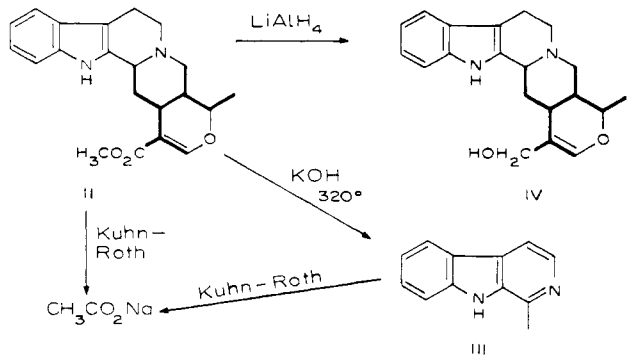
tions and degradations were carried out several times by different research workers so as to confirm the reproducibility of the results.

Scheme I



A summary of the results of the various experiments is given in Table I.

Table I. Results of Incorporation of Glycine into Ajmalicine (II)

Expt	Compd fed	% incorporation into ajmalicine	% of alkaloid specific activity in degradation products[a] CH_3CO_2Na	Harman (III)	Ajmalicinol (IV)
1	Glycine-1-^{14}C	0.0008			
2	Glycine-2-^{14}C	0.26	0.41		
3	Glycine-2-^{14}C	0.17	0.86	69	
4	Glycine-2-^{14}C	0.48	0.58	59	63
5	Glycine-2-^{14}C	0.31	0.78[b]	78	79

[a] The specific activity in ajmalicine is taken as 100%. [b] This value refers to sodium acetate obtained in Kuhn–Roth oxidation of harman. The values in experiments 2, 3, and 4 refer to oxidation on ajmalicine.

An analysis of the results quickly reveals that high levels of activity reside in two portions of the alkaloid: (1) the tryptophan unit containing 60–80%; (2) the methyl group of the ester containing approximately 20–35%. The C_{10} unit contains very little activity (approximately 1–4%).

Plausible explanations for the obtained results can be advanced. For example, it has been shown conclusively[6] that in microorganisms tryptophan is a product of the shikimate–chorismate pathway and that the final biosynthetic step, catalyzed by tryptophan synthetase, is the replacement of the glycerol phosphate moiety of indolyl-3-glycerol 3′-phosphate by serine to form the side chain of this amino acid. This same tryptophan synthetase activity has been demonstrated in plants.[7] Furthermore, the activity of the enzyme, serine aldolase, responsible in mammalian systems for the interconversion of glycine and serine has also been shown in plant systems.[8] Since both glycine and serine have very recently been shown to be present in *Vinca* plants,[9] it is attractive to postulate that glycine can be utilized in the biosynthesis of the tryptophan unit in *V. rosea*. The high level of activity found in the degradation product, harman (III), is explicable in these terms.

The presence of significant activity in the methyl group of the ester function is merely an indication that in *V. rosea*, degradation to a "C_1" can occur, a process observed previously.[2]

Of particular interest is the finding that very little activity is found in the C_{10} unit, in contrast to the results obtained by Gear and Garg[4] in their experiments with *Cephaelis ipecacuanha* plants. Our results suggest that in *V. rosea*, glycine-2-^{14}C is not a specific precursor of the C_{10} unit.

It is relevant at this point to note the recent studies by Shah and Rogers[10] on terpenoid biosynthesis in green plants. They suggest that acetyl CoA, an established intermediate, may be formed from carbon dioxide *via* the route, carbon dioxide → glycollate → glyoxylate → glycine → serine → pyruvate → acetyl CoA. The obvious implication of glycine involvement in acetyl CoA and, thereby in turn, in biosynthesis of the C_{10} unit required in ajmalicine does not receive strong support from our results. Whether the postulated involvement of glycine in the cephaeline biosynthesis[4] reveals a different biosynthetic pathway in that plant system relative to *V. rosea* remains an open question.

Finally, the nonincorporation of glycine-1-^{14}C into ajmalicine is readily understood. The conversion of glycine to both a "C_1" unit and tryptamine (*via* serine) entails the loss of the carboxyl group.[2, 10]

Further experiments to provide additional information relevant to the above are now in progress.[11]

Acknowledgment. Financial aid from the National Research Council of Canada is gratefully acknowledged.

(6) (a) J. R. Mattoon, "Biogenesis of Natural Compounds," 2nd ed, P. Bernfeld, Ed., Pergamon Press, New York, N. Y., 1967, p 34; (b) I. D. Spenser, *Compr. Biochem.*, **20**, 330 (1968).

(7) L. Fowden, "Plant Biochemistry," J. Bonner and J. E. Varner, Ed., Academic Press, New York, N. Y., 1965, p 381.

(8) Reference 7, p 379.

(9) R. R. Paris and R. L. Girre, *C. R. Acad. Sci. Paris, D*, **268**, 62 (1969).

(10) S. P. J. Shah and L. J. Rogers, *Biochem. J.*, **114**, 395 (1969).

(11) After this communication was submitted for publication, two communications have appeared: (a) A. K. Garg and J. R. Gear, *Tetrahedron Lett.*, 4377 (1969); (b) A. K. Garg and J. R. Gear, *Chem. Commun.*, 1447 (1969). In both instances, the specific incorporation of glycine into the C_{9-10} unit is reported. These authors suggest that "glycine may be a fundamental precursor of the C_{9-10} unit in alkaloids." Our results are not in agreement with that statement.

(12) To whom inquiries should be sent.

(13) Visiting professor, summer 1969.

James P. Kutney,[12] John F. Beck
Vern R. Nelson, Kenneth L. Stuart[13]
Chemistry Department, University of British Columbia
Vancouver 8, Canada

Ajay K. Bose
Department of Chemistry & Chemical Engineering
Stevens Institute of Technology
Hoboken, New Jersey

Received December 19, 1969

Thallium in Organic Synthesis. XIV. Orientation Control in an Electrophilic Aromatic Substitution Reaction[1,2]

Sir:

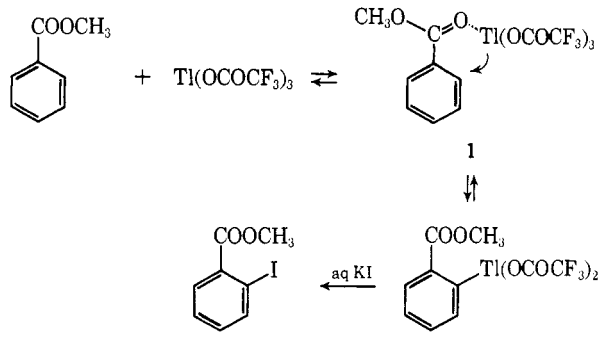
We describe in this paper control over *ortho*, *meta*, or *para* substitution in the same electrophilic aromatic substitution reaction (thallation), and the application

(1) We gratefully acknowledge financial support of this work by the Smith Kline & French Laboratories, Philadelphia, Pa. 19101.

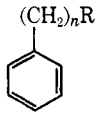
(2) Part XIII: A. McKillop, B. P. Swann, M. J. Zelesko, and E. C. Taylor, *Angew. Chem.*, in press.

of these findings to orientation control in the synthesis of substituted benzenoid compounds.

ortho **Substitution.** We have recently reported[3] the use of thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid as an effective reagent for the thallation of aromatic substrates, and a facile synthesis of aromatic iodides by treatment of the resulting arylthallium ditrifluoroacetates with aqueous potassium iodide.[4] It was observed that thallation of benzoic acid followed by treatment with potassium iodide gave *o*-iodobenzoic acid; the high ratio of *ortho* to *meta* substitution (95:5) is unprecedented. It was suggested[4] that this almost exclusive *ortho* substitution might have resulted from intramolecular delivery of thallium to the *ortho* position from a mixed thallium(III) carboxylate, presumably formed *in situ*.[5] We have now found that methyl benzoate, a compound unable to form a mixed carboxylate, gives identical results, indicating the intermediacy of a substrate–electrophile complex (**1**).



In order to examine the synthetic implications of these observations, we have studied the homologous series **2** in which the distance between the complexed



2, R = COOH, $COOCH_3$, OH, $OCOCH_3$, OCH_3

electrophile (TTFA) and the aromatic ring was systematically increased. Results are summarized in Table I and show clearly that the distance of the basic center in the side chain from the aromatic nucleus controls the extent of *ortho* substitution. Thus, benzyl alcohol and benzyl methyl ether give *only* *o*-iodo derivatives under the above conditions;[6] to our knowledge this is one of the very few examples of an electrophilic substitution reaction which gives only the *ortho* isomer.[7] Predominant *ortho* substitution is observed with phenylacetic acid (and its methyl ester) and with 2-phenylethyl methyl ether.

If *ortho* substitution is an intramolecular process, as indicated by the above results, then increasing the distance between the (complexed) electrophile and the ring should influence isomer distribution by decreasing *ortho* substitution. That this is indeed the case can be seen by inspection of the data in Table I.

Table I. Controlled Synthesis of Aromatic Iodides

Compd no.	Substrate	Reaction conditions	Isomer distribution, % *o*	*m*	*p*
3	$C_6H_5CH_2OH$	*a*	>99		
4	$C_6H_5CH_2OCH_3$	*a*	>99		
5	C_6H_5COOH	*b*	95	5	
6	$C_6H_5COOCH_3$	*b*	95	5	
7	$C_6H_5CH_2COOH$	*a*	92	3	5
8	$C_6H_5CH_2COOCH_3$	*a*	92	3	5
9	$C_6H_5CH_2CH_2OCH_3$	*a*	85	3	12
10	$C_6H_5CH_2CH_2COOH$	*a*	29	13	58
		b	19	58	23
11	$C_6H_5CH_2CH_2CH_2COOH$	*a*	6	10	84
12	$C_6H_5CH_2CH_2CH_2OH$	*a*	12	9	79
		b	7	64	29
13	$C_6H_5CH_2CH_2CH_3$	*a*	3	6	91
		b	9	78	13
14	$C_6H_5CH(CH_3)_2$	*a*	1	5	94
		b	12	85	3
15	$C_6H_5CH_2CH_2OH$	*a*	83	6	11
		b	6	56	38
16	$C_6H_5CH_2CH_2OCOCH_3$	*a*	3	13	84

[a] TTFA–TFA at room temperature, followed by aqueous KI (average yields, ≥80%). [b] TTFA–TFA under reflux, followed by aqueous KI (average yields, ≥80% based on recovered starting material).

para **Substitution.** In the absence of complexation factors such as those described above, the kinetically favored reaction in compounds activated toward electrophilic substitution (see Table I, compounds **13** and **14**) is *para* thallation.

meta **Substitution.** Electrophilic thallation, like the well-known mercuration reaction,[8] is freely reversible.[9] In principle, therefore, the orientation of substitution initially dictated by kinetic factors should also be susceptible to thermodynamic control. In practice, this can be accomplished by heating the thallation mixture. Thus, *n*-propylbenzene (compound **13**, Table I) gives 91% *para* substitution at room temperature but 78% *meta* substitution at 73° (refluxing TFA). Similarly, cumene (compound **14**, Table I) gives 94% *para* substitution at room temperature but 85% *meta* substitution upon heating.

Thus, by appropriate manipulation of conditions, it is possible to control orientation *in the same electrophilic substitution reaction* (thallation). *meta* substitution is achieved under conditions of thermodynamic control. Under conditions of kinetic control, *ortho* substitution results when chelation of the reagent (TTFA) with the directing substituent permits intramolecular delivery of the electrophile, and *para* substitution results when such capabilities are absent.

The potential synthetic utility of these results is illustrated by the selective conversion of 2-phenylethanol (compound **15**, Table I) to its *o*-, *m*-, or *p*-iodo derivative. Thallation at room temperature, followed by treatment with aqueous KI, gives predominantly *ortho* substitution (83%), while thallation at 73° gives predominantly *meta* substitution (56%).[10] Thallation

(3) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423 (1969).
(4) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *ibid.*, 2427 (1969).
(5) J. K. Kochi and T. W. Bethea, III, *J. Org. Chem.*, 33, 75 (1968).
(6) For comparison, mercuration of benzyl alcohol with mercury (II) diacetate gives 60% *ortho*, 15% *para*, and 25% *poly* substitution (T. Ukai, Y. Yamamoto, M. Yotsuzuka, and F. Ichimura, *J. Pharm. Soc. Jap.*, 76, 657 (1956)).
(7) Another example of an exclusive *ortho* substitution is found in the alkylation of primary and secondary aromatic amines with olefins in the presence of aluminum anilide catalysts; a cyclic mechanism is suggested here as well (G. G. Ecke, J. P. Napolitano, A. H. Filbey, and A. J. Kolka, *J. Org. Chem.*, 22, 639 (1957)).
(8) W. Kitching, *Organometal. Chem. Rev.*, 3, 35 (1968).
(9) A. McKillop, J. D. Hunt, and E. C. Taylor, to be published
(10) For comparison, mercuration of 2-phenylethanol with mercury(II) diacetate gives 20% *ortho*, 60% *para*, and 20% *poly* substitution (ref 6).

of the acetate of 2-phenylethanol (compound **16**), however (where the distance of the complexed TTFA from the ring has been increased; *i.e.*, $-O(H)\cdots TTFA \rightarrow -OC(CH_3)=O\cdots TTFA$), results in predominantly *para* substitution (84%).

Since arylthallium ditrifluoroacetates are versatile synthetic intermediates for the preparation of phenols,[11] thiophenols,[12] and nitriles,[11] as well as iodides,[4] control over the orientation of the thallation reaction, as demonstrated in the examples given above, has as its consequence control over isomer distribution in a spectrum of aromatic substitution reactions.

(11) E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, to be published.
(12) E. C. Taylor, M. Ochiai, and A. McKillop, to be published.
(13) NRCC Postdoctoral Fellow, 1968–1970.

Edward C. Taylor, Frank Kienzle,[13] Roger L. Robey
Department of Chemistry, Princeton University
Princeton, New Jersey 08540

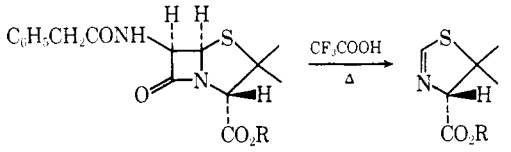
Alexander McKillop
School of Chemical Sciences, University of East Anglia
Norwich, England

Received November 15, 1969

Degradation of Penicillin G Methyl Ester and Penillonic Acid Methyl Ester to D-5,5-Dimethyl-Δ^2-thiazoline-4-carboxylic Acid Methyl Ester

Sir:

We wish to report a new and potentially useful chemical degradation of penicillin G (**1**). A solution of **1** in trifluoroacetic acid which had been heated at the boiling point exhibited nmr signals[1] at δ 1.75 (s, 3), 2.0 (s, 3), 5.35 (d, 1, J = 2 Hz), and 9.6 ppm (d, 1, J = 2 Hz) which are characteristic of 5,5-dimethyl-Δ^2-thiazoline-4-carboxylic acid (**2**).[2] To facilitate



1, R = H
3, R = CH_3

2, R = H
4, R = CH_3

$C_6H_5CH_2CONHCH_2CO_2COCF_3$ (**5**)

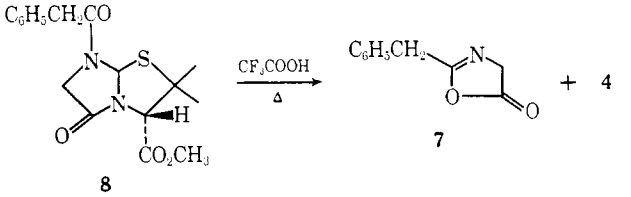
$C_6H_5CH_2CONHCH{=}C{=}O$ (**6**)

isolation of the thiazoline the degradation was performed on the methyl ester **3**.[3]

A 10% solution of compound **3** in CF_3COOH was heated at reflux for 15 min and evaporated *in vacuo* at room temperature. The residue was dissolved in methylene chloride and quenched with excess aqueous ammonia. Evaporation and distillation of the dried methylene chloride solution afforded a 50–60% yield of optically active thiazoline **4** [mp 50.5–51.5°; $[\alpha]^{25}D$ +51.9° (*c* 1, $CHCl_3$); lit.[4] mp 50°]. A solution infrared spectrum of this compound was identical with that of authentic racemic thiazoline.[5] The optical integrity of the carbon atom bearing the carbomethoxy group appears to have been preserved since the melting point of the thiazoline is the same as that reported for the thiazoline prepared from D-penicillamine.[4] Hydrolysis of compound **4** with hot 2 *N* HCl gave D-penicillamine hydrochloride [mp 177–179.5° dec; $[\alpha]^{25}D$ −49.8° (*c* 1, 1 *N* NaOH)][6] in 70% yield.

Although the precise fate of the N-phenylacetylglycyl fragment of **3** is not known, addition of the reaction mixture to an excess of benzylamine in pyridine led to the isolation of the benzylamide of N-phenylacetylglycine in 27% yield.[7] Formation of this product supports the view that the N-phenylacetylglycyl fragment is present in CF_3COOH as the mixed anhydride **5**,[8] the acylamino ketene **6**,[9] or the benzyloxazolone **7**.[10] The absence of nmr signals characteristic of oxazolone **7** and the stability of **7**[11] in CF_3COOH apparently eliminate the oxazolone as a final product in the CF_3COOH degradation of penicillin G.

However, when penillonic acid methyl ester (**8**)[12] was heated in CF_3COOH a clean conversion to oxazolone **7** and thiazoline **4** occurred. The nmr spectrum of the reaction mixture approximated that of equal parts of authentic **4** and **7**. Optically active **4** was isolated and the N-phenylacetylglycyl fragment was



8 **7**

characterized as the benzylamide derivative. Jansen and Robinson[10] reported the reverse reaction, **4** + **7** → **8**, occurs in benzene solution. Furthermore, they suggested that the penillonic acid rearrangement proceeds by dissociation of penicillin to **4** and **7** followed by recombination to **8**. The degradation of penicillin

(1) Nuclear magnetic resonance (nmr) spectra were measured on a Varian A-60 spectrophotometer using $(CH_3)_4Si$ as internal standard. Optical rotations were measured on a Rudolph 137 polarimeter. Infrared spectra were measured on a Perkin-Elmer 257 grating infrared spectrophotometer. Melting points are uncorrected.
(2) H. M. Crooks, Jr., in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, 1949, p 471.
(3) Prepared in 96% yield by methylation of potassium penicillin G with methyl iodide in dimethylformamide solution.
(4) Merck Report No. 63, p 18, April 1945, cited in ref 2, p 1057.
(5) A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968). These workers reported that DL-**4** could be prepared by heating DL-N-formylpenicillamine with boron trifluoride etherate in methanol. Prior to their publication we had synthesized DL-**4** by hydrogen chloride catalyzed esterification of DL-**2** in the presence of trimethyl orthoformate. The Merck group[4] prepared D-**4** by the reaction of ethyl formimidate hydrochloride and D-penicillamine methyl ester.
(6) An authentic sample of D-penicillamine hydrochloride (Aldrich Chemical Co.) had $[\alpha]^{25}D$ −50.6° (*c* 1, 1 *N* NaOH); "The Merck Index," P. G. Stecher, Ed., Merck and Co., Rahway, N. J., 1968, p 789, reports mp 177.5° dec; $[\alpha]^{25}D$ −55° (*c* 1, 1 *N* NaOH).
(7) R. L. Peck and K. Folkers in ref 2, p 190.
(8) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952), have shown that mixed anhydrides of carboxylic acids and trifluoroacetic acid react with primary amines to produce a mixture of amides.
(9) W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experientia*, **23**, 280 (1967), suggest an aminoketene or its equivalent to account for the products observed upon irradiation of an aqueous solution of 6-aminopenicillanic acid.
(10) A. B. A. Jansen and R. Robinson, *Monatsh. Chem.*, **98**, 1017 (1967). A more convenient procedure than that reported for the preparation of **7** is the treatment of phenylacetylglycine with dicyclohexylcarbodiimide in methylene chloride solution.
(11) The nmr spectrum of authentic 2-benzyl-5-oxazolone (**7**) in CF_3COOH is essentially unchanged after heating at reflux for 15 min.
(12) R. L. Peck and K. Folkers in ref 2, p 188.