[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. XIII. Allylic Rearrangement in the Reactions of *cis*- and *trans*-3,5-Dibromocyclopentenes with Dimethylamine[1]

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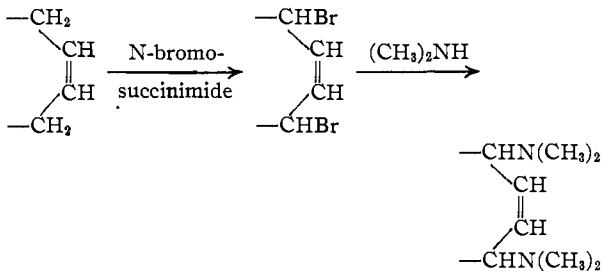
Bromination of cyclopentene with two molar equivalents of N-bromosuccinimide formed a mixture of *cis*- and *trans*-3,5-dibromocyclopentenes (I and II) in 63% yield. The reaction of I and II with dimethylamine proceeded with allylic rearrangement and formed *trans*-1,2-bis-(dimethylamino)-3-cyclopentene (III) in each case, in 65–67% yield. Identity of the samples of III formed from I and II was established by comparison of physical constants, solid derivatives (Table I) and infrared spectra (Fig. 1). Evidence for the structure of III was obtained by catalytic reduction to *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV). The samples of IV prepared from I and II *via* III were shown to be identical by comparison of physical properties, solid derivatives (Table II) and infrared spectra (Fig. 2). The structure of IV was established by an independent synthesis through the sequence: α-carbethoxycyclopentanone → 1,2-cyclopentanedione monoxime (V) → 1,2-cyclopentanedione dioxime (VI) → *trans*-1,2-diaminocyclopentane (VII) → *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV). The identity of IV prepared by this route with samples prepared from I and II *via* III was shown by comparison of physical properties, infrared spectra and properties of the picrates and picrylsulfonates, including X-ray diffraction patterns of the picrates.

This paper reports an investigation of the reaction of *cis*- and *trans*-3,5-dibromocyclopentenes (I and II) with dimethylamine as model reactions for a critical step in a procedure depending upon subsequent Hoffmann exhaustive methylation for conversion of an olefin to a triene:



The reaction of 3,8-dibromocycloöctene with dimethylamine previously was found to form a bis-(dimethylamino)-cycloöctene of unknown structure in very poor yield.[3] The 3,5-dibromocyclopentenes offered advantage for study as models because the structures of the *cis* and *trans* forms were established by Thiele by oxidation to *meso* and racemic α,α′-dibromoglutaric acids, respectively.[4] Proof of structure of the diamines formed by reaction of I and II with dimethylamine also was expected to be simpler than would be the case for corresponding products in the eight-membered series.

The bromination of cyclopentene with N-bromosuccinimide in the presence of benzoyl peroxide formed 63% of a mixture of *cis*- and *trans*-3,5-dibromocyclopentenes (I and II), which was partially separated by fractional distillation and crystallization of the *trans* isomer. The quantity of I and II required for study of the reaction with dimethylamine was prepared by the simpler method of addition of bromine to cyclopentadiene according to procedures described previously.[5] Both the *cis*- and *trans*-dibromides reacted readily with dimethylamine in benzene solution. The major product obtained from each dibromide was a bis-(dimethylamino)-cyclopentene, which was isolated in 65–67% yield. The diamines formed from I and II had very similar physical constants, as did their picrates and picrylsulfonates (Table I). Mixed melting points of the two picrates and of the two picrylsulfonates were not depressed, and infrared spectra (Fig. 1) of the diamines were identical within experimental error, indicating that the products were identical rather than isomeric.

TABLE I

PROPERTIES OF THE BIS-(DIMETHYLAMINO)-CYCLOPENTENE

	Derived from I	Derived from II	Mixed m. p., °C.
B.p., °C.	71–72 (9 mm.)	66–67 (8 mm.)	
$n^{25}D$	1.4682	1.4674	
d^{25}_4	0.8876	0.8870	
Dipicrate, m.p., °C.	182.6–183.5	184.5–185.7	183–184
Dipicrylsulfonate, m.p., °C.	215.5–216 dec.	214.5–215 dec.	214.5–215 dec.
Methiodide, m.p., °C.	197.8–198.4 dec.	200.6–201 dec.	198–199 dec.

The diamine samples obtained from I and II were hydrogenated in the presence of a palladium catalyst. The hydrogen absorptions in the two reductions were 117 and 108% of one molar equivalent, respectively, indicating partial cleavage at labile allylic positions with the formation of dimethylamine. The occurrence of cleavage as a side reaction was proved by the isolation of small amounts of dimethylamine as the hydrochloride (characterized by conversion to 1,1-dimethyl-3-phenylthiourea) in both cases. The properties of the bis-(dimethylamino)-cyclopentane samples which were obtained from the two hydrogenations and the melting points of the picrate and picrylsulfonate derived from each reduction product are summarized in Table II. The close corre-

TABLE II

PROPERTIES OF THE BIS-(DIMETHYLAMINO)-CYCL OPENTANE

	Derived from I	Derived from II	Mixed m. p., °C.
B.p., °C.	43–44.5 (1.5 mm.)	39–40 (1 mm.)	
$n^{25}D$	1.4567	1.4570	
d^{25}_4	0.8661	0.8668	
Dipicrate, m.p., °C.	222.5–223.5 dec.	223.5–224.5 dec.	222.5–223.5 dec.
Dipicrylsulfonate, m.p., °C.	207.6–208 dec.	207.8–208.2 dec.	207.8–208.2 dec.

(1) Supported in part by the Office of Naval Research under Contract N5ori-07822, Project Designation NR-055-96.

(2) Arthur D. Little Fellow, 1949–1950.

(3) A. C. Cope and L. L. Estes, Jr., THIS JOURNAL, **72**, 1128 (1950).

(4) J. Thiele, *Ann.*, **314**, 296 (1901).

(5) (a) E. H. Farmer and W. D. Scott, *J. Chem. Soc.*, 172 (1929); (b) A. T. Blomquist and W. G. Mayes, *J. Org. Chem.*, **10**, 134 (1945); (c) E. B. Reid and J. F. Yost, THIS JOURNAL, **72**, 1807 (1950).

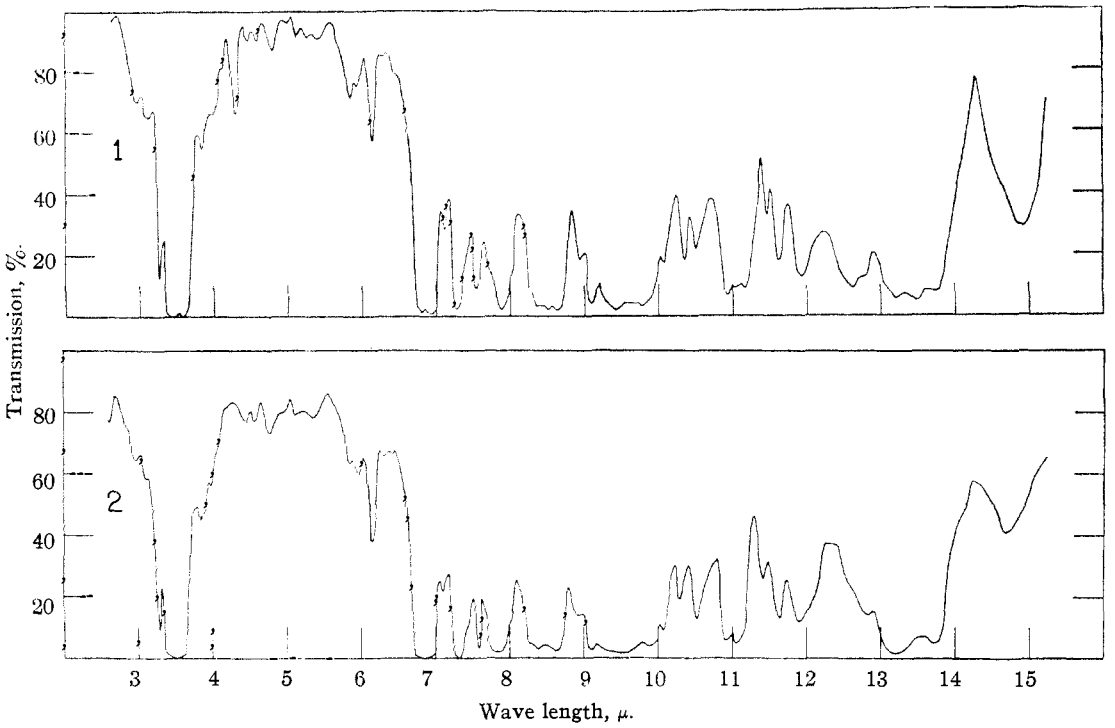


Fig. 1.—Infrared absorption spectra of samples of *trans*-1,2-bis-(dimethylamino)-3-cyclopentene (III): curve 1, sample prepared from I; curve 2, sample prepared from II.

spondence of physical constants, including melting points and mixed melting points of the solid derivatives, indicate that the diamines obtained by hydrogenation are identical. This conclusion is supported by the identity (within experimental error) of their infrared absorption spectra (Fig. 2).

It is concluded from these data that the same diamine is formed by the reaction of I and II with dimethylamine; the diamine is believed to be

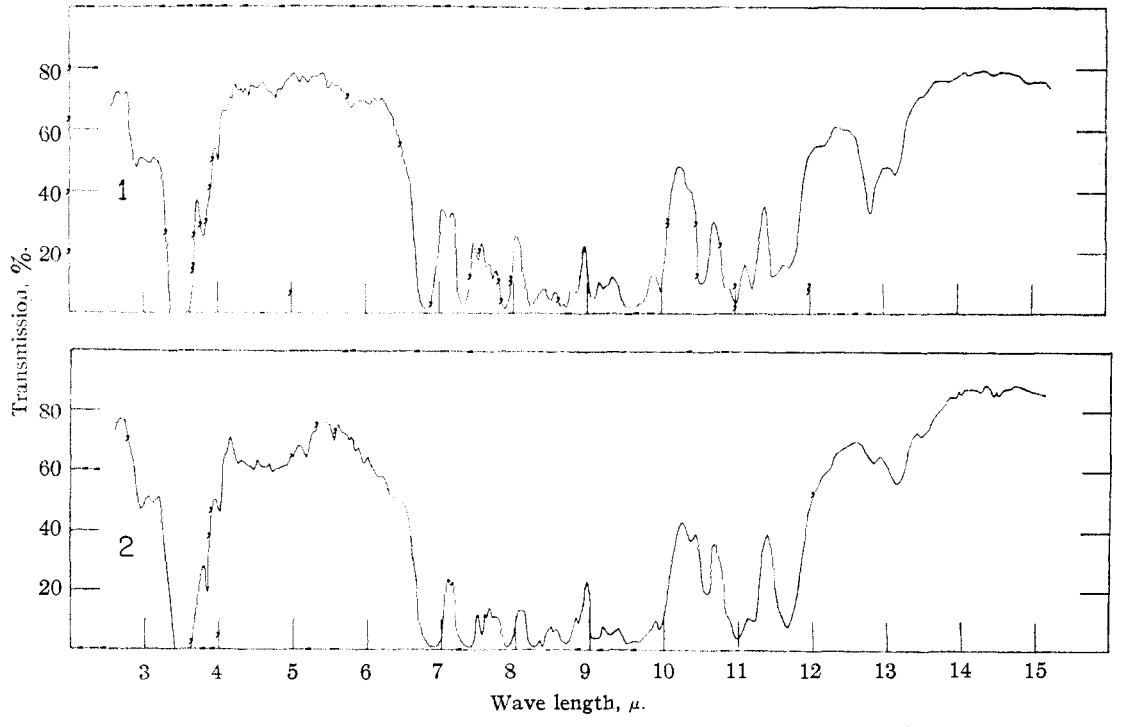
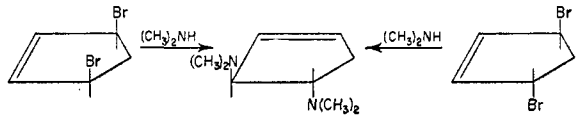


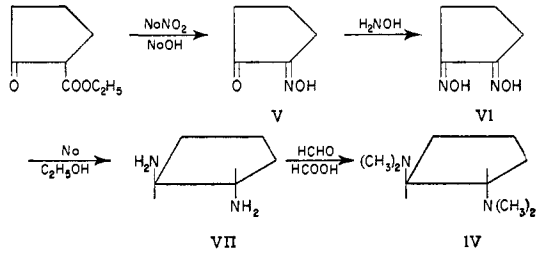
Fig. 2.—Infrared absorption spectra of samples of *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV): curve 1, sample prepared from III derived from I; curve 2, sample prepared from III derived from II.

trans-1,2-bis-(dimethylamino)-3-cyclopentene (III).



I III II

Evidence supporting this assignment of structure was obtained by an independent synthesis of the reduction product of III, *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV), by the following series of reactions. A similar method has been used for the preparation of *trans*-1,2-diaminocyclohexane from α-carbethoxycyclohexanone.[6]

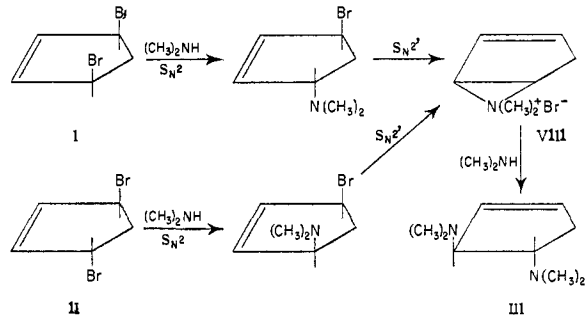


V VI VII IV

The product obtained from the reaction of α-carbethoxycyclopentanone with sodium nitrite and sodium hydroxide in water was chiefly a mixture of two monoximes (Va and Vb) of 1,2-cyclopentanedione. One monoxime (Va) crystallized from a mixture of ether and petroleum ether as a monohydrate which lost water of crystallization readily. The other monoxime (Vb) crystallized from the same solvents as a hemihydrate which was stable at room temperature. Both Va and Vb were converted into 1,2-cyclopentanedione dioxime (VI) by treatment with hydroxylamine hydrochloride and sodium acetate. The yield of the dioxime VI was 66–68% from α-carbethoxycyclopentanone when the monoximes were not isolated. The reduction of VI to *trans*-1,2-diaminocyclopentane (VII) was effected by treatment with sodium in absolute ethanol by a procedure previously described[7]; the *trans* configuration of the diamine has been proved by resolution into *d*- and *l*-forms.[7] The diamine VII was methylated by treatment with formaldehyde and formic acid,[8] which yielded *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV) (assuming that inversion of configuration did not occur during methylation).

The physical properties of the sample of *trans*-1,2-bis-(dimethylamino)-cyclopentane (IV) prepared from VII were very similar to the properties of IV derived from I and II (by conversion to III followed by hydrogenation). The infrared spectra of the three samples of IV also were identical within experimental error, except for the presence in IV prepared from VII of bands at 5.85 and 6.19 μ indicating contamination with an impurity, probably a carbonyl compound. The dipicrate and dipicrylsulfonate of IV prepared from VII had the same melting points and showed no depression in mixed melting points with corresponding derivatives of IV obtained from I and II. Since these derivatives melted with decomposition, additional confirmation of identity was sought, and was obtained by comparison of the X-ray diffraction patterns of samples of the dipicrate of IV derived from I, II and VII, which were identical within experimental error.

A possible course for the reaction of I and II with dimethylamine which would lead to the same product from both isomers consists in a normal displacement with inversion, followed by an intramolecular displacement by an S_N2' mechanism[9] forming an ethylenimmonium intermediate (VIII), which would be expected to lead to III by reaction with dimethylamine with inversion of configuration. A number of alternate paths could lead to III, but VIII is probably the final intermediate since the product has the *trans* configuration.



I VIII II III

Experimental[10]

Bromination of Cyclopentene.—A mixture of 25.3 g. of cyclopentene, 200 ml. of carbon tetrachloride, 132.4 g. of technical N-bromosuccinimide and 1 g. of benzoyl peroxide was heated under reflux for 4 hours, cooled with ice and filtered to remove succinimide. The filtrate was washed with 5% sodium carbonate solution and cold water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was distilled rapidly at 3 mm. and the light yellow distillate was fractionated through a 15 × 1.2 cm. Vigreux column. The mixture of *cis*- and *trans*-3,5-dibromocyclopentenes that was obtained was separated into seven fractions; the total yield was 53 g. (63%), b.p. 52–73° (3 mm.), $n^{25}D$ 1.5690–1.5889. Samples of fractions no. 2 (b.p. 54–55° at 3 mm., $n^{25}D$ 1.5700) and no. 7 (b.p. 73° at 3 mm., $n^{25}D$ 1.5889) were characterized by carbon-hydrogen analyses which were in agreement with the formula $C_5H_6Br_2$. Fractions no. 6 and 7 crystallized and after recrystallization from 30–60° petroleum ether melted at 43.4–44.2° (ref. 5b reports m.p. 45° for *trans*-3,5-dibromocyclopentene). The samples of *cis*- and *trans*-3,5-dibromocyclopentenes which were used to investigate the reaction with dimethylamine (described below) were prepared by the addition of bromine to cyclopentadiene.[5]

Reaction of *cis*-3,5-Dibromocyclopentene (I) **with Dimethylamine.**—*cis*-3,5-Dibromocyclopentene (I), 14.7 g., $n^{25}D$ 1.5751, prepared from cyclopentadiene and bromine in chloroform,[5b] was added to a solution of 35 g. of dimethylamine in 200 ml. of dry benzene that was cooled in an ice-bath. The mixture was allowed to stand overnight at room temperature, and then was extracted with 200 ml. of 15% hydrochloric acid. The aqueous phase was made alkaline by adding 60 g. of solid sodium hydroxide with cooling and stirring, and then was extracted with three 100-ml. and two 50-ml. portions of ether. The ether extracts were combined and concentrated, and the residue

(6) F. M. Jaeger and J. A. van Dijk, *Proc. Acad. Sci. Amsterdam*, **39**, 584 (1936) [*C. A.*, **30**, 6341 (1936)]; F. M. Jaeger and L. Bijkerk, *ibid.*, **40**, 12 (1937) [*C. A.*, **31**, 4960 (1937)]; T. A. Geissmann and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).

(7) F. M. Jaeger and H. B. Blumedal, *Z. anorg. allgem. Chem.*, **175**, 161 (1928).

(8) General procedure of H. T. Clark, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(9) R. E. Kepner, S. Winstein and W. G. Young, *ibid.*, **71**, 115 (1949).

(10) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates for analyses.

was dissolved in 150 ml. of 2 *N* hydrochloric acid and heated at 55–65° for 5 minutes to hydrolyze any vinyl-type amines. The solution was cooled, extracted with 75 ml. of ether, and made basic with 35 g. of sodium hydroxide. The product was extracted with three 75-ml. portions of ether, dried over sodium sulfate and distilled through a 17 × 1.0 cm. Vigreux column. The yield of a bis-(dimethylamino)-cyclopentene was 6.76 g. (67.6%), b.p. 71–72° (9 mm.), $n^{25}D$ 1.4682, d^{25}_4 0.8876.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76; N, 18.18. Found: C, 69.84; H, 11.91; N, 18.18.

A dipicrate was prepared from 0.3 g. of the amine and 1.0 g. of picric acid in 25 ml. of 95% ethanol and recrystallized twice from a mixture of ethanol and water; m.p. 182.6–183.5°.

Anal. Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.17; H, 3.94; N, 18.29. Found: C, 41.42; H, 3.96; N, 18.21.

The dipicrate was also obtained in a dimorphous form melting at 221.4–222.2° (dec.), which also was characterized by analysis.

A dipicrylsulfonate was prepared from 0.1 g. of the amine and 1.0 g. of picrylsulfonic acid in 25 ml. of 95% ethanol and recrystallized twice from a mixture of ethanol and water; m.p. 215.5–216° (dec.).

Anal. Calcd. for $C_{21}H_{24}N_8O_{18}S_2$: C, 34.05; H, 3.27; N, 15.13. Found: C, 34.13; H, 3.53; N, 14.81.

A solution of the diamine (8.86 g.) and 40.4 g. of methyl iodide in 300 ml. of absolute ethanol was heated under reflux on a steam-bath for 5 minutes, and then cooled slowly. The total yield of the dimethiodide obtained by filtration and concentration of the filtrate was 23.75 g. (94.5%). An analytical sample which was recrystallized from absolute ethanol melted at 197.8–198.4° (dec.).[11]

Anal. Calcd. for $C_{11}H_{24}I_2N_2$: N, 6.39. Found: N, 6.29.

A solution of 5.61 g. of the amine in 100 ml. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 1.0 g. of 10% palladium-on-Norit.[12] The absorption of hydrogen stopped after 7 hours and amounted to 117% of one molar equivalent. After filtration to remove the catalyst the ethanol was distilled at atmospheric pressure through a 24 × 1.2 cm. column packed with glass helices. The distillate contained dimethylamine, which was converted to the hydrochloride and identified by treatment with phenyl isothiocyanate in the presence of aqueous sodium hydroxide, which formed 1,1-dimethyl-3-phenylthiourea (m.p. 132–133° and mixed m.p. with a known sample 131.5–133°). Distillation of the residue yielded 3.6 g., b.p. 71.5–73° (10 mm.), which was redistilled through an 18 × 0.8 cm. column packed with glass helices. The bis-(dimethylamino)-cyclopentane which was obtained had b.p. 43–44.5° (1.5 mm.), $n^{25}D$ 1.4567; d^{25}_4 0.8661.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.90; N, 17.93. Found: C, 69.13; H, 12.85; N, 17.69.

The saturated diamine (0.1 g.) was treated with 0.5 g. of picric acid in 30 ml. of 95% ethanol and converted into a dipicrate, which was recrystallized twice from a mixture of ethanol and water; m.p. 222.5–223.5° (dec.).

Anal. Calcd. for $C_{21}H_{26}N_8O_{14}$: C, 41.04; H, 4.26; N, 18.24. Found: C, 41.15; H, 4.41; N, 18.17.

The saturated diamine (0.09 g.) also was treated with 0.5 g. of picrylsulfonic acid in 35 ml. of 95% ethanol and converted into the dipicrylsulfonate, which was recrystallized three times from a mixture of ethanol and water; m.p. 207.6–208° (dec.).

Anal. Calcd. for $C_{21}H_{26}N_8O_{18}S_2$: C, 33.96; H, 3.53; N, 15.09. Found: C, 34.08; H, 3.91; N, 15.23.

Reaction of *trans*-3,5-Dibromocyclopentene (II) with Dimethylamine.—*trans*-3,5-Dibromocyclopentene (II) (prepared from cyclopentadiene and bromine in petroleum ether[5b] and recrystallized from petroleum ether), 22.1 g., was added to a solution of 49 g. of dimethylamine in 400 ml. of dry benzene with cooling in an ice-bath. The mixture was allowed to stand at room temperature for 7 days. The bis-(dimethylamino)-cyclopentene which was formed was isolated in the same manner as the product obtained from I and dimethylamine (described above). The yield was 9.85 g. (65%), b.p. 69–70° (9 mm.). An analytical sample redistilled through a semimicro column[13] had b.p. 66–67° (8 mm.), $n^{25}D$ 1.4674, d^{25}_4 0.8870.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76; N, 18.18. Found: C, 70.21; H, 11.87; N, 18.46.

The dipicrate was prepared from the diamine and picric acid in 95% ethanol, and after two recrystallizations from a mixture of ethanol and water melted at 184.5–185.7°. A mixed melting point with the dipicrate of the diamine prepared from the *cis*-dibromide (I) and dimethylamine (described above) was 183–184°.

Anal. Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.17; H, 3.94; N, 18.29. Found: C, 41.42; H, 4.20; N, 18.35.

The dipicrylsulfonate prepared from the diamine and picrylsulfonic acid in 95% ethanol and purified by three recrystallizations from a mixture of ethanol and water melted at 214.5–215° (dec.). A mixed melting point with the dipicrylsulfonate of the diamine prepared from the *cis*-dibromide and dimethylamine (described above) was 214.5–215° (dec.).

Anal. Calcd. for $C_{21}H_{24}N_8O_{18}S_2$: C, 34.05; H, 3.27; N, 15.13. Found: C, 33.99; H, 3.51; N, 15.38.

A solution of 7.71 g. of the diamine and 33 g. of methyl iodide in 250 ml. of absolute ethanol was heated under reflux on a steam-bath for 5 minutes, allowed to stand overnight, and filtered. The dimethiodide collected plus the small quantity obtained by concentration of the filtrate amounted to 20.8 g. (95%). An analytical sample which was recrystallized from absolute ethanol melted at 200.6–201° (dec.).[11] A mixed m.p. with the dimethiodide of the diamine prepared from the *cis*-dibromide I and dimethylamine (described above) was 198–199° (dec.).[11]

Anal. Calcd. for $C_{11}H_{24}I_2N_2$: C, 30.15; H, 5.52; N, 6.39. Found: C, 30.07; H, 5.74; N, 6.27.

A solution of 4.36 g. of the diamine in 100 ml. of absolute ethanol absorbed 108% of one molar equivalent of hydrogen in the presence of 1.0 g. of 10% palladium-on-Norit[12] in a period of 6 hours. The reduction product was isolated in the same manner as the saturated diamine described in the preceding section. The ethanol distillate contained dimethylamine, identified as 1,1-dimethyl-3-phenylthiourea, m.p. 132.5–133°. The bis-(dimethylamino)-cyclopentane which was obtained had b.p. 39–40° (1 mm.), $n^{25}D$ 1.4570, d^{25}_4 0.8668.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.90; N, 17.93. Found: C, 69.21; H, 12.88; N, 17.72.

The dipicrate of the bis-(dimethylamino)-cyclopentane described above, prepared in 95% ethanol and purified by three crystallizations from a mixture of ethanol and water, melted at 223.5–224.5° (dec.). A mixed melting point with the dipicrate of the reduction product of the diamine obtained from the *cis*-dibromide (I) and dimethylamine was 222.5–223.5° (dec.).

Anal. Calcd. for $C_{21}H_{26}N_8O_{14}$: C, 41.04; H, 4.26; N, 18.24. Found: C, 41.10; H, 4.38; N, 18.13.

The dipicrylsulfonate of the bis-(dimethylamino)-cyclopentane described above, prepared in 95% ethanol and purified by two recrystallizations from ethanol and water, melted at 207.8–208.2° (dec.). A mixed melting point with the dipicrylsulfonate obtained from the reduction product derived from the *cis*-dibromide (I) and dimethylamine was 207.8–208.2° (dec.).

Anal. Calcd. for $C_{21}H_{26}N_8O_{18}S_2$: C, 33.96; H, 3.53; N, 15.09. Found: C, 33.83; H, 3.98; N, 14.82.

Reaction of *trans*-3,5-Dibromocyclopentene (II) with Trimethylamine.—A solution of 4.18 g. of II in 50 ml. of dry methanol was added slowly to an ice-cold solution of 15.5 g. of trimethylamine in 150 ml. of dry methanol. The mixture was allowed to stand at room temperature for 5 days. The methanol and excess trimethylamine were distilled under reduced pressure, and the brown, partially crystalline residue was washed with pentane. The light brown powder (3.08 g., 58.5%) was recrystallized twice from absolute

(11) The sample was introduced into the melting point bath 10° below the melting point and the temperature was increased at a rate of 2° per minute.

(12) "Organic Syntheses," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 32.

(13) C. W. Gould, G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

ethanol. The bis-(dimethylamino)-cyclopentene dimethobromide obtained in this manner was a white, crystalline salt which decomposed without melting at 200–250°. No evidence was obtained concerning its structure.

Anal. Calcd. for $C_{11}H_{24}Br_2N_2$: C, 38.38; H, 7.03; N, 8.14. Found: C, 38.15; H, 6.93; N, 7.96.

Preparation of 1,2-Cyclopentanedione Monoxime from α-Carbethoxycyclopentanone.—α-Carbethoxycyclopentanone[14] (31.2 g., b.p. 102–104° at 12 mm.) was added to a solution of 8.8 g. of sodium hydroxide in 160 ml. of water. A heavy white precipitate formed immediately. A solution of 13.8 g. of sodium nitrite in 32 ml. of water was added, and the mixture was shaken vigorously under nitrogen with a mechanical shaker for 44 hours at room temperature. The reaction mixture (a clear yellow solution) was cooled to 0° and treated with 70 ml. of 6 *N* sulfuric acid, which caused the evolution of carbon dioxide and oxides of nitrogen. The solution was extracted with ether in a continuous extractor for 5.5 hours, and the extract was concentrated in a nitrogen atmosphere under reduced pressure to a volume of 40 ml. A large part of the concentrate crystallized. Fractional crystallization from ether–petroleum ether of a portion of the crystalline solids obtained in this manner resulted in the separation of a small amount of adipic acid (m.p. and mixed m.p. with a known sample 151.5–152.5°) as the least soluble component. Dilution of the mother liquors with petroleum ether after separation of the adipic acid caused crystallization of two monoximes, which were separated mechanically. One form (Va), slightly less soluble than the other, crystallized in long needles which formed a fine yellow powder on exposure to the air. It melted in the range 63–80° after numerous crystallizations from a mixture of ether and petroleum ether or from water. This form sublimed on drying under reduced pressure, and satisfactory analytical results could not be obtained on the anhydrous oxime. A sample melting at 65.5–67° which was obtained by recrystallization from water was analyzed as the hydrate after air-drying.

Anal. Calcd. for $C_5H_7NO_2 \cdot H_2O$: C, 45.79; H, 6.92; N, 10.62; H_2O, 13.74. Found: C, 45.86; H, 7.04; N, 10.62; H_2O, 15.7 (loss on drying to approximately constant weight at 50° and 35 mm. for 8 hours).

The other monoxime (Vb) crystallized readily from water or from a mixture of ether and petroleum ether, forming colorless rhomboids melting at 78.5–81° from the latter solvent pair. It proved to be a hemihydrate which did not lose water of crystallization on drying at room temperature and 1 mm. over phosphorus pentoxide.

Anal. Calcd. for $C_5H_7NO_2 \cdot {}^1/_2H_2O$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.27; H, 6.46; N, 11.13.

Both monoximes were identified by conversion to 1,2-cyclopentanedione dioxime (described below). The hydrate (83 mg.) was added to a solution of 82 mg. of sodium acetate in 0.5 ml. of water. Addition of 70 mg. of hydroxylamine hydrochloride in 0.5 ml. of water caused immediate precipitation of the dioxime, which after 1 hour was separated by centrifugation, washed with water and dried; the yield of 1,2-cyclopentanedione dioxime was 75%, m.p. 210–225° (dec.). The monoxime hemihydrate (81 mg.) was treated in the same way and yielded 74 mg. (87%) of the dioxime, m.p. 210–225° (dec.).

1,2-Cyclopentanedione Dioxime (VI).—The crude mixture of 1,2-cyclopentanedione monoximes suspended in a small amount of ether, obtained by the procedure described above from 31.2 g. of α-carbethoxycyclopentanone, was treated with a solution of 13.9 g. of hydroxylamine hydrochloride and 8.0 g. of sodium hydroxide in 50 ml. of water. Some heat was evolved and a precipitate formed immediately. The mixture was allowed to stand overnight at 5° and then was filtered. The dioxime was obtained in a yield of 16.8 g. (66%) as a light tan powder, m.p. 230–240° (dec.). An analytical sample was prepared by dissolving 1 g. of the crude product in 25 ml. of 2% aqueous sodium hydroxide at room temperature, treating the slightly turbid solution with Norit, filtering and neutralizing with 1 *N* hydrochloric acid. The dioxime precipitated and when the mixture was just neutral to phenolphthalein, the solid was separated by filtration and washed twice with water and once with acetone. Recovery of the dioxime was 83%. Repetition of the process furnished an analytically pure sample of the dioxime. On heating, it darkened at 192–205° and decomposed without melting at 210–225°.

Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.90; H, 6.31; N, 21.97.

***trans*-1,2-Diaminocyclopentane (VII).**—The dioxime was reduced by treatment with sodium and absolute ethanol by a procedure described previously,[7] except that the diamine was isolated directly from the steam distillate containing the reduction products by making it strongly alkaline with sodium hydroxide and extracting with trichloroethylene. The yield of the diamine was 29%, b.p. 65° (13.5 mm.), $n^{25}D$ 1.4850–1.4858. The diamine also was isolated as the dihydrochloride by neutralizing the steam distillate with hydrochloric acid, concentrating the solution and crystallizing the residue from a mixture of absolute ethanol and ether; the yield of the dihydrochloride was 77%. An analytical sample that was recrystallized from a mixture of absolute ethanol and ether decomposed at 287–290° after gradual darkening which began at 230°.

Anal. Calcd. for $C_5H_{14}N_2Cl_2$: C, 34.69; H, 8.15; N, 16.19. Found: C, 34.73; H, 8.30; N, 15.85.

The dipicrate of 1,2-diaminocyclopentane was prepared from 0.18 g. of the diamine and 1 g. of picric acid in 25 ml. of 95% ethanol and recrystallized twice from a mixture of ethanol and water; m.p. 233–233.5° (dec.).

Anal. Calcd. for $C_{17}H_{18}N_8O_{14}$: C, 36.57; H, 3.25. Found: C, 36.64; H, 3.44.

The diacetyl derivative of 1,2-diaminocyclopentane was prepared by treating the diamine with an excess of acetic anhydride in water. The product was isolated by concentrating the mixture to dryness and crystallizing the residue from absolute ethanol by the addition of dry ether. The diacetyl derivative melted at 226.5–227.5°; ref. 7 reports m.p. 219–220°.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.76; N, 15.21. Found: C, 58.51; H, 8.70; N, 15.07.

***trans*-1,2-Bis-(dimethylamino)-cyclopentane (IV).**—To 25 ml. of 87% formic acid was added 4.9 g. of sodium bicarbonate, 5.0 g. of *trans*-1,2-diaminocyclopentane dihydrochloride and 20 ml. of 37% formalin. The mixture was heated under reflux for 45 hours, cooled and diluted with an equal volume of water containing 7 ml. of concentrated hydrochloric acid. The mixture was distilled to dryness under reduced pressure, and a solution of the residue in 25 ml. of water was extracted with ether to remove any nonbasic impurities. The aqueous solution was made basic by adding a solution of 25 g. of sodium hydroxide in 40 ml. of water, and then was extracted with five 50-ml. portions of ether. The combined extracts were dried over sodium sulfate, concentrated in a nitrogen atmosphere under reduced pressure and the residue was distilled through an 18 × 0.8 cm. semi-micro column[13] containing a platinum spiral. The yield of *trans*-1,2-bis-(dimethylamino)-cyclopentane was 1.1 g., b.p. 45–46° (6 mm.), $n^{25}D$ 1.4578.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.90; N, 17.93. Found: C, 68.81; H, 13.15; N, 17.97.

The dipicrate of this sample of *trans*-1,2-bis-(dimethylamino)-cyclopentane melted at 224.5–225.3° (dec.), and gave mixed melting points of 222.5–223° (dec.) and 223.5–224° (dec.), respectively, with samples obtained from *cis*- and *trans*-3,5-dibromocyclopentenes by reaction with dimethylamine, hydrogenation and preparation of the picrates. The dipicrylsulfonate melted at 208–208.9° (dec.), and gave mixed melting points of 208.4–208.9° (dec.) and 208.3–208.8° (dec.), respectively, with samples obtained from *cis*- and *trans*-3,5-dibromocyclopentenes by reaction with dimethylamine, hydrogenation and preparation of the picrylsulfonates.

X-Ray Diffraction Patterns.—X-Ray diffraction patterns of samples of the dipicrate of IV derived from I, II and VII by the reaction sequences described above were determined by Dr. W. O. Statton, to whom we are indebted for the following data. The patterns were obtained with a Debye–Scherrer powder camera, using the K_α radiation from a tube with a copper target and operated at 40 kv. and 15 ma. The data presented below show good agreement in both the intensity and spacing of the lines for each pattern, and indicate that the structures of the three dipicrates are identical.

(14) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 116.

X-RAY DIFFRACTION PATTERNS

Intensity	Interplanar spacings (in Å.) of samples of the dipicrate of IV obtained *via* I	II	VII
Very weak	1.67	(Absent)	1.65
Very weak	1.77	(Absent)	1.76
Medium	1.93	1.97	2.00
Strong	2.18	2.21	2.21
Weak	2.50	2.47	2.58
Medium	2.89	2.94	2.90
Weak	3.19	3.12	(Absent)
Very strong	3.80	3.77	3.65
Medium	5.22	5.04	4.98
Strong	7.76	7.90	7.38

Infrared Absorption Spectra.—We are indebted to Dr. R. C. Lord, Mr. R. S. McDonald and Miss B. J. Fax for the measurement and interpretation of the infrared absorption spectra of III and IV (Figs. 1 and 2). The absorption spectra were determined for samples of the pure liquids with a Perkin–Elmer Spectrophotometer Model 12B.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. I. Alpha Amino Monocyclic β-Lactams[1]

BY JOHN C. SHEEHAN AND JAMES J. RYAN[2]

A new general synthesis has been developed which furnishes β-lactams bearing an amino function alpha to the lactam carbonyl, a combination of structural features present in penicillin. By interaction of a diacylaminoacyl chloride and benzalaniline in the presence of triethylamine a good yield of a β-lactam is obtained.

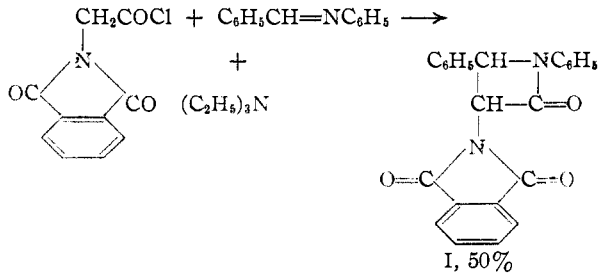
Procedures are given for the synthesis of 1,4-diphenyl-3-phthalimido-2-azetidinone, 1,4-diphenyl-(3-nitrophthalimido)-2-azetidinone, 1,4-diphenyl-3-dimethanesulfonylamino-2-azetidinone and 1,4-diphenyl-3-phenylacetamido-2-azetidinone.

The chemistry of β-lactams is of considerable current interest since this structure is the characteristic feature of the generally accepted formula for penicillin.

This communication reports a new and widely applicable synthesis[3] which furnishes β-lactams bearing an amino function alpha to the lactam carbonyl (position 3 of the azetidinone ring), a class of compounds for which there is no reported general synthesis. The combination of these structural components, β-lactam ring and α-amino function, is a key feature of the penicillin molecule.

Two new synthetic routes to β-lactams have been developed previously in this Laboratory.[4] This first communication of the series describes the preparation of a group of α-acylamino monocyclic β-lactams, and in particular the compound 1,4-diphenyl-3-phenylacetamido-2-azetidinone (III), which, like benzylpenicillin (penicillin G), is an α-phenylacetamido β-lactam. The fundamental reaction is illustrated by the preparation of 1,4-diphenyl-3-phthalimido-2-azetidinone (I).

Upon the addition of a benzene solution of phthaloylglycyl chloride to an equimolar amount of triethylamine and an excess of benzalaniline dissolved in benzene, a mild but essentially instantaneous reaction takes place, the β-lactam is formed, and a quantitative yield of triethylammonium chloride is precipitated. The lactam is isolated in good yield after removal of the amine



I, 50%

salt. Other inert solvents, such as ether, may be substituted for the benzene, and triethylamine may be replaced by other tertiary aliphatic amines. Also prepared in a similar manner were the lactams 1,4-diphenyl-3-(3-nitrophthalimido)-2-azetidinone and 1,4-diphenyl-3-(dimethanesulfonylamino)-2-azetidinone. The reaction apparently proceeds smoothly in cases where the nitrogen of the amino acid moiety is protected by substitution of both hydrogen atoms.

It is possible to visualize this reaction as proceeding by way of an intermediate "acylamino aldoketene," which adds to benzalaniline to yield the β-lactam. Since Staudinger[5] prepared the first β-lactam by the addition of diphenyl ketene to benzalaniline, there might appear to be a formal resemblance between the two methods. The ketene mechanism is probably not the true one, and from evidence to be given in a subsequent communication a different reaction course may be inferred.

A major advantage to the use of the phthaloyl group for protecting the nitrogen atom is its susceptibility to facile removal by means of hydrazine[6] with formation of the free amino compound. It has been shown that this cleavage proceeds rapidly under mild conditions without rupture of a normal peptide bond.[7] Treatment of I with hot alcoholic

(1) This communication is from part of a thesis submitted by J. J. R. to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of requirements for the Ph.D. degree, April, 1949.

(2) Monsanto Chemical Company, Merrimac Division, Everett, Mass.

(3) A preliminary report of extensions of this basic synthesis has been communicated, J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, THIS JOURNAL, **72**, 3828 (1950).

(4) J. C. Sheehan and P. T. Izzo, *ibid.*, **70**, 1985 (1948); **71**, 4059 (1949). J. C. Sheehan and A. J. Bose, *ibid.*, **72**, 5158 (1950). Footnotes in the latter communication refer to classical syntheses of β-lactams.

(5) H. Staudinger, *Ber.*, **40**, 1145 (1907).

(6) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(7) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **71**, 1855 (1949).