# Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted α-Aminomethyleneketones V. Synthesis of 1,2-Oxathiino[5,6-*c*]pyridine and 1,2-Oxathiino[5,6-*c*]quinoline Derivatives



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Reaction of sulfene with *N,N*-disubstituted 3-aminomethylene-1-(methyl, methylphenyl, phenyl)-4-piperidones and 3-aminomethylene-2,3-dihydro-1-phenyl-4(1*H*)quinolones gave *N,N*-disubstituted 4-amino-3,4,5,6,7,8-hexahydro-6-(methyl, methylphenyl, phenyl)-1,2-oxathiino-[5,6-*c*]pyridine 2,2-dioxides and 4-amino-6-phenyl-3,4,5,6-tetrahydro-1,2-oxathiino[5,6-*c*]quinoline 2,2-dioxides, respectively, whereas *N,N*-disubstituted 3-aminomethylene-2,3-dihydro-1-methyl-4(1*H*)quinolones did not react. Slow air oxidation in the cold of intermediates 2,3-dihydro-3-hydroxymethylene-1-(methyl, phenyl)-4(1*H*)quinolones gave the corresponding 1-substituted 1,4-dihydro-4-oxo-3-quinolinecarboxyaldehydes.

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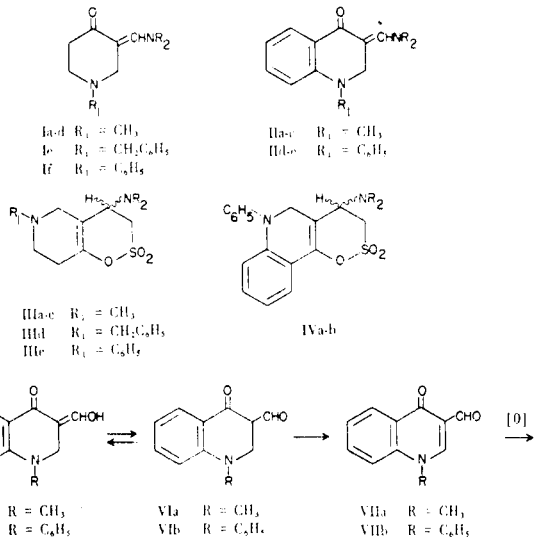
In previous work we described the synthesis of 1,2-oxathiin derivatives condensed with an oxygen or sulfur heterocycle, by 1,4-cycloaddition of *N,N*-disubstituted 3-aminomethylene-4-chromanones, -2,3-dihydro-4-thiochromanones, and -2,3,5,6-tetrahydro-4-thiopyranones to sulfene (1,2). We wish to report now the synthesis of derivatives of 1,2-oxathiin condensed with a nitrogen heterocycle, namely 1,2-oxathiino[5,6-*c*]quinoline and 1,2-oxathiino[5,6-*c*]pyridine; few derivatives of the latter were described previously by us (3).

For this purpose we synthesized in low to fair yield a series of *N,N*-disubstituted 3-aminomethylene-1-(methyl, methylphenyl)-4-piperidones Ia-e (Tables I and II) following a procedure described in the early literature (4), namely from amine hydrochloride and sodium salt of α-hydroxymethyleneketone. In the present circumstances it was indeed impossible to isolate the free α-hydroxymethyleneketone by acidification of the aqueous solution of its sodium salt owing to the fair basicity of ring nitrogen atom. On the other hand, *N,N*-disubstituted 3-aminomethylene-2,3-dihydro-1-(methyl, phenyl)-4(1*H*)-quinolones IIa-e (Tables III and IV) could be prepared, generally in high yield, from secondary amines and the crude readily isolable α-hydroxymethyleneketones Va-b. Also enamine If could be obtained in low yield from unstable 3-hydroxymethylene-1-phenyl-4-piperidone and piperidine; other secondary amines gave no results.




Enaminoketones I and II are probably E-isomers, at least as can be seen from the strong upfield shift of $NCH_2$ protons (~ 0.4-0.7 ppm) caused by the phenyl group in compounds Id and IIe (see Tables II and IV).

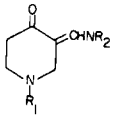
Reaction of enamines I and II with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) gave in good yield *N,N*-disubstituted 4-amino-3,4,5,6,7,8-hexahydro-1,2-oxathiino[5,6-*c*]pyridine 2,2-dioxides IIIa-e (Table V) and 4-amino-3,4,5,6-tetrahydro-1,2-oxathiino-[5,6-*c*]quinoline 2,2-dioxides IVa-b (Table VII), respectively, only when 1-substituent of the enamine was a phenyl group (enamines If and IId,e), but yields generally decreased or the reaction quite failed when 1-substituent was an alkyl group (enamines Ia,b,d and IIa,b,c). The adducts obtained showed ir and nmr spectra (Tables VI and VIII) in agreement with the proposed structure [compare (2)]. Therefore, when in enamines I and II, the 1-nitrogen is sufficiently nucleophilic, it appears that sulfene can interact with it instead of giving dipolar 1,4-cycloaddition.

We had already noticed (3) that in the preparation of 2,3-dihydro-3-hydroxymethylene-1-(methyl, phenyl)-4-(1*H*)quinolones Va-b two different by-products were obtained. One of these was also obtained in the present work as the main product in the reaction of enamines IIa,b with sulfene. The compounds have been now recognized as 1-substituted 1,4-dihydro-4-oxo-3-quinoline-

*0022-152X/79/010177-06$02.25*

Table I

*N,N*-Disubstituted 3-Aminomethylene-1-(methyl, methylphenyl, phenyl)-4-piperidones (Ia-f)



| Formula Number | $R_1$ | $NR_2$ | Yield % | B.p./mm Hg or M.p. °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|
| Ia | $CH_3$ | $N(C_2H_5)_2$ | 15 | 115-116/0.4 | $C_{11}H_{20}N_2O$ | 67.31<br>67.56 | 10.27<br>10.41 | 14.27<br>14.25 |
| Ib | $CH_3$ |  | 60 | 110-120/0.4 | $C_{11}H_{18}N_2O$ | 68.01<br>67.63 | 9.34<br>9.66 | 14.42<br>14.32 |
| Ic | $CH_3$ |  | 32 | 128-130/0.2 | $C_{12}H_{20}N_2O$ | 69.19<br>69.40 | 9.68<br>9.58 | 13.45<br>13.15 |
| Id | $CH_3$ | $N(CH_3)C_6H_5$ | 22 | 150-152/0.4 | $C_{14}H_{18}N_2O$ | 73.01<br>72.85 | 7.88<br>8.16 | 12.16<br>11.90 |
| Ie | $CH_2C_6H_5$ | $N(CH_3)C_6H_5$ | 16 | 160-170/0.2 | $C_{20}H_{22}N_2O$ | 78.40<br>78.08 | 7.24<br>7.54 | 9.14<br>9.18 |
| If | $C_6H_5$ |  | 25 | 121 (a) | $C_{17}H_{22}N_2O$ | 75.52<br>75.24 | 8.20<br>7.94 | 10.36<br>10.50 |

(a) After chromatography on Florisil ® with diethyl ether.
Enamines Ia-e were prepared according to (3), and If according to (1).

Table II

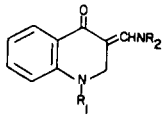
Uv, Ir and Nmr Spectral Data of Compounds Ia-f

| Compound | Uv λ max nm (log ε) | Ir, $cm^{-1}$ (tetrachloromethane) C=O | C=C | Nmr, δ (tetrachloromethane) |
|---|---|---|---|---|
| Ia | 328.5 (4.26) | 1653 | 1532 | 1.24 (t, J = 7.3, $2CH_3$), 2.1-3.0 (m, $CH_2$-5 + $CH_2$-6), 2.34 (s, $NCH_3$), 3.32 (q, J = 7.3, $2NCH_2$), 3.38 (near s, $CH_2$-2), 7.25 (m, =CHN) |
| Ib | 335 (4.29) | 1660 | 1548 | 1.92 (m, $2CH_2$ pyrr.), 2.05-2.75 (m, $CH_2$-5 + $CH_2$-6), 2.34 (s, $NCH_3$), 3.58 (m, $CH_2$-2 + $2NCH_2$ pyrr.), 7.45 (near s, =CHN) |
| Ic | 329 (4.23) | 1656 | 1542 | 1.65 (m, $3CH_2$ pip.), 2.1-2.8 (m, $CH_2$-5 + $CH_2$-6), 2.34 (s, $NCH_3$), 3,40 (m, $CH_2$-2 + $2NCH_2$ pip.), 7.16 (near s, =CHN) |
| Id | 235 (3.61)<br>332 (4.14) | 1683 | 1550 | 2.20 (s, $NCH_3$), 2.15-2.75 (m, $CH_2$-5 + $CH_2$-6), 2.98 (m, $CH_2$-2), 3.41 (s, $NCH_3$), 7.12 (m, $C_6H_5$), 7.40 (m, =CHN) |
| Ie | 250 (4.13)<br>308 (3.69) | 1667 | 1542 | 2.1-2.9 (m, $CH_2$-2 + $CH_2$-5 + $CH_2$-6), 3.33 (s, $NCH_3$), 3.40 (s, $NCH_2Ph$), 6.2-7.4 (m, $2C_6H_5$), 7.38 (m, =CHN) |
| If | 251.5 (4.06)<br>330 (4.24) | 1660 | 1548 | 1.68 (m, $3CH_2$ pip.), 2.56 (near t, J = 6, $CH_2$-5), 3.48 (m, $2NCH_2$ pip.), 3.58 (near t, J = 6, $CH_2$-6), 4.30 (near s, $CH_2$-2), 6.7-7.5 (m, $C_6H_5$), 7.60 (m, =CHN) (a) |

(a) In deuteriochloroform.

Table III

*N,N*-Disubstituted 3-Aminomethylene-1-(methyl, phenyl)-2,3-dihydro-4(1*H*)quinolones (IIa-e)




| Formula Number | $R_1$ | $NR_2$ | Yield % | M.p. °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|
| IIa | $CH_3$ | $N(C_2H_5)_2$ | 70 | 81 (a) | $C_{15}H_{20}N_2O$ | 73.74<br>73.45 | 8.25<br>8.44 | 11.47<br>11.52 |
| IIb | $CH_3$ |  | 82 | 111 (a) | $C_{16}H_{20}N_2O$ | 74.97<br>74.72 | 7.86<br>7.97 | 10.93<br>10.96 |
| IIc | $CH_3$ | $N(CH_3)C_6H_5$ | 10 | 140 (b) | $C_{18}H_{18}N_2O$ | 77.67<br>77.30 | 6.52<br>6.65 | 10.06<br>10.36 |
| IId | $C_6H_5$ |  | 73 | 138 (c) | $C_{21}H_{22}N_2O$ | 79.21<br>79.45 | 6.96<br>7.20 | 8.80<br>8.50 |
| IIe | $C_6H_5$ | $N(CH_3)C_6H_5$ | 67 | 99 (b) | $C_{23}H_{20}N_2O$ | 81.15<br>81.18 | 5.92<br>6.03 | 8.23<br>8.00 |

(a)From anhydrous diethyl ether. (b) From ethyl acetate. (c) From 95% ethanol.
Enamines IIa,b were prepared according to (1), and IIc,d,e according to (8).

Table IV

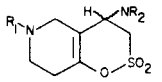
Uv, Ir and Nmr Spectral Data of Compounds IIa-e

| Compound No. | UV λ max nm (log ε) | Ir, $cm^{-1}$ C=O | C=C | Nmr, δ (deuteriochloroform) |
|---|---|---|---|---|
| IIa | 248.5 (4.44)<br>274 sh (3.86)<br>345 (4.15)<br>407 (3.97) | 1653 | 1546 (a) | 1.22 (t, J = 7.5, $2CH_3$), 2.83 (s, $NCH_3$), 3.26 (q, J = 7.5, $2NCH_2$), 4.12 (m, $CH_2$-2), 6.35-7.65 (m, H-6 + H-7 + H-8), 7.36 (m, =CHN), 7.7-7.9 (m, H-5) (a) |
| IIb | 250 (4.41)<br>274 sh (3.92)<br>347 (4.16) | 1640 | 1527 (b) | 1.64 (m, $3CH_2$ pip.), 2.90 (s, $NCH_3$), 3.40 (m, $2NCH_2$ pip.), 4.25 (m, $CH_2$-2), 6.4-7.5 (m, H-6 + H-7 + H-8), 7.58 (near s, =CHN), 7.85-8.05 (m, H-5) |
| IIc | 250.5 (4.60)<br>293 (3.78)<br>330 (4.07)<br>341.5 (4.05) | 1635 | 1556 (a) | 3.00 (s, $NCH_3$), 3.65 (s, $NCH_3$), 4.46 (near s, $CH_2$-2), 6.4-7.7 (m, 8H ar. + =CHN), 8.30-8.55 (m, H-5) |
| IId | 241.5 (4.34)<br>302 (4.08)<br>339 (4.12)<br>415 (3.84) | 1640 | 1528 (b) | 1.62 (m, $3CH_2$ pip.), 3.40 (m, $2NCH_2$ pip.), 4.73 (s, $CH_2$-2), 6.5-7.8 (m, 8H ar.), 7.60 (s, =CHN), 7.95 and 8.08 (2d, J ~ 2, H-5) |
| IIe | 240 (4.31)<br>294.5 (4.13)<br>361 (4.21)<br>424 (3.94) | 1643 | 1533 (b) | 3.45 (s, $NCH_3$), 4.02 (m, $CH_2$-2), 6.50-7.55 (m, 13H ar.), 7.73 (m, =CHN), 7.96 and 8.09 (2d, J~ 2, H-5) |

(a) In tetrachloromethane. (b) In chloroform.

Table V

*N,N*-Disubstituted 4-Amino-3,4,5,6,7,8-hexahydro-6-(methyl, methylphenyl, phenyl)-1,2-oxathiino[5,6-*c*]pyridine 2,2-Dioxides (IIIa-e)



| Formula Number | $R_1$ | $NR_2$ | Yield % | M.p. °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|
| IIIa | $CH_3$ | $N(C_2H_5)_2$ | 37 | 56 (a) | $C_{12}H_{22}N_2O_3S$ | 52.53<br>52.23 | 8.08<br>8.38 | 10.21<br>10.32 |
| IIIb | $CH_3$ |  | 27 | 116 (b) | $C_{12}H_{20}N_2O_3S$ | 52.92<br>53.28 | 7.40<br>7.39 | 10.29<br>10.57 |
| IIIc | $CH_3$ |  | 56 | 120 (b) | $C_{13}H_{22}N_2O_3S$ | 54.52<br>54.45 | 7.74<br>7.91 | 9.78<br>9.50 |
| IIId | $CH_2C_6H_5$ | $N(CH_3)C_6H_5$ | 40 | 152 (c) | $C_{21}H_{24}N_2O_3S$ | 65.60<br>65.52 | 6.29<br>6.25 | 7.29<br>7.61 |
| IIIe | $C_6H_5$ |  | 55 | 117 (b) | $C_{18}H_{24}N_2O_3S$ | 62.04<br>62.00 | 6.94<br>6.96 | 8.04<br>8.15 |

(a) After chromatography on Florisil ® with diethyl ether. (b) From anhydrous diethyl ether. (c) From 95% ethanol. All compounds were prepared according to (1), using anhydrous tetrahydrofuran as solvent.

Table VI

Ir and Nmr Spectral Data of Compounds IIIa-e

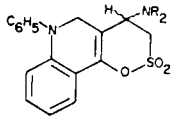
| Compound | Ir, $cm^{-1}$ (tetrachloromethane) C=C | O=S=O | | Nmr, δ (tetrachloromethane) |
|---|---|---|---|---|
| IIIa | 1678 | 1383 | 1187 | 1.10 (t, J = 7.2, $2CH_3$), 2.35 (s, $NCH_3$), 2.45 (q, J = 7.2, $2NCH_2$), 2.90 (m, $CH_2$-5), 2.03-3.05 (m, $CH_2$-7 + $CH_2$-8), 3.05-4.30 (m, $CH_2$-3 + CH-4). |
| IIIb | 1705 | 1383 | 1185 | 1.78 (m, $2CH_2$ pyrr.), 2.33 (s, $NCH_3$), 2.63 (m, $2NCH_2$ pyrr. + $CH_2$-7 + $CH_2$-8), 2.93 (m, $CH_2$-5), 3.1-4.3 (m, $CH_2$-3 + CH-4). |
| IIIc | 1692 | 1382 | 1186 | 1.53 (m, $3CH_2$ pip.), 2.33 (s, $NCH_3$), 2.48 (m, $2NCH_2$ pip. + $CH_2$-7 + $CH_2$-8), 2.89 (m, $CH_2$-5), 3.1-4.2 (m, $CH_2$-3 + CH-4). |
| IIId | 1705 | 1382 | 1182 (a) | 2.1-2.9 (m, $CH_2$-7 + $CH_2$-8), 2.76 (s, $NCH_3$), 3.02 (m, $CH_2$-5), 3.2-3.7 (m, $CH_2$-3 + $NCH_2Ph$), 4.90 (m, CH-4), 6.65-7.60 (m, $2C_6H_5$) (b) |
| IIIe | 1703 | 1387 | 1188 | 1.53 (m, $3CH_2$ pip.), 2.42 (m, $2NCH_2$ pip. + $CH_2$-8), 2.85-4.20 (m, $3CH_2$ + CH-4), 6.5-7.4 (m, $C_6H_5$). |

(a) In chloroform. (b) In deuteriochloroform.

carboxaldehydes VIIa-b on the following basis. Compound VIIa was already known and showed m.p. and uv spectrum in agreement with those described (5,6); moreover its structure, as well as that of VIIb, was confirmed by ir, nmr and ms data (see Experimental). Compounds VIIa-b could arise from a facile air oxidation of the tautomeric forms VIa-b originating from α-hydroxymethyleneketones Va-b; actually, VIIa-b could be obtained from Va-b in fair to good yield by slow air oxidation in the cold during about two months. Finally, we tried also the dipolar 1,4-cycloaddition of enamines I and II with dichloroketene [prepared *in situ* from dichloroacetyl chloride and tri-

Table VII

*N,N*-Disubstituted 4-Amino-6-phenyl-3,4,5,6-tetrahydro-1,2-oxathiino[5,6-*c*]quinoline 2,2-Dioxides (IVa-b)



| Formula Number | $NR_2$ | Yield % | M.p. °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| IVa |  | 84 | 178 (a) | $C_{22}H_{24}N_2O_3S$ | 66.64<br>66.65 | 6.10<br>6.14 | 7.07<br>6.78 |
| IVb | $N(CH_3)C_6H_5$ | 80 | 145 (a) | $C_{24}H_{22}N_2O_3S$ | 68.88<br>68.57 | 5.30<br>5.53 | 6.69<br>6.58 |

(a) From ethyl acetate.

All compounds were prepared according to (1), using anhydrous tetrahydrofuran as solvent.

Table VIII

Ir and Nmr Spectral Data of Compound IVa-b

| Compound No. | Ir, $cm^{-1}$ (chloroform) C=C | O=S=O | | Nmr, δ (deuteriochloroform) |
|---|---|---|---|---|
| IVa | 1675 | 1380 | 1188 | 1.45 (m, $3CH_2$ pip.), 2.44 (m, $2NCH_2$ pip.), 3.55 (m, $CH_2$-3), 3.7-4.3 (m, CH-4), 4.47 (m, $CH_2$-5), 6.55-7.75 (m, 9H ar.). |
| IVb | 1675 | 1384 | 1182 | 2.84 (s, $NCH_3$), 3.58 (m, $CH_2$-3), 4.43 (m, $CH_2$-5), 4.75-5.35 (m, CH-4), 6.50-7.75 (m, $2NC_6H_5$ + 4 H ar.). |

ethylamine, compare (7)], but in any case we were unable to isolate the adduct even if in a few cases (enamines Ie, IIe) its formation and/or that of dehydrochlorinated products could be inferred from ir absorptions of the reaction mixture.

## EXPERIMENTAL

Uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. Ir spectra were taken on a Perkin-Elmer Model 257 spectrometer and nmr spectra were recorded on a Perkin-Elmer Model R12 instrument (60 MHz; TMS as internal standard; J in Hz). Mass spectra were obtained with a GC/MS Varian Mat 111 spectrometer. Melting points were determined with a Fisher-Johns apparatus.

3-Hydroxymethylene-1-phenyl-4-piperidone was prepared (1) from 1-phenyl-4-piperidone (0,02 mole), ethyl formate (0.04 mole) and sodium methoxide (0.04 mole) in anhydrous benzene. The very unstable crude compound obtained by acidification at *p*H 5 (yield 97%) was used immediately without any purification; ir (tetrachloromethane): ν max 1710 (broad), 1633, 1587 $cm^{-1}$.

Compound VIIa.

A solution of Va (3) (7.56 g., 0.04 mole) in diethyl ether (80 ml.) was kept in a refrigerator in a loosely stoppered flask. Every five days the precipitate which formed was filtered and the solution was concentrated, total yield after 55 days, 5.23 g. (70%); m.p. 210° from 95% ethanol [lit. (5) 217-218°]; uv: λ max nm (log ε), 217 (4.43), 233.5 (4.37), 265 (3.91), 324 (4.21) [lit. (6), 233 (4.35), 264 sh (3.90), 325 (4.17)]; ir (chloroform): ν max 3020, 3005, 2850, 1681, 1633, 1612, 1553, 1503 $cm^{-1}$; nmr (deuteriochloroform): δ 3.95 (s, $NCH_3$), 7.58 (mc, CH-6 + CH-7 + CH-8), 8.30 (s, CH-2), 8.4-8.7 (m, CH-5), 14.53 (s, CHO); ms: m/e 187 ($M^{\cdot+}$, 11%), 160 (11), 159 (100), 131 (23), 130 (29), 77 (18), 57 (16), 55 (11), 45 (18), 44 (30), 40 (18), 31 (34), 29 (11).

*Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.30; H, 4.94; N, 7.36.

The same compound was also obtained as the main product (58-72%) in the reaction of enamines IIa,b with sulfene.

Compound VIIb.

Starting from Vb (3) (2.51 g., 0.01 mole) and following the above procedure, 0.78 g. (31%) of VIIb was obtained, m.p. 187° from 95% ethanol; uv: λ max nm (log ε), 216 (4.41), 232.5 (4.44), 264 sh (3.89), 318 sh (4.23), 3.27.5 (4.25); ir (chloroform): ν max, 3030, 3000, 2855, 1675, 1627, 1592, 1545 $cm^{-1}$; nmr (deuteriochloroform): δ 7.57 (mc, $NC_6H_5$ + 3H ar.), 8.30 (s, CH-2), 8.4-8.75 (m, CH-5), 14.3 (s, CHO); ms: m/e 249 ($M^{\cdot+}$, 6%), 222 (14), 221 (100), 220 (28), 204 (14), 193 (16), 192 (8), 191 (10), 165 (10), 110 (6), 89 (7), 77 (13), 57 (8), 55 (6),51 (13).

*Anal.* Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62.

Found: C, 76.81; H, 4.57; N, 5.57.

Acknowledgement.

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