progestational in rats or rabbits, even at high dose levels.

The unusual activity observed with the above compounds has led to the preparation of steroidal pyrazoles related to the progestational and cortical hormones, as well as to the fusion of steroids with other heterocyclic rings.

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TITANIUM TETRACHLORIDE–TRIALKYLALUMINUM COMPLEX—A CYCLIZING CATALYST FOR ACETYLENIC COMPOUNDS

Sir:

Heretofore reactions of acetylene and terminal acetylenic compounds with catalyst such as obtained from the reaction of triisobutylaluminum with titanium tetrachloride resulted only in the polymerization of these compounds to high polymers.[1] Using the same type of catalyst we have found that by regulating the ratio of $(i\text{-Bu})_3Al$ to $TiCl_4$ we can trimerize symmetrical acetylenic compounds to hexasubstituted benzenes. Thus (as shown in Fig. 1) diphenylacetylene can be

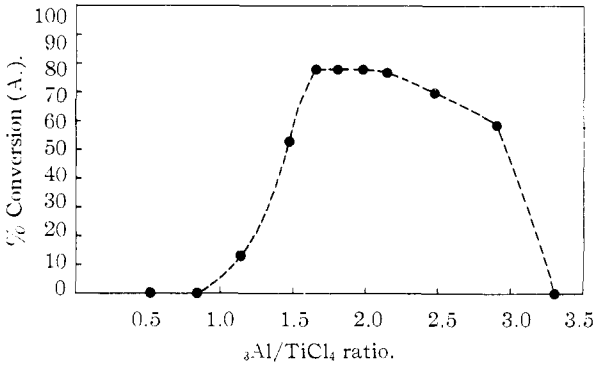


Fig. 1.—Conversion to hexaphenylbenzene *versus* mole ratio $(i\text{-Bu})_3Al/TiCl_4$: (A) conversions taken after 10 minutes at room temperature except those cases where there was 0% conversion, in which case more rigorous conditions were used after the 10 minutes had elapsed.

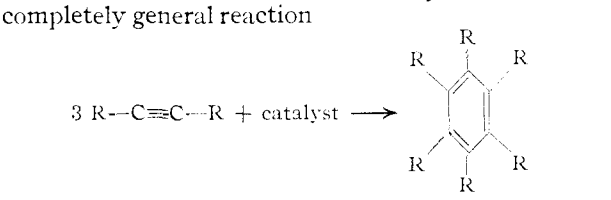
trimerized to hexaphenylbenzene only between $(i\text{-Bu})_3Al/TiCl_4$ ratios of 1/1 to 3/1, although polymerization of olefins readily occurs outside these limits. Control experiments demonstrated that neither triisobutylaluminum, titanium tetrachloride, nor titanium trichloride alone could effect cyclic trimerization. In fact the $(i\text{-Bu})_3Al/TiCl_3$ polymerization catalyst does not catalyze cyclic trimerization of any acetylenes reported in this paper.

This type of cyclic trimerization is not limited to diphenylacetylene. Any symmetrical dialkyl or diarylacetylene will trimerize at the proper catalyst ratio. Dimethylacetylene trimerizes to hexamethylbenzene in 100% yield at $(i\text{-Bu})_3Al/TiCl_4$ ratios of 1.8/1. The "crude" product melted at 161–162° compared to 162° obtained by Smith and Lux[2] after recrystallization. One hundred per cent. yields of hexaethylbenzene (m.p. "crude" product 127–128° compared to 126–128° obtained by Smith and Guss[3] after recrystallization) were obtained from diethylacetylene using the $(i\text{-Bu})_3Al$ $TiCl_4$ catalyst. Seventeen moles of cyclic trimer per mole of catalyst were obtained, indicating the "catalytic" nature of this reaction.

Identities of the hexasubstituted benzenes were established by comparison of infrared spectra with those of authentic samples. Hexamethylbenzene and hexaethylbenzene were available but hexaphenylbenzene was synthesized[4] by condensation of diphenylacetylene[5] with tetraphenylcyclopentadienone. The infrared and X-ray spectra of the authentic and unknown samples were identical.

Recently, using organometal compounds, Zeiss[6] has obtained cyclic trimers of two acetylenic compounds. The organometal compound was used in stoichiometric amounts, rather than in the small quantities normally considered as catalytic amounts, and the reaction has required specific organometal compounds for specific symmetrical acetylenes. Nevertheless, the similarity of products obtained from Zeiss' systems and the $(i\text{-Bu})_2Al$ $TiCl_4$ system might reflect a relationship between the two which will provide a valuable clue to the $(i\text{-Bu})_3Al$ $TiCl_4$ catalyst structure.

In summary, the catalytic system $(i\text{-Bu})_3Al$ $TiCl_4$ previously believed applicable only to the polymerization of olefins (or acetylenes) to form high polymers can now be used for cyclic trimerization of disubstituted acetylenes in the completely general reaction



(1) (a) G. Natta, P. Pino and G. Mazzanti, Belgian Patents 546,151, Mar. 16, 1956; (b) 548,927, June 22, 1956.

(2) L. I. Smith and A. R. Lux, THIS JOURNAL, **51**, 2997 (1929).
(3) L. I. Smith and C. O. Guss, *ibid.*, **62**, 2625 (1940).
(4) W. Dilthey and G. Hurtig, *Ber.*, **67B**, 495, 2005 (1934).
(5) L. I. Smith and M. M. Falkof, *Org. Syn.*, **22**, 50 (1942).
(6) (a) H. H. Zeiss and W. Herwig, THIS JOURNAL, **80**, 2913 (1958); (b) M. Tsutsui and H. Zeiss, p. 59-P, Abstracts of Papers, 134th Meeting American Chemical Society, September 7–12, Chicago, Illinois.

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PARTIAL ASYMMETRIC SYNTHESIS IN THE ADDITION OF DIPHENYLDIAZOMETHANE TO OLEFINS[1]

Sir:

Cram and Abd Elhafez[2] and Prelog and coworkers[3,4] have studied the course of asymmetric syntheses in a number of systems and have found

(1) This work was supported by a grant from the National Science Foundation.
(2) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).
(3) V. Prelog, *et al.*, *Helv. Chim. Acta*, **36**, 308 (1953).
(4) For a review of this work, see J. A. Mills and W. Klyne, Ch. 5 in "Progress in Stereochemistry," Vol. I, Academic Press Inc., New York, N. Y., pp. 198–201.

that it was dependent on the conformation of the asymmetric center. The concepts derived from this work have been applied, with success, to the correlation of configuration.[4] These studies involved addition reactions to a carbonyl function which was located adjacent to or near an asymmetric center. Asymmetric syntheses by the addition to an olefinic moiety in both catalytic[5] and non-catalytic[6] reactions also have been observed.

We wish to report that the addition of diphenyldiazomethane to (−)-menthyl acrylate (I, R = H) and (−)-menthyl methacrylate (I, R = CH_3) results in partial asymmetric synthesis.

When 1.48 g. (0.0076 mole) of diphenyldiazomethane was added slowly to 1.61 g. (0.0076 mole) of (−)-menthyl acrylate[7] an exothermic reaction accompanied by immediate decolorization and evolution of nitrogen occurred. In order to avoid any possibility of the resolution of the diastereoisomers that are formed, isolation of products at this point was avoided. The reaction mixture was saponified by refluxing with a solution of 0.85 g. of potassium hydroxide in 60 ml. of ethylene glycol for 52 hours to assure completeness.[8] The reaction mixture was diluted with water and extracted 4–5 times with ether. The residue from the ether extract showed less than 0.1% of carbonyl absorption at 1720 cm.$^{-1}$. The aqueous fraction was acidified with hydrochloric acid and yielded 1.08 g. (60%) of 2,2-diphenylcyclopropanecarboxylic acid (II, R = H), m.p. 163–164.5°, whose infrared spectrum was identical in all respects with an authentic sample[9] and which had a rotation of $[\alpha]^{24}D$ −4.7° ($CHCl_3$). This corresponds to 2.2% of asymmetric synthesis.

The above procedure was repeated using (−)-menthyl methacrylate[7,10,11] (I, R = CH_3) which after complete saponification yielded 1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II, R = CH_3) in 74% yield, m.p. 176–180.5°, whose infrared spectrum was identical with that of an authentic sample.[12] The rotation of $[\alpha]^{24}D$ +3.7° ($CHCl_3$) corresponds to 10% asymmetric synthesis.

It has been demonstrated that the addition of diazoalkanes to olefins proceeds in a stereospecific manner.[13] The resulting Δ′-pyrazolines in turn decompose stereospecifically.[13] The asymmetric synthesis can be visualized as proceeding by an attack of the diazoalkane predominantly in the direction indicated by the arrow in Fig. 1 to yield

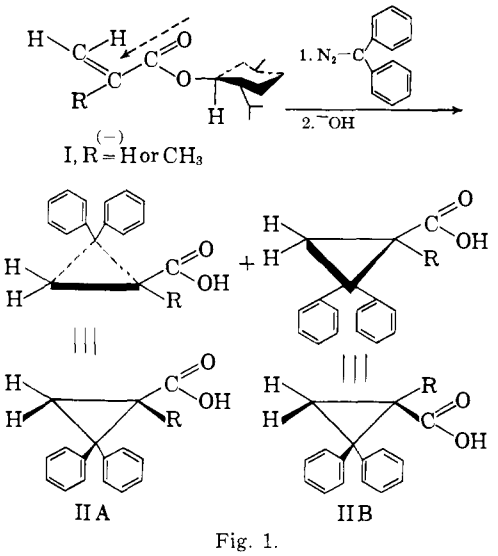
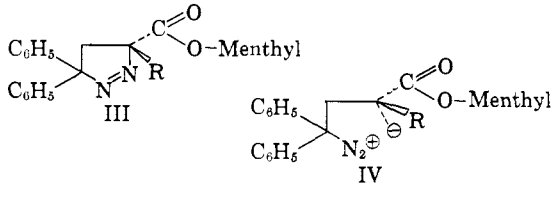


Fig. 1.

III in excess, which decomposes to yield a predominance of IIA. An alternative is the formation of a zwitterion intermediate IV which can collapse directly to product rather than proceed through III. That this reaction proceeds via a diphenyl-



methylene (carbene) addition[14] has been ruled out provisionally in this case[15] on the observation that the copper-catalyzed addition of diphenyldiazomethane to (−)-menthyl acrylate yielded totally inactive product.

On the basis of Prelog's[4] correlation we have assigned the D-configurations to (−)-IIA (R = H) and to (+)-IIA (R = CH_3). The detailed mechanism of the addition of various diazoalkanes to olefins and its application to the establishment of absolute configuration of other cyclopropanecarboxylic acids is currently under investigation.

(5) M. G. Vavon and B. Jakubowicz, *Bull. Soc. Chim.*, **53**, 1111 (1933); D. Lipkin and T. D. Stewart, THIS JOURNAL, **61**, 3295 (1939); C. L. Arcus and D. G. Smyth, *J. Chem. Soc.*, 35 (1955).

(6) M. P. Balfe, J. Kenyon and D. Y. Waddan, *ibid.*, 1367 (1954).

(7) C. S. Marvel and R. L. Frank, THIS JOURNAL, **64**, 1675 (1942).

(8) The use of alcoholic potassium hydroxide or shorter reaction time resulted in incomplete saponification as shown by the appearance of a carbonyl band at 1720 cm.$^{-1}$ in the infrared spectrum of the neutral fraction from the saponification. Incomplete saponification would be equivalent to partial resolution.[3]

(9) H. M. Walborsky and F. M. Hornyak, *ibid.*, **77**, 6026 (1955).

(10) C. E. Rehberg, M. B. Dixon and C. H. Fisher, *ibid.*, **67**, 210 (1945).

(11) We wish to thank Mr. A. Young for the preparation of this ester.

(12) H. M. Walborsky and F. J. Impastato, *Chem. and Ind.*, 1690 (1958).

(13) K. V. Auwers, *et al.*, *Ber.*, **66**, 1198 (1933); *Ann.*, **470**, 284 (1924); **496**, 252 (1932); J. van Alphen, *Rec. Trav. Chim.*, **62**, 210 (1943).

(14) P. S. Skell and A. Y. Garner, THIS JOURNAL, **78**, 5430 (1956); W. von E. Doering and P. M. LaFlamme, *ibid.*, **78**, 5447 (1956).

(15) Whether other methylenes will yield asymmetric synthesis is under investigation.

(16) To whom inquiries regarding this work should be sent.

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RECEIVED FEBRUARY 2, 1959

ENZYMATIC SYNTHESIS OF CARNOSINE FROM β-ALANYL ADENYLATE AND HISTIDINE

Sir:

Previous studies have provided evidence for enzymatic formation of amino acyl adenylates[1,2]; however, proof that such anhydrides are inter-

(1) M. Karasek, P. Castelfranco, P. R. Krishnaswamy and A. Meister, THIS JOURNAL, **80**, 2335 (1958).

(2) H. S. Kingdon, L. T. Webster and E. W. Davie, *Proc. Nat. Acad. Sci. (U.S.)*, **44**, 757 (1958).