

and a peak at 5.13  $\tau$  attributed to the CH<sub>2</sub> group in the tautomeric isoindolenine (III, R = C<sub>6</sub>H<sub>5</sub>). The ratio of the areas of the aromatic proton signal plus 1/2 of the CH<sub>2</sub> signal to the area of the N-H signal plus 1/2 of the CH<sub>2</sub> signal was found to be 10.2:1, within experimental error of 10:1.<sup>10</sup> The area of the CH<sub>2</sub> peak corresponds to a fraction of 9% isoindolenine. In CCl<sub>4</sub> the relative area of the CH<sub>2</sub> peak corresponds to 4% isoindolenine. The changes in tautomeric equilibrium are more drastic for 1-*p*-methoxyphenylisoindole. The n.m.r. spectra of one and the same sample were measured in ethyl ether-*d*<sub>10</sub> and in CDCl<sub>3</sub>. In ether-*d*<sub>10</sub>, the N-H signal was too broad to be integrated at -1.3 to 0.0  $\tau$ , aromatic protons at 1.9 to 3.1  $\tau$ , CH<sub>2</sub> at 5.2  $\tau$ . (very small), and OCH<sub>3</sub> at 6.32  $\tau$  (single sharp peak). The integrals of aromatic to CH<sub>3</sub> signals had the ratio 2.9:1. The isoindolenine content was very small, judged by the CH<sub>2</sub> area and the single OCH<sub>3</sub> peak. In CDCl<sub>3</sub>:N-H at -0.3 to +0.3  $\tau$ , aromatic protons at 1.9 to 3.2  $\tau$ , CH<sub>2</sub> at 5.19  $\tau$ , and two OCH<sub>3</sub> peaks at 6.26 and 6.29  $\tau$ , with relative peak heights about 1:2. The ratio NH + 1/2 CH<sub>2</sub>:1/2 CH<sub>2</sub> + aromatic CH:OCH<sub>3</sub> was measured as 1.01:9.04:3.00. From the relative area of the CH<sub>2</sub> peak an isoindolenine content of 30.8% is calculated. This is consistent with the relative heights of the OCH<sub>3</sub> peaks and with the above determination from the ultraviolet spectrum (30%).

1-Phenylisoindole readily forms a maleic anhydride adduct. Its ultraviolet spectrum is that of an isoindole (Table I). The infrared spectrum shows N-H (3280 cm.<sup>-1</sup>) and carboxanhydride (1861, 1831, 1770 cm.<sup>-1</sup>) (in KBr). It therefore seems to be a condensation product (in the 3 position?), rather than a Diels-Alder adduct.

We are further investigating the equilibria and chemical reactions of isoindoles.

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(10) Since the two CH<sub>2</sub> protons in the isoindolenine correspond to one aromatic and one NH proton in the isoindole, adding half of the CH<sub>2</sub> signal to the aromatic and half to the NH signals corrects to 100% isoindole.

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### A SYNTHESIS OF HOLOMYCIN

Sir:

Various *Streptomyces* species elaborate yellow, sulfur containing metabolites which exhibit high activity against fungi, Gram-positive and Gram-negative bacteria. Four representatives of this group of antibiotics are presently known in pure form. Degradative studies on thiolutin,<sup>1</sup> aureothricin,<sup>1</sup> holomycin<sup>2</sup> and isobutyropyrrrothine<sup>3</sup> revealed structures which differ only in the nature of the N-acyl side chain and the substituent attached to the lactam nitrogen atom of the pyrrothine<sup>1</sup> nucleus. The nine steps outlined below led to synthetic holomycin.<sup>4</sup>

S-Benzylcysteine ethyl ester<sup>5</sup> was acylated with di-

(1) W. D. Celmer and I. A. Solomons, *J. Am. Chem. Soc.*, **77**, 2861 (1955), and earlier papers cited.

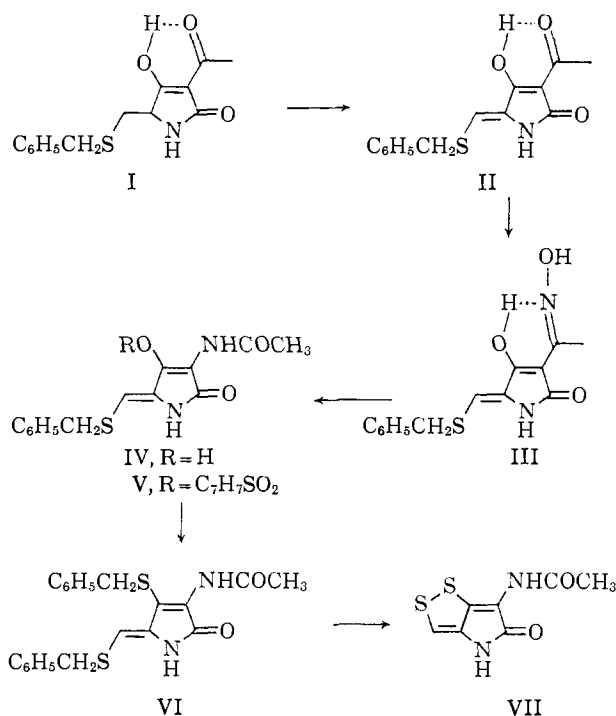
(2) L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog and H. Zähler, *Helv. Chim. Acta*, **42**, 563 (1959).

(3) D. S. Bhate, R. K. Hulyalkar and S. K. Menon, *Experientia*, **16**, 504 (1960).

(4) A synthesis of holomycin following a different sequence has been announced in a brief note by U. Schmidt and F. Geiger, *Ang. Chem.*, **74**, 328 (1962).

(5) C. R. Harington and R. V. Pitt Rivers, *Biochem. J.*, **38**, 417 (1944).

ketene in ethanol solution.<sup>6</sup> Dieckmann condensation<sup>6</sup> of the crude acetoacetamide with sodium ethoxide in ethanol-benzene (80°, 3 hr.) yielded  $\alpha$ -acetyl- $\gamma$ -benzylthiomethyltetramic acid (I) (42% for both steps), m.p. 114°;  $\nu_{\text{max}}^{\text{KBr}}$  3400-2500, 1710, 1665, 1610 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  244, 277 m $\mu$  ( $\epsilon$  5100, 12700). Dehydrogenation with thionyl chloride in benzene solution (25°, 24 hr.) provided the yellow benzylthiomethylene derivative (II or its stereoisomer) (84%), m.p. 170°,  $\nu_{\text{max}}^{\text{KBr}}$  3500-2500, 1710, 1690, 1660, 1600 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  288, 350 m $\mu$  ( $\epsilon$  18500, 11600); n.m.r. (*d*<sub>7</sub>-DMF) 0.85 (1H), 2.9 (5H), 3.7 (1H); 6.05 (2H), 7.85 (3H)  $\tau$ . Treatment with hydroxylamine in aqueous tetrahydrofuran (25°, 24 hr.) led to a single oxime (III) (71%), m.p. 160°,  $\nu_{\text{max}}^{\text{KBr}}$  3400-2600, 1680-1620, 1600 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  297, 334 m $\mu$  ( $\epsilon$  15600, 18700) which on heating with *p*-toluenesulfonyl chloride and sodium hydroxide in aqueous tetrahydrofuran (65°, 30 min.) was transformed to  $\alpha$ -acetylamino- $\gamma$ -benzylthiomethylenetetramic acid (IV) (28%), m.p. 200°,  $\nu_{\text{max}}^{\text{CHCl}_3}$  3440, 3390, 3250, 1690, 1650, 1600, 1525 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  235, 330 m $\mu$  ( $\epsilon$  10000, 23700); n.m.r. (CDCl<sub>3</sub>) -1.33 (1H), 2.7 (5H), 3.88 (1H), 6.0 (2H), 7.85 (3H)  $\tau$ .



Direct conversion<sup>7</sup> of tetramic acid (IV) to its benzylthio derivative (VI) was not possible but this intermediate became available by a two-stage sequence<sup>7,8</sup> when it was found that IV was converted readily to its O-toluenesulfonyl derivative (V) (80%) m.p. 200-204° (dec.) with tosyl chloride in a mixture of tetrahydrofuran and triethylamine (25°, 16 hr.). Displacement of the toluenesulfonate group with sodium benzylmercaptide in ethanol-tetrahydrofuran (70°, 8 hr.) produced the desired sulfide (VI) (40%); m.p. 180°;  $\nu_{\text{max}}^{\text{KBr}}$  3400, 3250, 1690, 1660, 1625, 1600, 1525 cm.<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  360 m $\mu$  ( $\epsilon$  23400); n.m.r. (CDCl<sub>3</sub>) 2.6 (10 H), 3.8 (1H), 6.05 (2H), 6.15 (2H), 7.9 (3H)  $\tau$ . Debenzylation with lithium in liquid ammonia<sup>9</sup> and air oxidation of the crude dithiol in methanol at pH 2 (25°) completed the synthesis. The product obtained (15%) had m.p.

(6) Method of R. N. Lacey, *J. Chem. Soc.*, 850 (1954).

(7) Method of R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 8336 (1959).

(8) R. B. Woodward, M. P. Cava, W. D. Ollis, W. D. Hunger, H. U. Daeniker and K. Schenker, *ibid.*, **76**, 4749 (1954).

(9) K.-D. Gundermann and G. Pape, *Chem. Ber.*, **95**, 2076 (1962).

264–272° dec.,  $\nu_{\text{max}}^{\text{KBr}}$  3400, 3200, 1660, 1630, 1595, 1540  $\text{cm}^{-1}$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  246, 302, 385  $\text{m}\mu$  ( $\epsilon$  5400, 3000, 10800) and was identical with natural holomycin (infrared and ultraviolet spectra, mixture m.p. determination and  $R_f$  value in paper chromatography<sup>10</sup>).

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(10) The authors wish to thank Professor V. Prelog and Dr. W. Keller for having performed this comparison.

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### METAL-AMMONIA REDUCTION OF ALLENES<sup>1</sup>

Sir:

The sodium–ammonia reduction of 1,2-cyclononadiene to *cis*-cyclononene was described recently.<sup>2,3</sup> Subsequent examination of additional members—both cyclic and acyclic—of the allene family has shown the reaction to be completely general and not peculiar to strained medium-rings. Moreover, it appears to be rapid and quantitative<sup>4</sup> and the product mixtures are free of rearrangement products.

The reduction of 2,3-nonadiene afforded *cis*- and *trans*-2-nonene (50/50) and less than 1% of two other substances, assumed to be *cis*- and *trans*-3-nonene. Similarly, 2-methyl-2,3-pentadiene gave rise to *trans*-4-methyl-2-pentene (48%), *cis*-4-methyl-2-pentene (34%) and 2-methyl-2-pentene (18%). 1,2-Cyclodecadiene gave only *cis*-cyclodecene while 1,2-cyclotridecadiene<sup>5</sup> afforded equal amounts of *cis*- and *trans*-cyclotridecene. The synthetic utility of the method is illustrated in the reduction of readily available<sup>6</sup> 1,2,6-cyclononatriene to pure *cis,cis*-1,5-cyclononadiene.<sup>7</sup> Finally, the reduction of 1,2-nonadiene, the only terminal allene studied, gave *cis*-2-nonene (85%), *trans*-2-nonene (8%) and 1-nonene (6%).

Excluding for the moment 1,2-nonadiene, these reductions share one very important feature; the most hindered double bond is reduced. The attack of an electron on the allene linkage is electrophilic and therefore probably occurs at the central atom<sup>7</sup> giving rise to intermediate radical-ion I. It is important to note that this species (and those formed from it) does not approach pi-symmetry (*i.e.*, become an allyl radical or allyl anion) as such symmetry would leave only the substituent effects of alkyl groups to dictate the site of protonation by solvent. It is clear that I retains the configurational identity of the allene and that the direction of approach taken by the electron in the formation of I determines which double bond is reduced. This direction appears to be determined by the relative magnitude of steric interaction of the enlarged pi-orbital containing the extra electron with R and R'.

(1) Supported by The Robert A. Welch Foundation.

(2) P. D. Gardner and M. Narayana, *J. Org. Chem.*, **26**, 3518 (1961).

(3) The reduction of tetraphenylpropadiene to 1,1,3,3-tetraphenylpropane [C. B. Wooster and J. F. Ryan, *J. Am. Chem. Soc.*, **56**, 1133 (1934)] is best considered in context. "The Reduction of Phenylated Olefins with Alkali Metals in Liquid Ammonia."

(4) Yields of *distilled* products were usually in the 80% range but no pot-residues were found; the loss is assumed to be manipulative. Analyses of alkene or cycloalkene mixtures were made by vapor–liquid chromatography on silver nitrate columns using authentic samples for retention time comparisons. Identity of products was established in some cases by comparing chromatogram charts of different runs. Product ratios described were obtained with sodium as the reductant although a brief study with lithium gave identical results.

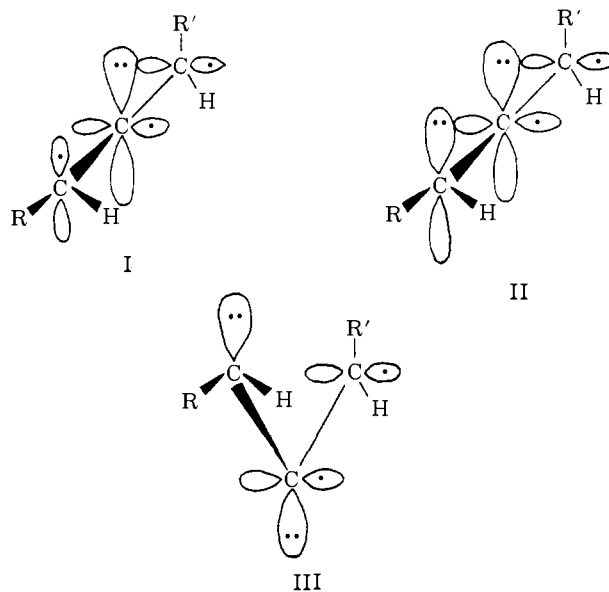
(5) This substance gave satisfactory analytical data. Its assignment of structure satisfies numerous items of chemical and physical data.

(6) L. Skätteböl, *Tetrahedron Letters*, **5**, 167 (1961).

(7) D. Devaprabhakara and P. D. Gardner, *J. Am. Chem. Soc.*, in press.

Thus, in representation I, R would be larger than R'. The attack of a second electron then precedes protonation (which would give an allyl radical) with consequent formation of dianion II. The configurational geometry of II must be as shown for reasons pointed out in the description of I; a 90° twist between the two charged atoms would give a species having symmetrical pi geometry. The rehybridized dianion (III)<sup>8</sup> in which coulombic repulsions are minimized at the expense of overlap energy cannot be discarded.<sup>9</sup> Structure II would appear to be more consistent with the observed *cis/trans* ratios of products.

The anomalous reduction of 1,2-nonadiene suggests that terminal allenes react by a different mechanism. This possibility is under investigation.



(8) Cf. A. J. Birch and H. Smith, *Quart. Rev.*, **12**, 17 (1958), and references cited therein.

(9) Likewise, orbital geometry analogous to that in II cannot be ruled out as a representation of the dianion formed in the reduction of a disubstituted acetylene. The observed *trans* geometry<sup>8</sup> of the resulting olefin would seem consistent with the type of orbital geometry shown in either II or III.

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### BICYCLIC ENAMINES. I. THE FORMATION OF A SUBSTITUTED NORTRICYCLENE FROM A BICYCLIC ENAMINE<sup>1</sup>

Sir:

It has been noted previously that the addition of a proton to an enamine takes place at the  $\beta$ -carbon atom to form an iminium salt<sup>2</sup> unless protonation at the  $\beta$ -carbon atom is sterically prohibited, in which case N-protonation takes place.<sup>2,3</sup> Iminium salts possessing endocyclic double bonds<sup>2,4,5</sup> and exocyclic double bonds<sup>6–8</sup> have been synthesized previously. It has been found in this laboratory that protonation of certain bicyclic enamines resulted in the formation of substituted nortricycloenes. The production of sub-

(1) Support of this work by a Frederick Gardner Cottrell Grant from the Research Corporation is gratefully acknowledged.

(2) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(3) C. A. Grob, A. Kaiser and E. Renk, *Chem. Ind. (London)*, 598 (1957).

(4) N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.*, **81**, 5627 (1959), previous papers and references cited therein.

(5) N. J. Doorenbos and C. L. Huang, *J. Org. Chem.*, **26**, 4106 (1961).

(6) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **82**, 6418 (1960), and references cited therein.

(7) G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962).

(8) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).