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The synthesis of some quinazolino[3,2-*a*][1,4]benzodiazepines from 2-bromomethyl-3-*o*-carbomethoxyphenyl-4(3*H*)quinazolone is described. Alkylation and acylation of N-6 led to a series of novel derivatives of this ring system.

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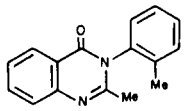
The quinazolones exhibit an extensive range of pharmacological activities (1) and, as part of our continuing studies on derivatives of the sedative-hypnotic 2-methyl-3-*o*-tolyl-4(3*H*)quinazolone, "Methaqualone" (**1**) (2,3), we considered the synthesis of fused derivatives of **1** in which the two methyl groups were inter-linked **2**.



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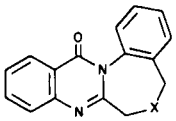
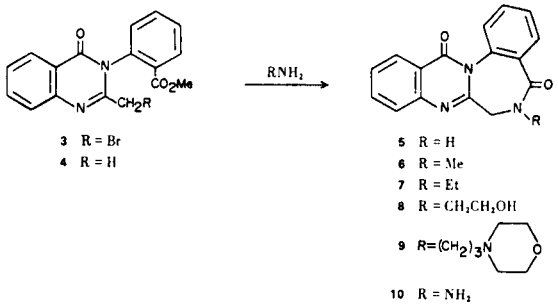


2

Such an investigation was prompted by observations of the nmr spectra of certain 2-substituted derivatives of **1** (2) which suggest that the *o*-tolyl ring in **1** is not co-planar with the quinazolone nucleus and that rotation around the *N*-tolyl bond is slow on the nmr time-scale (4). These conclusions have been supported by theoretical molecular orbital calculations (5). Examination of Drieding models showed that suitable one-atom bridges, linking the two methyl groups and creating a fused seven-membered ring, would allow the molecule to adopt a series of constrained conformations of **1**. In particular, if the bridging atom were nitrogen, the molecules would, in addition, be derivatives of the clinically important 1,4 benzodiazepines (6). This paper describes the synthesis of some new quinazolino [3,2-*a*][1,4]benzodiazepines (**2**) (X = NR).

The key intermediate for the synthesis of this ring system was 2-bromomethyl-3-(*o*-carbomethoxy)phenyl-4-(3*H*)quinazolone (**3**), which was prepared from the known 2-methyl derivative **4** (7) by bromination in acetic acid. Treatment of **3** with primary amines, ammonia or hydrazine in alcohol resulted in spontaneous cyclisation to give the appropriate quinazolino[3,2-*a*][1,4]benzodiazepines (**5**-**10**) (Scheme I).

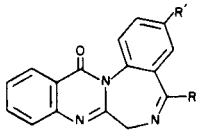
Scheme I



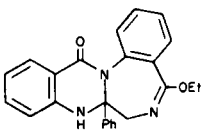
3 R = Br
4 R = H

5 R = H
6 R = Me
7 R = Et
8 R = CH_2CH_2OH
9 R = $(CH_2)_3N$O
10 R = NH_2

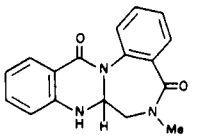
Further modifications of this basic structure were carried out along a number of lines. Thus alkylation of **5** by triethyloxonium fluoroborate gave the imino-ether **11** which was, however, surprisingly unreactive to nucleophilic attack condensing only under forcing conditions with *n*-butylamine, in the presence of boron trifluoride etherate, to give the amidine **12**. Phenyl magnesium bromide did not react with **11** at the imino-ether bond as desired to give **13** adding instead across the 7a-8 imine bond to give **14**. The same system was also produced by reduction of the quinazolone **6** with sodium cyanoborohydride in acetic acid to give **15**.



11 R = OEt, R' = H
12 R = NHn-Bu, R' = H
13 R = Ph, R' = H
16 R = Ph, R' = NO_2



14



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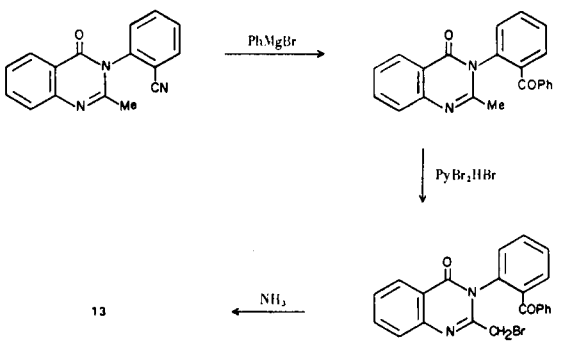
Since the quinazolone system of **13** was of particular interest because of its relationship to the sedative/hypnotic benzodiazepines two alternative routes to its synthesis were investigated. Thus, 1,3-dihydro-5-phenyl-7-nitro-2*H*-1,4-benzodiazepine-2-thione (8) was fused with anthranilic acid at 160° when cyclisation occurred to give the required nitro-substituted benzodiazepine **16**. Alternatively, the

Scheme II



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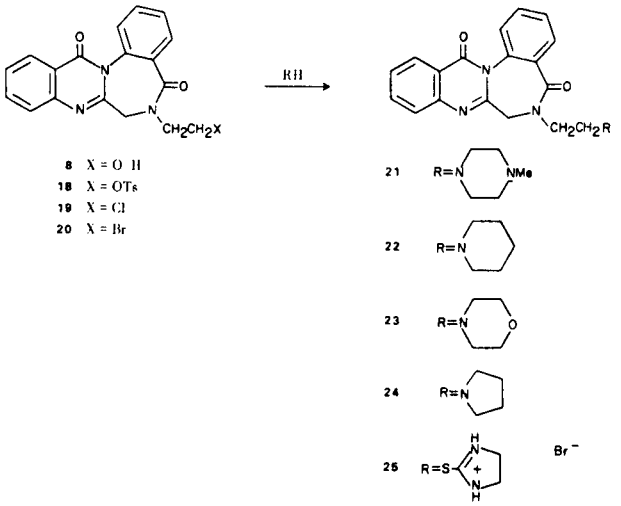
unsubstituted ring system **13** was obtained by the cyclisation with ammonia of **17**, prepared according to Scheme II.

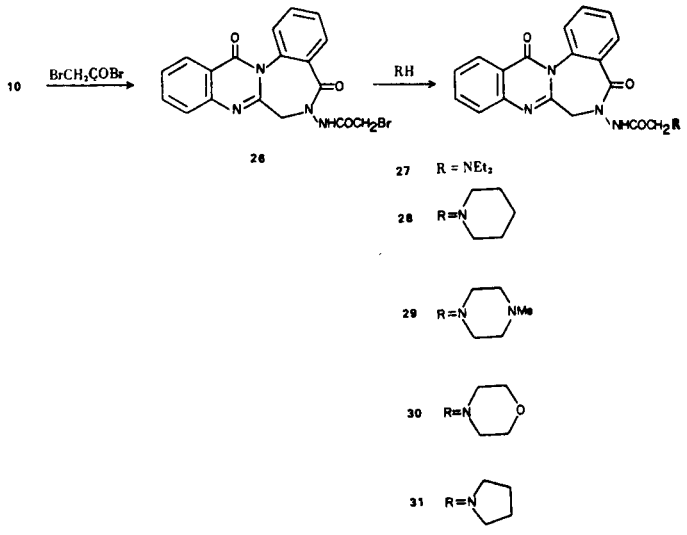
Compound **8** was the starting point for the synthesis of a further series of derivatives. It was hoped initially to prepare the tosylate **18** as the requisite reactive intermediate but, unexpectedly, **8** reacted with tosyl chloride in pyridine under the usual conditions not to give **18** but rather the chloroethyl derivative **19**. A hydrobromic acid-concentrated sulphuric acid mixture converted **8** to the more reactive bromoethyl derivative **20**, however, which was then condensed with a number of amines and imidazolidin-2-thione to give **21-25** (Scheme III).

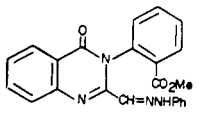
Scheme III



A third series of compounds was prepared from the amino compound **10** by its initial condensation with bromacetyl bromide to give **26** and subsequent displacement by secondary amines to give **27-31** (Scheme IV). Interestingly, an attempt to extend this series into the *N*-phenyl substituted derivatives by condensation of **3** with phenyl hydrazine failed because the product of this reaction was the phenyl hydrazone **32** and not a ring-closed compound.

Scheme IV





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A list of the 6-substituted quinazoline[3,2-*a*][1,4]-benzodiazepines prepared in this study is given in the Table.

None of these compounds showed significant CNS activity in a series of animal tests designed to discover sedative/hypnotic activity.

EXPERIMENTAL

All melting points are uncorrected and were obtained on a Kofler Hot-stage apparatus. Nmr spectra were recorded on a Perkin-Elmer R12 60m Hz instrument and shift values are recorded in τ units. Infra-red spectra were recorded as potassium bromide discs on a Pye-Unicam SP 100 spectrophotometer. Elemental analyses were performed by B.M.A.C., 41 High Street, Teddington, Middlesex, U.K.

2-Bromomethyl-3-*o*-carbomethoxyphenyl-4(3*H*)quinazolone (**3**).

Compound **4** (7) (5.0 g.) was dissolved in refluxing glacial acetic acid (50 ml.) and bromine (1.0 ml.) added dropwise over 15 minutes. After the addition was complete the solution was stirred and refluxed for 2 hours, cooled in ice and the solid thus precipitated filtered off. This was washed with ether, dried, stirred in water, filtered, dried and stirred in hot methanol (10 ml.) to remove starting material, filtered and recrystallised from acetonitrile-methanol to give **3**, 5.0 g. (78%), m.p. 200-203°; ir: ν C=O 1722, 1683 cm^{-1}; nmr (deuteriochloroform): 6.34 (3H, s, CH_3), 5.72, 6.13 (2H, q, J = 10 Hz, $-CH_2-$), 2.1-2.6 (6H, m, ArH), 1.65-1.85 (2H, m, ArH).

Anal. Calcd. for $C_{17}H_{13}BrN_2O_3$: C, 54.69; H, 3.49; N, 7.51; Br, 21.45. Found: C, 54.52; H, 3.53; N, 7.50; Br, 21.74.

6-Methylquinazolino[3,2-*a*][1,4]benzodiazepine-5,13(6*H*,13*H*)-dione (**6**).

Compound **3** (2.0 g.) was suspended in benzene (20 ml.) and treated with methylamine (6 ml., 33% solution in ethanol). After stirring at room temperature for 2 hours, water was added, the organic layer separated, dried (magnesium sulfate) evaporated and the residue crystallised from methanol to give **5**, 1.0 g. (64%); ir: ν C=O 1700, 1658; nmr (deuteriochloroform): 6.76 (3H, s, NMe), 5.46, 5.95 (2H, q, J = 15 Hz, $-CH_2-$), 1.95-2.6 (7H, m, ArH), 1.67 (1H, d, C_{12}-H).

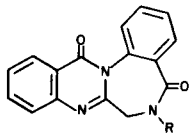
Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.98; H, 4.35; N, 14.29.

6-Aminoquinazolino[3,2-*a*][1,4]benzodiazepine-5,13(6*H*,13*H*)dione (**10**).

A solution of **3** (3.0 g.) and hydrazine hydrate (2.5 g.) in ethanol (30 ml.) and benzene (30 ml.) was heated at 60° for 18 hours, cooled and poured into water (100 ml.). The benzene layer was separated, the organic layer extracted with benzene and the combined organic layers washed with water, dried (magnesium sulfate) and evaporated to give a gum crystallisation of which, from methanol, gave **10**, 0.93 g. (39%), m.p. 220-223°; ir: ν NH 3320, ν C=O 1685, 1660 cm^{-1}; nmr (deuteriochloroform): 5.44 (2H, s, $-CH_2$), 5.17 (2H, s, NH_2 lost with deuterium oxide), 2.0-

Table

6-Substituted Quinazolino[3,2-*a*][1,4]benzodiazepines[



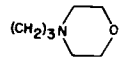
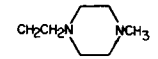
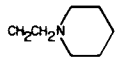
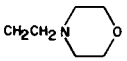
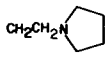
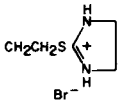
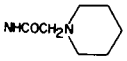
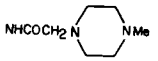
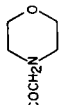
Compound No.	R	M.p.	Crystallisation Solvent	Analysis Expected C	H	N	Found C	H	N
5	H	312-315°	Acetic Acid	69.31	4.00	15.15	69.70	3.82	15.03
6	Me	182-184°	Methanol	70.09	4.50	14.42	69.98	4.35	14.29
7	Et	175-177°	Methanol	70.81	4.95	13.76	70.74	5.04	13.91
8	CH_2CH_2OH	190-193°	Methanol	67.28	4.71	13.08	66.92	4.82	12.86
9		77-82°	Methanol-water	68.30	5.98	13.85	68.28	6.03	13.92
10	NH_2	220-223°	Methanol	65.75	4.14	19.17	65.41	4.36	19.03
19	CH_2CH_2Cl	205-207°	Benzene-methanol	63.63	4.15	12.37	63.89	4.08	12.53
20	CH_2CH_2Br	181-184°	Methanol	56.20	3.65	10.94	55.91	3.85	11.39
21		195-197°	Benzene-ether	68.47	6.25	17.36	68.54	6.35	17.31
22		144-146°	Benzene-petrol	71.11	6.23	14.42	71.28	6.36	14.48
23		175-178°	Benzene-petrol	67.68	5.68	14.35	67.65	5.78	14.18
24		140-142°	Benzene-petrol	70.57	5.92	14.96	70.85	6.08	15.06
25		195-198°	Methanol-ether	50.00	4.39	13.88 (+ 1*M* H_2O)	50.16	4.37	13.89
26	$NHCOCH_2Br$	248-250°	Methanol	52.32	3.17	19.34	52.31	3.26	19.13
27	$NHCOCH_2NEt_2$	150-152°	Methanol-ether	65.17	5.72	17.27	65.37	5.73	17.23
28		254-256°	Methanol-ether	65.10	5.81	16.15 (+ 0.5*M* MeOH)	65.46	6.17	15.91
29		130-132°	Benzene-petrol	61.32	5.81	18.65 (+ 1*M* H_2O)	60.98	5.48	18.48

Table (continued)

Compound No.	R	M.p.	Crystallisation Solvent	Analysis					
				Expected			Found		
				C	H	N	C	H	N
30		240-242°	Methanol-ether	63.00	5.05	16.70	62.89	5.25	16.63
31		222-224°	Benzene-ether	65.50	5.25	17.36	65.60	5.56	17.37

2.6 (7H, m, ArH), 1.70 (1H, d, J = 8 Hz, C_{12}-H).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.41; H, 4.36; N, 19.03.

5-Ethoxyquinazolino[3,2-*a*][1,4]benzodiazepin-13(13*H*)one (**11**).

Compound **5** (6.0 g.) was suspended in 1,2-dichloroethane (200 ml.) and heated to 60°. Triethyloxonium fluoroborate (10 g.) was added and after 10 minutes stirring and refluxing, most of the solid dissolved. On further refluxing a new precipitate appeared and after 4 hours, a fresh batch of triethyl oxonium fluoroborate (5 g.) was added. After a further 3 hours, the solution was cooled, poured into saturated sodium bicarbonate (500 ml.), the organic layer separated and the aqueous layer extracted with chloroform. The combined organic layers were washed, dried (magnesium sulfate), and evaporated to give an oil which crystallised from cold methanol to give **11**, 3.55 g. (53%), m.p. 130-133°; ir: ν C=O 1698, ν C=N 1640 cm^{-1}; nmr (deuteriochloroform): 8.65 (3H, t, J = 7 Hz, CH_3), 5.70 (2H, q, J = 7 Hz, $-OCH_2$), 5.32, 5.98 (2H, q, J = 13 Hz, ring CH_2), 2.1-2.6 (7H, m, ArH), 1.69 (1H, m, C_{12}-H).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.87; H, 5.11; N, 13.69.

5-(*n*-Butylamino)quinazolino[3,2-*a*][1,4]benzodiazepin-13(13*H*)-one (**12**).

A solution of **11**, *n*-butylamine (5.0 ml.) and boron trifluoride etherate (1.0 ml.) in toluene (50 ml.) was refluxed for 48 hours, cooled, washed with water and the aqueous layer extracted with chloroform. The combined organic layers were dried (magnesium sulfate), evaporated and the residue crystallised from methanol to give **12**, 1.7 g. (52%), m.p. 204-205°; ir: ν NH 3370, ν C=O 1678 cm^{-1}; nmr (deuteriochloroform): 9.10 (3H, t, CH_3), 8.2-8.8 (4H, m, $-CH_2CH_2-$), 6.68 (2H, m, NH-CH_2), 5.43, 6.05 (2H, q, J = 12 Hz, CH_2 (ring)), 5.4 (1H, broad, lost with deuterium oxide, NH), 2.2-2.7 (7H, m, ArH), 1.73 (1H, d, J = 7 Hz, C_{12}-H).

Anal. Calcd. for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.03; N, 16.85. Found: C, 72.04; H, 6.21; N, 17.04.

5-Phenylquinazolino[3,2-*a*][1,4]benzodiazepin-13(13*H*)one (**13**).

(a) 2-Methyl-3-*o*-cyanophenyl-4(3*H*)quinazolone.

Phosphorus trichloride (2.0 ml.) in toluene (10 ml.) was added dropwise to a solution of anthranilonitrile (5.0 g.) and *N*-acetylanthranilic acid (7.5 g.) in toluene (65 ml.) stirred at 80°. After stirring and refluxing for 4 hours, the solution was cooled, poured into saturated sodium carbonate solution (100 ml.), the organic layer separated and the aqueous layer extracted with chloroform. The combined organic layers were washed with water, dried (magnesium sulfate) and evaporated to give an oil which crystallised from methanol to give 2-methyl-3-*o*-cyanophenyl-4(3*H*)quinazolone, 3.9 g. (35%), m.p. 165-166°; ir: ν C≡N 2235, ν C=O 1700 cm^{-1}; nmr (deuteriochloroform): 7.78 (3H, s, 2-CH_3), 2.1-2.8 (7H, m, ArH), 1.71 (1H, d, J = 7 Hz, C_5-H).

(b) 2-Methyl-3-(*o*-benzoyl) phenyl-4 (3*H*)quinazolone.

Phenyl magnesium bromide [30 ml. of an ether solution from bromobenzene (4.7 g.) and magnesium (0.72 g.) in ether (45 ml.)] was added to the above compound (3.5 g.) in benzene (130 ml.). The solution was stirred and refluxed for 1 hour, cooled, hydrochloric acid (30 ml.) added and the mixture stirred and refluxed for a further 2 hours. After cooling, the organic layer was separated, washed with water, dried (magnesium sulfate) and evaporated to give a gum which crystallised from methanol to give 2-methyl-3-(*o*-benzoyl)phenyl-4(3*H*)quinazolone, 1.5 g. (33%), m.p. 210-217°; ir: ν C=O 1695, 1660 cm^{-1}; nmr (deuteriochloroform): 7.64 (3H, s, 2-CH_3), 1.8-2.8 (13H, m, ArH).

(c) 2-Bromomethyl-3-(*o*-benzoyl)phenyl-4(3*H*)quinazolone.

Pyridinium hydrobromide perbromide (6.0 g.) was added in portions over 20 minutes to a stirred solution of the above compound (6.0 g.) and sodium acetate (5.0 g.) in dioxane (170 ml.) at 95-100°. When the addition was complete, heating was continued for 10 minutes, the solution was cooled and poured into water (1 l.) to give a precipitate of 2-bromomethyl-3-(*o*-benzoyl)phenyl-4(3*H*)quinazolone, 6.2 g. (83%), m.p. 186-195° which, after washing with water and methanol, was shown by tlc and nmr to be largely the required compound and was used in the next stage without further purification; ir: ν C=O 1700, 1655 cm^{-1}; nmr (deuteriochloroform): 5.54, 5.95 (2H, q, J = 10.65 Hz, $-CH_2-$), 1.8-2.7 (13H, m, ArH).

(d) Compound **13**.

Ammonia was bubbled over 3 hours into a stirred solution of the above compound (6.2 g.) in methanol (100 ml.) and benzene (100 ml.) at 60°. The solution was cooled, poured into water (200 ml.), the benzene layer separated and the aqueous layer extracted with benzene. The combined extracts were washed with water, dried (magnesium sulfate) and evaporated to give a gum which gave **13** on crystallisation from methanol-benzene, 1.3 g. (26%), m.p. 228-229°; ir: ν C=O 1692, ν C=N 1615 cm^{-1}; nmr (deuteriochloroform): 4.88, 5.82 (2H, q, J = 12 Hz, $-CH_2$), 2.1-2.7 (12H, m, ArH), 1.74 (1H, d, J = 8 Hz, C_{12}-H).

Anal. Calcd. for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.45. Found: C, 78.26; H, 4.55; N, 12.50.

5-Ethoxy-8-hydro-7a-phenylquinazolino[3,2-*a*][1,4]benzodiazepin-13(13*H*)one (**14**).

Phenyl magnesium bromide [4.0 ml. of a solution from 1.56 g. of bromobenzene and 0.24 g. of magnesium in ether (30 ml.)] was added to **11** (200 mg.) in dry toluene (10 ml.) and the solution heated at 100° for 15 hours. A further batch of the Grignard (4.0 ml.) was added, heating continued for 2 hours, the solution was cooled and 2*N* hydrochloric acid added until the precipitate dissolved. The mixture was re-basified with sodium bicarbonate solution, the organic layer separated and the aqueous layer extracted with toluene. The combined organic layers were washed with water, dried (magnesium sulfate) and evaporated to give a gum crystallisation of which, from methanol, gave **14**, 80 mg. (31%), m.p. 225-228°; ir: ν NH 3300, ν C=O 1660 cm^{-1}; nmr (deuteriochloroform-D_6DMSO): 8.64 (3H, t, J = 7 Hz, CH_3), 6.10, 6.80 (2H, q, J = 12 Hz, $-CH_2-N$), 5.64 (2H, q, J = 7 Hz), 2.2-3.5 (13H, m, ArH), 1.97 (1H, m, ArH).

Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 74.95; H, 5.67; N, 10.86.

3-Nitro-5-phenylquinazolino[3,2-*a*][1,4]benzodiazepin-13(13*H*)-one (**16**).

An intimate mixture of 7-nitro-5-phenyl[1,4]benzodiazepine-2-thione (8) (3.0 g.) and anthranilic acid (9.0 g.) was heated at 160° for 30 minutes, cooled, digested with hot methanol (20 ml.), cooled and filtered. The solid was recrystallised from chloroform-methanol to give **16**, 1.0 g. (27%), m.p. 290-293°; ir: ν C=O 1700 cm^{-1}; nmr (TFA): 4.47, 5.23 (2H, q, J = 15 Hz, $-CH_2$), 2.3-2.7 (8H, m, ArH), 1.8-2.2 (3H, m, C_1,C_4, C_{12}-H), 1.50 (1H, dd, J = 7 Hz, 2 Hz, C_2-H).

Anal. Calcd. for $C_{22}H_{14}N_4O_3 \cdot 0.5MH_2O$: C, 67.51; H, 3.86; N, 14.32. Found: C, 67.57; H, 3.71; N, 14.36.

6-(2-Chloroethyl)quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-(6*H*,13*H*)dione (**19**).

p-Toluenesulphonyl chloride (5.0 g.) was added to a solution of **7** (4.8 g.) in dry pyridine (30 ml.), the solution heated to 60° for 30 minutes, cooled, poured into water and the gum extracted with chloroform. The organic layer was washed with water, dried (magnesium sulfate), evaporated and the residue recrystallised from methanol to give **19**, 2.3 g. (45%), m.p. 203-207°; ir: ν C=O 1690, 1650 cm^{-1}; nmr (deuteriochloroform): 5.8-6.3 (4H, m, $-CH_2CH_2-$), 5.40, 5.78 (2H, q, J = 15 Hz, ring CH_2), 2.0-2.6 (7H, m, ArH), 1.69 (1H, d, J = 7 Hz, C_{12}-H).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C, 63.63; H, 4.15; N, 12.37. Found: C, 63.81; H, 4.08; N, 12.53.

6-(2-Bromoethyl)quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-(6*H*,13*H*)dione (**20**).

Concentrated sulphuric acid (5.0 ml.) was added dropwise over 5 minutes to a stirred solution of compound **7** (2.7 g.) in 40% hydrobromic acid (30 ml.), and the solution was heated to 100° for 1 hour. The cooled mixture was poured into saturated sodium bicarbonate solution (100 ml.), the mixture extracted with chloroform (2 x 100 ml.) and the organic extract washed successively with sodium bicarbonate and water, dried (magnesium sulfate) and evaporated to give a solid which was recrystallised from methanol-benzene to give **20**, 2.5 g. (77%), m.p. 181-184°; ir: ν C=O 1690, 1650 cm^{-1}; nmr (deuteriochloroform): 5,8-6.5 (4H, m, $(CH_2)_2$), 5.38, 5.75 (2H, q, J = 15 Hz, CH_2 of ring), 2.0-2.6 (7H, m, ArH), 1.64 (1H, d, J = 7 Hz, C_{12}-H).

Anal. Calcd. for $C_{18}H_{14}BrN_3O_2$: C, 56.20; H, 3.65; N, 10.94. Found: C, 55.91; H, 3.85; N, 11.39.

6-[2-(*N*-Methylpiperazino)ethyl]quinazolino[3,2-*a*][1,4]benzodiazepine-5,13(6*H*,13*H*)dione (**21**).

A solution of **20** (1.0 g.) and *N*-methylpiperazine (1.0 ml.) in dry benzene (15 ml.) was stirred at 60° for 18 hours, cooled, washed with water, dried (magnesium sulfate) and evaporated to give an oil which on crystallisation from benzene-ether gave **21**, 770 mg. (73%), m.p. 195-197°; ir: ν C=O 1690, 1662 cm^{-1}; nmr (deuteriochloroform): 7.92 (3H, s, NCH_3), 7.0-8.0 (10H, m, $-CH_2N$ + piperazino ring protons), 5.9-6.6 (2H, m, $-CH_2NCO$), 5.49, 5.83 (2H, q, J = 15 Hz, ring CH_2), 2.0-2.6 (7H, m, ArH), 1.69 (1H, d, J = 6 Hz, C_{12}-H).

Anal. Calcd. for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.54; H, 6.35; N, 17.31.

Compounds **22-24** were prepared analogously.

6-(2-[(2'-Imidazolin-2'-yl)thiol]ethyl)quinazolino[3,2-*a*][1,4]-benzodiazepine-5,13(6*H*,13*H*)dione Hydrobromide (**25**).

A solution of **18** (1.0 g.) and imidazolidine-2-thione (300 mg.) in acetonitrile (15 ml.) was heated and stirred at 80° for 4 hours, cooled to 0°, the precipitate filtered off, washed with ether and and recrystallized from methanol-ether to give **25**, 1.0 g. (79%), m.p. 195-198°. Methanol of crystallisation could be removed by heating at 60° *in vacuo* for 2 hours; ir: ν NH 3250, ν C=O 1680, ν C=N 1665, 1620 cm^{-1}; nmr (D_6DMSO): 6.2-6.5 (6H, m, CH_2S + $CH_2\overset{+}{N}$), 5.8-6.2 (2H, m, $-CH_2-NCO$), 5.54 (2H, s, ring CH_2), 2.0-2.4 (7H, m, ArH), 1.80 (1H, d, J = 6 Hz, C_{12}-H).

Anal. Calcd. for $C_{21}H_{20}BrN_5O_2S \cdot H_2O$: C, 50.00; H, 4.39; N, 13.88; S, 6.35; Br, 15.84. Found: C, 50.16; H, 4.37; N, 13.89; S, 6.45; Br, 16.18.

6-(Bromacetylamino)quinazolino[3,2-*a*][1,4]benzodiazepine-5,13-(6*H*,13*H*)dione (**26**).

Bromacetyl bromide (0.75 ml.) was added to a suspension of **10** (2.3 g.) and sodium bicarbonate (1.0 g.) in methylene chloride (50 ml.), the mixture stirred at room temperature for 3 hours, water (10 ml.) added, the organic layer separated, washed with water, dried (magnesium sulfate) and evaporated to give a gum crystallisation of which, from methanol, gave **26**, 2.5 g. (76%), m.p. 248-250°; ir: ν NH 3218, 3260, ν C=O 1720, 1665 cm^{-1}; nmr (D_6DMSO): 6.03 (2H, s, CH_2Br), 5.07, 5.87 (2H, q, J = 13 Hz, ring CH_2), 2.0-2.4 (7H, m, ArH), 1.74 (1H, d, J = 7 Hz

C_{12}-H), -1.0 (1H, s, NH lost with deuterium oxide).

Anal. Calcd. for $C_{18}H_{13}BrN_4O_3$: C, 52.33; H, 3.17; N, 13.56; Br, 19.34. Found: C, 52.31; H, 3.26; N, 13.71; Br, 19.13.

6-[(Diethylaminoacetyl)amino]quinazolino[3,2-*a*][1,4]benzodiazepine-5,13(6*H*,13*H*)dione (**27**).

A solution of **28** (1.4 g.) and diethylamine (0.6 ml.) in dry benzene (25 ml.) and methanol (5 ml.) was stirred at room temperature for 18 hours, water added, the organic layer separated and the aqueous layer extracted with benzene. The combined organic layers were washed with water, dried (magnesium sulfate), evaporated and the residue recrystallised from ether-methanol to give **27**, 1.1 g. (80%), m.p. 150-152°; ir: ν NH 3280, 3340, ν C=O 1715, 1690, 1683 cm^{-1}; nmr (deuteriochloroform): 8.93 (6H, t, J = 7 Hz, ethyl CH_3), 7.35 (4H, q, J = 7 Hz, ethyl CH_2), 6.80 (2H, s, $COCH_2$-), 5.11, 5.62 (2H, q, J = 15 Hz, ring CH_2), 1.9-2.5 (7H, m, ArH), 1.69 (1H, d, J = 7 Hz, C_{12}-H).

Anal. Calcd. for $C_{22}H_{23}N_5O_3$: C, 65.17; H, 5.72; N, 17.27. Found: C, 65.36; H, 5.73; N, 17.23.

Dompounds **28-31** were prepared analogously.

2-(Phenylhydrazino)methyl-3-*o*-carbomethoxyphenyl-4(3*H*)quinazolone (**32**).

A solution of **3** (0.5 g.) and phenylhydrazine (0.5 g.) in benzene (5 ml.) and ethanol (5 ml.) was heated at 60° for 20 hours, cooled, water added, the organic layer separated and the aqueous layer extracted with benzene. The combined organic extracts were washed with water, dried (magnesium sulfate), evaporated and the residue recrystallised from methanol-benzene to give **32**, 350 mg. (65%), m.p. 209-210°; ir: ν NH 3500-3400 (broad), ν C=O 1721, 1690, ν C=N 1610 cm^{-1}; nmr (deuteriochloroform): 6.34 (3H, s, CH_3), 3.68 (1H, s, =CH), 2.1-2.8 (11H, m, ArH), 1.6-1.8 (2H, m, ArH).

Anal. Calcd. for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.21; H, 4.57; N, 14.28.

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(3) A Combination of Methaqualone and Diphenydramine is marketed as Mandrax (R) by Roussel Laboratories, Ltd.

(4) See for instance the non-equivalence of the 2-methylene protons in **3** which can only arise because of restricted rotation around the *N*-(2-carbomethoxyphenyl) bond.

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