TABLE I

STARTING MATERIALS FOR, YIELDS, PHYSICAL CHARACTERISTICS, AND ANALYSES OF OXATHIOLANES

Carbonyl compound	Yield, % BF_3–Et_2O	Yield, % TsOS–PhH	Mp or bp, °C (mm)	n_D (temp, °C)	Formula	Registry no.	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found	Ref
Acylic ketones													
Diethyl ketone	82	72.5[a]	63 (17)	1.4775 (25)	$C_7H_{14}OS$	16047-97-5	57.53	57.25	9.59	9.74	21.92	22.07	
Isopropyl methyl ketone	81	64[a]	50 (1.0)	1.4762 (24)	$C_7H_{14}OS$	16047-98-6	57.53	57.37	9.59	9.77	21.92	22.05	
Diisopropyl ketone	63	57[a]	43 (0.3)	1.4850 (24)	$C_8H_{16}OS$	16047-99-7	62.04	62.12	10.41	10.53	18.30	18.47	
1-Butenyl methyl ketone	70		84–86 (19)	1.4890 (20)	$C_8H_{14}OS$	16048-00-3	60.76	60.94	8.86	8.96	20.25	20.34	
Dibenzyl ketone[b]	92	90	41–42		$C_{17}H_{18}OS$								*c*
Acetophenone[d]	83	78	85 (1.2)	1.5641 (25)	$C_{10}H_{12}OS$								*c, e*
Benzophenone	56	28.5	52–53		$C_{15}H_{14}OS$								*f*
Cyclic ketones													
Cyclopentanone	74	78[a]	35 (0.6)	1.5092 (27)	$C_7H_{12}OS$	176-38-5							*c, e*
Cyclohexanone[g]	96	92	45 (0.2)	1.5158 (25)	$C_8H_{14}OS$								*c, e*
Cycloheptanone	92		77–78 (1.2)	1.5165 (25)	$C_9H_{16}OS$	184-31-6	62.79	62.56	9.30	9.48	18.60	18.85	
3-Cholestanone[i]	74	89	129–130										*c, h*
Norcamphor[j]	94		62 (0.6)	1.5326 (21)		172-68-9	63.53	63.59	8.23	8.40	18.82	18.62	
Aldehydes													
Propanal	57	24[a]	63–64 (36)	1.4780 (27)	$C_6H_{10}OS$	16048-04-7	50.85	51.01	8.47	8.54	27.12	27.26	
Butyral[k]	88	82	61–62 (18)	1.4779 (24)	$C_6H_{12}OS$								*l*
Benzaldehyde[m]	83	80	87–88 (0.6)	1.5830 (25)	$C_9H_{10}OS$								*e, n*

[a] This work. [b] Lit. mp 42–43. [c] See ref 4. [d] Lit. bp 96° (2 mm), 98° (1.3 mm); $n^{24}D$ 1.5663, $n^{25}D$ .15640. [e] E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962). [f] See ref 6. [g] Lit. Bp 47° (0.6 mm), 106–107° (21 mm); $n^{24}D$ 1.5155, $n^{25}D$ 1.5152. [h] See ref 5. [i] Lit. mp 135–136°, 133–134°. [j] Mixture of geometric isomers. [k] Lit. bp 84° (34 mm). [l] B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963). [m] Lit. bp 98–100° (1.3 mm), 86–87° (5 mm); $n^{25}D$ 1.5850. [n] See ref 3*a*.

remained at 92%. With cyclohexanone, however, the maximum conversion can be achieved in 2 hr even with a 2:3 molar ratio of boron trifluoride. These results can be explained in terms of the relative magnitudes of the equilibrium constants for the equilibria involved.

$$H_2O + BF_3 \rightleftharpoons H_2O{\cdot}BF_3$$

$$H_2O + H_2O{\cdot}BF_3 \rightleftharpoons 2H_2O{\cdot}BF_3$$

The oxathiolanes formed were characterized by spectral and elemental analyses. The infrared spectra indicated the absence of ketone absorption, and there were present envelopes in the nmr spectra[8] at 3.8–4.1 and 2.3–2.9 ppm downfield from TMS, characteristic of methylene groups adjacent to sulfur and oxygen atoms, respectively.

Experimental Section[9]

General Method of Preparation of Oxathiolanes.—To a stirred, refluxing solution of 56.1 g (0.5 mol) of cycloheptanone and 29.1 g (0.5 mol) of 2-mercaptoethanol in 400 ml of anhydrous ether was added dropwise over a 1-hr period 71 g (0.5 mol) of boron trifluoride etherate. After an additional hour of being heated under reflux, the solution was allowed to cool, washed twice with 100 ml of 0.1 *M* sodium bicarbonate solution and once with 100 ml of saturated sodium chloride solution, and dried over magnesium sulfate. After removal of the solvent under vacuum on a rotary evaporator, the residue was distilled under vacuum to yield a small forerun which was followed by 79.2 g (92%) of 2-oxa-5-thiaspiro[4.6]undecane: bp 77–78° (1.2 mm); $n^{25}D$ 1.5165.

2,2-Diphenyl-1,3-oxathiolane.—The reaction was run as above using 72.8 g (0.4 mol) of benzophenone and 31.2 g (0.4 mol) of boron trifluoride etherate in 400 ml of anhydrous ether. The residue after removal of most of the solvent was filtered to remove the majoritiy of the crude solid oxathiolane. To the filtrate was added 50 ml of methanol, and the mixture was cooled at 0° to precipitate additional solid oxathiolane. The combined solid fractions (55 g, 56%) were recrystallized from isopropyl alcohol to give 52.8 g (54%) of 2,2-diphenyl-1,3-oxathiolane, mp 52–53° (lit.[10] mp 52°).

Registry No.—2-Mercaptoethanol, 60-24-2.

(8) A detailed analysis of the nmr spectra of 1,3-oxathiolanes is available: D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, **89**, 4368 (1967).

(9) Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrometer. Nmr spectra were recorded with a Varian Associates Model A-60 spectrometer. Vpc analyses were carried out on an Aerograph Model 1520 vapor phase chromatograph employing helium as the carrier gas and columns of either XF1150 or DC11 on 60/80 mesh Chromosorb P. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. We wish to thank Mr. H. Talts for the spectral analyses and Miss N. Essig for technical assistance.

(10) See Table I, footnote *e*.

The Preparation of 6-Aryltetrahydro-1,3-oxazin-2-ones and Their Hydrolysis to 3-Substituted Propylamines

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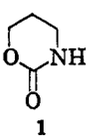
Tetrahydro-1,3-oxazin-2-one (1) has been prepared by the condensation of 3-aminopropanol with deriva-



1

tives of carbonic acid.[2] However, the generality and convenience of this synthesis for certain substituted analogs of **1** is severely limited by lack of availability of the appropriate amino alcohols. We wish to report a convenient route to 6-aryltetrahydro-1,3-oxazin-2-ones (**7**) starting from the readily available β-aroylpropionic acids (**2**). The over-all yields of tetrahydrooxazines from γ-keto acids were in the range 35–50%.

The aryl group was varied to cover a broad range of electronic characteristics. New compounds prepared by Scheme I are listed in Tables I and II.

(1) Taken in part from the undergraduate research report of H. F. E.

(2) (a) R. Delaby, R. Damiens, and G. D'Huyteza, *Compt. Rend.*, **239**, 674 (1954); (b) E. K. Dreschel, U. S. Patent 2,701,246; *Chem. Abstr.*, **50**, 2686h (1956).

TABLE I

γ-ARYL-γ-HYDROXYBUTYRYL HYDRAZIDES (4)

Aryl group	Registry no.	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	% yield
Phenyl[a]		124.5–126							75
p-Chlorophenyl	16047-73-7	161.5–162.5	52.49	52.69	5.73	5.82	12.25	12.31	74
p-Bromophenyl	16047-74-8	169–169.5	43.97	44.10	4.80	4.81	10.26	10.34	86
p-Tolyl	16047-75-9	140–141	63.44	63.36	7.75	7.69	13.45	13.38	57
p-Anisyl	16047-76-0	148–150	58.91	58.91	7.19	7.17	12.49	12.45	92
p-Nitrophenyl	16047-77-1	163–163.5	50.20	50.01	5.47	5.48	17.56	17.56	95

[a] Preparation by this method previously reported by J. M. S. See P. A. S. Smith and J. M. Sullivan, *J. Org. Chem.*, **26**, 1132 (1961).

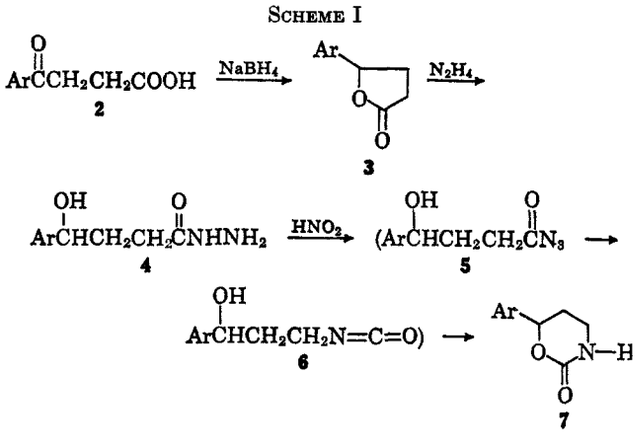
TABLE II

6-ARYLTETRAHYDRO-1,3-OXAZIN-2-ONES (7)

Aryl group	Registry no.	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	% yield
Phenyl[a]		180–181							50
p-Chlorophenyl	16047-78-2	164.5–165	61.38	61.17	5.15	5.09	7.16	7.07	41
p-Tolyl	16047-79-3	186–187	96.09	69.19	6.85	6.97	7.33	7.50	64
p-Anisyl	16047-80-6	199–200.5	63.75	63.86	6.32	6.35	6.76	6.74	45
p-Nitrophenyl	16047-81-7	201–204	54.05	54.12	4.54	4.56	12.58	12.62	39

[a] See Table I, footnote *a*.

SCHEME I



Borohydride reduction of **2** to γ-aryl-γ-butyrolactones (**3**) was efficiently accomplished as reported by Julia, Julia, and Bemont.[3] Conversion of **3** into γ-aryl-γ-hydroxybutyryl hydrazides (**4**) also proceeded smoothly in high yield.

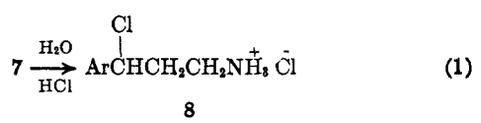
These hydrazides were found to react with nitrous acid normally and to undergo the Curtius rearrangement through the azides (**5**) and isocyanates (**6**) to produce 6-aryltetrahydro-1,3-oxazin-2-ones (**7**).

The success of these Curtius rearrangements was gratifying since the reaction of γ-hydroxyacyl hydrazides with nitrous acid has been reported in some cases to result only in reversion to the corresponding lactones.[4] Lactonization occurred through loss of hydrazine by the hydrazide or through loss of hydrazoic acid by the azide. Careful work-up of our reactions did reveal that in some cases, partial reversion to the lactone had indeed occurred, but to an extent of less than 10%.

No correlation was found between the yields of our Curtius rearrangements and the electronic nature of the aryl group. However, the presence of the γ-aryl group is apparently essential to the success of the reaction, because in those cases where complete reversion to the lactone has been reported,[4] no γ-aryl group was present. The aryl group possibly is exerting a steric effect, which interferes with lactonization owing to crowding in the vicinity of the hydroxide group.

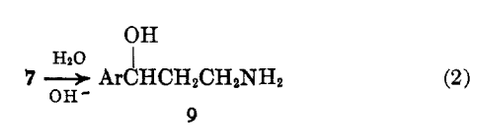
A study of the hydrolytic cleavage of 6-aryltetrahydro-1,3-oxazin-2-ones (**7**) revealed that these compounds can serve as a convenient source of 3-substituted-3-arylpropylamines.

Acidic hydrolysis with hydrochloric acid proceeded smoothly to produce 3-chloro-3-arylpropylamine hydrochlorides (**8**). Physical and analytical data for the compounds prepared by the reaction in eq 1 are listed in Table III.



(1)

Basic hydrolysis proved less satisfactory, producing the expected 3-hydroxy-3-arylpropylamines (**9**) (isolated as salts) in some cases, although failing in others. Physical and analytical data for the compounds prepared by the reaction in eq 2 are listed in Table III.



(2)

Experimental Section[5]

γ-Aryl-γ-butyrolactones (3).—γ-(*p*-Nitrophenyl)-γ-butyrolactone was prepared by the nitration of γ-phenyl-γ-butyrolactone.[6] The remaining lactones were prepared by the method of Julia, Julia, and Bemont,[3] except that sodium borohydride was substituted for potassium borohydride.

γ-Aryl-γ-hydroxybutyryl Hydrazides (4).—The appropriate lactone (0.10 mol) and 99+% hydrazine (0.10 mol) were dissolved in 200 ml of 95% ethanol and refluxed for 6 hr. The hydrazide crystallized upon cooling and was recrystallized from 95% ethanol.

6-Aryltetrahydro-1,3-oxazin-2-ones (7).—The appropriate hydrazide (0.10 mol) was dissolved in 17 ml of 6 *N* HCl and 50 ml of water. Ether (100 ml) was added and while the mixture

(3) M. Julia, S. Julia, and B. Bemont, *Bull. Soc. Chim. Fr.*, **1960**, 304.

(4) P. A. S. Smith in "Organic Reactions," Vol. 3, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p 349 ff.

(5) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are corrected and were taken on a Mel-Temp capillary melting point apparatus.

(6) S. J. Cristol and R. F. Helmreich, *J. Amer. Chem. Soc.*, **74**, 4083 (1952)

TABLE III
PRODUCTS FROM HYDROLYTIC CLEAVAGE OF 7

Aryl group	Registry no.	X	Y	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	% yield
p-Chlorophenyl	16047-82-8	Cl	Cl	251–254 dec	44.93	45.29	5.03	5.24	5.82	5.79	69
p-Tolyl	16047-83-9	Cl	Cl	234–237 dec	54.56	55.16	6.87	7.00	6.36	6.44	87
p-Nitrophenyl	16047-84-0	Cl	Cl	148–150	43.04	43.11	4.82	5.03	11.15	11.15	62
Phenyl[a]		$^1/_2C_2O_4$	OH	194–195							
p-Tolyl	16052-65-6	HC_2O_4	OH	161–162	56.46	56.34	6.71	6.82	5.48	5.41	72
p-Chlorophenyl	16047-85-1	$^1/_2C_2O_4$	OH	212–214[b]	52.29	52.14	5.27	5.36	6.10	6.07	23

[a] See Table I, footnote *a*. [b] Another form melts at 163–164°.

was stirred at 0–5°, a solution of 7.5 g (0.10 mol) of sodium nitrite in 50 ml of water was added dropwise. The ether layer was separated, washed with 5% $NaHCO_3$ and water, and dried over anhydrous magnesium sulfate. An equal volume of benzene was added and the mixture was refluxed for 12 hr. During this time, the 6-aryltetrahydrooxazin-2-one crystallized in an extremely pure condition, as evidenced by the fact that recrystallization did not raise the melting point. Evaporation of the mother liquors yielded an additional, less pure sample which could be recrystallized from benzene.

Acidic Hydrolysis of 6-Aryltetrahydro-1,3-oxazin-2-ones.—A sample of **7** was covered with concentrated HCl and allowed to stand for 12 hr at room temperature. An exception was 6-(*p*-nitrophenyl)tetrahydro-1,3-oxazin-2-one, which requires steam bath temperature. The reaction mixture was then evaporated to dryness, leaving the 3-chloro-3-arylpropylamine hydrochloride (**8**) as a crude solid which could be recrystallized from ethanol or ethanol–benzene.

Basic Hydrolysis of 6-Aryltetrahydro-1,3-oxazin-2-ones.—A solution of **7** in alcoholic KOH was prepared, using 2 ml of 6 *N* KOH in ethanol for each millimole of **7**. The reaction mixture was refluxed for 5 hr, diluted with an equal volume of water, and acidified to pH 2 with 6 *N* HCl, during which CO_2 was evolved. The solution was then extracted with ether to remove nonbasic impurities, the water layer was made basic with 6 *N* NaOH, and the liberated organic base was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate followed by removal of ether, leaving the 3-hydroxy-3-arylpropylamine (**9**) as an oil. This was isolated as the oxalate or acid oxalate by precipitating it from ethanol solution by adding a saturated solution of oxalic acid in ethanol. The salt was recrystallized from aqueous ethanol.

Acknowledgment.—The authors are grateful to Research Corporation for partial support of this project in the form of a Frederick Gardner Cottrell grant in aid.

Anisomycin. III.[1] Conformational Studies of the Pyrrolidine Ring

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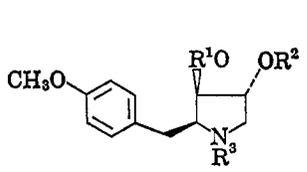
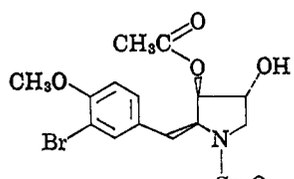
The first structural studies of anisomycin were carried out by classical chemical methods[2] and lead to the proposal of an all-*trans* relationship for the substituents on the pyrrolidine ring. However, recent X-ray crystallographic studies on N-acetylbromoanisomycin (**14**) have shown that the original stereochemical assignments were in error.[3] The correct structure for anisomycin (**1**) is shown above.





14

1, $R^1 = CH_3CO$; $R^2 = R^3 = H$
2, $R^2 = CH_3CO$; $R^1 = R^3 = H$
3, $R^1 = R^2 = R^3 = H$
4, $R^1 = CH_3CO$; $R^2 = H$; $R^3 = C_6H_5CH_2OCO-$
5, $R^1 = R^3 = CH_3CO$; $R^2 = H$
7, $R^1 = R^2 = R^3 = CH_3CO$
12, $R^1 = R^2 = H$; $R^3 = CH_3CO$
13, $R^1 = R^2 = CH_3CO$; $R^3 = H$

In the course of the initial investigation of anisomycin, attempts were made to use nuclear magnetic resonance spectra to elucidate the stereochemistry but without success. However, now that we know the stereochemistry of anisomycin, it is possible to explain some of the anomalies observed in the nmr spectra and to shed some light on the conformational properties of the pyrrolidine ring.

The proton magnetic resonance spectrum of anisomycin (**1**) in $CDCl_3$–D_2O and the assignments for chemical shifts are shown in Table I. Signals for the aromatic protons h and g indicate an A,B^2 pattern typical of a 1,4-disubstituted benzene ring, and the occurrence of a singlet at 3.78 ppm (methoxy) substantiates our previous observations that anisomycin contains a *p*-methoxyphenyl group. A single peak observed at 2.12 ppm is due to the methyl (a) of the acetate group. The benzyl methylene of anisomycin is adjacent to an asymmetric carbon atom (C-2), so that we should expect the methylene function to give rise to two separate and distinct nmr signals for the two diastereomeric methylene protons. Each signal should be split by the neighboring hydrogen atom at C-2 to produce a quartet of peaks due to the benzyl methylene, and this is observed at about 3.4 ppm, but the quartet is complicated further by splitting which is not so readily assigned. The diastereoisomerism of the benzyl methylene protons should be independent of conformation, for no matter how rapid the rate of torsion around the C–C bond, the environments of the

(1) Anisomycin. II: K. Butler, *J. Org. Chem.*, **31**, 317 (1966).
(2) J. J. Beereboom, K. Butler, F. C. Pennington, and I. A. Solomons, *J. Org. Chem.*, **30**, 2334 (1965).
(3) J. P. Shaefer and P. J. Wheatley, personal communication.