Novel Heterocycles. 5. Lactone Fused Quinazolines

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Quinazoline fused lactones were synthesized. The six-membered lactone **7** was prepared by the interaction of ethyl pyruvate with hydroxyethylanthranilamide **11**, followed by hydrolysis and cyclization using 1-methyl-2-choropyridinium iodide. The corresponding seven-membered lactone **10** was prepared by reaction of **11** with ethyl propiolate, followed by hydrolysis and cyclization as above. Quinazolines possessing functionalities capable of forming either a six- or seven-membered lactone were cyclized in xylene in the presence of sodium methoxide. Only the six-membered lactone **14** formed.

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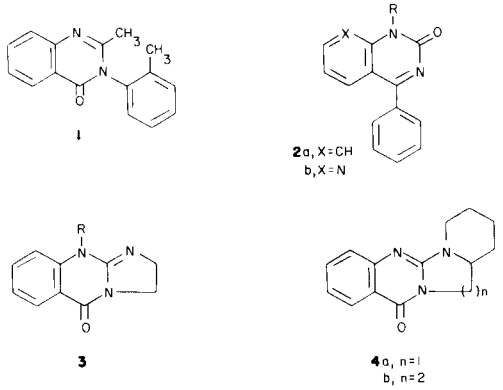
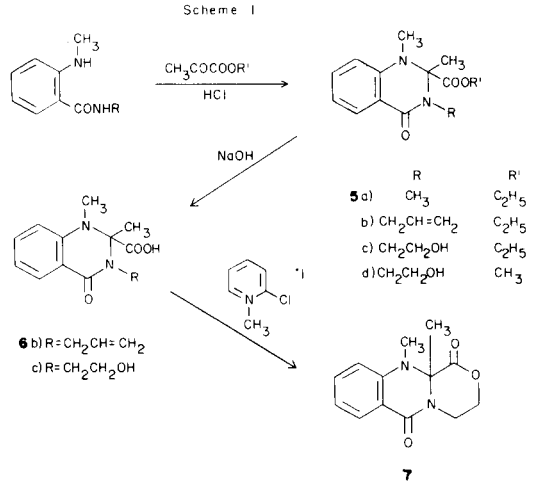
It has been demonstrated that the quinazoline nucleus is capable of exhibiting a wide variety of pharmacological activities. For example, methaqualone (**1**) (1), a sedative, resembles short acting barbiturates; 1-alkyl-4-aryl-2(1*H*)-quinazolinones and 1-alkyl-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)ones (**2a,b**) (2,3) are potent antiinflammatory agents; 2,3-dihydroimidazo[2,1-*b*]quinazolin-5-(10*H*)ones (**3**) (4) represent a new class of bronchodilators and tetracyclic quinazolinones (**4a,b**) possess CNS-depressant activities (5).



In a continuing search for compounds possessing interesting biological activity, it seemed logical that the quinazoline ring system would be a good starting substrate for such investigations.

One such project involved elaboration of this ring system by fusing on a lactone. The construction of the lactone moiety fused to a quinazoline requires that both an acid (or ester) and an alcohol functionality, or their equivalents, be present in close enough proximity to one another to allow lactonization to occur. The synthesis of 2-substituted-1,2,3,4-tetrahydroquinazolin-4-ones has been accomplished in high yields by the reaction of anthranilamides with aldehydes or ketones in the presence of an acid catalyst (6-8). The use of ethyl (or methyl) pyruvate in such a reaction would result in the introduction of a carboxylic ester into the 2-position of the quinazoline. When 2-methylamino-*N*-methylbenzamide was allowed to react with ethyl pyruvate in the presence of hydrochloric acid, the expected 1,2,3,4-tetrahydro-1,2,3-trimethyl-4-oxoquinazoline-2-carboxylic acid ethyl ester (**5a**) was isolated in essentially quantitative yield (Scheme 1). An analogous reaction with the corresponding *N*-allylbenzamide furnished **5b** in 93% yield.

Scheme I



The first requirement, the incorporation of an ester into the quinazoline ring, being satisfied left the introduction of an appropriate alcohol functionality. It has been shown that the reaction of *N*-methylisatoic anhydride with ethanolamine yields *N*-2-hydroxyethyl-2-methylaminobenzamide (9). Subsequent reaction with ethyl pyruvate or methyl pyruvate as with model compounds **5a** and **5b**, produced the desired **5c** and **5d** in 84% and 72% yield, respectively.

The second requirement having been met, lactonization could now be attempted. Refluxing the hydroxyester in xylene did not result in ring closure and the starting material was recovered. A similar reaction in xylene using a catalytic quantity of sodium methoxide was attempted and it also did not yield the lactone. Prolonged reaction time led to unidentified decomposition products.

It was then decided that hydrolysis of the ester function to an acid should enhance the possibility of lactonization.

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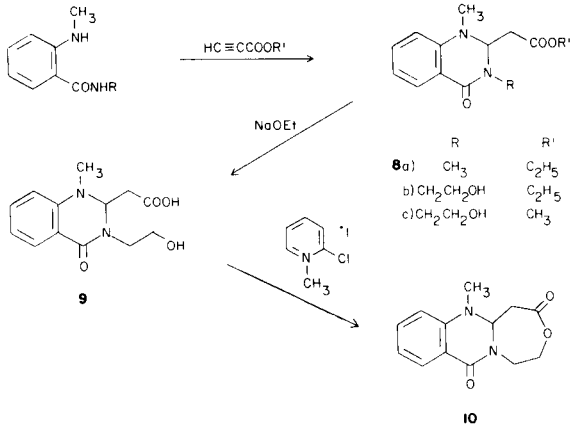
Reaction of **5b** with aqueous sodium hydroxide at room temperature resulted in the free acid **6b**, in 89% yield. In an analogous manner, **5c** was hydrolyzed to **6c** in 82% yield. Subsequent treatment of hydroxy acid **6c** with 1-methyl-2-chloropyridinium iodide in the presence of triethylamine (10) furnished the desired lactone **7** in quantitative yield.

A 6-membered lactone now in hand, it was of interest to synthesize a quinazoline fused to a 7-membered lactone ring. The possibility of an acetate group being introduced into the 2-position of the quinazoline was investigated.

Scheme 2



The treatment of 2-methylamino-*N*-methylbenzamide with ethyl propiolate, in the presence of sodium ethoxide, resulted in the formation of the 2-quinazolineacetic acid ethyl ester (**8a**) in 63% yield (Scheme 2). This cyclization occurs *via* a Michael addition of the aromatic methylamino group at the terminal end of the acetylene followed by a second Michael addition of the amide nitrogen on the resulting acrylate intermediate. When an analogous reaction was attempted using *N*-2-hydroxyethyl-2-methylaminobenzamide, **8b** was isolated in 78% yield. The use of methyl propiolate in this reaction resulted in the isolation of the corresponding methyl ester (**8c**) in 70% yield.

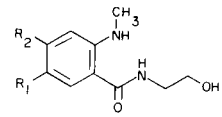
As in the previous case, attempted lactonization of **8b** in refluxing xylene resulted in no reaction. The addition of a catalytic amount of sodium methoxide did not help and only induced decomposition of **8b**. By analogy with **5a**, hydrolysis of the ester furnished the crucial intermediate hydroxy acid (**9**) required for lactonization. Treatment of **9** with *N,N'*-dicyclohexylcarbodiimide resulted in the desired lactonization but the product was severely contaminated with dicyclohexylurea. The use of 1-methyl-2-chloropyridinium iodide smoothly converted **9** to **10** in 85% yield.

Since the formation of a 6 or 7 membered ring appeared to be of equal ease, it was decided to study a system in which competitive lactonizations can occur. A search of the literature disclosed the synthesis of quinazolines bearing both carbomethoxy and acetic acid methyl ester functionalities at the 2-position resulting from the interaction of anthranilamides with dimethyl acetylene dicarboxylate (11,12). If this reaction was applied to *N*-2-hydroxyethyl-2-methylaminobenzamide, the resulting product would possess the capability of forming either a 6-membered lactone, if cyclization was to occur with the carbomethoxy, or a 7-membered lactone if cyclization occurs with the acetate group. The reaction was performed and the desired intermediate **12** was isolated in 91% yield.

The nmr spectrum of the diester (e.g. **12a**) exhibited two distinct ester OCH_3 singlets at δ 3.85 and 3.2. The dramatic upfield shift of one of the ester signals is interesting in that the corresponding methyl signals of **5d** and **8c** are observed at δ 3.65 and 3.55 respectively. Molecular models indicate that it is possible that the acetic acid methyl ester can be in a conformation which places the methyl group over the aromatic ring. Spacial geometry of this type may explain this type of shift.

Contrary to the cases of the 6- and 7-membered lactones previously discussed, refluxing **12** in xylene for four days produced a pure lactone in 45% yield. The addition of a catalytic quantity of sodium methoxide facilitated the

Table 1



No.	R_1	R_2	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	
11a	H	H	77-80	94					(9)
11b	Cl	H	129-131	74	$C_{10}H_{13}ClN_2O_2$				(a)
11c	OCH_3	OCH_3	149-151	57	$C_{12}H_{18}N_2O_4$	56.7 (56.3	7.1 6.8	11.0 10.8)	
11d	-O-CH_2-O-		98-100	68	$C_{11}H_{14}N_2O_4$	55.4 (55.7	5.9 6.2	11.8 12.2)	

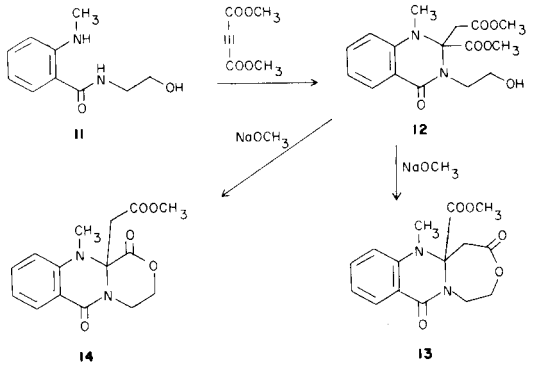
(a) Used without further purification.

reaction and a 68% yield of a pure lactone was realized after only seven hours (Scheme 3). It is interesting to note that in the preparation of **12**, prolonged reaction time resulted in the contamination of the reaction mixture with partial lactone formation.

Spectrally, as expected, the elucidation of the structure as to which lactone (either **13** or **14**) formed was very difficult. The proton nmr spectrum of the product was similar in nature to **7** and **10**. The remaining methyl ester signal was observed at δ 3.6 which is approximately at the midpoint of the methyl resonances of the starting material (e.g. **12a**) This approach did not allow a definitive assignment. Analysis of Carbon-13 nmr data (see Table 4) provided insight into the differentiation between **13** and **14**. It was noted that, in comparison to **7** and **10**, the shifts of the product resemble **7** more than they do **10**. Therefore, it was concluded that the 6-membered lactone **14** was the product.

Additional proof of structure **14** was obtained by analysis of various coupling constants in 360 MHz proton spectra. Complete results and data will be published in a separate report.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60 or EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 1 molar in deuteriodimethylsulfoxide in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25 μs, corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra 8K time-domain data points were used. All shifts reported are referenced to internal TMS, and are estimated to be accurate to ±0.05 ppm.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

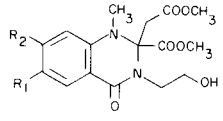
1,2,3,4-Tetrahydro-1,2,3-trimethyl-4-oxoquinazoline-2-carboxylic Acid Ethyl Ester (**5a**).

A mixture of 3.0 g. of 2-methylamino-*N*-methylbenzamide (13), 2.1 g. of ethyl pyruvate, and 2 drops concentrated hydrochloric acid in 40 ml. of ethanol was refluxed for 48 hours. An additional 3 drops of hydrochloric acid were added and the mixture refluxed for five more hours. The solvent was removed under reduced pressure and the residue chromatographed on a column of silica gel using a 1% solution of ethanol/chloroform to elute the product, 4.7 g. (99%) of **5a**, m.p. = 53-56°; ir (potassium bromide): 1735, 1660, 1605 cm^{-1}; nmr (deuteriochloroform): δ 8.0 (m, 1), 7.6-6.7 (m, 3), 4.15 (q, 2), 3.15 (s, 3), 2.95 (s, 3), 1.8 (s, 3), 1.15 (t, 3). ^{13}C nmr (deuteriochloroform): δ 14.1 (CH_3), 20.0 (CH_3), 29.4 (CH_3), 33.1 (CH_3), 62.2 (CH_2), 79.8 (C), 112.9 (CH), 117.1 (C), 119.3 (CH), 129.0 (CH), 134.0 (CH), 147.5 (C), 164.0 (CO), 171.7 (CO_2).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9; N, 10.7. Found: C, 64.1; H, 7.2; N, 10.7.

3-Allyl-1,2-dimethyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid Ethyl Ester (**5b**).

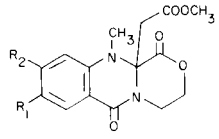
Table 2



No.	R_1	R_2	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	
12a	H	H	143-145	91	$C_{16}H_{20}N_2O_6$	57.1	6.0	8.3		
						(57.4	6.3	8.8)		(a)
12b	Cl	H	79-82	40	$C_{16}H_{19}ClN_2O_6$	51.8	5.2	7.6	9.6	
						(51.9	5.2	7.5	10.0)	
12c	OCH_3	OCH_3	149-151	60	$C_{18}H_{24}N_2O_8$	54.5	6.1	7.0		
						(54.8	6.4	6.8)		(b)
12d	-O-CH_2-O-		FOAM	50	$C_{17}H_{20}N_2O_8$					

(a) Reanalysis did not improve the value. (b) Used without further purification.

Table 3

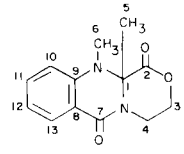


No.	R_1	R_2	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	
14a	H	H	134-136	68	$C_{15}H_{16}N_2O_5$	59.2	5.3	9.2		
						(58.8	5.3	9.1)		
14b	Cl	H	171-173	59	$C_{15}H_{15}ClN_2O_5$	53.2	4.5	8.3	10.5	
						(53.2	4.8	8.1	10.6)	
14c	OCH_3	OCH_3	181-183	55	$C_{17}H_{20}N_2O_7$	56.0	5.5	7.7		
						(55.8	5.6	7.5)		
14d	-O-CH_2-O-		182-184	83	$C_{16}H_{16}N_2O_7$	55.2	4.6	8.0		
						(54.9	5.1	7.8)		(a)

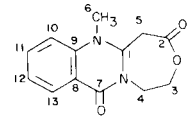
(a) Reanalysis did not improve the value.

Table 4

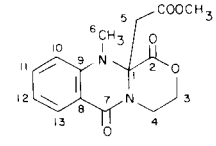
Carbon-13 Chemical Shifts for **7**, **10** and **14** (a)



7



10



14

Assignment	**7**	**10**	**14**
1	77.0	72.4	77.1
2	166.2	172.0	165.1
3	69.2	69.0	70.2
4	37.0	40.1	38.8
5	21.7	39.3	39.7
6	37.5	35.3	35.9
7	161.1	162.6	161.4
8	119.9	114.8	119.8
9	147.8	146.0	147.7
10	119.5	112.9	117.3
11	134.3	134.9	134.7
12	122.3	118.8	121.9
13	128.4	129.0	129.1
CO_2			171.0
OCH_3			52.1

(a) In ppm from TMS.

A mixture of 13.5 g. of *N*-allyl-2-methylaminobenzamide (13), 9.0 g. of ethyl pyruvate, and 15 drops of concentrated hydrochloric acid in 150 ml. of ethanol was refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a 1% solution of ethanol/chloroform to elute the product, 19 g. (93%) of **5b**. This material was used without further purification; ir (chloroform): 1740, 1640, 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.5-6.6 (m, 3), 6.3-5.6 (m, 1), 5.2 (m, 2), 4.4-3.9 (m, 2), 4.05 (q, 2), 2.9 (s, 3), 1.8 (s, 3), 1.05 (t, 3).

1,2-Dimethyl-3-(2-hydroxyethyl)-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid Ethyl Ester (**5c**).

A mixture of 5.0 g. of **11a** (9), 3.2 g. of ethyl pyruvate, and 10 drops of concentrated hydrochloric acid in 75 ml. of ethanol was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 6.3 g. (84%) of **5c**. This material was used without further purification; ir (chloroform): 1735, 1640, 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.55-6.65 (m, 3), 4.05 (q, 2), 3.75 (m, 5), 2.95 (s, 3), 1.85 (s, 3), 1.0 (t, 3).

1,2-Dimethyl-3-(2-hydroxyethyl)-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid Methyl Ester (**5d**).

A mixture of 1.5 g. of **11a** (9), 0.9 g. of methyl pyruvate, and three drops of concentrated hydrochloric acid in 20 ml. of ethanol was refluxed for 48 hours. The solvent was removed under reduced pressure and the

residue was chromatographed on a column of silica gel using ethyl acetate to elute the product, 1.55 g. (72%) of **5d**. This material was used without further purification; ir (chloroform): 3425, 1730, 1635, 1605 cm^{-1}; nmr (deuteriochloroform): δ 8.0 (m, 1), 7.65-6.7 (m, 3), 3.85 (m, 5), 3.65 (s, 3), 2.95 (s, 3), 1.9 (s, 3).

3-Allyl-1,2-dimethyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid (**6b**).

A mixture of 19.0 g. of **5b** and 180 ml. of 2*N* sodium hydroxide was stirred at room temperature for 24 hours. The solution was washed with methylene chloride and the aqueous phase was acidified with 2*N* hydrochloric acid. The resulting precipitate was filtered, washed with water and dried to give 14.4 g. (89%) of **6b**. An analytical sample was crystallized from methanol/ethyl acetate, m.p. = 172-176° dec.; ir (potassium bromide): 1740, 1610 cm^{-1}; nmr (DMSO-d_6): δ 11.0-8.2 (s, broad, 1, COOH), 7.65 (m, 1), 7.4 (m, 1), 6.85 (m, 2), 6.3-5.6 (m, 1), 5.15 (m, 2), 4.8-3.7 (m, 2), 2.95 (s, 3), 1.8 (s, 3).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8. Found: C, 64.4; H, 6.2; N, 10.5.

1,2-Dimethyl-3-(2-hydroxyethyl)-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid (**6c**).

A mixture of 3.8 g. of **5c** and 50.0 ml. of 1.0 *N* sodium hydroxide was stirred at room temperature for 24 hours. Exactly 50.0 ml. of 1.0 *N* hydrochloric acid was added and the solution was concentrated to one-third volume. The resulting precipitate was filtered, washed with water, and dried to give 2.8 g. (82%) of **6c**. An analytical sample was crystallized from methanol/ethyl acetate, m.p. = 146-149°; ir (potassium bromide): 3540, 3230, 1720, 1620 cm^{-1}; nmr (DMSO-d_6): δ 7.7-7.2 (m, 2), 6.8 (m, 2), 7.1-5-0 (broad peak, 2, COOH and OH), 3.5 (s, 4), 2.9 (s, 3), 1.8 (s, 3).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C,59.1; H, 6.1; N, 10.6. Found:C, 60.4; H, 6.3; N, 10.5. Reanalysis of carbon did not improve the value.

3,4-Dihydro-11,11a-dimethyl[1,4]oxazine[3,4-*b*]quinazoline-1,6(11*H*,-11a*H*)dione (**7**).

To refluxing solution of 2.1 g. of 1-methyl-2-chloropyridinium iodide (10) in 200 ml. of acetonitrile was added a solution of 0.5 g. of **6c** and 1.6 g. of triethylamine in 100 ml. of acetonitrile dropwise over a period of 5 hours. After addition the mixture was refluxed an additional 30 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 0.47 g. (100%) of **7**. An analytical sample was crystallized from ether/pentane, m.p. = 105-108°; ir (chloroform): 1745, 1650 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (m, 1), 7.7-7.0 (m, 3), 5.0-4.5 (m, 3), 3.65-3.0 (m, 1), 2.9 (s, 3), 1.65 (s, 3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.0; H, 5.7; N, 11.1.

1,3-Dimethyl-4-oxo-2-quinazolineacetic Acid Ethyl Ester (**8a**).

A mixture of 3.0 g. of 2-methylamino-*N*-methyl benzamide (13) and 1.9 g. of ethyl propiolate in 50 ml. of ethanol was refluxed for 18 hours. After allowing to cool to room temperature, 100 mg. of sodium ethoxide was added and the mixture was refluxed for one hour. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a 2% solution of ethanol/chloroform to elute the product. Distillation on a Kugelrohr apparatus at 0.2 mm furnished 3.0 g. (63%) of **8a**; ir (chloroform): 1730, 1650, 1615 cm^{-1}; nmr (deuteriochloroform): δ 7.95 (m, 1), 7.4 (m, 1), 7.0-6.5 (m, 2), 5.0 (t, 1), 4.1 (q, 2), 3.1 (s, 3), 2.95 (s, 3), 2.65 (d, 2), 1.25 (t, 3); ^{13}C nmr (deuteriochloroform): δ 14.1 (CH_3), 33.3 (CH_3), 35.8 (CH_2), 36.9 (CH_3), 61.3 (CH_2), 75.7 (CH), 113.4 (CH), 114.7 (C), 119.1 (CH), 128.9 (CH), 134.0 (CH), 146.5 (C), 163.0 (CO), 170.8 (CO_2).

3-(2-Hydroxyethyl)-1-methyl-4-oxo-2-quinazolineacetic Acid Ethyl Ester (**8b**).

A mixture of 6.0 g. of **11a** and 3.0 g. of ethyl propiolate in 100 ml. of ethanol was refluxed for 4 days. After allowing to cool to room temperature, 100 mg. of sodium ethoxide was added and the mixture was refluxed for one hour. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a 2% solution of methanol/chloroform to elute the product, 7.0 g. (78%) of **8b**. This material was used without further purification; ir (chloroform): 3400, 1735, 1645, 1615 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.4 (m, 1), 7.0-6.5 (m, 2), 5.15 (t, 1), 4.05 (q, 2), 3.9-3.2 (m, 5), 2.95 (s, 3), 2.65 (d, 2), 1.2 (t, 3).

3-(2-Hydroxyethyl)-1-methyl-4-oxo-2-quinazolineacetic Acid Methyl Ester (**8c**).

This reaction, using methyl propiolate, was performed similar to the one described for the preparation of **8b** and the product **8c** was isolated in 70% yield. An analytical sample was crystallized from ether/pentane, m.p. = 69-72°; ir (chloroform): 3400, 1730, 1630, 1605 cm^{-1}; nmr (deuteriochloroform): δ 7.85 (m, 1), 7.6-6.5 (m, 3), 5.1 (t, 1), 4.1-3.1 (m, 5), 3.55 (s, 3), 2.95 (s, 3), 2.65 (d, 2).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.4; H, 6.5; N, 10.1. Found: C, 60.8; H, 6.8; N, 10.0.

3-(2-Hydroxyethyl)-1-methyl-4-oxo-2-quinazolineacetic Acid (**9**).

To a solution, resulting from the reaction of 0.3 g. of sodium with 30 ml. of ethanol, was added a solution of 3.3 g. of **8b** in 35 ml. of ethanol and the mixture was refluxed for one hour. The reaction mixture was concentrated to 20 ml. and the resulting precipitate was filtered, washed with ethanol, and dissolved in 25 ml. of water. The solution was acidified with 2*N* hydrochloric acid and the mixture was extracted into ethyl acetate. After drying over sodium sulfate, the solvent was removed under reduced pressure to give 1.5 g. (50%) of **9**, m.p. = 142-144°; ir (Nujol): 3450, 1695, 1620 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 7.9 (m, 1), 7.7-6.6 (m, 3), 5.25 (t, 1), 4.3-3.15 (m, 3), 3.05 (s, 4), 2.7 (d, 2). The acid and hydroxy protons are not observed as any discernible signals.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.1; H, 6.1; N, 10.6. Found: C, 59.2; H, 6.5; N, 10.4.

6-Methyl-1,2,5,5a-tetrahydro-4*H*[1,4]oxazepino[5,4-*b*]quinazoline-4,11(6*H*)-one (**10**).

To a refluxing solution of 2.1 g. of 1-methyl-2-chloropyridinium iodide (10) in 200 ml. of acetonitrile was added a solution of 0.5 g. of **9** and 1.6 g. of triethylamine in 125 ml. of acetonitrile dropwise over a period of 6 hours. After addition, the mixture was refluxed an additional 30 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a solution of 1% methanol/chloroform to elute the product, 0.4 g. (85%) of **10**. An analytical sample was crystallized from methylene chloride/ether, m.p. = 207-209°; ir (chloroform): 1740, 1655, 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.8 (m, 1), 7.45 (m, 1), 6.8 (m, 2), 5.4 (m, 1), 4.9-4.3 (m, 3), 3.65-2.7 (m, 3), 2.9 (s, 3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.7; H, 6.0; N, 11.1.

Preparation of **11a-d**. General Procedure:

A mixture of 0.1 mole of the appropriate isatoic anhydride (14) and 0.11 mole of ethanolamine in 250 ml. of dioxane was stirred at 60° for 1.5 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a solution of 5% methanol/chloroform to elute the product. These products were usually crystallized from methylene chloride/ether. The results are summarized in Table 1.

Preparation of **12a-d**. General Procedure:

A mixture of 0.06 mole of **11a-d** and 0.06 mole of dimethyl acetylenedicarboxylate in 150 ml. of methanol was refluxed for 3 hours. The mixture was allowed to cool to room temperature and 0.3 g. of sodium methoxide was added then the mixture was refluxed for one hour. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a solution of 2% methanol/chloroform to elute the product. These products were usually

crystallized from methylene chloride/ether. The results are summarized in Table 2.

Representative Spectra, *e.g.* **12a**:

This compound had the following spectral data; ir (chloroform): 3420, 1750, 1650, 1615 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.6-6.5 (m, 3), 4.25-3.4 (m, 5), 3.85 (s, 3), 3.2 (s, 3), 3.15 (s, 2), 2.85 (s, 3). ^{13}C nmr: δ 33.5 (CH_3), 37.4 (CH_2), 49.8 (CH_2), 52.0 (CH_3), 53.8 (CH_3), 61.4 (CH_2), 83.5 (C), 111.0 (CH), 113.9 (C), 118.6 (CH), 128.3 (CH), 134.5 (CH), 145.8 (C), 163.7 (CO), 169.6 (CO_2), 170.1 (CO_2).

Preparation of **14a-d**. General Procedure:

A mixture of 0.025 mole of **12a-d** and 0.2 g. of sodium methoxide in 100 ml. of xylene was refluxed for 7-10 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product. These products were usually crystallized from methylene chloride/ether. The results are summarized in Table 3.

Representative Spectra, *e.g.* **14a**:

This compound had the following spectral data; ir (chloroform): 1740, 1645 cm^{-1}; nmr (deuteriochloroform): δ 7.95 (m, 1), 7.65-6.8 (m, 3), 4.9-4.45 (m, 3), 4.15-3.4 (m, 1), 3.6 (s, 3), 3.1 (d, 2), 2.85 (s, 3).

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