Synthesis of Azepinoquinazolones from 2-Methyl-3-(*o*-tolyl)-4-quinazolone

John B. Taylor, Derek R. Harrison and Ferdinand Fried

Roussel Laboratories, Ltd., Kingfisher Driver, Covingham, Swindon, Wilts., England

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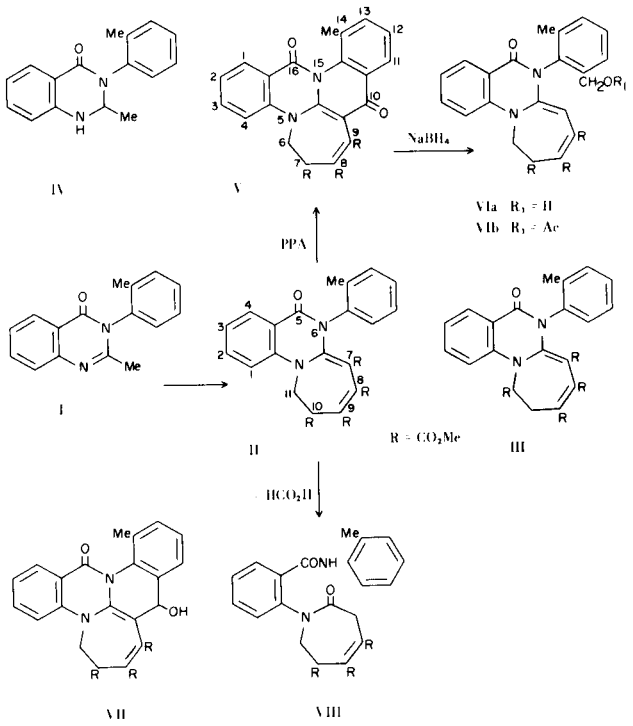
Some new azepinoquinazolones were synthesized from 2-methyl-3(*o*-tolyl)-4(3*H*)quinazolone (methaqualone) as potential hypnotic agents. Methaqualone (I) reacted with dimethyl acetylenedicarboxylate (dmad) to give the azepinoquinazolone (II) which on treatment with PPA gave the pentacyclic ketone (V). Subsequent sodium borohydride reduction of the ketone (V) gave the fused azepine (VIa). Reaction of the azepinoquinazolone (II) with formic acid resulted in cleavage of the quinazolone nucleus to give the azepine (VIII). None of the compounds synthesized exhibited significant hypnotic activity.

In view of the biological interest in quinazolones (1), in particular the hypnotic methaqualone (I) (2), the reaction of methaqualone with dimethylacetylenedicarboxylate (dmad) was investigated as a source of novel azepinoquinazolones incorporating the 2-methyl-3-*o*-tolylquinazolone nucleus, in a search for potential hypnotic agents.

Reaction of methaqualone with dmad in refluxing acetonitrile gave a product containing one major component. Chromatography on alumina gave the azepine (II) in good yield, the significant evidence for which structure was the following. The mass spectrum showed a molecular ion at m/e 534 consistent with the addition of two moles of dmad, and the fragmentation pattern, in particular a base peak at M-86, was characteristic of the loss of methyl acrylate from the azepine (II or III) (3). The nmr spectrum was compatible with azepine (II) rather than III, and showed a high field ester signal assigned to the 7-ester group of azepine (II), which was confirmed by subsequent chemistry of the azepine.

The nmr spectrum of the azepine (II) was of particular interest since it exists at room temperature as a pair of diastereomeric rotamers (4), exhibiting double resonances for the *o*-tolyl methyl and the four ester signals, due to slow rotation about the *N*-aryl bond. The relative populations of the preferred conformations were 70:30 measured from the tolyl 2′-methyl signal in the 100 MHz nmr. Variable temperature examination resulted in collapsing of the signals at 150°. Dihydromethaqualone (IV) also exhibits atropisomerism (5), the tolyl 2′-methyl signal appearing as a doublet, and the 2-methyl as a pair of doublets, in the nmr spectrum.

Cyclisation of the azepine (II) with polyphosphoric acid gave the pentacyclic ketone (V) whose nmr now



showed two low field aromatic protons attributable to the deshielding produced by the two pericarbonyl groups (6), the loss of the high field ester function, and the collapse of the tolyl-methyl to a singlet in the rigid structure (V). The mass spectrum was consistent with this assignment.

Reduction of the ketone (V) with sodium borohydride gave the azepine (VIa), plausibly arising from the alcohol (VII) *via* protonation at C-9a and a subsequent retro-Aldol reaction. Its structure was assigned from a consideration of the mass spectral, ir, uv and nmr data of the

azepine. In particular, the presence of the hydroxymethyl group was established by the presence of an AB quartet in the nmr spectrum, which moved downfield on acetylation, the non-equivalence of the protons again resulting from restricted rotation about the *N*-aryl bond.

Attempted reduction of the azepine (II) with refluxing formic acid gave the crystalline azepinone (VIII) characterised by its nmr and mass spectral data. Feasibly hydrolysis of the 7-ester is followed by a facile decarboxylation of the β-imminium acid and subsequent cleavage of the quinazolone nucleus. That the azepine (VIII) was not in fact a reduction product was confirmed by its isolation as a by-product from the cyclisation of the azepine (II) with polyphosphoric acid.

None of the compounds showed significant CNS depressant activity at 400 mg./Kg. in the mouse.

EXPERIMENTAL

Ir spectra were measured with a Pye-Unicam SP1000 on potassium bromide discs, and uv spectra on a Perkin-Elmer 402 spectrophotometer in methanol solutions. Nmr spectra were recorded on a Perkin-Elmer R12A (60 MHz) and a Varian HA100 (100 MHz) spectrophotometer in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were measured on an A.E.I. MS902 instrument.

Tetramethyl-10,11-dihydro-5(6*H*)oxo-6-(*o*-tolyl)azepino[1,2-*a*]-quinazoline-7,8,9,10-tetracarboxylate (II).

Methaqualone (2.0 g.) and dmad (2.26 g.) in acetonitrile (20 ml.) were refluxed for 30 hours. Evaporation gave a brown residue which was chromatographed on neutral alumina (150 g.) and eluted with benzene, followed by benzene-chloroform in increasing proportions to 1:1. The first fractions yielded starting material (230 mg.) whilst subsequent fractions yielded the azepine (II) as pale yellow needles (1.2 g., 28%); m.p. 174-176°; ir: 1755, 1724, 1708, 1698 cm^{-1}; nmr: τ 1.95 (1H, d (broad), J 8Hz, 4-H), 2.3-3.0 (7H, m, ArH), 6.21 (major isomer), 6.32 (major isomer), 6.25, 6.28 (both isomers), 6.32 (9H, ester O Me), 6.3-6.7 (2H, m, 10, 11-H), 6.91, 6.93, (3H, 3:7 intensity ratio, 7-ester OMe), 7.4-7.7 (1H, m, 11-H), 7.65, 7.73 (3H, 7:3 intensity ratio, tolyl-Me); mass spectrum: m/e 534 (M^+), 448 (100%).

Anal. Calcd. for $C_{28}H_{26}N_2O_9$: C, 62.9; H, 4.9; N, 5.2. Found: C, 62.8; H, 4.9; N, 5.1.

Trimethyl-6,7-dihydro-14-methyl-10,16(15*H*)dioxoazepino[3,2,1-*gh*]quino[2,1-*b*]quinazoline-7,8,9-tricarboxylate (V).

The azepine (II) (10 g.) and polyphosphoric acid (200 g.) were heated at 140° for 1 hour, until effervescence ceased, cooled and poured into ice-water. The precipitate was extracted into chloroform and the extracts washed successively with aqueous sodium bicarbonate solution and water, dried and evaporated. Trituration of the residue with benzene gave a pale yellow solid which on recrystallisation from methanol gave the product (V) as colourless rhombs (5.2 g., 57%) m.p. 250-252°; ir (C=O): 1760, 1750, 1730, 1718, 1633 cm^{-1}; nmr: 1.75-1.90 (2H, m, 2,11-H), 2.2-2.8 (5H, m, ArH), 6.20 (6H, s, O Me), 6.28 (3H, s, O Me), 6.2-7.4 (3H, m, 6,7-H, partially obscured), 7.70 (3H, s, 14-Me); mass spectrum: m/e 502 (M^+), 416 (100%).

Anal. Calcd. for $C_{27}H_{22}N_2O_8$: C, 64.6; H, 4.4; N, 5.6. Found: C, 64.8; H, 4.5; N, 5.5.

The benzene filtrate from the trituration was evaporated and the residue chromatographed on neutral alumina (70 g.). Elution with benzene followed by benzene-chloroform (1:1) gave compound VIII (0.83 g.), m.p. 238-241°*(vide infra)*.

Trimethyl-10,11-dihydro-5(6*H*)oxo-6-(6′-hydroxymethyl-2′-tolyl)-azepino[1,2-*a*]quinazoline-8,9,10-tricarboxylate (VIa).

The azepine (II) (5.0 g.) and sodium borohydride (1.0 g.) in ethanol (100 ml.) were stirred at room temperature for 17 hours, the solvent evaporated and water added to the residual gum. Acidification with 2*N* hydrochloric acid gave a white precipitate which on recrystallisation from methanol gave the product as colourless rods (3.1 g., 62%), m.p. 154-158°; ir: 3400 (OH), 1770, 1751, 1745, 1728, (C=O) cm^{-1}; nmr: τ 5.19, 5.45 (2H, q, J 12 Hz, $-CH_2O$); mass spectrum: m/e 506 (M^+), 361 (100%).

Anal. Calcd. for $C_{27}H_{26}N_2O_8$: C, 64.0; H, 5.2; N, 5.5. Found: C, 63.8; H, 5.1; N, 5.4.

Compound VIa (1.5 g.) and acetyl chloride (3 ml.) were stirred at room temperature for 15 minutes, poured into water and extracted with chloroform. The extracts were washed with water, dried and evaporated, giving a pale yellow gum which on trituration with methanol gave the acetate (VIb) as colourless rods (from methanol) (0.8 g., 50%); m.p. 133-135°; ir: (C=O) 1760, 1743 (broad) cm^{-1}; nmr: τ 4.51, 4.84 (2H, q, J 14 Hz, $-CH_2O$); mass spectrum: m/e 548 (M^+), 403 (100%).

Anal. Calcd. for $C_{29}H_{28}N_2O_9$: C, 63.5; H, 5.2; N, 5.1. Found: C, 63.8; H, 5.3; N, 4.9.

Trimethyl-1,3,6,7-tetrahydro-1-(2′-*o*-tolylcarbamoyl)phenyl-2*H*-azepin-2-one-4,5,6-tricarboxylate (VIII).

The azepine (II) (5.0 g.) in formic acid (50 ml.) was refluxed for 15 hours, and the cooled solution poured into water. Basification with 2*N* aqueous sodium hydroxide solution gave a white precipitate which on recrystallisation from methanol gave the azepine (VIII) as colourless rods (4.5 g., 90%); m.p. 239-242°; ir: 3315 (NH), 1775, 1765, 1732, 1727, 1690 (C=O) cm^{-1}; nmr: τ 1.52 (1H, s, NH), 5.9-6.7 (2H, m, 6,7-H), 7.13 (2H, q, J 15 Hz, 3 $-CH_2$), 7.4-7.8 (1H, m, 7-H); mass spectrum: m/e 494 (M^+), 288 (100%).

Anal. Calcd. for $C_{26}H_{26}N_2O_8$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.3; H, 5.2; N, 5.9.

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