A Facile Synthesis of (2-Oxo-1,2-dihydroquinoxalin-3-yl)-methyl Ketones and (Quinoxalin-2-yl)-methyl Ketones

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Quinoxalinyl ketones are normally prepared either by reacting *o*-phenylenediamine with appropriately substituted α-diketones[1,2] or by nucleophilic substitution of 2-chloro-, 2,3-dichloro-, or 2-methanesulphonyl quinoxalines with ketones in the presence of sodamide[3,4]. While the latter method is a patent procedure, the former suffers from the fact that the α-diketones are difficult to prepare.

In the present paper, we report a new method for the facile synthesis of (2-oxo-1,2-dihydroquinoxalin-3-yl)-methyl ketones and (quinoxalin-2-yl)-methyl ketones by reacting qui-

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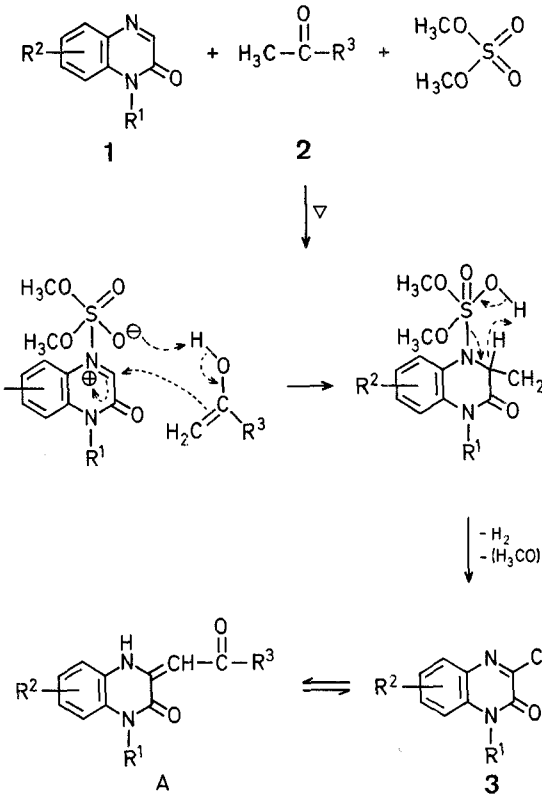
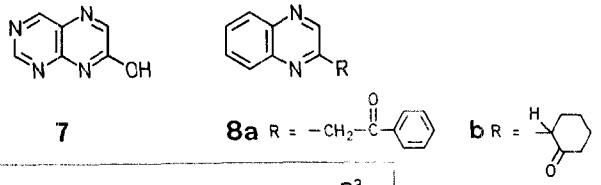
noxalines **1** with ketones **2** in the presence of dimethyl sulphate. This is essentially a Michael type of reaction, for which the use of dimethyl sulphate as a catalyst has hitherto not been reported.



In a typical reaction, equimolar quantities of quinoxaline **1** and the corresponding methyl ketone **2** were refluxed in the presence of catalytic amount of anhydrous dimethyl sulphate[5] to yield the quinoxalinyl ketone **3** (see Table). Ketones having an active methylene group gave the quinoxalines **4**, **5**, and **6** (see Table).

The probable mechanism for this conversion is shown above and is supported by using sulphur dioxide as a catalyst instead of dimethyl sulphate. The use of sulphur dioxide to form complexes with tertiary amines is known[6]. The compounds **3a-k** exist as enamines A and not as enols B. This type of tautomerism has been extensively studied[7].

The use of mineral acid instead of dimethyl sulphate as a catalyst in our reaction yielded a mixture of reduced and oxidised products, with higher yields of reduced products. Similar reduced products are reported[8] in the case of 7-hydroxypteridine (**7**) with ambient nucleophiles in the presence of mineral acid as catalyst. The oxidation of these reduced products entails a lot of difficulties, as they are not easily oxidised with normal oxidising agents like hydrogen peroxide and sodium hypochlorite.



Quinoxalin-2-yl ketones (**8a** and **8b**) were prepared by reacting the parent quinoxaline (**8**, R = H) with acetophenone and cyclohexanone, respectively, in the presence of dimethyl sulphate.

Table. (Quinoxalin-2-yl)-methyl Ketones **3-6** prepared

Product No.	R^1	R^2	R^3	Yield [%] by Method A	Yield [%] by Method B	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	H	H	CH_3	91	—	257–258°	267°[1]	°680, 1650	insufficiently soluble
3b	CH_3	H	CH_3	80	—	192–194°	200°[1]	1678, 1655	2.25 (s, 3H); 3.60 (s, 3H); 6.20 (s, 1H); 7.10 (s, 4H); 13.3 (br. s, 1H)
3c	CH_3	7-O_2N	CH_3	44	—	254–256°	$C_{12}H_{11}N_3O_4$ (261.2)	1720, 1690	2.26 (s, 3H); 3.60 (s, 3H); 7.6–8.5 (m, 3H); 12.9 (br. s, 1H)[b]
3d	CH_3	7-Br	CH_3	70	—	179–180°	$C_{12}H_{11}BrN_2O_2$ (294.9)	1690, 1640	insufficiently soluble
3e	H	H	C_2H_5	94	—	203–205°	$C_{12}H_{12}N_2O_2$ (216.2)	1700, 1640	insufficiently soluble
3f	CH_3	H	C_2H_5	78	—	146–148°	$C_{13}H_{14}N_2O_2$ (230.3)	1680, 1640	1.18 (t, 3H, J = 8 Hz); 2.60 (q, 2H, J = 8 Hz); 3.60 (s, 3H); 6.32 (s, 1H); 7.10 (s, 4H); 13.4 (br. s, 1H)
3g	H	H	*i*-C_4H_9	90	—	245–247°	$C_{14}H_{16}N_2O_2$ (244.3)	1690, 1630	0.94 (d, 6H, J = 7 Hz); 2.0–2.2 (m, 2H); 3.15 (s, 1H); 6.00 (s, 1H); 7.0–7.4 (m, 4H); 14.50 (s, 1H); 15.2 (br. s, 1H)[b]
3h	CH_3	H	*i*-C_4H_9	72	55	151–152°	$C_{15}H_{18}N_2O_2$ (258.3)	1690, 1630	0.96 (d, 6H, J = 7 Hz); 1.5–2.5 (m, 3H); 3.60 (s, 3H); 6.22 (s, 1H); 7.10 (s, 4H); 13.0 (br. s, 1H)
3i	CH_3	H	C_6H_5	94	87	180–182°	180°[2]	1700, 1640	3.60 (s, 3H); 5.98 (s, 1H); 7.18 (s, 4H); 7.3–8.1 (m, 5H); 14.0 (br. s, 1H)
3j	CH_3	H	3-Br—C_6H_4	90	85	133–134°	$C_{17}H_{13}BrN_2O_2$ (357.0)	1690, 1640	3.67 (s, 3H); 6.97 (s, 1H); 7.20 (s, 4H); 7.3–8.2 (m, 4H); 14.1 (br. s, 1H)
3k	H	H	2-H_3CO—C_6H_4	75	—	241–243°	$C_{17}H_{14}N_2O_3$ (294.3)	1680, 1640	insufficiently soluble

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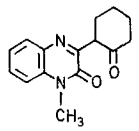
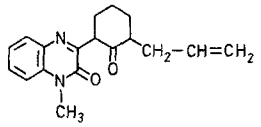
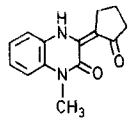
Table. (Continued)

Product No.	R^1	R^2	R^3	Yield [%] by Method A	Yield [%] by Method B	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4				70	45	182–183°[b]	$C_{15}H_{16}N_2O_2$ (256.3)	1730, 1670, 1630	1.6–2.8 (m, 8H); 3.70 (s, 3H); 4.30 (dd, 1H, J = 10 Hz, 10 Hz); 7.1–8.0 (m, 4H)
5				64	42	162–164°[b]	$C_{18}H_{20}N_2O_2$ (296.4)	1660, 1640	insufficiently soluble
6				68	34	190–191°[b]	$C_{14}H_{14}N_2O_2$ (242.3)	1690, 1630, 1610	1.7–3.6 (m, 3H); 3.50 (s, 3H); 7.16 (s, 4H); 13.2 (br. s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.07, H ±0.09, N ±0.23, Br ±0.43.
[b] In DMSO-d_6 solution.

(2-Oxo-1,2-dihydroquinoxalin-3-yl)-methyl Ketones 3; General Procedure:

Method A, using dimethyl sulphate as catalyst: To a refluxing mixture of the quinoxaline **1** (R^1 = CH_3; 10 mmol) and the ketone **2** (10 mmol), freshly purified[5] dimethyl sulphate (0.5 ml) is added. The reaction mixture darkens considerably within 5 min and is heated further till the completion of the reaction is indicated by T.L.C. (silica gel; benzene/acetone, 9 : 1). The reaction mixture is then poured into aqueous sodium hydroxide (10%, 20 ml) and extracted with chloroform (3 × 50 ml). The chloroform layer is washed with water (3 × 100 ml) till neutral and then dried with sodium sulphate. Chloroform is evaporated and the crude product obtained is purified by column chromatography (silica gel, 30 × 2 cm column; eluent: benzene and mixture of benzene/acetone of increasing polarity) and crystallised from acetone.

For quinoxalines **1** (R^1 = H) the reaction is performed as described above for R^1 = CH_3, except for the work-up. The reaction mixture is poured into aqueous sodium hydroxide (10%, 20 ml), acidified with dilute hydrochloric acid and the product obtained is purified by column chromatography and crystallisation from acetone. Methylation of the product (**3**, R^1 = H) with dimethyl sulphate in aqueous sodium hydroxide gives a product which is identical with the product (**3**, R^1 = CH_3) obtained from 1-methyl-2-oxo-1,2-dihydroquinoxaline (**1**, R^1 = CH_3) as described above.

Method B, with sulphur dioxide as catalyst: A steady stream of sulphur dioxide is passed through a refluxing mixture of the quinoxaline **1** (10 mmol) and the appropriate ketone **2** (10 mmol) till the T.L.C. analysis (silica gel; benzene/acetone, 9 : 1) indicates completion of the reaction. The reaction mixture is then worked up as described for Method A.

(Quinoxalin-2-yl)-methyl Ketones 8; General Procedure:

To a refluxing mixture of quinoxaline **8** (R = H; 10 mmol) and the corresponding ketone (acetophenone or cyclohexanone; 10 mmol), dimethyl sulphate (0.5 ml) is added. The reaction mixture is worked up as described for Method A.

(Quinoxalin-2-yl)-methyl phenyl ketone **(8a)**; yield: 70%; m.p. 154–155 °C (Ref.[4], m.p. 155–156 °C).

2-(Quinoxalin-2-yl)-cyclohexanone **(8b)**; yield: 62%; m.p. 135–136 °C (Ref.[4], m.p. 129–130 °C).

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