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1,2,4-TRIAZINES AND CONDENSED DERIVATIVES—XVI[a]

1-OXO-1,2-DIHYDRO- AND 1-OXO-1,2,6,7-TETRAHYDRO[1,2,4]TRIAZINO[1,6-*c*]-QUINAZOLIN-5-IUM SALTS. SYNTHESIS AND SOME REACTIONS[b]

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Abstract—Methylation of the type **1** and **2** triazinoquinazoliumolates yields the oxotriazinoquinazolinium salts of types **7** and **8**, respectively. **4a** similarly furnishes **9**. Acid induced degradations and $NaBH_4$ reductions of compounds **7–9**, their conversions into the corresponding pseudobases (**10**, **11**) as well as methods of synthesis of the novel oxotriazinoquinazoliniumolates (**16**) are described.

The 3-methylthio[1,2,4]triazino[1,6-*c*]quinazolin-5-ium-1-olates **1a**,[3] **1b**[3] and **1c**, the 7-acetyl-6,7-dihydro derivatives **2a–b**[3] (obtained by condensation of the triazinone **3a** with orthoesters and oxo compounds, respectively,[c] and acetylation of the products of the latter reaction) as well as the related triazinoindole **4a**[4] were treated with MeI to yield the corresponding deep purple red methiodides **7a–c**, **8a–b** and **9** in excellent yields. (The chlorides, tetrafluoroborates and trifluoracetates corresponding to compounds **7a** and **b**, respectively, are colourless, and the colour of the iodides may therefore possibly be due to charge-transfer interactions.) The sites of attachment of the newly introduced Me groups follow (1) from the IR spectra of the compounds **7** and **8** which exhibit *one more* amide I band than those of the respective starting compounds, (2) from the acid catalyzed degradations of the compounds **7a–b**, **8b** and **9** and (3) from the structure proving synthesis of compound **7b**. The degradations had either to be carried out in the presence of $NaHSO_3$ or the iodides had to be converted via their pseudobases **10** and **11**, respectively (see below), into the corresponding chlorides or fluoroborates prior to hydrolysis with aqueous HCl. Compounds **7a–b** and **8a** furnished the dione **12a** as the common hydrolysis product; the latter proved identical with an authentic sample obtained by methylation with diazomethane of **3a**,[4] separation of the resulting 2- (**3b**) and 4-methyl derivatives (**13**) and hydrolysis of the latter. The assignment of the structures to the two isomers is based on their IR spectra. Treatment of **11** with HCl in boiling acetic anhydride and addition of KI furnished an authentic sample of **7b**. Hydrolysis of **9** with $NaHSO_3$ aq furnished **14**,[6] an authentic sample of which was obtained by treatment of **3b** with HCl aq and ring closure of the resulting **12b** with AcOH.

The sites of methylation of compounds **1** and **2** are incompatible with the alternative structures **5** and **6**. Aromatic 1,2,4-triazines of type **15** have namely been shown to react with methylating agents under neutral conditions at N(1) and/or N(2) rather than at N(4),[7] which is in agreement with our observation concerning the site of methylation of compound **4a**.

Since 3-quinazolinium cations and related compounds are known to be attacked by nucleophiles at C(4),[8,9] we prefer structures **10** and **11** for the pseudobases corresponding to the salts **7** and **8**, respectively, although other structures are conceivable, cf Ref. 10.

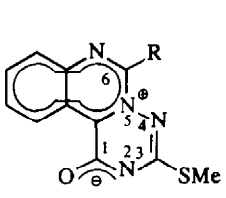
Thermal treatment of the pseudobase **10** (R = H) furnishes, under elimination of MeSH, the triazinoquinazoliniumolate **16a** whose structure assignment rests on its alternative synthesis by condensation of compound **12a** and acetic formic anhydride in the presence of dry HCl. The related compound **16b** was formed when **12a** was treated with HCl in acetic anhydride. Compounds **12a** and the related **12c** were cyclized to the 2H-[1,2,4]triazino[5,6-b]indol-3(4H)-ones **17a** and **17b**, respectively, by refluxing with acetic acid.

Sodium borohydride reduction of the iodides **7** and **8** in EtOH or DMF furnished the corresponding compounds **19**. The pseudobase **10** (R = H), however, is reduced by $NaBH_4$ only in the presence of acids. In the course of the reduction of the type **7** compounds attack of the hydride anion therefore appears to be directed first towards C-6 (yielding thereby, after protonation, a type **8** intermediate with H replacing Ac) and subsequently towards C-11b. Reduction of **7b** furnished, according to the NMR spectrum of the product, a mixture of the two diastereomeric racemates of structure **19b** in unequal amounts, but only one of the two possible racemates of structures **19c** and **e** was obtained as the product of reduction of compounds **7c** and **8b**, respectively. Acetylation of the mixture of the two racemates of **19b** furnished a single racemate in moderate yield which proved identical with the racemate **19e** obtained by reduction of **8b**. When dissolved in TFA, the compounds **19a–c** suffer profound decomposition (red colouration, profound changes in the NMR spectrum) even at r.t. to yield complex mixtures. In the case of compound **19a** TFA treatment causes, according to the NMR spectrum, formation of mainly one product to which structure **21** has been tentatively assigned on the basis of NMR evidence (three Me signals,

[a] For Part XV, see Ref. 1.

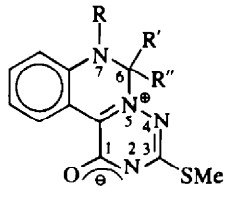
[b] Part of the present work has been described in a preliminary communication.[2]

[c] Originally structures **5** and **6**, respectively, have been assigned to the condensation products mainly on the basis of IR and NMR evidence[3] as well as of the observation that part of the condensation products formed with oxo compounds furnish, under elimination of R'–CO–R'', type **4b** ring contraction products on heating and/or treatment with acids.[5] On the basis of the present methylation studies and of an X-ray structure determination of compound **2c**[1] these structure assignments had, however, to be revised.



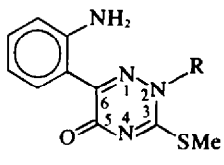
1

a: R = H
b: R = Me
c: R = Ph



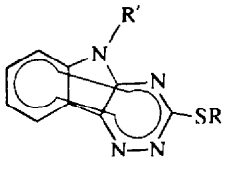
2

	R	R′	R″
a	Ac	H	H
b	Ac	H	Me
c	H	Me	Me
d	H	Ph	H



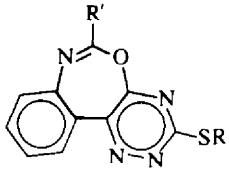
3

a: R = H
b: R = Me



4

a: R = Me, R′ = Ac
b: R′ = H



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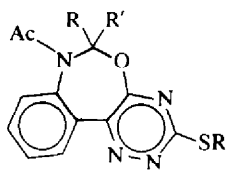

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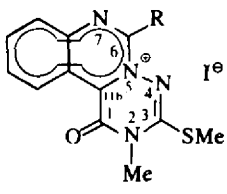
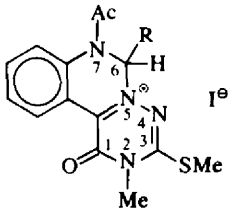


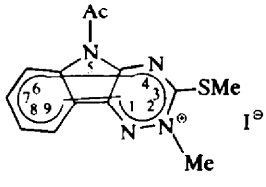
7

a: R = H
b R = Me
c: R = Ph



8

a: R = H
b: R = Me



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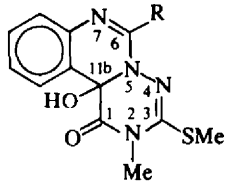

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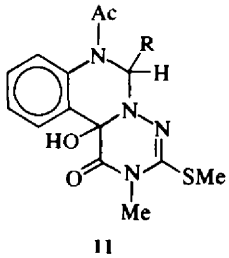

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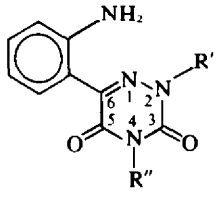


12

a: R′ = H; R″ = Me
b: R′ = Me; R″ = H
c: R′ = R″ = Me

no methylene and methine signals). Formation of **21** from **19a** may be rationalized by assuming the intermediacy of compound **20**. For a rearrangement which is similar to that assumed to lead from **20** to **21**, see Ref.[12]

$NaBH_4$ reduction of compound **9** similarly furnished compound **22**.

Careful alkaline hydrolysis of compound **19c** furnished benzaldehyde, isolated in form its condensation product **2d**[3] with **3a**.[4] The reaction sequence PhCOOH → → **1c** → **7c** → → **19c** → PhCHO offers a novel method of potential generality for the selective reduction of the carboxyl into the aldehyde group. Attempts to replace the reagent **3a** and the type **1**, **7** and **19** intermediates by simpler ones have met with success and resulted in the development of three simple and selective reduction methods.[13-15]

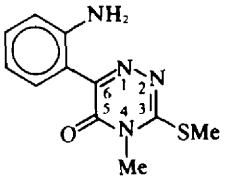
EXPERIMENTAL

6-(2-Benzoylaminophenyl)-3-methylthio-1,2,4-triazin-5(2H)-one

A mixture of **3a**[4] (3.0 g; 12.8 mmole), anhyd dioxane (20 ml) and benzoyl chloride (1.75 ml; 15 mmole) was refluxed for 30 min. The mixture was allowed to cool and treated with 5% $NaHCO_3$ aq until neutral. The solid product was washed with water and recrystallized from 50% aqueous DMF (30 ml) to yield 1.8 g (41%) of the title substance, colourless needles, m.p. 264–265° from DMF–ether. (Found: C, 60.51; H, 4.40; N, 16.26; S, 9.33. $C_{17}H_{14}N_4O_2S$ (338.38) requires: C, 60.34; H, 4.17; N, 16.26; S, 9.47%); IR (KBr): 1635 + 1650 (sh), Amide I bands.

3-Methylthio-6-phenyl-[1,2,4]triazino[1,6-c]quinazolin-5-ium-1-olate (**1c**)

A mixture of **3a**[4] (10 g; 42.7 mmole), anhyd dioxane (50 ml) and benzoyl chloride (6.0 ml; 52 mmole) was refluxed for 30 min. The N-benzoyl derivative of **3a** which separated on cooling was mixed



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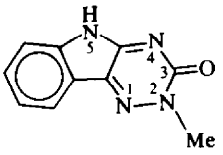

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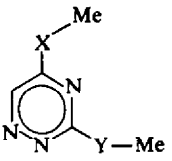
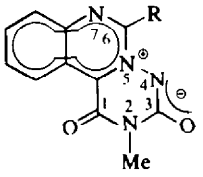


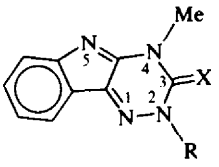
15

a: X = O, Y = S
b: X = S, Y = O
c: X = Y = O



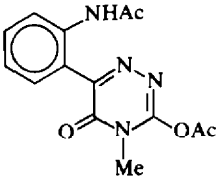
16

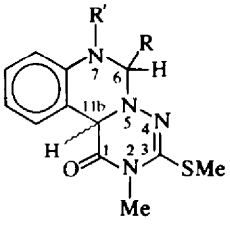
a: R = H
b: R = Me



17

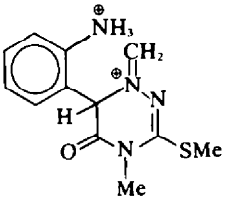
a: R = H; X = O
b: R = Me; X = O
c: R = H; X = S





19

a: R = R′ = H
b: R = Me; R′ = H
c: R = Ph; R′ = H
d: R = H; R′ = Ac
e: R = Me; R′ = Ac



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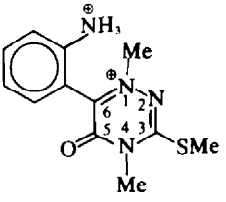
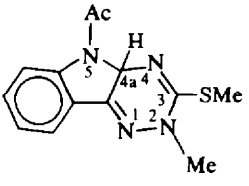


21



22

with Ac_2O (50 ml). Dry HCl was introduced under stirring for 15 min (heat was evolved). The mixture was allowed to cool. The crystalline product was filtered off, washed with two portions of ether (30 ml, each) and triturated with 5% $NaHCO_3$ aq (300 ml); if necessary, crystalline $NaHCO_3$ was added until the aqueous phase finally remained slightly alkaline. The insoluble product was filtered off, washed with water and recrystallized from EtOH (600 ml) to yield 3.8 g (28%) of **1c**, lemon yellow needles, m.p. 215–216°. (Found: C, 63.58; H, 3.60; N, 17.56; S, 10.11. $C_{17}H_{12}N_4OS$ (320.30) requires: C, 63.74; H, 3.77; N, 17.49; S, 10.01%); IR (KBr): 1660, $\nu C{=}N^{\oplus}$.

1 - *Oxo* - 1,2 - *dihydro*[1,2,4]*triazino*[1,6-c]*quinazolin* - 5 - *ium salts* (**7**) *and the corresponding pseudobases* (**10**)

(a) A mixture of **1a**[3] (8.0 g; 32 mmole), MeI (10 ml; 162 mmole) and nitromethane (40 ml) was stirred for 3 hr on a boiling steam bath. The mixture remained heterogeneous throughout. The mixture was allowed to cool and the resulting **7a** (12 g; 98%) was filtered off and washed with ether. Purple needles, m.p. 228–229° from nitromethane. (Found: C, 37.05; H, 3.40; I, 32.83; S, 8.34. $C_{12}H_{11}IN_4OS$ (386.23) requires: C, 37.31; H, 2.87; I, 32.86; S, 8.30%); IR (KBr): 1720 cm $^{-1}$. NMR (TFA; external TMS) of the corresponding *colourless* trifluoroacetate, obtained by dissolving the pseudobase **10** (R = H) of **7a** (see below) in TFA: δ 9.62, dd, $J \approx 8$ and 1.5 Hz, 1H, 11-H; 9.32, s, 1H, 6-H; 8.25–7.85, m, 3H, 8-H–10-H; 3.45, s, 3H, N-Me; 2.5, s, 3H, S-Me.†

(b) Compound **7b** (4.8 g; 83%), purple needles, m.p. above 210° (dec.; from nitromethane–EtOAc), was similarly obtained from **1b**[3] (3.8 g) and MeI (10 ml) in nitromethane (30 ml). According to its IR spectrum, this product proved identical with an authentic sample obtained as described below.

(c) Compound **7c** (4.6 g; 99%), m.p. 198–200° (dec), was similarly obtained from **1c** (3.8 g) and MeI (10 ml) in nitromethane (30 ml). IR (KBr): 1720 cm^{-1}.

(d) Compound **7a** (27 g; 70 mmole) was stirred with 5% $NaHCO_3$ aq (500 ml) for 15 min at r.t. The purple colour disappeared. The resulting **10** (R = H) (15.7 g; 81%) was filtered off, washed with water, dried over P_2O_5 and purified by rapid dissolution in DMF under gentle heating and reprecipitation with water. Small colourless needles which turn yellow under considerable sintering at 145–150° and decompose above 250°. (Found: C, 52.20; H, 4.00; N, 20.32; S, 11.55. $C_{12}H_{12}N_4O_2S$ (276.32) requires: C, 52.16; H, 4.38; N, 20.28; S, 11.55%); IR (KBr): 1720 cm^{-1}.

Treatment of the pseudobase with KI in AcOH reconverted it into **7a**. When a soln of the pseudobase (0.5 g) in DMF (10 ml) was treated with a mixture of $NaBF_4$ (6.0 g), water (20 ml) and AcOH

†This spectrum is completely analogous to that of **1a** taken in TFA (internal DSS) [9.87, dd, $J \approx 8$ and 1.5 Hz, 1H, 11-H; 9.67, s, 1H, 6-H; 8.55–8.20, m, 3H, 8-H–10-H; 2.86, s, 3H, S-Me] which is further proof in favour of structure **1a** and against the alternative type **5** structure (at least in the sense that it is the former from which the salts are derived).

(1 ml), 0.2 g (32%) of the *colourless* crystalline tetrafluoroborate **7a** (with $BF_4^{\ominus}$ replacing $I^{\ominus}$), m.p. 280–282° (dec), was obtained. The IR spectrum was, apart from the intensive $BF_4^{\ominus}$ band, identical with that of the iodide.

(e) The pseudobase **10** (R = Me) corresponding to **7b** was similarly obtained in 78% yield. All attempts of recrystallization of the crude product failed. M.p. (crude product) 160°; dec. above 210°. IR (KBr): 1725 cm^{-1}.

7 - *Acetyl* - 1 - *oxo* - 1,2,6,7 - *tetrahydro*[1,2,4]*triazino*[1,6-*c*]*quinazolin* - 5 - *ium salts* (**8**)

(a) A mixture of **2a**[3] (4.5 g; 15.6 mmole), MeI (10 ml) and nitromethane (30 ml) was refluxed for 2 hr. Another portion of MeI (10 ml) was added and refluxing was continued for another 2 hr. The mixture was kept overnight in a refrigerator to yield 5.5 g (82%) of **8a**, purple red crystals, m.p. 188–191° (dec); from nitromethane. (Found: C, 38.71; H, 3.62; I, 29.89; S, 7.42. $C_{14}H_{15}IN_4O_2S$ (430.28) requires: C, 39.08; H, 3.51; I, 29.50; S, 7.45%); IR (KBr): 1720, 1675 cm $^{-1}$. NMR (DMSO-d_6): δ 8.7, dd, $J \approx 8$ and 2 Hz, 1H, 11-H; 8.0–7.85, m, 3H, 8-H–10-H; 6.05, s, 2H, CH_2; 3.55, s, 3H, N–Me; 2.8, s, 3H, S–Me; 2.3, s, 3H, Ac.

(b) Compound **8b** m.p. above 230° (dec); from DMF, was similarly obtained from **2b**[3] in 95% yield. (Found: C, 40.68; H, 4.14; I, 28.23; S, 7.02. $C_{15}H_{17}IN_4O_2S$ (444.31) requires: C, 40.55; H, 3.86; I, 28.56; S, 7.20%); IR (KBr: 1710, 1685 cm^{-1}.

5 - *Acetyl* - 2 - *methyl* - 3 - *methylthio* - 5H - [1,2,4]*triazino*[5,6-*b*]*indol* - 2 - *ium iodide* (**9**)

A mixture of **4a**[4] (7.7 g; 29.8 mmole), MeI (10 ml) and $CHCl_3$ (40 ml) was refluxed for 6 hr to yield 5.0 g (42%) of **9**, m.p. above 200° (dec); from nitromethane–EtOAc. (Found: C, 39.68; H, 3.56; I, 31.64; N, 14.44; S, 8.41. $C_{13}H_{13}IN_4OS$ (400.25) requires: C, 39.01; H, 3.27; I, 31.70; N, 14.01; S, 8.01%); IR (KBr): 1750 cm^{-1}.

Degradation of compounds **7–9**

(a) A mixture of the pseudobase **10** (R = H) (10 g; 36.3 mmole) corresponding to **7a**, 37% HCl aq (30 ml) and water (80 ml) was refluxed for 5 hr. MeSH was vigorously evolved. The light yellow soln was evaporated to dryness *in vacuo*, the residue was dissolved in water (30 ml) and treated with 5% $NaHCO_3$ aq to yield 5.95 g of crude **12a** which was purified through its HCl salt.

Thus, the crude product was dissolved in anhyd MeOH (100 ml) and treated with dry HCl gas until precipitation of the salt started. Dry ether (200 ml) was added and the mixture was kept overnight in a refrigerator to yield 5.8 g (63%) of **12a**·HCl, colourless plates, m.p. above 190° (dec). (Found: C, 47.81; H, 4.72; Cl, 14.14. $C_{10}H_{10}N_4O_2$·HCl (254.68) requires: C, 47.16; H, 4.35; Cl, 13.92%); IR (KBr): 1740, 1660 cm $^{-1}$.

The salt was dissolved in water (50 ml), the soln was treated with Norite and then with 5% $NaHCO_3$ aq. to yield 4.0 g of the base which was recrystallized from i-PrOH (100 ml) to furnish 2.7 g (34%) of pure **12a**, m.p. 198.5°, identical with an authentic sample (see below).

(b) Compound **7b** (1.0 g; 2.5 mmole) was treated with 5% $NaHCO_3$ aq. (60 ml). The insoluble pseudobase (**10**, R = Me) was filtered off and refluxed with a mixture of 37% HCl aq. (3.5 ml) and water (7 ml). The mixture was worked up as above to yield 0.50 g (92%) of crude **12a** which, according to m.p., m. m.p. and IR spectra proved identical with the product obtained from the pseudobase **10** (R = H) of **7a**.

(c) Compound **8b** (0.5 g; 11 mmole) was dissolved in 10% NaOH aq. (5 ml) and treated with warm 20% $NaBF_4$ aq. (10 ml). Acidification with AcOH furnished 0.35 g of the brick-red fluoroborate (**8b**, with $BF_4^{\ominus}$ instead of $I^{\ominus}$), m.p. 262–264° (dec), whose IR spectrum proved identical—apart from the presence of a strong $BF_4^{\ominus}$ band—with that of the iodide. The fluoroborate was hydrolyzed as described above to yield 0.09 g (36%) of pure **12a**, identical according to m.p., m. m.p. and IR spectra with the product obtained from the pseudobase of **7a**.

(d) A mixture of **9** (0.5 g; 1.25 mmole), $NaHSO_3$ (2.0 g) and water (15 ml) was refluxed for 1 hr (vigorous MeSH evolution) to yield 0.15 g (60%) of **14**, yellow plates, m.p. above 320° (dec) from AcOH, which, according to its IR spectrum, proved identical with an authentic sample (see below).

6 - (2 - *Aminophenyl*) - 2 - *methyl* - (**3b**) *and* - 4 - *methyl* - 3 - *methylthio* - 1,2,4 - *triazin* - 5(2H) - *one* (**13**)

Compound **3a**[4] (1.0 g; 4.27 mmole) was treated at r.t. with a slight excess of freshly prepared ethereal diazomethane soln until the evolution of N_2 ceased and an almost clear soln resulted. n-Pentane (30 ml) was added to yield an oily ppt which was worked up by preparative TLC (adsorbent: Kieselgel G, Merck; activated for 2 hr at 105°; solvent: benzene–MeOH, 4:1; detection I_2 vapour) to yield **3b**, m.p. 207–208°, R_f 0.52, and **13**, m.p. 137°, R_f 0.65, the ratio of the two isomers being 2:1.

Alternatively, 1.7 g of the crude methylation product was stirred at r.t. with two portions of ether (300 ml, each), and the insoluble residue was recrystallized from i-PrOH to yield 0.41 g (12%) of **3b**, m.p. 207–208°, which proved chromatographically pure. (Found: N, 22.88; S, 12.98. $C_{11}H_{12}N_4OS$ (248.31) requires: N, 22.56; S, 12.91%) IR (KBr): 1640, 1620 cm^{-1}. UV (EtOH): 204 (4.36); 237 (4.44); 294 (3.95), sh; 364 (3.50).

The combined ethereal solns were evaporated to dryness and the residue was recrystallized from i-PrOH to yield 0.38 g (11%) of chromatographically pure **13**, m.p. 135–137°. (Found: C, 53.16; H, 4.89. $C_{11}H_{12}N_4OS$ (248.31) requires: C, 53.20; H, 4.89%); IR (KBr): 1675, 1610 cm $^{-1}$.

6 - (2 - *Aminophenyl*) - 1,2,4 - *triazine* - 3,5(2H,4H) - *diones* (**12**) (authentic samples)

(a) A mixture of **13** (0.2 g; 0.81 mmole) 37% HCl aq. (5 ml) and water (2.5 ml) was refluxed for 4 hr. The mixture turned initially red but became rapidly colourless, and MeSH was evolved vigorously. The soln was evaporated to dryness *in vacuo*. The residue was dissolved in water and the soln was treated with 5% $NaHCO_3$ aq. until neutral. The crude **12a** was filtered off and recrystallized from i-PrOH to yield 0.08 g (45%) of pure **12a**, m.p. 198.5°. (Found: C, 54.97; H, 4.57; N, 24.90. $C_{10}H_{10}N_4O_2$ (218.21) requires: C, 55.04; H, 4.62; N, 25.68%); IR (KBr): 1730 (w), 1660 cm^{-1} (s). NMR (DMSO-d_6): δ 7.3–6.4, m, 4H, ArH's; 5.25, bs, 2H, NH_2; 3.2, s, 3H, N–Me.

(b) Hydrolysis of **3b** (0.25 g; 1.0 mmole) was carried out similarly than the hydrolysis of **13** and furnished 0.15 g (68%) of **12b**, m.p. 210–235° (sintering); dec above 320°. (Found: C, 55.07; H, 4.87; N, 25.37. $C_{10}H_{10}N_4O_2$ (218.21) requires: C, 55.04; H, 4.62; N, 25.68%); IR (KBr): 1710, 1685 cm $^{-1}$.

(c) Compound **12b** (0.3 g; 1.4 mmole), dissolved in EtOH, was treated at r.t. with a slight excess of ethereal diazomethane soln. The mixture was evaporated to dryness and the oily residue was triturated with ether until it turned crystalline. Recrystallization from i-PrOH furnished 0.12 g (37%) of **12c**, m.p. 154°. (Found: C, 56.50; H, 5.21; N, 24.40. $C_{11}H_{12}N_4O_2$ (232.24) requires: C, 56.88; H, 5.21; N, 24.13%); IR (KBr): 3410, 3320, 1715, 1660 cm $^{-1}$; NMR ($CDCl_3$): δ 7.75–6.65, m, 4H, ArH's; 4.5, bs, 2H, NH_2; 3.7 and 3.4, both s, 3H, each, two N-Me's.

(d) Compound **12a** (2.0 g; 9.2 mmole) was similarly methylated to yield 1.4 g (66%) of **12c**, yellow needles, m.p. 154° which, according to m.p., m. m.p. and IR spectra, proved identical with the authentic product obtained as described above.

2,6 - *Dimethyl* - 3 - *methylthio* - 1 - *oxo* - [1,2,4]*triazino*[1,6-*c*]*quinazolin* - 5 - *ium iodide* (**7b**) (authentic sample)

Dry HCl gas was introduced for 5 min into a refluxing soln of **13** (0.2 g; 0.81 mmole) in Ac_2O (3 ml). The soln was allowed to cool and ether (15 ml) was added to give the *light yellow* crystals of the chloride (**7b**, with $Cl^{\ominus}$ instead of $I^{\ominus}$). The chloride was triturated with an aqueous (3 ml) soln of KI (1.0 g) to yield 0.22 g (68%) of the purple red crystals of the iodide **7b** which were filtered off, washed with 20% KI aq. and EtOH and recrystallized from nitromethane–EtOAc, m.p. above 210° (dec). (Found: C, 38.93; H, 3.68; N, 13.98; S, 8.09. $C_{13}H_{13}IN_4OS$ (400.25) requires: C, 39.01; H, 3.27; N, 14.01; S, 8.01%); IR (KBr): 1720 cm^{-1}.

2 - *Methyl* - 5H - [1,2,4]*triazino*[5,6-b]*indol* - 3(2H) - *one* (**14**) (authentic sample)

A mixture of **12b** (0.1 g; 0.46 mmole) and AcOH (5 ml) was refluxed for 30 min and evaporated to dryness. The residue was triturated with Et_2O to yield 0.04 g (43%) of **14**, m.p. 320° (dec.; from AcOH), lit.[6] m.p. 327°. The IR (KBr) (1650 cm^{-1}) and UV spectra were identical with those reported.[6]

2 - Methyl - 1 - oxo - 1,2 - dihydro[1,2,4]triazino[1,6-c]quinazolin - 5 - ium - 3 - olate (**16a**)

(a) A mixture of the pseudobase **10** (R = H) (1.2 g; 4.34 mmole) and anhyd. DMF (10 ml) was refluxed for 15 min (vigorous MeSH evolution) and allowed to cool. Ether (15 ml) was added to yield 0.45 g (45%) of **16a**, small stout yellow crystals, m.p. 328° (dec) from AcOH. The product proved identical with an authentic sample (see below).

(b) The same product was obtained in 21% yield when the pseudobase was heated for 15 min at 150–160° in the absence of any solvent and the product reprecipitated with ether from its AcOH soln.

(c) *Authentic sample.* Dry HCl gas was introduced into a refluxing mixture of **12a** (2.0 g; 9.2 mmole) and acetic formic anhydride (15 ml) for 15 min. Precipitation of a crystalline product started immediately and was completed by the addition of anhyd Et_2O (20 ml). This product was triturated with 5% $NaHCO_3$ aq. (two 30 ml portions) to yield 1.5 g (71%) of **16a**, m.p.: 328° (dec); from AcOH or DMF. (Found: C, 58.07; H, 3.87; N, 24.47. $C_{11}H_8N_4O_2$ (228.21) requires: C, 57.89; H, 3.53; N, 24.55%); IR (KBr): 1690 (m), 1635 cm^{-1} (s).

Reactions of compound **12a**

(a) Compound **12a** (0.4 g; 1.8 mmole) was refluxed for 3 hr with AcOH (10 ml) and the resulting soln was evaporated to dryness *in vacuo*. The residue was triturated with water (10 ml) to yield 0.2 g (55%) of **17a**, m.p. above 310° (dec) from DMF which, according to its IR spectrum, proved identical with an authentic sample prepared as described below.

(b) Compound **12a** (1.1 g; 5.0 mmole) was refluxed for 5 min with Ac_2O (10 ml). The mixture was filtered and allowed to cool. Ether (40 ml) was added to yield 0.4 g (26%) of **18**, colourless needles, m.p. 178–180° (dec) from benzene. (Found: C, 55.86; H, 4.71; N, 18.66. $C_{14}H_{14}N_4O_4$ (302.28) requires: C, 55.62; H, 4.67; N, 18.54%); IR (KBr): 1750, 1710 + 1690 (sh), i.e. *three* C=O bands. NMR ($CDCl_3$): δ 8.4–7.95, m, 2H and 7.8–7.15, m, 2H, ArH's; 3.45, s, 3H, N–Me; 2.82 and 2.22, both s, 3H, each, Ac groups.

(c) Dry HCl gas was introduced for 15 min into a refluxing soln of **12a**·HCl (3.0 g; 11.8 mmole) in Ac_2O (20 ml). The heterogeneous mixture was allowed to cool. Anhyd ether (30 ml) was added and the product was filtered off and triturated with 5% $NaHCO_3$ aq. to yield 2.3 g (81%) of **16b**, small prisms, m.p. 274–276° (dec) from DMF. (Found: C, 59.23; H, 4.09; N, 23.60. $C_{12}H_{10}N_4O_2$ (242.20) requires: C, 59.50; H, 4.16; N, 23.13%); IR (KBr): 1690 (m), 1625 cm^{-1} (vs). NMR (TFA; external TMS): δ 9.5, dd, J ≈ 8 and 1.5 Hz, 1H, 11-H; 8.1–7.85, m, 3H, 8-H–10-H; 3.38 and 2.8, both s, 3H each, 2- and 6-Me.

2H - [1,2,4]Triazino[5,6-b]indol - 3(4H) - ones and thiones (**17**)

(a) A mixture of isatine (6.0 g; 40.8 mmole), 4-methylthiosemicarbazide (4.3 g; 40.8 mmole) and EtOH (80 ml) was refluxed for 20 min to yield 7.5 g (79%) of isatine-β-(4-methylthiosemicarbazone), yellow needles, m.p. 264–266° (dec) from DMF–EtOH. (Found: C, 51.70; H, 4.58; S, 13.35. $C_{10}H_{10}N_4OS$ (234.28) requires: C, 51.26; H, 4.30; S, 13.69%); IR (KBr): 3180 b, 1695, 1670, 1620 cm^{-1}.

The above product (6.8 g; 25.6 mmole) was refluxed for 1 hr with an aqueous (30 ml) soln of KOH (1.68 g; 30 mmole). The mixture was allowed to cool, diluted with water (30 ml) and acidified with AcOH to yield 5.25 g (95%) of **17c**, yellow crystals, m.p. above 340° (dec) from DMF or pyridine–EtOH. (Found: C, 55.68; H, 3.88; N, 25.59. $C_{10}H_8N_4S$ (216.26) requires: C, 55.53; H, 3.73; N, 25.91%); IR (KBr): 3200–2350 (b, vs), 1610, 1585, 1560 cm^{-1} (vs).

(b) Compound **17c** (2.16 g; 10 mmole) was dissolved in an aqueous (20 ml) soln of KOH (0.67 g; 12 mmole); MeI (1.25 ml; 20 mmole) was added to the red soln and the mixture was stirred at r.t. for 30 min. The S–Me derivative (1.7 g; 74%), orange–yellow needles, m.p. 187°, separated gradually. (Found: C, 57.37; H, 4.48; N, 24.14; S, 13.59. $C_{11}H_{10}N_4S$ (230.29) requires: C, 57.37; H, 4.38; N, 24.33; S, 13.92%); IR (KBr): 1580, 1550 cm^{-1}.

†For the method of oxidation, cf Ref. 11.

‡The two outside peaks of the 4.9 quartet are submerged into the noise.

A mixture of this product (0.5 g; 2.2 mmole), 20% HCl aq. and EtOH (10 ml, each) was refluxed for 2 hr (vigorous evolution of MeSH) and evaporated to dryness. The residue was dissolved in 10% NaOH aq. and acidified with AcOH to yield 0.35 g (80%) of **17a**, m.p. above 320° (dec) from DMF. (Found: C, 59.78; H, 4.15; N, 28.53. $C_{10}H_8N_4O$ (200.20) requires: C, 59.99; H, 4.03; N, 27.99%); IR (KBr): 3200, 3050, 2900, 1685 vs, 1625, 1590, 1570 vs.

(c) An aqueous (100 ml) soln of $KMnO_4$ (3.16 g; 20 mmole) was added within 15 min under ice-cooling and continuous stirring to the soln of **17c** (1.6 g; 7.4 mmole) and NaOH (0.6 g; 15 mmole) in water (20 ml). Stirring was continued for another 15 min. EtOH (15 ml) was added and the MnO_2 was filtered off after further stirring for 15 min. The orange coloured filtrate was acidified with AcOH to yield 0.8 g (54%) of **17a** which was filtered off after the mixture had been boiled up and allowed to cool again. The product was identical with the sample obtained as described under (b).†

(d) Compound **12c** (0.6 g; 2.6 mmole) was refluxed for 30 min with AcOH (6 ml). The mixture was allowed to cool and ether (30 ml) was added to yield 0.28 g (50%) of **17b**, orange–yellow needles, m.p. 237° from DMF. (Found: C, 61.85; H, 4.74; N, 26.53. $C_{11}H_{10}N_4O$ (214.22) requires: C, 61.67; H, 4.71; N, 26.16%); IR (KBr): 1700, 1630, 1590, 1570 cm^{-1}.

$NaBH_4$ *reductions of compounds* **7–10**

(a) $NaBH_4$ (0.79 g; 21 mmole) was added in small portions at 0° under continuous stirring to a soln of **7a** (4.0 g; 10.3 mmole) in EtOH (40 ml). After the effervescence had ceased, water (60 ml) was added to the soln and the excess $NaBH_4$ was decomposed with AcOH. 2.0 g (73%) of **19a**, colourless glittering plates, m.p. 163° from EtOH, were obtained. (Found: C, 55.22; H, 5.83; N, 21.10; S, 11.93. $C_{12}H_{14}N_4OS$ (262.32) requires: C, 54.94; H, 5.38; N, 21.36; S, 12.22%); IR (KBr): 3400 m, 1700, 1600; NMR ($CDCl_3$): δ 7.45–6.5, m, 4H, ArH's; 5.05, s, 1H, 11b-H; 4.62 and 4.38, AB qu, J = 12.6 Hz, 2H, CH_2; 4.05, bs, 1H, NH; 3.23, s, 3H, N–Me; 2.28, s, 3H, S–Me. NMR (TFA, external TMS; spectrum of the cation **21**): δ 7.65–6.85, m, 4H, ArH's; 3.9, s, 3H, N^{①}–Me; 3.3, s, 3H, N–Me; 2.45, s, 3H, S–Me.

(b) The same product was obtained (0.95 g; 70%) when **7a** (2.0 g; 5.15 mmole) was reduced with $NaBH_4$ (0.55 g; 15 mmole) in anhyd DMF (20 ml) and, after the soln became colourless, the product was precipitated by the addition of water (40 ml).

(c) $NaBH_4$ (0.2 g; 5.2 mmole) was added in portions to a soln of the pseudobase **10** (R = H; 0.5 g; 1.3 mmole) in EtOH (10 ml) as described under (a). The mixture was acidified with AcOH to yield 0.32 g (94%) of **19a**, identical with the product obtained according to (a).

An attempt to reduce **10** (R = H) in DMF as described under (b) failed; the starting compound was recovered in 71% yield.

(d) Compound **7b** (3.0 g; 7.5 mmole) was reduced with $NaBH_4$ (0.55 g; 15 mmole) in EtOH (30 ml) as described under (a) to yield 1.8 g (86%) of **19b**, colourless glistering prisms, m.p. 154° from EtOH. (Found: C, 56.69; H, 6.25; N, 20.79; S, 11.73. $C_{13}H_{16}N_4OS$ (276.36) requires: C, 56.49; H, 5.84; N, 20.27; S, 11.60%); IR (KBr): 3350, 1700, 1605 cm^{-1}. NMR ($CDCl_3$): δ 7.35–6.5, m, 4H, ArH's; 5.1, somewhat broadened s, 1H, 11b-H; 4.9, w + 4.5, s, both qu‡, J = 6.5 and 6.0 Hz, respectively, total intensity 1H, 6-H; 3.85, bs, 1H, NH; 3.25, s, 3H, N–Me; 2.32, s, 3H, S–Me; 1.57, s + 1.37, w, both d, J = 6.0 and 6.5 Hz, respectively, total intensity 3H, 6-Me.

(e) Reduction of **7c** (4.0 g; 9 mmole) with $NaBH_4$ (0.92; 25 mmole) in EtOH (30 ml) was carried out as described under (a) and furnished 2.8 g (92%) of **19c**, m.p. 161–162° from EtOH. (Found: C, 64.13; H, 5.35; S, 9.09. $C_{18}H_{18}N_4OS$ (338.41) requires: C, 63.88; H, 5.36; S, 9.47%); IR (KBr): 3250, 1700, 1600 cm^{-1}; NMR ($CDCl_3$): δ 7.75–6.5, m, 9H, ArH's; 5.45, s, 1H, 6-H; 5.2, s, 1H, 11b-H; 4.2, vb s, 1H, NH; 3.2, s, 3H, N–Me; 2.15, s, 3H, S–Me.

(f) Reduction of **8a** (4.2 g; 9.8 mmole) with $NaBH_4$ (1.8 g; 47 mmole) in EtOH (60 ml) was carried out as described under (a) and gave 2.5 g (84%) of **19d**, colourless needles, m.p. 163° from EtOH. (Found: C, 55.36; H, 5.38; N, 18.56; S, 10.16. $C_{14}H_{16}N_4O_2S$ (304.37) requires: C, 55.24; H, 5.30; N, 18.41; S, 10.53%); IR (KBr): 1700, 1660, 1610 cm^{-1}; NMR ($CDCl_3$): δ 7.7–7.0, m, 4H, ArH's; 5.65 and 4.45, AB qu, J = 12 Hz, 2H, CH_2; 5.1, s, 1H, 11b-H; 3.25, s, 3H, N–Me; 2.4 and 2.3, both s, 3H, each, Ac and S–Me.

(g) The same compound **19d** (0.7 g; 60%) was obtained by refluxing **19a** (1.0 g; 3.8 mmole) with a mixture of Ac_2O and pyridine (4 ml, each) for 30 min, evaporating the mixture to dryness *in vacuo* and triturating the residue with ether, m.p. and m. m.p. with the product obtained as described under (f) 163° from EtOH.

(h) Compound **8b** (1.0 g; 2.3 mmole) was reduced with $NaBH_4$ (0.5 g; 13 mmole) in EtOH (10 ml) as described under (a) to yield 0.6 g (84%) of **19e**, small colourless plates, m.p. 173° from i-PrOH. (Found: C, 56.92; H, 5.48; N, 17.74; S, 10.05. $C_{15}H_{18}N_4O_2S$ (318.39) requires: C, 56.68; H, 5.70; N, 17.60; S, 10.07%); IR (KBr): 1700, 1685, 1610 cm^{-1}; NMR ($CDCl_3$): δ 7.75–7.1, m, 4H, ArH's; 5.95, qu, J = 7.2 Hz, 1H, 6-H; 5.1, s, 1H, 11b-H; 3.25, s, 3H, N–Me; 2.35 and 2.30, both s, 3H, each, Ac + S–Me; 1.45, d, J = 7.2 Hz, 3H, 6-Me.

(i) The same product was obtained in 17% yield when 0.5 g of a mixture of the two stereoisomers of **19b** was refluxed with a mixture of Ac_2O and pyridine (2 ml, each), worked up as described under (g) and recrystallized from i-PrOH.

(j) Compound **9** (2.0 g; 4.9 mmole) was reduced with $NaBH_4$ (0.6 g; 15.8 mmole) in EtOH (20 ml) as described under (a) to yield 1.2 g (87%) of **22**, colourless needles, m.p. 189° from EtOH. (Found: C, 56.56; H, 5.16; N, 20.10; S, 11.67. $C_{13}H_{14}N_4OS$ (274.33) requires: C, 56.91; H, 5.14; N, 20.43; S, 11.69%); IR (KBr): 1690 cm^{-1}. NMR ($CDCl_3$): δ 8.5, dd, J ≈ 8 and 1.5 Hz, 1H, 6-H; 7.75, dd, J ≈ 8 and 1.5 Hz, 1H, 9-H; 7.55–7.15, m, 2H, 7-H and 8-H; 4.98, s, 1H, 4a-H; 3.62, s, 3H, N–Me; 2.58 and 2.50, both s, 3H, each, Ac and S–Me; NMR (TFA; external TMS): δ 7.6–6.95, m, 4H, ArH's; 5.15, s, 1H, 4a-H; 3.42, s, 3H, N–Me; 2.40 and 2.30, both s, 3H, each, Ac and S–Me.

Alkaline hydrolysis of **19c**

A mixture of **19c** (3.0 g; 8.9 mmole), 10% NaOH aq. (15 ml) and EtOH (30 ml) was refluxed for about 5 min, until a clear soln resulted, rapidly cooled to r.t. and acidified with AcOH. Water (100 ml) was added and the mixture was extracted with three portions of ether (30 ml, each). The ethereal soln was washed with water and dried over $MgSO_4$. The solvent was distilled off and the residue was refluxed for 2 min with a mixture of **3a**[4] (2.1 g; 8.9 mmole), EtOH (15 ml) and AcOH (2 ml). On cooling, 1.5 g (5.2%) of **2d**, m.p. 252–253° (dec) from DMF, identical according to m. m.p. and IR spectra with an authentic product,[3] separated.

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