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DEPARTMENT OF CHEMISTRY
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STEREOCHEMISTRY OF METAL ADDITION TO CONJUGATED SYSTEMS. II. DIENES

Sir:

Evidence has been submitted[1] that metal additions to benzil, and presumably to α-diketones in general, consistently exhibit a pronounced *cis* stereochemical preference which is especially accentuated in nonpolar solvents and further that a novel stereoelectronic effect which should be operative to a greater or lesser extent in metal additions to all conjugated systems is responsible for the observed stereospecificity. This latter conclusion has now been reinforced with data for another common type of conjugated system, the 1,3-dienes.

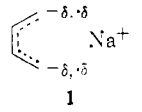
TABLE I

Diene	Temp., °C.	% *cis*-Olefin
Butadiene	−33	13
Butadiene	−78	50
1,3-Pentadiene	−33, −78	68

Table I contains v.p.c. analyses of the *cis–trans* composition of the olefin produced (in 60–75% yield) in the liquid ammonia reductions of butadiene and 1,3-pentadiene. Controls established the absence of olefin isomerization and also that any allylic sodium intermediates were configurationally stable. The latter was accomplished for the butadiene system by reducing *trans*-γ-methylallyl (crotyl) acetate in the media used in this study to essentially pure *trans*-2-butene. The intermediate butenyl sodium is involved in both this reduction and that of butadiene. Therefore a minimum conclusion is that no isomerization from *trans* to *cis* occurs and the *cis* olefin content accurately reflects the minimum percentage of *cis* addition to the diene.

In every instance the *cis* content exceeds that expected on the basis of the low (3–7% at room temperature[2]) *cis* conformer population of the diene (assuming indiscriminate addition). The results for butadiene are especially telling. Though reduction at the boiling point of ammonia (−33°) was rather indiscriminate, giving but 13% *cis* addition, that at −78° produced 50% *cis* addition, *i.e.*, completely overcame the large adverse conformational factor, which is *ca.* 10[2] at −78°, the stabler *trans* conformer being "frozen in" at low temperatures.

These facts demonstrate a temperature dependent factor acting to promote *cis* addition. Undoubtedly this is the same factor suggested to account for the *cis* stereospecificity of diketone additions, namely, preferential stabilization of the *cis*-anion radical (**1**) relative to its *trans* counterpart (**2**).



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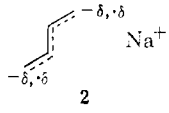
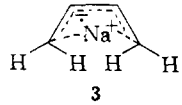


2

It is especially noteworthy that the *cis*-directing effect, shown earlier to be maximal in nonpolar solvents, already has reached a magnitude sufficient to nullify the adverse conformational effect in one of the least favorable solvents, ammonia (though at −78°). The implication is that, just as in the diketone case, addition should be *cis* specific in nonpolar solvents, though it is doubtful that diene reductions should have the same high specificity as those of diketones for reasons easily gleaned from a more detailed picture of the *cis* anion radicals of the two systems (**3** and **4**). Ion pair interaction is optimum in **4** but in **3** the Na^+



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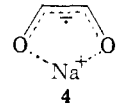

4

is displaced from the ideal location (midway between the termini of the system and coplanar with it) it occupies in **4** by the two inside hydrogens. The distinction should become more apparent the more intimate the ion pair, *i.e.*, the less polar the solvent. Consequently the limit of practically attainable specificity may be somewhat lower for systems **3** than **4**. Unfortunately the data necessary to test this surmise could not be obtained since mainly polymerization occurs in aprotic media and pertinent polymer stereostudies on butadiene are not yet available.

Reduction in nonpolar media using added proton donors is only a partial solution to the problem. Ziegler, *et al.*,[3] reported the reduction of butadiene by lithium in ether with added N-ethylaniline to furnish mainly *cis*-2-butene, but no quantitative measure of the olefin composition was ascertained. Our v.p.c. measurements for the same reaction in THF solvent (ether interfered with the analysis) indicated only a very slight (50–60%) *cis* excess. Even so, this confirms the expected greater stereospecificity in more nonpolar solvents since even at −33°, the ammonia reduction was 87% *trans*. Very probably, then, metal additions in pure aprotic solvents will be at least somewhat more *cis*-stereospecific.

Results for 1,3-pentadiene were similar. The more specific (68% *cis*) reduction is ascribed to a combination of a selectivity–reactivity effect (pentadiene should be less reactive than butadiene) and the circumstance that *trans* addition to the (25%) *cis* component of our pentadiene (*i.e.*, addition to the *trans* conformer of *cis*-1,3-pentadiene) can lead to some *cis* olefin. Finally, the absence of a perceptible temperature dependency in this case is noted as curious.

It appears, then, that the formation of a cyclic anion radical renders *cis* additions to 1,3-systems generally more apt than would otherwise be anticipated and in the majority of solvents actually dominant over or exclusive of *trans* addition.

(1) Part I of this series, *J. Am. Chem. Soc.*, **84**, 4345 (1962).

(2) W. B. Smith and J. L. Masingill, *ibid.*, **83**, 4301 (1961), and references cited therein.

(3) K. Ziegler, F. Hoffner and H. Grimm, *Ann.*, **528**, 101 (1937).

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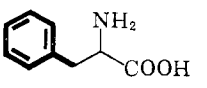
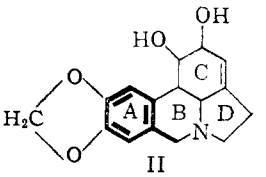
THE BIOGENETIC ORIGIN OF THE C_6–C_1 UNIT OF LYCORINE[1]

Sir:

It has been shown experimentally that the phenolic compounds 2-C^{14}-tyrosine,[2–4] 3-C^{14}-tyrosine[5,6] and 2-C^{14}-tyramine[7] are directly incorporated into rings C and D of the *Amaryllidaceae* alkaloids. In addition, 1-C^{14}-norbelladine,[8,9] 1,1′-C^{14}-norbelladine[10] and partially methylated derivatives of norbelladine[11] are able to serve as intermediates in the biosynthesis of these alkaloids. The purpose of this report is to provide information about the nature of the precursor(s) of the C_6–C_1 unit of the *Amaryllidaceae* alkaloid, lycorine (II, heavy bonds).



I



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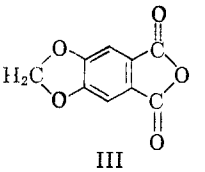

III

man[13] and carbon atom-5 was isolated as the dimedone derivative according to the procedure of Humber, *et al.*[14]

The percentage incorporation of 2- and 3-C^{14}-phenylalanine and the specific activities of lycorine and its degradation product, hydrastic anhydride (Table I), show that 3-C^{14}-phenylalanine can serve as the precursor of the C_6–C_1 unit of lycorine, *but only one phenylalanine unit is utilized in the biosynthesis of lycorine* (II, heavy bonds). However, this incorporation of phenylalanine into

TABLE I

INCORPORATION OF RADIOACTIVE COMPOUNDS INTO LYCORINE AND RELATIVE ACTIVITIES OF DEGRADATION PRODUCTS[a]

	Injected[b]		Incorporated[c]		Lycorine		Hydrastic anhydride		Carbon atom-5 of lycorine[d]	
	Mg.	mμc.	mμc.	%	Specific activity, mμc./mM	Relative activity	Specific activity, mμc./mM	Relative activity	Specific activity, mμc./mM	Relative activity
3-C^{14}-DL-Phenylalanine	20	13,000	48.0	0.37	92.5	100	87.0	94		
3-C^{14}-DL-Phenylalanine	12	9,850	17.5	0.18	5.81	100	4.9	84		
2-C^{14}-DL-Phenylalanine	15	25,000	0.0	0.0	0.0					
3-C^{14}-DL-Tyrosine	4	11,000	20.0	0.18	9.2	100	0.0	0		
2-C^{14}-Tyramine	4	15,600	158.0	1.01	32.4	100	0.0	0		
H^3-Protocatechuic aldehyde	66	6,650	15.0	0.23	7.4					
2-C^{14}-DL-Tyrosine	12	20,800	44.8	0.22	11.1	100			8.41	76

[a] Samples were counted in a Packard Tri-Carb Scintillation Counter in toluene or ethanol–dioxane–naphthalene scintillator solutions. [b] All radioactive compounds were injected into the corm with the exception of 2-C^{14}-phenylalanine. This was injected into the stem. [c] Based on incorporation after recrystallization of lycorine to constant specific activity. [d] Isolated as the formaldehyde dimedone derivative.

The labeled compounds were injected at three separate time intervals into *Narcissus incomparabilis* Mill. The alkaloids were extracted from all of the tissue.[12] The amounts of radioactive compounds administered, incorporation into lycorine, the degradation of lycorine to hydrastic anhydride (III) and the isolation of carbon atom-5 as formaldehyde are shown in Table I. The lycorine was degraded to hydrastic anhydride according to the procedure of Warnhoff and Wild-

lycorine does not proceed *via* tyrosine. This can be seen by (1) the lack of incorporation of 2-C^{14} phenylalanine into rings C and D of lycorine (Table I) and (2) the tyrosine isolated, after hydrolysis of the plant protein from the phenylalanine experiments, was not radioactive. On the other hand, 3-C^{14}-tyrosine can be incorporated into lycorine only as a C_6–C_2 unit (rings C and D of II). Similar results, on the incorporation of 3-C^{14}-tyrosine to haemanthamine, haemanthidine and tazettine have been reported by Wildman, Fales and Battersby[5] and Jeffs.[6] Since the haemanthamine from the 3-C^{14}-phenylalanine experiment appears to be radioactive, it may well be that this aromatic amino acid is the C_6-C_1 precursor for the pyrrolophenanthridine and 5,10b-ethanophenanthridine alkaloids. Experiments are in progress to demonstrate these inter-relationships.

The conversion of phenylalanine to the dihydroxylated, C_6-C_1 precursor of lycorine, without going through tyrosine, might be explained on the

(1) This work was supported by a grant-in aid from the National Science Foundation.
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(3) A. R. Battersby, R. Binks and W. C. Wildman, *ibid.*, 410 (1960).
(4) R. J. Suhadolnik and A. G. Fischer, Abstracts, Am. Chem. Soc., Chicago, Ill., 1961, p. 39-Q.
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(7) A. G. Fischer and R. J. Suhadolnik, *Fed. Proc.*, **21**, 399 (1962).
(8) A. R. Battersby, R. Binks, S. W. Breuer, H. M. Fales and W. C. Wildman, *Proc. Chem. Soc.*, 243 (1961).
(9) A. R. Battersby, H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **83**, 4089 (1961).
(10) W. C. Wildman, H. M. Fales, R. J. Highet, S. W. Breuer and A. R. Battersby, *Proc. Chem. Soc.*, 180 (1962).
(11) D. H. R. Barton, G. W. Kirby, J. B. Taylor and G. M. Thomas, *ibid.*, 254 (1961).
(12) H. G. Boit and H. Ehmke, *Ber.*, **89**, 163 (1956).
(13) E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.*, **79**, 2192 (1957).
(14) L. E. Humber, H. Kondo, K. Kotera, S. Takogi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).