2-Amino-2-oxazolin-4-ones. I. Synthesis[1a]

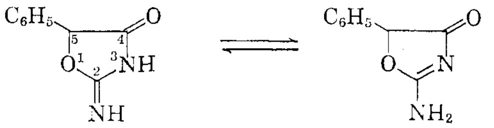
Charles F. Howell, Nicanor Q. Quinones, and Robert A. Hardy, Jr.

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

Received November 6, 1961

A series of new 5-aryl-2-dialkylamino-2-oxazolin-4-ones has been prepared by (a) condensation of mandelic acid derivatives with dialkylcyanamides, (b) aminolysis or (c) alkylation of 2-amino-5-aryl-2-oxazolin-4-ones, and (d) aminolysis of 5-aryl-2-thio-2,4-oxazolidinediones with secondary amines. Pharmacological results indicate that 2-dimethylamino-5-phenyl-2-oxazolin-4-one (II)[1b] is particularly interesting as a mild stimulant and anorexic agent.

The reported stimulant action[2,3] of 2-imino-5-phenyl-4-oxazolidinone (5-phenylpseudohydantoin, Ia)[4] on the central nervous system prompted us to prepare a number of related compounds. In the course of this investigation, a series of 5-aryl-2-disubstituted amino-2-oxazolin-4-ones, a type of compound not previously described, was synthesized. Comparison of these compounds with the unsubstituted derivative, previously formulated as Ia, indicates that tautomer Ib (2-amino-5-phenyl 2-oxazolin-4-one) is the predominant form of I and monosubstituted derivatives with alkyl or aralkyl (but not phenyl) substituents on the exocyclic nitrogen atom. These results are reported in paper II.[5] The nomenclature in both papers is consistent with our conclusions on tautomerism in this series. The present paper describes four new syntheses of 2-amino-2-oxazolin-4-ones and some of their limitations.



Ia Ib

The chemistry of 2-amino-2-oxazolin-4-ones has been adequately reviewed by Clark-Lewis.[6] Although additional work has been reported,[7,8] new preparative procedures have not been described since this review. Synthetic methods include: (1) the condensation of α-hydroxy esters with guanidine,[4,6,7a] with potassium hydrogen cyanamide,[9] or with thiourea and sodium ethoxide[8,10]; (2) aminolysis of 2-ethylthio-2-oxazolin-4-ones[11]; and (3) cyclization of intermediate α-haloacylureas (prepared by several methods) to yield either unsubstituted or 2-monosubstituted amino derivatives.[7b,12]

Condensations of α-hydroxy esters with dialkylcyanamides have not been described. However, Schubert has reported the reaction of diethylcyanamide with mercaptoacetic acid in the presence of triethylamine to yield 2-diethyl-amino-2-thiazolin-4-one.[13] Only starting materials were recovered when we attempted the analogous condensation of mandelic acid or the ethyl ester with dimethylcyanamide and triethylamine. The desired condensation was effected, however, when dimethylcyanamide was refluxed with a benzene solution of ethyl mandelate which had been treated with a catalytic amount of sodium hydride. 2-Dimethylamino-5-phenyl-2-oxazolin-4-one (II) was isolated in 60% yield. This product was identical with a sample prepared by reaction of the anion of 2-amino-5-phenyl-2-oxazolin-4-one (Ib) with dimethyl sulfate,[5] or by treatment of Ib with excess dimethylamine. The structure was proved by hydrolysis to the known 5-phenyl-2,4-oxazolidinedione (III) and dimethylamine (isolated as the *p*-toluenesulfonamide).[5] These results establish the nature of the heterocyclic ring and the position of the methyl groups in the alkylation reaction.

This condensation probably involves nucleophilic addition of the ethyl mandelate anion to dimethylcyanamide forming the pseudourea anion IV.[14]

Loss of alkoxide then gives II. Apparently the ethoxide ion then catalyses further reaction (by proton exchange with ethyl mandelate) more rapidly than it reacts with dimethylcyanamide. The condensation could also be accomplished in methanol (22% yield) even though formation of 2,3,3-trimethylpseudourea (V) is probably an important

---

[1] (a) Presented in part before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 26, 1962; (b) The generic name "thozalinone" has been proposed for this compound.

[2] L. Schmidt, *Arzneimittel-Forsch.*, **6**, 423 (1956).

[3] G. A. Lienert and W. Janke, *Arzneimittel-Forsch.*, **7**, 436 (1957); B. Knick, *Münch. Med. Wochschr.*, **102**, 2102(1960).

[4] W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913).

[5] C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1686 (1962).

[6] J. W. Clark-Lewis, *Chem. Revs.* **58**, 63 (1958).

[7] (a) H. Najer, R. Giudicelli, E. Joannic-Voisinet, and M. Joannic, *Bull. soc. chim., France*, 1226 (1961); (b) H. Najer and R. Giudicelli, *Bull. soc. chim., France*, 1231 (1961).

[8] D. T. Elmore and J. R. Ogle, *Tetrahedron*, **3**, 310 (1958).

[9] O. Mertens, *J. prakt. Chem.*, **17** [II], 1 (1878).

[10] (a) E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 280 (1908); (b) E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **42**, 319 (1909).

[11] J. S. H. Davies, W. H. Hook, and F. Long, *J. Chem. Soc.*, 36 (1950).

[12] (a) H. Asplund, *Acta Acad. Aboensis, Math. et Phys.* **11**, 14 (1939); *Chem. Zentr.* **110** [II], 3092 (1939); (*b*) *idem.*, *Acta Acad. Aboensis, Math. et Phys.* **12**, 5 (1939); *Chem. Abstr.*, **41**, 2413 (1947); (c) H. Asplund, *Finska Kemistsamfundets Medd.* **49**, 49 (1940); *Chem. Abstr.*, **35**, 2143 (1941).

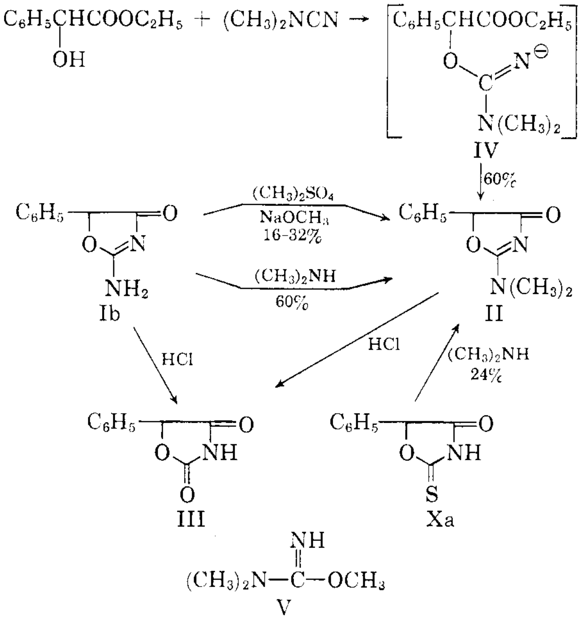
[13] H. Schubert, German Patent 930,563 (1955); *Chem. Abstr.*, **52**, 20199 (1958).

[14] The reaction of dialkylcyanamides with alkoxides to give 2,3,3-trialkylpseudoureas is well established, *Cf.*, F. H. S. Curd, D. G. Davey, and D. N. Richardson, *J. Chem. Soc.*, 1732 (1949) and R. H. McKee, *Am. Chem. J.*, **42**, 1 (1909).

TABLE I. SODIUM HYDRIDE-CATALYZED REACTIONS[a] OF DIALKYL CYANAMIDES WITH α-HYDROXY ESTERS

R¹	R²	R³	Equivalents of NaH	Reflux Period., Hr.	Yield, %	M.P.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3	CH_3	C_6H_5	0.16	1	61	132–135	$C_{11}H_{12}N_2O_2$	64.69	64.50	5.92	6.03	13.71	13.43
CH_3	CH_3	CH_3[b]	0.16	1	27	39–40	$C_6H_{10}N_2O_2$	50.69	50.40	7.09	6.84	19.71	19.42
CH_3	CH_3	o-F-C_6H_4[c]	0.2	1.5	58	175–177	$C_{11}H_{11}N_2O_2F$	59.45	59.77	4.99	5.09	12.61	12.45
CH_3	CH_3	o-EtOC_6H_4[c]	0.15	1.5	41	120–121	$C_{13}H_{16}N_2O_3$	62.89	62.92	6.50	6.54	11.29	11.21
CH_3	CH_3	2,4-DiClC_6H_3	0.2	1	55	154–155	$C_{11}H_{10}N_2O_2Cl_2$	48.37	48.49	3.70	4.02	10.26	10.36
C_2H_5	CH_3	C_6H_5[d]	0.5	1.5	30	102–103[e]							
C_2H_5	C_2H_5	C_6H_5	0.16	20	15[f]	133–135[f]	$C_{20}H_{24}N_2O_5S$	59.39	59.50	5.98	6.08	6.92	6.59
n-C_4H_9	n-C_4H_9	C_6H_5	0.16	20	8[f]	160–162[f]	$C_{24}H_{37}N_2O_5S$	62.63	62.47	7.00	7.20	6.09	6.23

[a] All reactions were conducted by the general procedure described for 2-dimethylamino-5-phenyl-2-oxazolin-4-one (II). [b] Commercial ethyl lactate (12 ml.) was dried by azeotropic distillation with benzene. The condensation product, 5.6 g. (39%), b.p. 116–120° (0.1 mm.), solidified and was recrystallized from ether. [c] Preparations of ethyl o-fluoro- and o-ethoxymandelate are described in the Experimental. [d] Ethylmethylcyanamide, prepared in 52% yield from ethylmethylamine hydrochloride by the procedure of R. H. McKee *Am. Chem. J.*, **36**, 208 (1906), boiled 72–73° (20 mm.). *Anal.* Calcd. for $C_4H_8N_2$: C, 57.11; H, 9.59; N, 33.30. Found: C, 56.99; H, 9.59; N, 32.99. [e] This product was identical with the material, m.p. 104–105°, prepared from 2-methylamino-5-phenyl-2-oxazolin-4-one and diethyl sulfate in ethanolic sodium ethoxide.[5] [f] It was found that neither 2-diethylamino- nor 2-di-n-butylamino-5-phenyl-2-oxazolin-4-one was efficiently extracted from benzene by 10% hydrochloric acid. Therefore, as much as possible of the volatile material was removed from the washed benzene solution, and the weighed residue was treated with an equivalent quantity, p-toluenesulfonic acid monohydrate. Yields, melting points, formulas, and analyses refer, therefore, to these crystalline salts which were recrystallized from acetone or acetone–ethyl acetate.



competing reaction. However, when the dimethylcyanamide and sodium methoxide were refluxed in methanol (to form the pseudourea V)[14] and the mandelic ester was then added, no cyclic product II could be isolated.

Ethyl mandelate could be replaced by mandelamide (10% yield) or *N*,*N*-dimethylmandelamide (30%) to obtain the same product. Aliphatic, substituted aromatic, and even α,α-disubstituted α-hydroxy esters gave the expected 2-dimethylamino-2-oxazolin-4-ones (Table I) in yields ranging from 27 to 61%. Progressively longer reaction times were required with ethylmethyl-diethyl- and di-*n*-butylcyanamides and the yields were decreased (Table I).

A second new and useful synthesis of 2-dialkylamino-2-oxazolin-4-ones was aminolysis[15] of the readily available 2-amino-5-phenyl-2-oxazolin-4-one (Ib) with secondary amines (Table II). Hindered amines reacted slowly and yielded less than the the 60–90% generally observed. For example, 60% of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (II) was obtained by heating Ib and dimethylamine at 125° for two hours. Under similar conditions diisopropylamine yielded 26% of the 2-dialkylamino compound and 20% of the starting material was recovered even after seventy-two hours.

With primary amines, the aminolysis was more complex. Treatment of Ib with refluxing allylamine (b.p. 56.5°) gave the normal product, 2-allylamino-5-phenyl-2-oxazolin-4-one, but refluxing aniline (b.p. 184°) yielded an abnormal, acid-stable product isomeric with the expected compound. The melting point, 204–205°, of this substance agreed with that reported[16] for 1,5-diphenylhydantoin

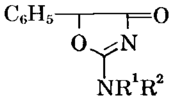
---

(15) Aminolysis of 5,5-diphenyl-2-imino-4-imidazolidinone and derivatives with amines and ammonia has been described by J. Breuer and K. Lempert, *Experientia*, **16**, 107 (1960).

(16) E. Testa and R. Ettorre, *Arch. Pharm.*, **290**, 532 (1957).

TABLE II

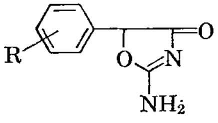
5-PHENYL-2-SUBSTITUTED AMINO-2-OXAZOLIN-4-ONES BY AMINOLYSIS OF 2-AMINO-5-PHENYL-2-OXAZOLIN-4-ONE (Ib)



Structure		Equivalents of Amine	Reaction Solvent[a] (if any)	Reflux Period, Hr.	Yield, % (Recovery,[b] %)	M.P.	Recryst. Solvent[a]	Formula	Carbon		Hydrogen		Nitrogen	
R¹	R²								Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3	CH_3	4	A	2(125°)[c]	60[d]	133–135	B							
C_2H_5	C_2H_5	4	A	2(125°)[c]	64	76–77	C + D	$C_{13}H_{16}N_2O_2$	67.22	67.02	6.94	7.14	12.01	11.81
CH_3	$C_6H_5CH_2CH_2$	2	...	0.3	60	146–148	A + E	$C_{18}H_{18}N_2O_2$	73.45	73.43	6.17	6.31	9.50	9.57
$C_6H_5CH_2$	$C_6H_5CH_2$	3	F	16	48 (8)	117–120	G	$C_{23}H_{20}N_2O_2$	77.51	77.43	5.66	5.77	7.86	7.75
$—(CH_2)_2NCH_3(CH_2)_2—$		2	...	0.5	96	144–146	A + E	$C_{14}H_{17}N_3O_2$	64.90	64.56	6.60	6.75	16.18	16.51
$—(CH_2)_5—$		2	...	0.3	64	128–129	B	$C_{14}H_{16}N_2O_2$	68.88	68.75	6.60	6.81	11.47	11.61
$—(CH_2)_2—O—(CH_2)_2—$		5	...	0.5	90	167–169	A	$C_{13}H_{14}N_2O_3$	63.40	63.47	5.74	5.96	11.38	11.70
n-C_3H_7	n-C_3H_7	3	F	24	64[b]	76–77	E	$C_{15}H_{20}N_2O_2$	69.20	69.32	7.73	7.98	10.75	10.41
i-C_3H_7	i-C_3H_7	5	F	72	26 (20)	136–138	H	$C_{15}H_{20}N_2O_2$	69.20	69.42	7.73	8.11	10.75	10.55
i-C_4H_9	i-C_4H_9	3	F	22	45 (12)	...[e]	..	$C_{17}H_{24}N_2O_2$	70.82	70.50	8.40	8.58	9.72	9.75
$C_6H_5CH_2$	H	7	...	1(100°)	71	180–181[f]	C	$C_{16}H_{14}N_2O_2$	72.20	72.01	5.31	5.71	10.52	10.73
$CH_2=CHCH_2$	H	7	...	1	37	123–124	D	$C_{12}H_{12}N_2O_2$	66.64	66.32	5.60	5.91	12.96	12.98
C_6H_5	H	11	A	100(80°)	45[b]	218–219[g]	A	$C_{15}H_{12}N_2O_2$	71.45	70.77	4.78	4.97	11.11	11.25

[a] Solvents: A = ethanol; B = ethyl acetate; C = acetone; D = water; E = petroleum ether; F = 2-methoxyethanol; G = methanol; H = ether. [b] Starting material (%) was recovered by extraction with 10% sodium hydroxide or by precipitation with ether. [c] Reaction conducted in a steel bomb at 125°. [d] This reaction used 1.75 moles of I and the infrared spectrum of the product was identical with that of a sample prepared from ethyl mandelate and dimethylcyanamide. [e] This compound was a hygroscopic liquid, b.p. 150–158° (*ca.* 10^{-5} mm.). [f] Lit.,[7b] m.p. 186°. For preparation of 1-benzyl-5-phenylhydantoin (VIIb), see Experimental. [g] Lit.,[12b] m.p. 219°. For preparation of 1,5-diphenylhydantoin see Experimental.

TABLE III. 2-AMINO-5-ARYL-2-OXAZOLIN-4-ONES FROM MANDELIC ESTERS[a] AND GUANIDINE



R	Procedure[b]	Yield,[c] %	M.P. (dec.)	Recryst. Solvent[d]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
H	1	68	254-256[e]	..									
o-F	1	37	235-237	B	$C_9H_7N_2O_2F$	55.69	55.84	3.64	3.76	14.43	14.94	9.78	9.96
o-Cl	2	57	260-263[f]	B	$C_9H_7N_2O_2Cl$	51.32	51.03	3.35	3.61	13.30	13.29	16.83	16.59
o-Br	[b]	15	262-264	B	$C_9H_7N_2O_2Br$	42.38	42.53	2.77	3.05	10.99	10.95	31.33	30.99
m-Cl	1	69	260-261	A	$C_9H_7N_2O_2Cl$	51.32	51.32	3.35	3.47	13.30	13.47	16.83	16.70
p-Cl	2	24	268-269[g]	B	$C_9H_7N_2O_2Cl$	51.32	51.34	3.35	3.62	13.30	13.62	16.83	16.45
p-Br	1	71	261-262	A	$C_9H_7N_2O_2Br$	42.38	42.22	2.77	3.10	10.99	11.03	31.33	31.20
2,4-DiCl	1	24	256-257	A	$C_9H_6N_2O_2Cl_2$	44.11	44.08	2.47	2.57	11.43	11.73	28.93	29.07
p-CH_3	1	16	252-254	B	$C_{10}H_{10}N_2O_2$	63.19	62.28	5.31	5.43	14.73	14.65	...	...
o-OCH_3	1	15	240-242[h]	B	$C_{10}H_{10}N_2O_3$	58.20	57.67	4.88	5.12	13.62	13.95	...	...
o-OC_2H_5	2	27	240-242	B	$C_{11}H_{12}N_2O_3$	60.00	59.37	5.49	5.56	12.71	13.05	...	...
H,5-CH_3[i]	1	17	206-207[i]	...[i]	$C_{10}H_{10}N_2O_3$	63.19	62.85	5.31	5.55	14.73	14.45	...	...

[a] Mandelic esters were prepared by literature procedures and had properties in agreementwith the reported values. Preparations of ethyl o-fluoro- and o-ethoxymandelate are described in the Experimental. [b] See Experimental. [c] Yields of crude product melting within 5° of purified product. [d] A = ethanol; B = dimethylformamide–water. [e] Lit.,[4] m.p. 256°. [f] Lit.,[7a] m.p. 273°. (Maquenne block). [g] Lit.,[7a] m.p. 301°. [h] Lit.,[7a] m.p. 253°. [i] 2-Amino-5-methyl-5-phenyl-2-oxazolin-4-one, recrystallized from water, also melted at 215–216° when heated slowly (1°/min.).

(VIIa). This structure was confirmed by comparison with a sample of VIIa prepared by treatment of α-chlorophenylacetylurea with aniline.[12b] Subsequently it was found that the normal product VIa could be obtained from Ib and aniline by prolonged refluxing in ethanol. The properties of VIa agreed with those reported by Aspelund[12b] and 5-phenyl-2,4-oxazolidinedione (III) was obtained upon hydrolysis. Benzylamine, b.p. 184°, yielded similar products (VIb and VIIb) under comparable conditions but formation of the hydantoin was slower, requiring *ca.* two hours of refluxing instead of one hour as with aniline. 1,3-Disubstituted ureas VIII, corresponding to the amines used, were also isolated from the high temperature reaction mixtures.

It would appear that VIa and VIb might undergo intramolecular rearrangement to the hydantoins VII at these high temperatures.[17] However, VIa was recovered unchanged when a sample was heated at 180–190° for one hour. A probable course for the reaction involves nucleophilic attack by the primary amine at C-5 to give an intermediate like IX which can either cyclize to yield VII or undergo aminolysis to the ureas VIII. Isolation of these ureas in which the carbonyl oxygen atom is probably derived from the oxygen atom of the oxazole ring favors this interpretation. A similar intermediate IX (R = C_6H_5, R′ = H) is probably involved in the preparation of VIIa from α-phenylchloroacetylurea and aniline.[12b] Also when VIa was refluxed with excess benzylamine, VIIb and VIIIb were formed; conversely VIb yielded the phenyl derivatives VIIa and VIIIa with aniline. Reactions of amines with oxazole derivatives to yield imidazoles have been observed previously[18] but are little understood.

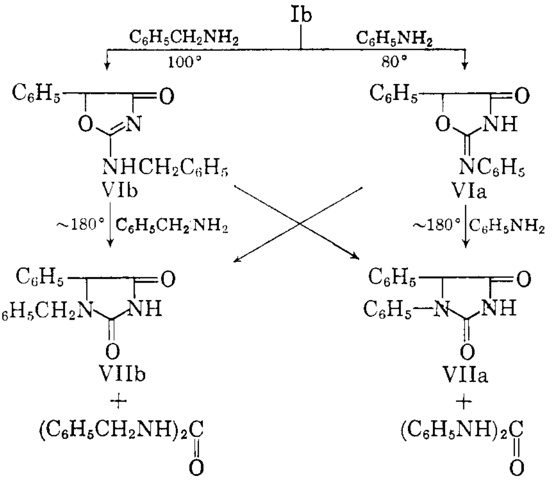
Most reported 2-amino-2-oxazolin-4-ones have been prepared by the action of guanidine on α-hydroxy esters,[4] including the compounds of Najer[7a] who was also interested in the stimulant properties of this series. Seven new 5-aryl derivatives (Table III) were obtained by this method in yields ranging from 15 to 71%. The alternative condensation of ethyl mandelate with thiourea and sodium ethoxide[10,12a] gave a smaller amount (43% *vs.* 68%) and poorer quality of Ib than the guanidine procedure. Extraneous infrared bands at 5.7 and 8.7 μ indicated the probable presence of 5-phenyl-2-thio-2,4-oxazolidinedione (Xa)[19] in the crude product. Elimination of ammonia (to yield Xa) as well as hydrogen sulfide (to yield Ib) is possible in this reaction as noted by Elmore and Ogle.[8]

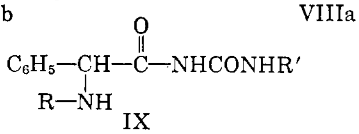
---

(17) Such a process might be analogous to the Chapman rearrangement of imidates to amides. *Cf.*, R. Roger and D. G. Neilson, *Chem. Revs.*, **61**, 179 (1961).

(18) For a review see J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, 1957, pp. 330 and 401.

(19) N. K. Ushenko and T. E. Gorizdra, *Ukrain. Khim. Zhur.*, **16**, 552 (1950); *Chem. Abstr.*, **48**, 11391 (1954).

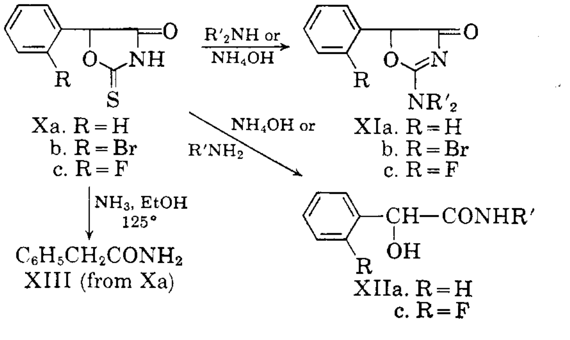




$C_6H_5-CH(NHR)-C(=O)-NHCONHR'$

IX

Aminolysis of 5-aryl-2-thio-2,4-oxazolidinediones (X)[11,19] was another method for preparing 2-amino-5-aryl-2-oxazolin-4-ones and is analogous to the ammonolysis of 2-ethylthio-5,5-dimethyl-2-oxazolin-4-one.[11] However, this route was useful only under carefully selected conditions. Treatment of Xa with dimethylamine or morpholine produced the expected derivatives XIa. Compound XIa (R′ = CH_3) was identical with other samples of II, but this method offered no advantages over the three previous syntheses. Ammonium hydroxide reacted with Xa and the *o*-bromo derivative Xb to give modest amounts of XIa (R′ = H) and XIb (R′ = H), respectively. The *o*-fluoro derivative Xc gave *o*-fluoromandelamide (XIIc, R′ = H, 83%) under these conditions, probably because the more soluble 2-amino-5-(*o*-fluorophenyl)-2-oxazolin-4-one (XIc, R′ = H) did not precipitate from the solution but reacted further with ammonia. Similarly, Xa and aqueous methylamine yielded *N*-methylmandelamide (XIIa, R′ = CH_3, 78%).[12b] Another type of side reaction was encountered when Xa was treated with ethanolic ammonia at 125°. Instead of XIa or XIIa (R′ = H), phenylacetamide (XIII, 20%) and sulfur (65%) were isolated. These products may have resulted from reduction of initially formed I by ammonium sulfide at the benzylic 5-position.



Pharmacological testing of this series[20] indicates that II is a particularly interesting mild stimulant and anorexic agent with properties different from the amphetamines. This compound has been selected for clinical trial in man. Several 2-dialkylamino-5-phenyl-2-oxazolin-4-ones (including II), 2-methylamino-5-phenyl-2-oxazolin-4-one[7b,12b] and the *o*-chloro and *o*-fluoro derivatives of I show better properties than I. The other modifications reported in our work have either diminished stimulant activity or none at all. For example, 2-dimethylamino-5-methyl-5-phenyl-2-oxazolin-4-one is a depressant rather than a stimulant.

Experimental

2-Dimethylamino-5-phenyl-2-oxazolin-4-one (II) (General Procedure of Table I).—A mixture of 0.37 g. (8.2 mmoles) of 54% sodium hydride in mineral oil[21] and 9 g. (0.05 mole) of ethyl mandelate in 25 ml. of benzene was warmed until evolution of hydrogen was complete. The solution was treated with 3.5 g. (0.05 mole) of dimethylcyanamide and heated under reflux for 1 hr. The solution was washed with 25 ml. of water, and the product was extracted into 25 ml. of 10% hydrochloric acid and precipitated by the addition of solid potassium carbonate. 2-Dimethylamino-5-phenyl-2-oxazolin-4-one [II, 6.2 g. (61%)] was obtained which had the properties listed in Table I and was identical with a sample prepared from 2-amino-5-phenyl-2-oxazolin-4-one (Ib) and dimethylamine (Table II).

Reactions of other α-hydroxy esters and dialkylcyanamides are described in Table I. Ethyl mandelate could be replaced by mandelamide and *N*,*N*-dimethylmandelamide when 2 equiv. of dimethylcyanamide were employed in the reaction to yield 10 and 22% of II, respectively. When methanol instead of benzene was used as a solvent, the yield of II was lower (22%). However, when methanolic sodium methoxide and dimethylcyanamide were heated under reflux for 1.5 hr. before adding the ethyl mandelate, only methyl mandelate, 5.5 g. (60%), m.p. 38–40°, was found. No effort was made to isolate 2,3,3-trimethylpseudourea (V) which may also have been present. A more detailed study of conditions affecting the reaction of mandelic esters with dimethylcyanamide will be published.[22] Preliminary indications are that use of more than about 0.2 equiv. of sodium hydride or reflux periods longer than 3 hr. are deleterious.

2-Dimethylamino-5-phenyl-2-oxazolin-4-one (II) yielded an acid sulfate salt, m.p. 175–178°, with concd. sulfuric acid in ethanol.

Anal. Calcd. for $C_{11}H_{14}N_2O_6S$: C, 43.70; H, 4.47; N, 9.27; S, 10.61. Found: C, 43.44; H, 5.00; N, 9.13; S, 10.88.

Compound II was hydrolyzed to 5-phenyl-2,4-oxazolidinedione (III)[4] by 10% hydrochloric acid.[5] It did not yield salts with anhydrous weak organic acids and did not react with methyl iodide in refluxing methanol (16 hr.).

2-Dimethylamino-5-methyl-5-phenyl-2-oxazolin-4-one.—A solution of 25 g. of ethyl atrolactate[23] in 100 ml. of benzene was added to a suspension of 2 g. of 50% sodium hydride–mineral oil dispersion in 50 ml. of benzene. The solution was treated with 13 g. of dimethylcyanamide and

---

[20] Pharmacological screening and evaluation studies were carried out by A. C. Osterberg, E. N. Greenblatt, *et al.*, of the Experimental Therapeutics Research Section of these laboratories. Details will be reported elsewhere.

[21] Supplied by Metal Hydrides Corp., 12–24 Congress, Beverly, Mass.

[22] C. F. Howell, S. Peluso, and H. G. Arlt, Jr., to be published.

[23] K. Freudenberg, J. Todd, and R. Seidler, *Ann.*, **501**, 199 (1933).

heated under reflux overnight. The reaction mixture was washed with 30 ml. of water, dried over sodium sulfate, and concentrated. Recrystallization of the residue from 200 ml. of 50% ether–petroleum ether afforded 14 g. (49%) of 2-dimethylamino-5-methyl-5-phenyl-2-oxazolin-4-one, m.p. 63–66°. Two more recrystallizations gave analytically pure material, m.p. 68–69°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.04; H, 6.47; N, 12.85. Found: C, 66.23; H, 6.32; N, 12.66.

Ethyl *o*-Fluoromandelate.—*o*-Fluoromandelic acid, prepared by the method of Hager and Starkey,[24] as very soluble in water and the yield of acid, m.p. 115–116.4° (lit.,[24] m.p. 116.5°), was increased from 6 to 90% by saturation of an aqueous solution with sodium chloride before continuous extraction with ether. Treatment of 13.6 g. of the acid with ethanol and a trace of *p*-toluenesulfonic acid[25] gave 11.5 g. (72%) of ethyl *o*-fluoromandelate, b.p. 71–72° (0.2 mm.), n^{29}D 1.4938.

Anal. Calcd. for $C_{10}H_{11}O_3F$: C, 60.60; H, 5.60; F, 9.59. Found: C, 60.64; H, 5.93; F, 9.70.

Ethyl *o*-ethoxymandelate, prepared similarly from *o*-ethoxybenzaldehyde, boiled at 135–137° (3 mm.) and was not characterized further.

2-Dialkylamino-5-phenyl-2-oxazolin-4-ones by Aminolysis (Table II).—A mixture of 3.5–8 g. (0.02–0.05 mole) of 2-amino-5-phenyl-2-oxazolin-4-one (I) and an excess of the required amine was heated to reflux (or in a steel bomb with volatile amines) as indicated in Table II. When no ammonia was evolved and the starting material did not dissolve, ethanol or 2-methoxyethanol was added to the refluxing solution. When no more ammonia was evolved the excess amine was removed by distillation under reduced pressure and the products described in Table II were obtained.

5-Phenyl-2-piperidino-2-oxazolidin-4-one.—A mixture of 2 g. of 2-allylamino-5-phenyl-2-oxazolin-4-one and 4 g. of piperidine was heated on a steam bath for 30 min. Volatile material was removed by distillation under reduced pressure and the residue was recrystallized once from ethyl acetate. The crude product [1.2 g. (53%) m.p. 112–114°] was not quite pure but had an infrared spectrum essentially identical with that of 5-phenyl-2-piperidino-2-oxazolin-4-one (Table II, m.p. 128–129°) and clearly distinguishable from that of the starting material.

Reactions of Primary Amines with Ib, VIa, and VIb at 180°. A. Reactions of Aniline with: (1) 2-Amino-5-phenyl-2-oxazolin-4-one (Ib).—A mixture of 3.5 g. of Ib and 10 ml. of purified aniline[26] was heated under reflux for 1.5 hr. The cooled mixture was added to 75 ml. of cold ether and filtered after 2 hr. The resulting solid (2.75 g.) was stirred with 100 ml. of 1 *M* potassium carbonate until no more material appeared to dissolve and then filtered. The insoluble fraction, (0.60 g., 14%, m.p. 228–238°) was identified as crude 1,3-diphenylurea (carbanilide (VIIIa), lit.,[27] m.p. 235°) by the infrared spectrum. Acidification of the potassium carbonate solution yielded 2.0 g. (38%) of 1,5-diphenylhydantoin (VIIa), m.p. 205–206°, (lit.,[16] m.p. 204–206°) with an infrared spectrum identical with a sample, m.p. 196–198°, prepared by the method of Aspelund[12b] from α-chlorophenylacetylurea and aniline. A sample of 1,5-diphenylhydantoin (2.0 g.) was heated on a steam bath with 20 ml. of 3 *N* hydrochloric acid for 2 hr. Filtration yielded 1.5 g. (75%) of unchanged 1,5-diphenylhydantoin, m.p 195–198°.

(2) **5-Phenyl-2-phenylimino-4-oxazolidinone (VIa).**—A mixture of 2.0 g. of VIa (Table II) and 5 ml. of aniline was heated under reflux for 2 hr., cooled and diluted with 50 ml. of petroleum ether. The resulting solid was stirred with 200 ml. of 10% sodium carbonate for 0.5 hr., filtered from an insoluble residue, and isolated by acidification with concd. hydrochloric acid. The precipitate was treated with 20 ml. of boiling acetone and filtered. The filtrate, diluted with 30 ml. of petroleum ether yielded 0.6 g. (30%) of crude recovered starting material (VIa), m.p. 206–209°. Concentration of the filtrate to 10 ml. gave 0.5 g. (25%) of 1,5-diphenylhydantoin (VIIa), m.p. 191–194°, identified by comparison of its infrared spectrum with that of an authentic sample.

A 50-mg. sample of 5-phenyl-2-phenylimino-4-oxazolidinone (VIa, m.p. 219–220°) was kept at 180–190° for 1 hr. with only slight discoloration. The recovered starting material melted at 216–217° and the infrared spectrum was unchanged.

(3) **2-Benzylamino-5-phenyl-2-oxazolin-4-one (VIb).**—A mixture of 2.5 g. of VIb (Table III) and 5 g. of aniline was heated under reflux for 2 hr., cooled, and diluted with 150 ml. of ether. The solution was washed with 10% hydrochloric acid and with water, and dried over calcium chloride. Concentration to 25 ml. yielded 1.0 g. (40%) of 1,5-diphenylhydantoin (VIIa, m.p. 200–203°), identified by its infrared spectrum.

B. Reactions of Benzylamine with: (1) 2-Amino-5-phenyl-2-oxazolin-4-one (Ib).—A mixture of 7 g. of Ib and 20 g. of benzylamine was heated to boiling during 0.5 hr. and refluxed for 2 hr. The solution was cooled, diluted with 250 ml. of ether, and filtered to remove 3.0 g. (31%) of 1,3-dibenzylurea, m.p. 165–168° (lit.,[28] m.p. 167–169°). The filtrate was extracted with 100 ml. of 10% sodium hydroxide. Acidification of the lower layer with 10% hydrochloric acid yielded 0.75 g. (7%) of 1-benzyl-5-phenylhydantoin [VIIb, m.p. 210–212° (uncorr.)]. Sublimation at 170° (0.1 mm.) gave a pure sample, m.p. 222–224° (corr.).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.95; H, 5.54; N, 10.64.

A sample of VIIb (0.10 g.) was recovered (90%) unchanged after heating with 5 ml. of 10% hydrochloric acid at 95–100° for 15 min. The infrared spectrum was similar to but not identical with that of 1,5-diphenylhydantoin (VIIa).

(2) **2-Benzylamino-5-phenyl-2-oxazolin-4-one (VIb).**—Refluxing 3.0 g. of VIb with 6 g. of benzylamine for 1.8 hr. gave 1.25 g. (46%) of 1,3-dibenzylurea, m.p. 160–164°, and 0.11 g. (4%) of 1-benzyl-5-phenylhydantoin, m.p. 210–212° (uncorr.) which were isolated as above and identified by their infrared spectra.

(3) **5-Phenyl-2-phenylimino-4-oxazolidinone(VIa).**—Similarly, a mixture prepared by refluxing 2.0 g. of VIa and 4 g. of benzylamine yielded 0.6 g. (30%) of 1,3-dibenzylurea, m.p. 168–170°, and 0.4 g. (20%) of VIIb, m.p. 210–212° (uncorr.).

5-Aryl-2-amino-2-oxazolin-4-ones (Table III): Procedure 1.—A solution of 0.02 mole of the substituted ethyl mandelate in 10 ml. of absolute ethanol was heated and stirred under reflux for 2 hr. with 10 ml. of 2.05 *M* ethanolic guanidine prepared from guanidine hydrochloride and sodium ethoxide. Evolution of ammonia was observed during the early part of the reaction and had ceased by the end of 2 hr.[4] The products are described in Table III.

In the cases of 5-(*o*-fluorophenyl)- and 5-(2,4-dichlorophenyl)-2-amino-2-oxazolin-4-one, by-products containing excess nitrogen were encountered. The crude products were best purified by suspending them in 1 equiv. of *N* sodium hydroxide and filtering to remove the impurities. Acidification of the filtrate with an equal volume of 2 *N* acetic acid then yielded the desired product in a nearly pure condition.

Procedure 2.—Guanidine hydrochloride (9.55 g.) and 5.6 g. of potassium hydroxide pellets were mixed in 100–200 ml. of absolute ethanol. The substituted ethyl mandelate (0.1 mole) was added and the mixture was heated under reflux for 1 hr. The mixture was diluted with 3–4 vol. of water and cooled. Filtration gave 15–57% of the 5-aryl-2-amino-2-oxazolin-4-ones reported in Table III.

---

(24) G. P. Hager and E. B. Starkey, *J. Am. Pharm. Assoc.*, **32**, 44 (1943).

(25) S. L. Shapiro, I. M. Rose, F. C. Testa, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5646 (1959).

(26) A. V. Few and J. W. Smith, *J. Chem. Soc.*, 753 (1949).

(27) T. L. Davis and K. C. Blanchard, *Org. Syntheses*, Coll. Vol. I, 453 (1941).

(28) O. C. Dermer and J. King, *J. Org. Chem.*, **8**, 168 (1943).

2-Amino-5-phenyl-2-oxazolin-4-one (Ib) from Ethyl Mandelate and Thiourea.—To a solution of sodium ethoxide prepared from 2.3 g. of sodium in 50 ml. of absolute ethanol was added 7.6 g. of thiourea followed by 18.0 g. of ethyl mandelate in 50 ml. of ethanol.[10] The solution was refluxed for 1 hr. and concentrated to dryness. The residue was dissolved in 50 ml. of water and acidified with 50 ml. of 2 *N* acetic acid (hydrogen sulfide evolution). The mixture was cooled overnight and filtered to give 10.5 g. of crude product, m.p. 225–230° dec., which had extraneous absorption bands at 5.72 and 8.7 μ in the infrared. [These bands are strong in the spectrum of 5-phenyl-2-thio-2,4-oxazolidinedione (Xa)]. The crude material was recrystallized from aqueous dimethylformamide to give 7.7 g. (43%) of 2-amino-5-phenyl-2-oxazolin-4-one (Ib) which was identical with that prepared from guanidine and ethyl mandelate.

5-Aryl-2-thio-2,4-oxazolidinediones (Xa, b, c).—These compounds were prepared from the appropriate aromatic aldehydes, sodium cyanide, and potassium thiocyanate, following the procedure used for the preparation of 5-methyl-2-thio-2,4-oxazolidinedione.[11] Crude products were purified by dissolving them in 2 equiv. of 1 *M* sodium bicarbonate and precipitation with hydrochloric acid.

5-Phenyl-2-thio-2,4-oxazolidinedione (Xa, 45% yield) was recrystallized from chloroform, m.p. 144–145° (lit.,[19] m.p. 130°).

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.95; H, 3.66; N 7.25; S, 16.59. Found: C, 56.34; H, 4.03; N, 7.06; S 16.32.

5-(*o*-Bromophenyl)-2-thio-2,4-oxazolidinedione (Xb, 16% yield) was recrystallized from benzene–carbon tetrachloride, m.p. 145–146°.

Anal. Calcd. for $C_9H_6NO_2SBr$: C, 39.72; H, 2.20; S, 11.79; Br, 29.37. Found: C, 39.85; H, 2.41; S, 11.90; Br, 29.57.

5-(*o*-Fluorophenyl)-2-thio-2,4-oxazolidinedione (Xc, 34% yield) was recrystallized from benzene–carbon tetrachloride, m.p. 132–133°.

Anal. Calcd. for $C_9H_6NO_2SF$: C, 51.18; H, 2.87; S, 15.19; F, 8.99. Found: C, 51.33; H, 3.04; S, 14.80; F, 8.86.

Reactions of 5-Aryl-2-thio-2,4-oxazolidinediones (X) with Amines. A. With Secondary Amines. (1) **2-Morpholino-5-phenyl-2-oxazolin-4-one.**—A mixture of 2.4 g. of Xa and 6.4 ml. of morpholine was warmed until hydrogen sulfide evolution began. When the reaction moderated, the mixture was refluxed for 5 min. and poured on ice. The product, 2.4 g. (80%), m.p. 164–166°, was recrystallized from ethanol and had the same infrared spectrum as the sample of 2-morpholino-5-phenyl-2-oxazolin-4-one listed in Table II.

(2) **2-Dimethylamino-5-phenyl-2-oxazolin-4-one (II).**—A mixture of 3.8 g. of Xa, 1.8 g. of dimethylamine, and 20 ml. of ethanol was heated in a steel bomb at 105° for 1.5 hr. The mixture was concentrated to dryness and the residue was purified as in the preceding preparations of this compound. 2-Dimethylamino-5-phenyl-2-oxazolin-4-one, 0.98 g. (24%), m.p. 136–139°, was obtained and had the same infrared spectrum as samples listed in Tables I and II.

B. With Ammonium Hydroxide at 25°. (1) **2-Amino-5-(*o*-bromophenyl)-2-oxazolin-4-one (XIb).**—A solution of 2.7 g. of 5-(*o*-bromophenyl)-2-thio-2,4-oxazolidinedione (Xb) in 5 ml. of concd. ammonium hydroxide was stored at room temperature for 16 hr. and filtered. After 2 days a second crop was collected from the filtrate. The two crops were recrystallized from aqueous dimethylformamide to give 0.39 g. (15%) of 2-amino-5-(*o*-bromophenyl)-2-oxazolin-4-one, m.p. 259–262° dec. An analytical sample recrystallized twice from aqueous dimethylformamide was crushed and dried *in vacuo* at 100° for 4 hr.; it had the properties listed in Table III.

(2) **2-Amino-5-phenyl-2-oxazolin-4-one (Ib).**—Similarly, a solution of Xa in ammonium hydroxide slowly deposited 2-amino-5-phenyl-2-oxazolin-4-one (Ib) which was identified by its infrared spectrum.

(3) **_o_-Fluoromandelamide (XIIc).**—A solution of 12.6 g. of 5-(*o*-fluorophenyl)-2-thio-2,4-oxazolidinedione (Xc) in 30 ml. of concd. ammonium hydroxide was stored at room temperature for 4 days, but no precipitate was formed. The solution was continuously extracted with methylene chloride for 12 hr. and the solvent was removed by distillation. The residue was dissolved in cold water, filtered, and concentrated to give 8.4 g. (83%) of crude *o*-fluoromandelamide, m.p. 79–85°. A sample for analysis was sublimed, recrystallized again and resublimed, m.p. 75–76°.

Anal. Calcd. for $C_8H_8NO_2F$: C, 56.80; H, 4.77; N, 8.28; F, 11.23. Found: C, 56.93; H, 4.97; N, 8.37; F, 10.90.

C. With Aqueous Methylamine at 25°. (1) **_N_-Methylmandelamide (XIIa. R′ = CH_3).**—A mixture of 4.8 g. of Xa and 10 ml. of 40% aqueous methylamine stored at room temperature for 4 days yielded 3.2 g. (78%) of *N*-methylmandelamide, m.p. 88–95°. Recrystallization from water raised the melting point to 96–98° (lit.,[12b] m.p. 95°).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.72; N, 8.48. Found: C, 65.22; H, 6.76; N, 8.35.

D. With Ammonia at 125°.—A mixture of 4.8 g. of Xa and 1.7 g. (4 equiv.) of ammonia in 25 ml. of ethanol was heated at 125° for 2 hr. in a steel bomb. Concentration yielded a residue which was recrystallized from about 100 ml. of ethyl acetate (charcoal). A yellow product, 0.52 g. (65%), m.p. 120–134°, was removed by filtration. Recrystallization from ethanol gave pure sulfur, m.p. 122–123°, identified by the blue flame and choking odor on combustion and the virtual lack of an infrared spectrum.

The ethyl acetate–mother liquor yielded 0.66 g. (20%) of phenylacetamide (XIII), m.p. 144–152°. Recrystallization from ethyl acetate and then from water afforded a pure sample, m.p. 157–158°, undepressed upon admixture with an authentic sample which had the same infrared spectrum.

5-Phenyl-2,4-oxazolidinedione (III).—An authentic sample of 5-phenyl-2,4-oxazolidinedione prepared from 3.0 g. of 2-amino-5-phenyl-2-oxazolin-4-one by the method of Traube and Ascher[4] was recrystallized from water and sublimed, m.p. 111–112° (lit.,[4] m.p. 108°).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.00; H, 3.98; N, 7.91. Found: C, 60.92; H, 4.06; N, 7.82.

Similar hydrolysis of 2-dimethylamino- (II), 2-piperidino-, 2-benzylamino-, 2-allylamino-5-phenyl-2-oxazolin-4-one, and 5-phenyl-2-phenylimino-4-oxazolidinone gave 45–61% of III which was identified by the melting point and infrared spectrum.

Acknowledgment.—We are indebted to L. Brancone and associates for microanalyses and to Dr. A. C. Osterberg and associates for the pharmacological data. Special appreciation is due to Dr. M. G. Howell for many helpful discussions and assistance with the technical literature.