The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)dione (Isatoic Anhydride). 7. Reactions with Anions of Active Methylenes to Form Quinolines

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The reaction of isatoic anhydrides with carbanions of various active methylene compounds is described. The isolation of 2-oxo or 4-oxoquinolines is possible by varying the functional groups flanking the methylene carbon.

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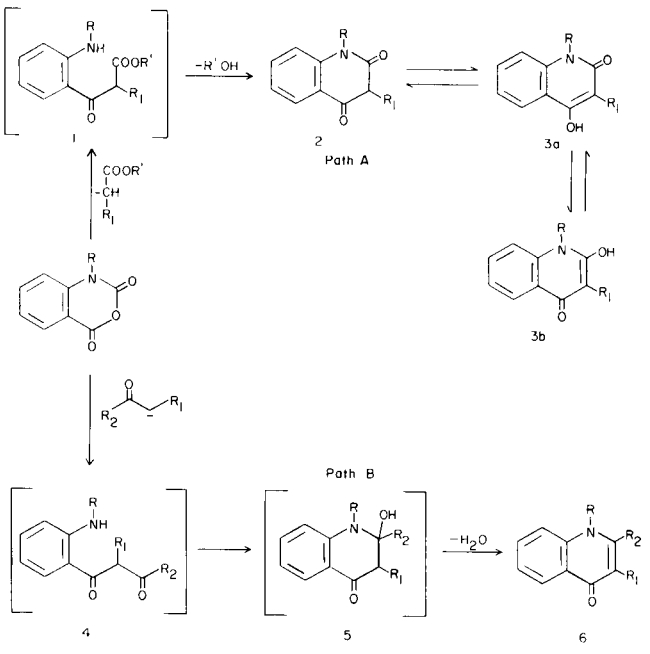
The use of 2*H*-3,1-benzoxazine-2,4(1*H*)dione (isatoic anhydride) (1) in heterocyclic synthesis has proven to be invaluable to the organic chemist. In earlier publications (2,3) we described the syntheses of a variety of complex heterocycles using substituted isatoic anhydrides as intermediates.

A particular reaction we found interesting was opening of the heterocyclic ring of isatoic anhydride by the anion of active methylene compounds such as diethylmalonate (3). The present publication will further describe this reaction and demonstrate its potential for the synthesis of a wide variety of novelly substituted quinolines.

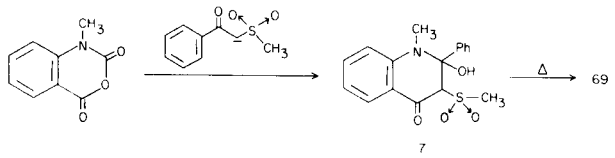
When a carboxylic acid ester was situated α to the active methylene group, the reaction proceeded along path A (Scheme I), with concomitant loss of alcohol, and afforded quinoline-2,4-diones (**2**). These compounds were found to exist in the enolized form **3a**, the enol proton generally appearing between δ 12 and 15 in the nmr.

Scheme I

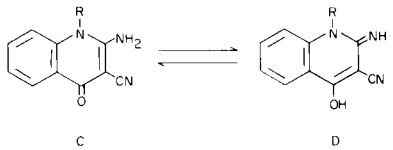


The use of a ketonic carbonyl function as one of the components of the active methylene system causes the reaction to proceed along path B and, upon loss of water, 4-oxoquinolines (**6**) were isolated.

In only one case were we able to isolate and characterize intermediates of type **5**. When *N*-methylisatoic anhydride was allowed to react with the anion of α-methylsulfonylacetophenone under normal conditions (see experimental), **7** was isolated in moderate yield. Subsequent sublimation at 200° afforded **69** in 90% yield.



Employing a nitrile functionality α to an active methylene group (e.g malononitrile) similarly produced compounds of type **6** with $R_2 = NH_2$. The double bond was assigned as predominantly endocyclic (C) rather than exocyclic (D) because the nmr spectrum exhibited two equivalent exchangeable protons, attributable to an NH_2 group, in the aromatic region and the distinct absence of a signal attributable to an enolic proton.



In certain instances in which the active methylene group was flanked by nonequivalent functional groups, each capable of reaction with the liberated amino group (intermediates **1** and **4**), two products (one of the type **3a** and one of type **6**) could be isolated from the reaction. For example, when *N*-methylisatoic anhydride was allowed to react with ethyl butyrylacetate in the presence of sodium hydride, **50** and **75** were isolated in yields of 17% and 22% respectively. When ethyl benzoylacetate was used as the active methylene component, the major products were the corresponding 1,4-dihydro-4-oxo-2-phenyl-3-quinoline-

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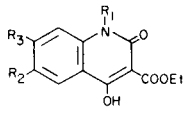
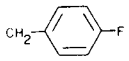
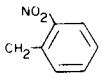
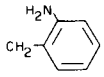
Table I



Compound No.	R_1	R_2	R_3	M.p. °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
8	CH_3	H	H	100-102	B, 67	$C_{13}H_{13}NO_4$	63.2	5.3	5.7	
							(63.2	5.6	5.4)	
9	CH_3	Cl	H	132-135	B, 53	$C_{13}H_{12}ClNO_4$	55.4	4.3	5.0	12.6
							(55.1	4.5	4.7	12.6)
10	CH_3	OCH_3	H	130-133	A, 50	$C_{14}H_{15}NO_5$	60.6	5.5	5.1	
							(60.4	5.6	5.1)	
11	CH_3	$O-CH_2-O$		212-215	A, 62	$C_{14}H_{13}NO_6$	57.7	4.5	4.8	
							(57.5	4.4	4.7)	
12	CH_3	NO_2	H	184-186	A, 52	$C_{13}H_{12}N_2O_6$	53.4	4.1	9.6	
							(53.3	4.0	9.6)	
13	CH_3	H	NO_2	196-198	A, 54	$C_{13}H_{12}N_2O_6$	53.4	4.1	9.6	
							(53.1	4.3	9.6)	
14	Et	H	H	68-71	A, 58	$C_{14}H_{15}NO_4$	64.4	5.8	5.4	
							(64.0	5.8	5.2)	
15	$(CH_2)_3CH_3$	H	H	54-55	A, 32	$C_{16}H_{19}NO_4$	66.4	6.6	4.8	
							(66.3	6.7	4.7)	
16	$(CH_2)_3CH_3$	H	Cl	125-127	A, 81	$C_{16}H_{18}ClNO_4$	59.3	5.6	4.3	10.9
							(59.2	5.4	3.9	11.3)
17	$(CH_2)_5CH_3$	H	H	64-66	A, 63	$C_{18}H_{23}NO_4$	68.1	7.3	4.4	
							(68.1	7.4	4.1)	
18	$CH_2CH=CH_2$	H	H	88-91	A, 83	$C_{15}H_{15}NO_4$	65.9	5.5	5.1	
							(65.8	5.5	5.1)	
19	$CH_2C\equiv CH$	H	H	171-174	A, 70	$C_{15}H_{13}NO_4$	66.4	4.8	5.2	
							(66.3	5.0	4.8)	
20		H	H	180-183	A, 74	$C_{18}H_{15}NO_4$	69.9	4.9	4.5	
							(70.2	5.0	4.4)	
21		H	H	136-138	A, 88	$C_{19}H_{16}FNO_4$	66.8	4.7	4.1	
							(66.9	4.7	3.9)	
22		H	H	152-155	A, 28	$C_{19}H_{16}N_2O_6$	62.0	4.4	7.6	
							(62.2	4.4	7.8)	
23		H	H	171-172	65	$C_{19}H_{18}N_2O_4$	67.4	5.9	8.3	
							(67.3	5.8	8.3)	

carboxylic acid ethylesters (compounds **59** to **64**). The corresponding 3-benzoyl-1,4-dihydro-4-hydroxy-2-oxoquinolines (compounds **52** to **55**) were isolated from the same reaction mixture in only low yields.

EXPERIMENTAL

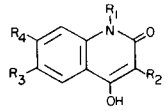
Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

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.

Procedure A. (Preparation of Compounds of Type **3a**).

To a solution of 0.05 mole of the appropriate active methylene compound in 100 ml. of dimethylacetamide was added 2.4 g. (0.05 mole) of sodium hydride (50%, pentane washed) in portions. When the evolution of hydrogen ceased, the mixture was placed in an oil bath at 120°. To this was added dropwise a solution of 0.05 mole of the appropriate isatoic anhydride in 75 ml. of dimethylacetamide over a period of 10 minutes and the mixture was stirred at 120° for 18 hours (carbon dioxide evolution occures). The solvent was removed under reduced pressure and water was added to the residue. The resulting solution was washed with methylene chloride and the aqueous phase was acidified with 6*N* hydrochloric acid. The resulting precipitate was filtered, washed well with water and was recrystallized from either ethanol or ether to furnish the product.

Table II



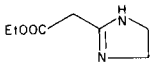
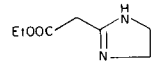
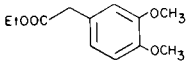
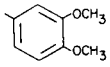
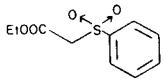
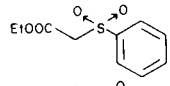
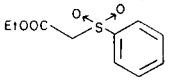
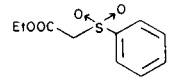
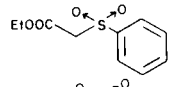
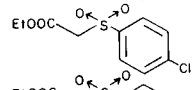
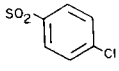
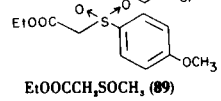
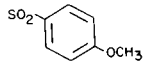
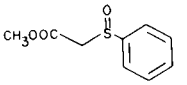
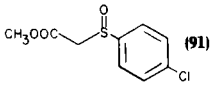
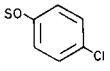
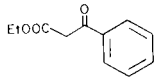
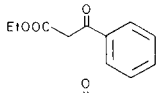
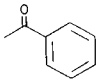
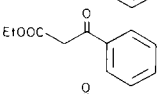
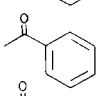
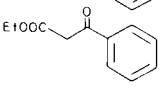
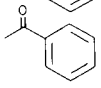
Compound No.	Active Methylene Component	R_1	R_2	R_3	R_4	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	S
24	$CH_2(COOtBu)_2$	$CH_2C{\equiv}CH$	COOtBu	H	H	168-170	A, 57	$C_{17}H_{17}NO_4$	68.2 (68.0)	5.7 5.9	4.7 4.6)		
25	$CH_3OOCCH_2CON(CH_3)_2$ (87)	CH_3	$CON(CH_3)_2$	H	H	161-163	A, 37	$C_{13}H_{14}N_2O_3$	63.4 (63.3	5.7 5.8	11.4 11.6)		
26	$EtOOCCH_2CN$	CH_3	CN	H	H	290-293	A, 36	$C_{11}H_8N_2O_2$	66.0 (65.7	4.0 4.3	14.0 14.4)		
27	$EtOOCCH_2NO_2$	CH_3	NO_2	H	H	168-169	B, 42	$C_{10}H_8N_2O_4$	54.6 (54.3	3.7 3.9	12.7 12.4)		
28	$EtOOCCH_2NO_2$	$CH_2CH{=}CH_2$	NO_2	H	H	125-127	B, 34	$C_{12}H_{10}N_2O_4$	58.5 (58.8	4.1 4.3	11.4 11.3)		
29	$EtOOCCH_2NO_2$	$CH_2C{\equiv}CH$	NO_2	Cl	H	222-225	B, 17	$C_{12}H_7ClN_2O_4$	51.7 (51.7	2.5 2.9	10.1 10.2	12.7 12.4	
30		CH_3	$NHCOCH_3$	H	H	196-199	78	$C_{12}H_{12}N_2O_3$	62.1 (61.9	5.2 5.3	12.1 11.8)		
31		CH_3		H	H	199-201	B, 13	$C_{13}H_{13}N_3O_2$	64.2 (64.2	5.4 5.4	17.3 17.3)		
32				H	H	269-271	B, 5	$C_{19}H_{17}N_3O_2$	71.5 (71.6	5.4 5.8	13.2 13.4)		
33		CH_3		H	H	252-253	A, 3.6	$C_{19}H_{17}NO_4$	69.4 (68.9	5.5 5.7	4.5 4.5)		
34	$EtOOCCH_2SO_2CH_3$ (88)	CH_3	SO_2CH_3	H	H	169-172	A, 70	$C_{11}H_{11}NO_4S$	52.2 (52.5	4.4 4.5	5.5 5.8		12.7 12.5)
35	$EtOOCCH_2SO_2CH_3$	CH_3	SO_2CH_3	O-CH_2-O		263-265	A, 33	$C_{12}H_{11}NO_6S$	48.5 (48.6	3.7 3.8	4.7 4.6		10.8 10.9)
36	$EtOOCCH_2SO_2CH_3$	$CH_2C{\equiv}CH$	SO_2CH_3	H	H	206-209	A, 50	$C_{13}H_{11}NO_4S$	56.3 (55.9	4.0 4.1	5.1 4.8		11.6 11.8)
37		CH_3		H	H	212-214	A, 67	$C_{16}H_{13}NO_4S$	60.9 (60.7	4.2 4.3	4.4 3.8		10.2 10.1) (a)
38		CH_3		Cl	H	245-246	A, 55	$C_{16}H_{12}ClNO_4S$	54.9 (54.8	3.5 3.6	4.0 3.9	10.1 10.2	9.2 9.4)
39		CH_3		OCH_3	OCH_3	285-287	A, 52	$C_{18}H_{17}NO_6S$	57.6 (57.5	4.6 4.3	3.7 3.6		8.5 8.6)
40		$CH_2CH{=}CH_2$		H	H	186-189	A, 58	$C_{16}H_{15}NO_4S$	63.3 (63.5	4.4 4.8	4.1 4.1		9.4 9.4)
41		$CH_2C{\equiv}CH$		H	H	233-236	A, 64	$C_{16}H_{13}NO_4S$	63.7 (63.8	3.9 4.1	4.1 4.1		9.4 9.4)
42		CH_3		H	H	233-234	A, 57	$C_{16}H_{12}ClNO_4S$	54.9 (54.8	3.5 3.5	4.0 4.1	10.1 10.0	9.2 8.9)
43		CH_3		H	H	203-206	A, 63	$C_{17}H_{15}NO_5S$	59.1 (59.1	4.4 4.6	4.1 3.8		9.3 9.4)
44	$EtOOCCH_2SOCH_3$ (89)	CH_3	$SOCH_3$	H	H	197-200	B, 40	$C_{11}H_{11}NO_3S$	55.7 (55.6	4.7 4.9	5.9 5.9		13.5 13.5)
45	 (90)	CH_3		H	H	180-183	B, 45	$C_{16}H_{13}NO_3S$	64.2 (64.2	4.4 4.6	4.7 5.1		10.7 10.9)
46	 (91)	CH_3		H	H	214-215	B, 55	$C_{16}H_{12}ClNO_3S$	57.4 (57.8	3.6 3.6	4.2 4.3	10.6 10.5	9.6 9.5)
47	$EtOOCCH_2COCH_3$	CH_3	$COCH_3$	H	H	143-146	B, 9	$C_{13}H_{11}NO_3$	61.4 (61.6	5.1 5.6	6.5 6.2		

Table II continued

Compound No.	Active Methylene Component	R_1	R_2	R_3	R_4	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	S
48	$EtOOCCH_2COCF_3$	CH_3	$COCF_3$	H	H	167-169	B, 13	$C_{12}H_8F_3NO_3$	53.1	3.0	5.2		
									(53.2	3.2	5.1)		
49	$EtOOCCH_2COCF_3$	Et	$COCF_3$	H	H	147-150	B, 5.5	$C_{13}H_{10}F_3NO_3$	54.7	3.5	4.9		
									(54.5	3.8	4.8)		
50	$EtOOCCH_2CO(CH_2)_2CH_3$	CH_3	$CO(CH_2)_2CH_3$	H	H	95-96	B, 17	$C_{14}H_{18}NO_3$	68.6	6.2	5.7		
									(68.2	6.3	5.6)		
51	$EtOOCCH_2COCH(CH_3)_2$	CH_3	$COCH(CH_3)_2$	H	H	94-96	B, 22	$C_{14}H_{18}NO_3$	68.6	6.2	5.7		
									(68.4	6.3	5.4)		
52		CH_3		H	H	178-180	A, 3.5	$C_{17}H_{13}NO_3$	73.1	4.7	5.0		
									(72.9	4.9	5.4)		
53		CH_3		Cl	H	200-202	B, 5.2	$C_{17}H_{12}ClNO_3$	65.1	3.9	4.5	11.3	
									(65.0	3.9	4.4	11.5)	
54		CH_3		$O-CH_2-O$		239-243	B, 5	$C_{18}H_{13}NO_5$	66.9	4.1	4.3		
									(67.4	4.0	4.3)		(a)
55		Et		H	H	101-104	B, 2.4	$C_{19}H_{15}NO_3$	73.7	5.2	4.8		
									(73.2	5.5	4.8)		(a)
56	$EtOOCCH_2PO(OEt)_2$	CH_3	$PO(OEt)_2$	H	H	63-66	A, 57	$C_{14}H_{18}NO_5P$	54.0	5.8	4.5		
									(53.9	6.0	4.2)		
57	$EtOOCCH_2PO(OEt)_2$	CH_3	$PO(OEt)_2$	Cl	H	64-67	A, 41	$C_{14}H_{17}ClNO_5P$	48.6	5.0	4.1	10.3	
									(48.4	4.9	4.3	10.4)	
58	$EtOOCCH_2PO(OEt)_2$		$PO(OEt)_2$	H	H	oil	A, 51	$C_{20}H_{22}NO_5P$					

(a) Reanalysis of the sample did not improve the values.

Procedure A (Preparation of Compounds of Type **6**).

The reaction was carried out similar to that of procedure A for the preparation of compounds of type **3a**. The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water and recrystallized from either ethanol or ether to furnish the product.

Procedure B. (Preparation of Compounds of Type **3a**).

To a solution of 0.05 mole of the appropriate active methylene compound in 100 ml. of dimethylacetamide was added 2.4 g. (0.05 mole) of sodium hydride (50%, pentane washed) in portions. When the evolution of hydrogen ceased a solution of 0.05 mole of the appropriate isatoic anhydride in 75 ml. of dimethylacetamide was added all at once. The mixture was placed in an oil bath at 60° and the temperature was raised slowly to 120° (over a period of 30 minutes) and kept there for 5 hours (carbon dioxide evolution occurs). The solvent was removed under reduced pressure and water was added to the residue. The resulting solution was washed with methylene chloride and the aqueous phase was acidified with 6*N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and was recrystallized from either ethanol or ether to furnish the product.

Procedure B (Preparation of Compounds of Type **6**).

The reaction was carried out similar to that of procedure B for the preparation of compounds of type **3a**. The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water and was recrystallized from either ethanol or ether to furnish the product.

General Procedure for Hydrolysis of Esters.

A suspension of 0.01 mole of the appropriate ester in 150 ml. of 6*N* sodium hydroxide was refluxed in 18 hours. The mixture was cooled then acidified with 6N hydrochloric acid. The resulting precipitate was filtered, washed with water and recrystallized from ethyl acetate to furnish the product.

2,3-Dihydro-2-hydroxy-1-methyl-3-methylsulfonyl-2-phenyl-4(1*H*)quinolinone (**7**).

The reaction was carried out similar to that of procedure A. The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water and was crystallized from methylene chloride/ether to yield 5.0 g. (30%) of **7**, m.p. = 178-180°; ir (chloroform): 3500, 1620, 1320, 1150 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (m, 1), 7.5 (m, 9), 3.5 (s, 3), 3.3 (s, 3), 2.1 (s, 1).

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.6; H, 5.2; N, 4.2; S, 4.7. Found: C, 61.6; H, 5.4; N, 3.9; S, 4.3.

1-(1-Aminobenzyl)-1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (**23**).

A solution of 1.0 g. of **22** in 50 ml. of acetic acid was hydrogenated in the presence of platinum oxide (0.1 g.) at one atmosphere for 10 minutes. The catalyst was filtered and the solvent was removed under reduced pressure. The resulting solid was crystallized from methlene chloride/ethyl acetate to yield 0.6 g. (65%) of **23**, m.p. = 171-172°; molecular ion at m/e 338.

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.4; H, 5.9; N, 8.3. Found: C, 67.3; H, 5.8; N, 8.3.

3-Acetylamino-1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline (**30**).

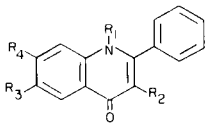
A suspension of 1.0 g. of **27** in 35 ml. of acetic acid containing 5 ml. of acetic anhydride was hydrogenated in the presence of platinum oxide (200 mg.) at 3.5 atmospheres for 1.5 hours. The catalyst was filtered and the filtrate was poured on 100 ml. of cold water. The resulting precipitate was washed with water and dried *in vacuo* to yield 0.8 g. (78%) of **30**, m.p. = 196-199°; ir (chloroform): 3320, 1645, 1620, 1590, 1520 cm^{-1}; nmr (DMSO-d_6): δ 10.8 (s, broad, 1), 9.6 (s, 1), 7.9 (m, 1), 7.5 (m, 3), 3.6 (s, 3), 2.2 (s, 3).

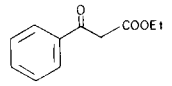
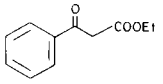
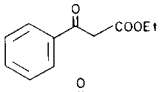
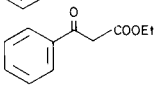
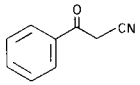
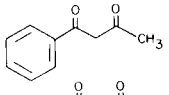
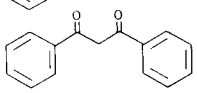
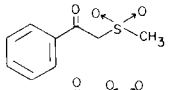
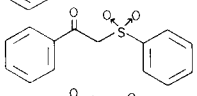
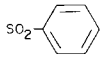
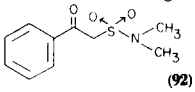
Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2; N, 12.1. Found: C, 61.9; H, 5.3; N, 11.8.

N,N-Dimethylmalonamic Acid Methylester (**87**).

Dimethylamine was bubbled through a solution of 10.0 g. of methyl

Table III



Compound No.	Active Methylene Component	R_1	R_2	R_3	R_4	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	S
59		CH_3	COOEt	H	H	167-168	B, 27	$C_{19}H_{17}NO_3$	74.2 (74.1	5.6 5.6	4.6 4.5)		
60		CH_3	COOH	H	H	222-223	80 (a)	$C_{17}H_{13}NO_3$	73.1 (72.6	4.7 4.3	5.0 4.8)		(b)
61		CH_3	COOEt	Cl	H	188-190	B, 41	$C_{19}H_{16}ClNO_3$	66.8 (66.9	4.7 5.1	4.1 4.1	10.4 10.4)	
62		CH_3	COOH	Cl	H	244-245	61 (a)	$C_{17}H_{12}ClNO_3$	65.1 (65.2	3.9 4.1	4.5 4.3	11.3 11.3)	
63		CH_3	COOEt	O-CH_2-O		221-223	B, 32	$C_{20}H_{17}NO_5$	68.4 (68.2	4.9 5.2	4.0 3.9)		
64		Et	COOEt	H	H	148-150	B, 37	$C_{20}H_{19}NO_3$	74.7 (74.5	6.0 6.2	4.4 4.3)		
65		Et	COOH	H	H	206-208	76 (a)	$C_{18}H_{15}NO_3$	73.7 (73.7	5.2 5.4	4.8 5.0)		
66		CH_3	CN	H	H	220-222	B, 65	$C_{17}H_{12}N_2O$	78.4 (78.5	4.7 4.7	10.8 10.8)		
67		CH_3		H	H	195-197	A, 17	$C_{18}H_{15}NO_2$	78.0 (77.4	5.5 5.7	5.1 5.0)		(b)
68		CH_3		H	H	216-218	A, 18	$C_{23}H_{17}NO_2$	81.4 (81.6	5.1 5.5	4.1 4.2)		
69		CH_3	SO_2CH_3	H	H	215-218	A, 30	$C_{17}H_{15}NO_3S$	65.1 (64.7	4.8 4.9	4.5 4.4		10.2 10.3)
70		CH_3		H	H	268-270	A, 36	$C_{22}H_{17}NO_3S$	70.4 (70.0	4.6 4.8	3.7 3.6		8.5 8.5)
71	 (92)	CH_3	$SO_2N(CH_3)_2$	H	H	166-168	B, 52	$C_{18}H_{18}N_2O_3S$	63.1 (63.1	5.3 5.4	8.2 8.0		9.4 9.4)

(a) See general procedure for hydrolysis of esters (Experimental). (b) Reanalysis of the sample did not improve the values.

malonyl chloride in 125 ml. of tetrahydrofuran for 15 minutes and the mixture was stirred at room temperature for an additional 30 minutes. The resulting precipitate was filtered and the filtrate was concentrated under reduced pressure to furnish 7.1 g. (60%) of **87**. An analytical sample was distilled on a Kugelrohr apparatus (5) at 0.5 mm, 49-52°: ir (chloroform): 1740, 1650 cm^{-1}; nmr (deuteriochloroform): δ 3.7 (s, 3), 3.5 (s, 2), 3.05 (s, 3), 2.95 (s, 3).

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.6; H, 7.6; N, 9.7. Found: C, 49.3; H, 7.9; N, 9.9.

Methylsulfonylacetic Acid Ethyl Ester (**88**).

To a solution of 30.0 g. of methylthioacetic acid ethyl ester (6) in 1.5 l. of methylene chloride cooled to 5° was added dropwise a solution of 88.5 g. of *m*-chloroperoxybenzoic acid in 50 ml. of methylene chloride (during the addition the temperature was kept below 10° by intermittant cooling). The resulting mixture was stirred at room temperature for 24 hours. The resulting precipitate was filtered and the filtrate was washed with 2*N* sodium carbonate. The solvent was removed under reduced pressure to yield 34.5 g. (84%) of **88**. An analytical sample was distilled on a Kugelrohr apparatus at 0.5 mm, 100-102°: ir (chloroform): 1740, 1335, 1110 cm^{-1}; nmr (deuteriochloroform): δ 4.4 (q, 2), 4.15 (s, 2), 3.25 (d, 3), 1.35 (t, 3).

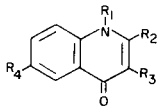
Anal. Calcd. for $C_5H_{10}O_4S$: C, 36.1; H, 6.1; S, 19.3. Found: C, 36.5; H, 6.1; S, 18.9.

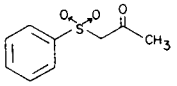
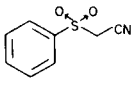
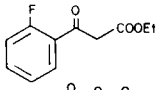
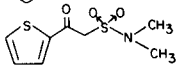
Methylsulfinylacetic Acid Ethyl Ester (**89**) (7).

To a solution of 25.0 g. of methylthioacetic acid ethyl ester (6) in 650 ml. of methanol cooled to 10° was added dropwise a solution 43.0 g. of sodium metaperiodate in 160 ml. of water over a period of 10 minutes. The mixture was then stirred at room temperature for 5 hours. The resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. Water was added to the residue and the resulting oil was extracted into methylene chloride. Evaporation of the solvent under reduced pressure yielded 19.7 g. (70%) of **89**: molecular ion at m/e 150.

(4-Chlorophenyl)sulfinylacetic Acid Methyl Ester (**91**) (7).

Table IV



Compound No.	Active Methylene Component	R_1	R_2	R_3	R_4	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl	S
72	CH_3COCH_2COOEt	CH_3	CH_3	COOEt	H	142-144	B, 43	$C_{14}H_{15}NO_3$	68.6	6.2	5.7		
									(68.3	6.5	5.6)		
73		CH_3	CH_3	COOH	H	244-247	85 (a)	$C_{12}H_{11}NO_3$	66.4	5.1	6.5		
									(66.3	5.3	6.3)		
74		CH_3	CH_3		H	232-234	A, 40	$C_{17}H_{15}NO_5S$	65.1	4.8	4.5		10.2
									(64.9	5.0	4.3		10.6)
75	$CH_3(CH_2)_3COCH_2COOEt$	CH_3	$(CH_2)_3CH_3$	COOEt	H	102-104	B, 22	$C_{16}H_{19}NO_3$	70.3	7.0	5.1		
									(70.3	7.2	5.0)		
76		CH_3	$(CH_2)_3CH_3$	COOH	H	139-142	87 (a)	$C_{14}H_{15}NO_3$	68.6	6.2	5.7		
									(68.6	6.5	5.5)		
77	$EtOOCCH_2COCOOEt$	CH_3	COOEt	COOEt	H	96-98	B, 16	$C_{16}H_{17}NO_5$	63.4	5.7	4.6		
									(63.6	5.8	4.6)		
78	$CO(CH_2COOEt)_2$	CH_3	CH_2COOEt	COOEt	H	130-133	B, 30	$C_{17}H_{19}NO_5$	64.3	6.0	4.4		
									(64.2	5.8	4.3)		
79	$NCCH_2CN$	CH_3	NH_2	CN	H	>300	A, 52	$C_{11}H_9N_3O$	66.3	4.6	21.1		
									(66.8	4.8	20.4		(b)
80	$CH_3SO_2CH_2CN$	CH_3	NH_2	SO_2CH_3	H	219-222	A, 8	$C_{11}H_{12}N_2O_3S$	52.4	4.8	11.1		12.7
									(52.1	5.1	10.8		12.8)
81		CH_3	NH_2		H	290-293	A, 52	$C_{16}H_{14}N_2O_3S$	61.1	4.5	8.9		10.2
									(61.1	4.8	8.7		9.9)
82	$(EtO)_2POCH_2CN$	CH_3	NH_2	$PO(OEt)_2$	H	193-196	B, 74	$C_{14}H_{19}N_2O_4P$	54.2	6.2	9.0		
									(53.8	6.2	9.0)		
83	$(EtO)_2POCH_2CN$	CH_3	NH_2	$PO(OEt)_2$	Cl	203-206	B, 58	$C_{14}H_{18}ClN_2O_4P$	48.8	5.3	8.1	10.3	
									(48.5	5.3	8.1	10.7)	
84	$(EtO)_2POCH_2CN$ 		NH_2	$PO(OEt)_2$	H	137-140	B, 30	$C_{20}H_{25}N_2O_4P$	62.2	6.0	7.3		
									(61.8	6.0	7.3)		
85		CH_3		COOEt	H	183-185	A, 54	$C_{19}H_{15}FN_2O_3$	61.6	4.0	7.6		
									(61.3	4.2	7.5)		
86		CH_3		$SO_2N(CH_3)_2$	H	146-148	B, 29	$C_{16}H_{16}N_2O_3S_2$	55.1	4.6	8.0		18.4
									(55.2	4.9	7.7		18.0)

(93)

(a) See general procedure for hydrolysis of esters (Experimental Section). (b) Reanalysis of the sample did not improve the values.

Using the procedure for **89**, 15.0 g. of methyl *p*-chlorophenylmercaptoacetate and 16.0 g. of sodium metaperiodate with a reaction time of 5 days yielded 14.7 g. (91%) of **91**: molecular ion at m/e 232.

1-Benzoyl-*N,N*-dimethylmethanesulfonamide (**92**).

To a solution of 9.1 g. of *N,N*-dimethylmethanesulfonamide in 100 ml. of tetrahydrofuran was added dropwise 48 ml. of 15% *n*-butyllithium in hexane, keeping the temperature of the reaction below 20°. Then a solution of 5.5 g. of ethyl benzoate in 20 ml. of tetrahydrofuran was added dropwise, keeping the temperature of the reaction below 10°. The mixture was allowed to warm to room temperature and was stirred there for 15 minutes. The solvent was removed under reduced presure and water was added to the residue. The resulting solution was acidified with 2*N* hydrochloric acid and the oil which separated was extracted into methylene chloride. Removal of the solvent under reduced pressure furnished an oil which, upon addition of ether, yielded 5.4 g. (65%) of **92**, m.p. = 78-80°: ir (chloroform): 1680, 1350, 1160 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (m, 2), 7.1 (m, 3), 4.6 (s, 2), 2.9 (s, 6).

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.8; H, 5.8; N, 6.2; S, 14.1. Found: C, 52.9; H, 6.4; N, 6.2; S, 14.3. Reapeated analysis of hydrogen did not improve the value.

N,N-Dimethyl-β-oxo-2-thienylethanesulfonamide (**93**).

Using the procedure for **92**, 10.0 g. of ethyl 2-thiophenecarboxylate and 16.0 g. of *N,N*-dimethylmethanesulfonamide, with a reaction time of 2 hours, yielded 8.4 g. (62%) of **93**, m.p. = 80-83°: ir (chloroform): 1660, 1350, 1160 cm^{-1}; nmr (deuteriochloroform): δ 7.8 (m, 2), 7.2 (m, 1), 4.5 (s, 2), 2.9 (s, 6).

Anal. Calcd. for $C_8H_{11}NO_3S_2$: C, 41.2; H, 4.8; N, 6.0; S, 27.5. Found: C, 41.3; H, 4.7; N, 6.0; S, 27.1.

REFERENCES AND NOTES

(1) Throughout this paper the names "isatoic anhydride" and "2*H*-3,1-benzoxazine-2,4(1*H*)dione" are used interchangeably. Commercial sources still prefer the first whereas Chemical Abstracts subscribes to the latter. We have adopted the Chemical Abstract numbering system for substituted isatoic anhydrides, but we feel that it will be easier to read if we use the expression "*N*-substituted isatoic anhydride" rather than "*N*-substituted-2*H*-3,1-benzoxazine-2,4(1*H*)dione".

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(3) G. M. Coppola, G. E. Hardtmann and O. R. Pfister, *J. Org. Chem.*, **41**, 825 (1976).

(4) G. Barnikow and G. Strickmann, *Chem. Ber.*, **100**, 1661 (1966).

(5) All Kugelrohr distillations were done on an Aldrich Kugelrohr distillation apparatus and the boiling points given are approximate.

(6) M. Protiva, V. Mychajlysyn, L. Novák, M. Borovička, J. O. Jílek, E. Aderová and V. Hach, *Cesk, Farm.*, **6**, 425 (1957).

(7) The material was used without further purification.