIMENTAL

M.p.s were taken with a Fisher–Johns hot-stage apparatus. Spectra were obtained with Perkin-Elmer models 137 and 621 (i.r.), Cary model 14 (u.v.), and Varian A-60 (n.m.r.) spectrophotometers. For n.m.r., carbon tetrachloride was used as solvent [except for (VIII)] and tetramethylsilane as internal standard. Analyses were performed by C. F. Geiger, 312 E. Yale Street, Ontario, California. Reactions of the enamines were carried out under nitrogen.

3,4-*Dihydro*-1-*pyrrolidinonaphthalene* (III).—In an adaptation of the Stork procedure,[3b] (I)[17] (19·1 g., 0·131 mole) [$\nu_{max.}$ (neat) 1688 cm.$^{-1}$ (C=O)] was refluxed for 72 hr. in a solution of dried, distilled pyrrolidine (35·5 g., 0·500 mole) and toluene-*p*-sulphonic acid (0·2 g.) in dried benzene under a Dean–Stark head. More pyrrolidine (12·0 g., 0·169 mole) was added after 8 hr. to replace any that had evaporated off. Evaporation of solvent and excess of pyrrolidine followed by vacuum distillation gave the enamine (III) (19·8 g., 76%), b.p. 102—107°/0·3 mm., n_D^{25} 1·5917,

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* We thank a referee for directing our attention to ref. 13.

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$\nu_{max.}$ (neat) 1618 cm.$^{-1}$ (N–C=C), $\lambda_{max.}$ (cyclohexane) 236 (ε 13,000) and 289 (4100) mμ, τ 4·95 (1H, t, *J* 4·5 c./sec., vinyl H) [lit., yield 54—58%, b.p. 117—119°/0·7 mm., $\nu_{max.}$ (neat) 1615 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 233 (ε 12,500) and 288 (3500) mμ;[4a] τ 5·0 (1H, t, *J* 5·0 c./sec.)[4b]] (Found: C, 84·55; H, 8·4. Calc. for $C_{14}H_{17}N$: C, 84·35; H, 8·6%). The calculated[18] coupling constant for the vinyl proton was 4·3 c./sec.

8,9-*Dihydro*-5-*pyrrolidino*-7H-*benzocyclohept*-5-*ene* (IV).—As for (III), a mixture of pyrrolidine (14·2 g., 0·200 mole) (II) (8·0 g., 0·050 mole) [from cinnamaldehyde and malonic acid (47% overall);[19,20] $\nu_{max.}$ (neat) 1678 cm.$^{-1}$ (C=O)], and toluene-*p*-sulphonic acid (0·2 g.) in benzene (85 ml.) was refluxed under a water trap for 17 hr. Evaporation and vacuum distillation gave a viscous *liquid* (IV) [9·4 g., 88%), b.p. 108—110°/0·65 mm., n_D^{25} 1·5822, $\nu_{max.}$ (neat) 1618 cm.$^{-1}$ (N–C=C), $\lambda_{max.}$ (cyclohexane) 228 (ε 14,000) and 288 (3700) mμ (Found: C, 84·05; H, 9·2. $C_{15}H_{19}N$ requires C, 84·45; H, 9·0%). Three other preparations gave 80—85% yields.

8,9-*Dihydro*-5-*morpholino*-7H-*benzocyclohept*-5-*ene* (XI).—A mixture of (II) (9·7 g., 0·046 mole), morpholine (15·4 g., 0·177 mole), and toluene-*p*-sulphonic acid (0·2 g.) in benzene (65 ml.) gave [procedure as for (III); 25 hr. reflux] (XI) (11·4 g., 82%), a low-melting *solid*, b.p. 110—111°/0·13 mm., $\nu_{max.}$ (neat) 1618 cm.$^{-1}$ (N–C=C), $\lambda_{max.}$ (cyclohexane) 226 (ε 12,400) and 277 (3450) mμ, τ 5·04 (1H, t, *J* 6·7 c./sec., vinyl H) (Found: C, 78·85; H, 8·5. $C_{15}H_{19}NO$ requires C, 78·6; H, 8·3%). The calculated[18] vinyl proton coupling constant was 6·7 c./sec.

3,4-*Dihydro*-2-*methylnaphthalene*-1(2H)-*one* (V).—The alkylation procedure of Brizzolara[8] was adapted. To benzene (100 ml.) and (III) (6·3 g., 0·032 mole) was added methyl iodide (17·9 g., 0·128 mole), and the mixture was heated under reflux for 18 hr. Two more additions of methyl iodide (each 3·6 g., 0·025 mole) were made *ca.* 4 and 16 hr. after refluxing was begun (final molar ratio of methyl iodide to (III) was 5·5 : 1). The mixture was set aside at room temperature for 10 hr., the water (10 ml.) was added, and the mixture was refluxed for another 1 hr. Sodium chloride (0·5 g.) and concentrated hydrochloric acid (3·5 ml.) were added and the cooled solution was then extracted with diethyl ether (4 × 30 ml.). The combined extracts were washed with aqueous 5% sodium thiosulphate (4 × 10 ml.). The combined thiosulphate washings were extracted with ether (3 × 10 ml.). All the organic extracts were combined and dried ($MgSO_4$), filtered, and distilled until the head temperature reached 90°. G.l.c. of the distillation residue on a silicone grease column (2 m.) at 200° (Perkin-Elmer model 154D) showed a 14% yield of (V).

Methylation with a 1 : 1 molar ratio of methyl iodide to (III) in benzene gave only hydrolysed starting material (I) (94% recovery); use of a 4 : 1 ratio in methanol gave (V) (11%) (g.l.c.).

Authentic (V) *for the* g.l.c. analyses was isolated by column chromatography of the combined distillation residues from the first and third preparations on silica gel (Matheson, Coleman, and Bell, 60—80 mesh) in diethyl ether–hexane mixtures; $\nu_{max.}$ (neat) 1689 cm.$^{-1}$ (C=O), τ 8·76 (3H, d, *J* 6·6 c./sec., α-Me); 2,4-dinitrophenylhydrazone, m.p. 242—244° (lit.,[21] 235—236°).

6,7,8,9-*Tetrahydro*-6-*methyl*-5H-*benzocyclohepten*-5-*one* (VI).—Brizzolara's procedure[8] was used: (12·3 g., 0·0866 mole) methyl iodide (12·3 g., 2 mol.) and (IV) (9·38 g., 0·0433 mol.) were refluxed in benzene (50 ml.) for 19 hr. Water (20 ml.) was added and heating was continued until all solid had dissolved. N-Hydrochloric acid (10 ml.) and sodium chloride (2 g.) were added, and the mixture was worked up as described for (V). Flash distillation removed all benzene and ether; vacuum distillation of the residue then yielded a colourless liquid (6·13 g.), b.p. 81·3—83·9°/0·65 mm. Preparative g.l.c. of the distillate on a silicone gum rubber column (20 ft. × $\frac{3}{8}$ in.) at 218° (Wilkens Autoprep A-700) revealed a conversion of 43% into (VI) and a yield [based on unrecovered (II)] of 53%. When the reaction was carried out in benzene with a 1 : 1 ratio of methyl iodide to (IV), 34% conversion into (VI) and a 48% yield were observed.

The fractions from g.l.c. were identified as their 2,4-dinitrophenylhydrazones: for (II), m.p. 214—215° (lit.,[22] 213—214°); for (VI), m.p. 196—200° (lit.,[23] 192°). The n.m.r. spectrum of a mixture of (II) and (VI) showed a doublet (*J* 6·5 c./sec.) at τ 8·86 due to the α-methyl in (VI).

3,4-*Dihydro*-2-(3-*oxobutyl*)*naphthalen*-1(2H)-*one* (VII).—To (III) (4·82 g., 0·0242 mole) dissolved in anhydrous dioxan (25 ml.) was added redistilled methyl vinyl ketone (1·80 g., 0·0257 mole). After 19 hr. stirring at room temperature, the dioxan was removed. A solution of sodium acetate (14 g.), water (14 ml.), acetic acid (14 ml.), and methanol (55 ml.)[3b] was added and the mixture was refluxed for 4 hr. After neutralization with aqueous 2N-sodium hydroxide (90 ml.), the mixture was evaporated under vacuum to *ca.* 100 ml. Several extractions with diethyl ether followed by drying of the extracts and evaporation left a thick oil. T.l.c. [silica gel with benzene–ethyl acetate (19 : 1)] showed the presence of (I) and (VII). Column chromatography on silica gel (75 g.) in hexane containing increasing amounts of diethyl ether gave (I) (1·00 g.) [29% based on hydrolysed (III)] and (VII) (2·04 g., 38%), $\nu_{max.}$ (neat) 1689 and 1721 cm.$^{-1}$ (two C=O) (lit.,[24] 1678 and 1718 cm.$^{-1}$), τ 7·84 (3H, s, Ac). The diketone (VII) was further characterized as its bis-2,4-dinitrophenylhydrazone, dark red *needles*, m.p. 176—178°, $\nu_{max.}$ (KBr) 1608 and 1634 cm.$^{-1}$ (two C=N) (Found: C, 53·95; H, 4·5. $C_{26}H_{24}N_8O_8$ requires C, 54·15; H, 4·2%).

An earlier preparation yielded the authentic sample of (VII) used in the t.l.c. It was separated from (I) by repeated extraction with light petroleum (b.p. 30—60°); m.p. 34—36° (from light petroleum) (lit.,[24] 33—35°).

1,9,10,10a-*Tetrahydro*-3(2H)-*phenanthrone* (IX).—A previously described method[24] was adapted. 3,4-Dihydro-2-(3-oxobutyl)naphthalen-1(2*H*)-one (VII) (2·04 g., 0·0944 mole) was refluxed for 30 min. in 95% ethanol (50 ml.) with potassium hydroxide (0·2 g.), after which most of the solvent was removed under vacuum. The organic material was taken up in diethyl ether (3 × 30 ml.), the combined extracts were dried, and the solvent was removed. The crude oily residue was recrystallized from methanol–water at −70° and then from hexane, yielding (IX) (0·82 g., 45%),

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m.p. 78—79° (lit.,[24] 83°; lit.,[25] 79—80°; lit.,[26] 80—81°), $\nu_{max.}$ (KBr) 1667 cm.$^{-1}$ (lit.,[26] $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$), τ 3·54 (1H, d, $J \pm 2{\cdot}1$ c./sec., vinyl H); the calculated [18] coupling constant was $-2{\cdot}6$ c./sec. However, despite the sharp m.p., analysis of the n.m.r. spectrum of (IX) suggested it to be only 80% pure. Presumably the remainder was the βγ-unsaturated ketone isomeric with (IX); such a mixture was obtained from the base-catalysed reaction of (I) with methyl vinyl ketone (u.v. spectrum).[24]

The deep red 2,4-dinitrophenylhydrazone of (IX) had m.p. 205—206° (decomp.) (from ethanol–methylene chloride) [lit.,[25] 204—206° (decomp.)], $\lambda_{max.}$ (CHCl$_3$) 402·5 mμ (ε 34,100) (Found: C, 63·25; H, 5·0. Calc. for $C_{20}H_{18}N_4O_4$: C, 63·5; H, 4·8%).

3,4,4a,5,6,7-*Hexahydrodibenzo*[a,c]*cyclohepten*-2-*one* (X).—To a mixture of (IV) (5·0 g., 0·0235 mole) in benzene (100 ml.) was added methyl vinyl ketone (1·64 g., 0·0235 mole). After 6 hr. at room temperature, the mixture was refluxed for 17 hr., then hydrolysed [35] by adding a solution of sodium acetate (12·5 g.) in acetic acid (25 ml.) and water (25 ml.) and refluxing for 4 hr. The benzene phase and benzene extracts were combined, washed successively with 10% hydrochloric acid and 5% sodium hydrogen carbonate solutions, and dried, and the solvent was removed under vacuum. The residue consisted only of 6,7,8,9-tetrahydro-6-(3-oxobutyl)-5*H*-benzocyclohepten-5-one (VIII), τ (CHCl$_3$) 8·00 (3H, s, Ac), no vinyl hydrogen; the *bis*-2,4-*dinitrophenylhydrazone* of (VIII) had m.p. 228—229° (from methanol–chloroform), $\nu_{max.}$ (KBr) 1592 and 1621 cm.$^{-1}$ (two C=N) (Found: C, 54·75; H, 4·7. $C_{27}H_{26}N_8O_8$ requires C, 54·9; H, 4·45%).

The residue was cyclised as in the conversion of (VII) into (IX), yielding (X) (3·2 g., 64%), m.p. 97·2—99·0° (lit.,[27] 98—100°), $\nu_{max.}$ (KBr) 1672 cm.$^{-1}$ (C=O), τ 4·08 (1H incompletely resolved d, $J \sim \pm 0{\cdot}6$ c./sec., vinyl H). The calculated [18] coupling constant was $-1{\cdot}0$ c./sec. Analysis of the n.m.r. spectrum of (X) suggested it to be only 85% pure; presumably the remainder was the βγ-unsaturated ketone isomeric with (X) [see (IX)]. The 2,4-dinitrophenylhydrazone of (X) had m.p. 184—187° (lit.,[27] 186—187°).

We acknowledge support of part of this research by a Frederick Gardner Cottrell grant from Research Corporation and the National Science Foundation Undergraduate Research Participation Program (to R. N. W.). We thank Arne Fredga, Uppsala University, Sweden, for providing facilities permitting this manuscript to be largely completed, and the American Scandinavian Foundation for a travel grant-in-aid. J. M. Holleran carried out some early exploratory work in this area.

[9/892 *Received, May* 28*th*, 1969]

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