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Studies in the Cyclopentane Series. I. The Synthesis of 1,2-Ureylenecyclopentane and Related Compounds

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Methods are described for the preparation of 1,2-ureylenecyclopentane. Differences in the behavior toward hydrazine of dimethyl *cis*-cyclobutane-1,2-dicarboxylate and dimethyl *cis*-cyclopentane-1,2-dicarboxylate are discussed. The reaction of the diazide of 1-cyclopentene-1,2-dicarboxylic acid with methanol and aniline was investigated.

Although ureylenecyclobutane[4] and ureylenecyclohexane[5] derivatives have been described, no information is available on the preparation and properties of 1,2-ureylenecyclopentane (I). Essentially three routes to the preparation of this ring system were explored: (1) the transformation of ethyl cyclopentanone-2-carboxylate (II) into ethyl 2-acetamido-1-cyclopentenecarboxylate (III), its reduction to ethyl *cis*-2-acetamidocyclopentanecarboxylate and conversion of the latter substance into (I) through the intermediates (IV), (V) and (XIII-A); (2) The Curtius and K. F. Schmidt degradation of *cis*-cyclopentane-1,2-dicarboxylic acid (IX) followed by ring closure of the resulting *cis*-1,2-diaminocyclopentane derivatives, and (3) the conversion of 1-cyclopentene-1,2-dicarboxylic acid (VIII) into 1,2-dicarbomethoxyamino-1-cyclopentene, its reduction to *cis*-1,2-dicarbomethoxyaminocyclopentane and ring closure.

Attempts to transform ethyl cyclopentanone-2-carboxylate (II) into ethyl 2-aminocyclopentanecarboxylate by catalytic hydrogenation of its oxime or its oxime acetate proved unpromising. Under our experimental conditions the yield of the desired amino acid ester was negligible and large amounts of non-nitrogenous materials and ammonia were obtained. Therefore, the hydrogenation of ethyl 2-acetamido-1-cyclopentenecarboxylate (III) was investigated. This compound absorbed one mole of hydrogen when reduced in glacial acetic acid over Adams catalyst. The resulting products were converted into a mixture of *cis*- and *trans*-2-benzamidocyclopentanecarboxylic acids (IV) by hydrolysis and benzoylation. Treatment with hydrazine of the methyl esters of these benzoylamidocarboxylic acids afforded a mixture of hydrazides which was separated by fractional crystallization into the *trans* hydrazide (VI) and a more soluble, lower melting fraction representing a mixture of the *cis* and *trans* hydrazides (V) and (VI). These hydrazides were converted to the azides and the latter decomposed with ethanol. Chromatographic separation of the reaction products gave *trans*-1-carbethoxyamino-2-benzamidocyclopentane and N-benzoyl-1,2-ureylenecyclopentane (XIII-A). The structure of the latter compound followed from its conversion into (I) by hydrolysis with barium hydroxide. *trans*-1-Carbethoxyamino-2-benzamidocyclopentane also resulted from the Curtius degradation of the *trans* hydrazide (VI). Poor yields of 1,2-ureylenecyclopentane (5%) were realized by this procedure due to the predominant formation of *trans* isomers. These may have originated from a *trans* addition of hydrogen to (III) or from inversion of the original *cis* hydrogenation product during its further transformations.

Buchman, *et al.*,[4] observed that degradation of *cis*- or *trans*-cyclobutane-1,2-dicarboxylic acids, either through their hydrazides or directly by the K. F. Schmidt procedure, gave the *cis*- and *trans*-1,2-diaminocyclobutanes, respectively. No inversion of the *cis* to the *trans* isomer was noted. These findings prompted the application of these schemes to the preparation of (I). Treatment of dimethyl *cis*-cyclopentane-1,2-dicarboxylate (X) with hydrazine hydrate led, in poor yield, to the formation of a mixture of hydrazides. Fractional crystallization of this mixture gave the *cis* dihydrazide (XI) and the *trans* dihydrazide (XII). The latter isomer also was obtained from dimethyl *trans*-cyclopentane-1,2-dicarboxylate. Reaction of the *cis* dihydrazide (XI) with nitrous acid yielded a diazide which upon refluxing in methanol decomposed with the formation of N-carbomethoxy-1,2-ureylenecyclopentane (XIII); this was converted into (I) by hydrolysis with barium hydroxide. The over-all yield in the conversion of (X) into (I) by this route was 6%. 1,2-Ureylenecyclopentane also was obtained in 19% yield by the K. F. Schmidt degradation of *cis*-cyclopentane-1,2-dicarboxylic acid (IX), followed by phosgene treatment of the intermediate, *cis*-cyclopentane-1,2-diamine (VII).

Although these results are essentially comparable to those reported in the cyclobutane series,[4] the pronounced tendency for *cis-trans* inversion in the cyclopentane series should be noted. The *cis* dihydrazide (XI) is so unstable that even its recrystallization from methanol causes a partial rearrangement to the more stable *trans* form (XII). In addition, the Curtius degradation of *cis*-cyclobutane-1,2-dicarboxylic acid dihydrazide gave the respective *cis* diurethan in contrast to (XI), which under comparable conditions underwent cyclization to form (XIII). This behavior parallels that observed with phthalic acid diazide[6] which on treatment with methanol affords 1-carbomethoxybenzimidazolone and not N,N'-dicarbomethoxy-*o*-phenylenediamine. Our findings, coupled with other similar observations,[7,8] indicate that the treatment of cyclic *cis* 1,2-dicarboxylic esters with hydrazine

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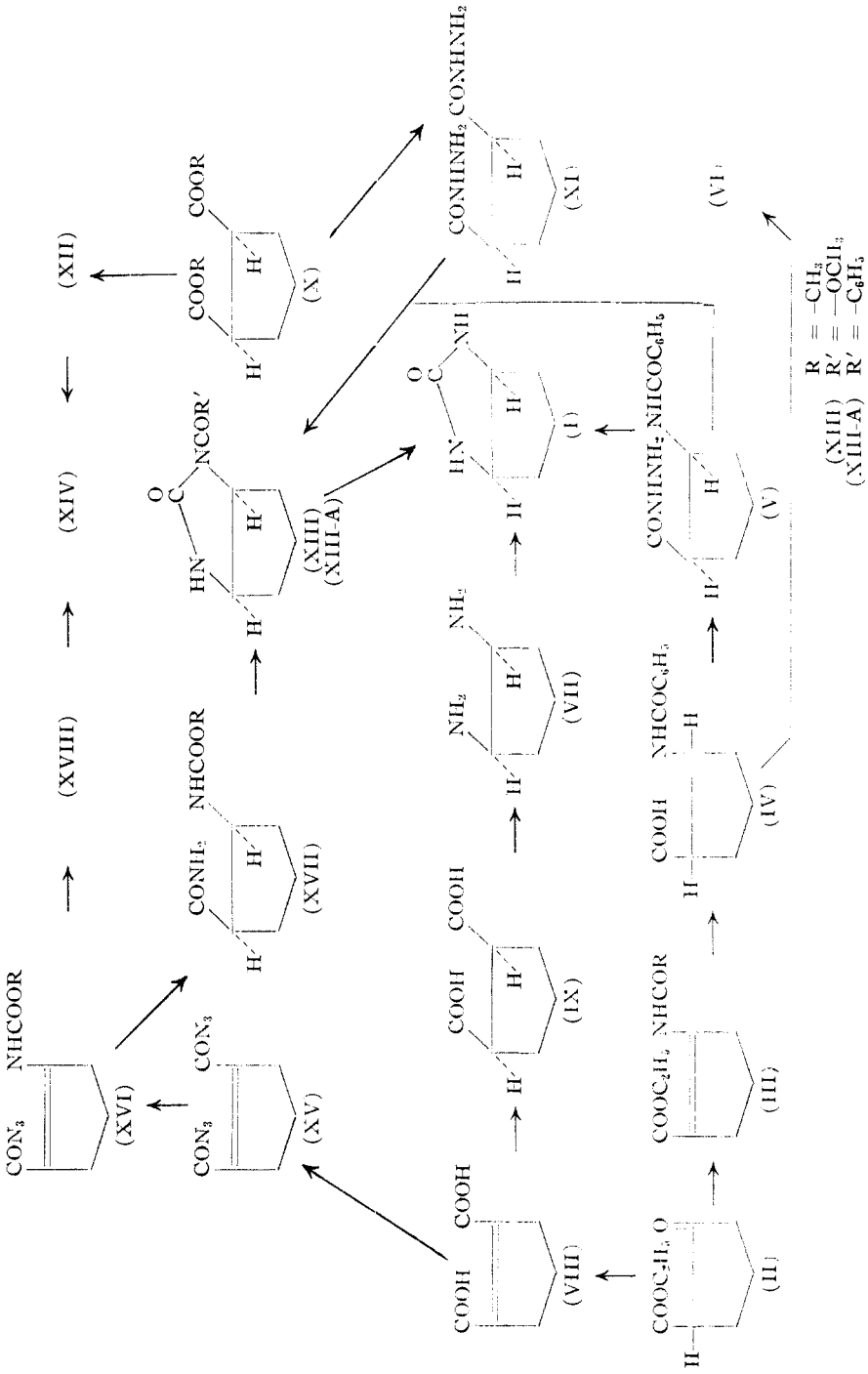
(4) E. R. Buchman, A. O. Reims, T. Skei and M. T. Schlatter, THIS JOURNAL, **64**, 2696 (1942).

(5) J. P. English, R. C. Clapp, Q. P. Cole, I. F. Halverstadt, J. O. Lampen and R. O. Roblin, Jr., *ibid.*, **67**, 295 (1945).

(6) H. Lindemann and W. Schultheis, *Ann.*, **464**, 237 (1928).

(7) B. R. Baker, M. V. Querry, S. R. Safir and S. Bernstein, *J. Org. Chem.*, **12**, 138 (1947).

(8) G. B. Brown, B. R. Baker, S. Bernstein and S. R. Safir, *ibid.*, **12**, 155 (1947).



frequently results in inversion with the formation of the corresponding *trans* hydrazides. This method is thus not as generally applicable to the preparation of cyclic *cis* 1,2-diamines as could have been expected on the basis of previous work.[4]

Rather unexpected results were obtained during attempts to convert 1-cyclopentene-1,2-dicarboxylic acid (VIII) into 1,2-dicarbomethoxyamino-1-cyclopentene. The acid chloride of (VIII) reacted with sodium azide to give the highly explosive diazide (XV). This azide, when decomposed in methanolic solution, did not afford the expected unsaturated diurethan but gave a compound of the composition $C_8H_{10}O_3N_4$. This was identified as the azide of 2-carbomethoxyamino-1-cyclopentenecarboxylic acid (XVI) in the following manner: Hydrogenation of (XVI) in methanol over a palladium-on-charcoal catalyst yielded the amide of 2-carbomethoxyamino-1-cyclopentenecarboxylic acid. The same compound also was obtained from (XVI) by treatment with methanolic ammonia. Hydrogenation of (XVI) over a platinum oxide catalyst in glacial acetic acid, on the other hand, gave the amides of *cis*- and *trans*-2-carbomethoxyaminocyclopentanecarboxylic acid (XVII) and (XVIII), which were separated by fractional crystallization. Degradation of the *cis* isomer (XVII) by a modified Hofmann degradation[9] yielded (XIII), which was in every respect identical with the material obtained by the Curtius degradation of (XI). Under similar conditions, the *trans* isomer (XVIII) was converted into (XIV). The same compound was obtained from (XII) by treatment with nitrous acid followed by decomposition of the azide with methanol. Decomposition of (XV) in benzene solution in the presence of aniline failed to yield the expected 1,2-diphenylureido-1-cyclopentene but instead gave the azide of 2-phenylureido-1-cyclopentenecarboxylic acid. These results demonstrate a difference in the reactivity of the two azide groups in (XV) similar to that observed with phthalic acid diazide.[9]

Experimental[10]

Ethyl 2-Acetamido-1-cyclopentenecarboxylate (III).—A solution of ethyl 2-amino-1-cyclopentenecarboxylate[11] (17 g.) in acetic anhydride (35 ml.) was heated on a steam-bath

(9) E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, Chapter 7, John Wiley & Sons, Inc., New York, N. Y., 1946, p. 273.

(10) (a) The microanalyses were performed in our microanalytical laboratories by Mr. George L. Stragand. (b) The melting points were determined with short-stem Anschütz thermometers and are uncorrected. (c) All hydrogenations were conducted at atmospheric pressure.

(11) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1946).

for 4 hours; then the solvent was removed *in vacuo*. The residue was dissolved in ether, the solution washed with 2 *N* hydrochloric acid and 2 *N* sodium carbonate and dried over sodium sulfate. The ether was removed and the acetyl derivative recrystallized from a mixture of petroleum ether (b.p. 30–60°) and ether; yield, 17.2 g. (79%); m.p. 53–54°.

Anal. Calcd. for $C_{10}H_{15}O_3N$: C, 60.9; H, 7.7; N, 7.1. Found: C, 60.7; H, 7.4; N, 7.0.

cis and *trans*-2-Benzamidocyclopentanecarboxylic Acids (IV).—A solution of ethyl 2-acetamido-1-cyclopentenecarboxylate (III) (3.94 g.) in glacial acetic acid (30 ml.) was added to platinum oxide (1 g.) previously reduced in glacial acetic acid (40 ml.), and the mixture was shaken until one mole of hydrogen had been absorbed and the uptake of hydrogen ceased (approximately thirty minutes). The catalyst was removed by filtration and the glacial acetic acid removed *in vacuo*. The residue was dissolved in 4 *N* hydrochloric acid (100 ml.); the solution was refluxed for four hours and evaporated to dryness *in vacuo*. The crystalline residue, representing a mixture of the hydrochlorides of *cis*- and *trans*-2-aminocyclopentanecarboxylic acids, was washed with acetone and dried over phosphorus pentoxide *in vacuo;* yield 3.2 g. The above hydrochlorides were benzoylated in the usual manner with benzoyl chloride (2.6 ml.) and 4 *N* sodium hydroxide, and the resulting benzoates recrystallized from 50% aqueous ethanol; yield, 3.3 g. (66%); m.p. 162–170°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: N, 6.0. Found: N, 5.9.

cis- and *trans*-1-Benzamido-2-cyclopentanecarboxylic Acid Hydrazides (V) and (VI).—The benzoates (IV) (3.2 g.) were dissolved in methanol (50 ml.) and an ethereal solution of diazomethane added until the yellow color remained for ten minutes. A few drops of glacial acetic acid were added and the solvents removed *in vacuo*. The residue was dissolved in ether; the solution was washed with 2 *N* sodium carbonate and water, and dried over sodium sulfate. Evaporation of the ether gave a mixture of stereoisomeric methyl esters (m.p. 83–95°) which were dissolved in absolute ethanol (6 ml.). Hydrazine hydrate (1.5 ml.) was added; the solution was refluxed for 20 hours and allowed to cool to room temperature. The resulting crystals were collected, washed with a mixture of absolute ethanol and ether, and dried; yield, 2.3 g.; m.p. 173–190°. Fractional recrystallization from 95% ethanol gave two fractions. The less-soluble *trans* isomer (VI) melted at 204–206°; yield, 1.2 g. (35%). A sample of this compound was sublimed at 175–180°, 0.03 mm., for analysis.

Anal. Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.1; H, 6.9; N, 17.0. Found: C, 63.3; H, 6.9; N, 17.4.

Evaporation of the mother liquors afforded a mixture of the *cis* and *trans* hydrazides (V) and (VI) which melted at 171–172°; yield, 1.1 g. (32%). A sample for analysis was sublimed at 150–170°, 0.03 mm.

Anal. Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.1; H, 6.9; N, 17.0. Found: C, 63.1; H, 6.8; N, 17.1.

N-Benzoyl-1,2-ureylenecyclopentane (XIII-A).—The hydrazide mixture of m.p. 171–172° (1.1 g.) was dissolved in 2 *N* hydrochloric acid (8 ml.) and the solution cooled in an ice-bath. Sodium nitrite solution (10%) (4 ml.) was added with stirring and the resulting gummy azide extracted with ice-cold ether. The ethereal solution was washed with sodium carbonate and water, dried over sodium sulfate and evaporated to dryness *in vacuo* at room temperature. The residue was refluxed with anhydrous ethanol (10 ml.) for one hour and the solvent removed. The resulting crystalline material was dissolved in benzene (20 ml.) and the solution poured on a column prepared from aluminium oxide (25 g.) (Fisher adsorption alumina). Elution of the column with a mixture of benzene and ether (3:2) gave *trans*-1-benzamido-2-carbethoxyaminocyclopentane, which was recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°); yield, 237 mg. (20%); m.p. 178–179°.

Anal. Calcd. for $C_{15}H_{20}O_3N_2$: C, 65.3; H, 7.3; N, 10.1. Found: C, 65.0; H, 7.0; N, 10.0.

Further elution of the column with ether afforded N-benzoyl-1,2-ureylenecyclopentane (XIII-A), which was recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°); yield, 314 mg. (31%); m.p. 175–176°. A mixture of this material with *trans*-1-benzamido-2-carbethoxyaminocyclopentane melted at 145–160°.

Anal. Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.8; H, 6.1; N, 12.2. Found: C, 67.5; H, 5.9; N, 12.1.

trans-1-Benzamido-2-carbethoxyaminocyclopentane.—In the manner described above, the *trans* hydrazide (VI) (1.13 g.) was converted into the *trans* urethan; this was recrystallized from ethyl acetate and petroleum ether (b.p. 30–60°); yield, 1.05 g. (72%); m.p. 175–177°. The material was, by mixed melting-point determination, identified with the *trans* urethan described above.

Anal. Calcd. for $C_{15}H_{20}O_3N_2$: N, 10.1. Found: N, 10.4.

cis-Cyclopentane-1,2-dicarboxylic Acid Dihydrazide (XI).—A mixture of dimethyl *cis*-cyclopentane-1,2-dicarboxylate[12] (X) (7.92 g.) and hydrazine hydrate (1 ml.) was heated in an oil-bath at 160–170°. This temperature was maintained while additional hydrazine hydrate (3 ml.) was slowly added over a period of fifty minutes. Following the addition of the hydrazine, the mixture was refluxed for one hour with mixing being effected by passing a stream of nitrogen through the solution. The mixture was cooled to 50°, methanol (24 ml.) added, and the solution kept at room temperature for 24 hours. The resulting *trans* dihydrazide (XII) was recrystallized from methanol; yield, 1.4 g. (18%); m.p. 223–224°. The substance was identified, by mixed-melting point determination, with the material described below. The mother liquors from the crystallization of the *trans* compound were concentrated to a small volume *in vacuo* and ether was added to the residue. The mixture was placed in a refrigerator for 12 hours and the resulting crystals of the *cis* hydrazide collected. The crude material was dried *in vacuo* over sulfuric acid for several days; yield, 2.17 g. Recrystallization from methanol and ether gave 1.76 g. (22%) of the *cis* hydrazide (XI) which melted at 125–126°. Prolonged refluxing of the *cis* isomer in methanol solution led to the formation of the sparingly methanol-soluble *trans* compound.

Anal. Calcd. for $C_7H_{14}O_2N_4$: C, 45.2; H, 7.6; N, 30.1. Found: C, 45.4; H, 7.3; N, 29.9.

trans-Cyclopentane-1,2-dicarboxylic Acid Dihydrazide (XII).—A mixture of dimethyl *trans*-cyclopentane-1,2-dicarboxylate (1.89 g.) (prepared from the *cis* dimethyl ester (X) by refluxing with sodium methoxide in methanol[13]), hydrazine hydrate (11 ml.) and dry ethanol (11 ml.) was refluxed for 18 hours at a bath temperature of 140–160°. The solvent was evaporated *in vacuo;* the resulting crystals were recrystallized from 95% ethanol and dried; yield, 600 mg. (32%); m.p. 224–225°.

Anal. Calcd. for $C_7H_{14}O_2N_4$: C, 45.2; H, 7.6; N, 30.1. Found: C, 45.2; H, 7.4; N, 30.3.

Azide of 2-Carbomethoxyamino-1-cyclopentenecarboxylic Acid (XVI).—Phosphorus pentachloride (20.3 g.) was added slowly with shaking to an ice-cold suspension of 1-cyclopentene-1,2-dicarboxylic acid[14] (VIII) (7 g.) in anhydrous ether (65 ml.). The mixture was removed from the ice-bath, shaken at room temperature for an additional twenty minutes and the remaining small quantity of undissolved phosphorus pentachloride removed by filtration. The ether was evaporated *in vacuo* under anhydrous conditions and the resulting sirupy acid chloride dissolved in dry benzene (20 ml.). The benzene was removed *in vacuo* at a bath temperature of 50°. This procedure was repeated twice more in order to free the acid chloride from phosphorus oxychloride. The resulting oily acid chloride was dissolved in ether (150 ml.) and stirred vigorously in an ice-bath with a solution of sodium azide (58.8 g.) in water (150 ml.) for 2 hours. The ether layer was separated, the aqueous phase reëxtracted with ether (150 ml.) and the combined ether extracts dried over anhydrous sodium sulfate. All operations were carried out at ice-bath temperatures, and the azide was used immediately. The azide (XV) is highly explosive and should not be kept free of solvent. Anhydrous methanol (70 ml.) was added to the above ether solution of the azide and the mixture was slowly heated to 55° when evolution of nitrogen indicated the decomposition of the azide. The temperature was slowly increased and the ether and approximately half of the methanol removed by distillation. Water (3 ml.) was added and the solution placed in a refrigerator for one hour. The resulting solid was recrys-

(12) A. Wassermann, *Helv. Chim. Acta*, **13**, 223 (1930).
(13) W. Hückel and E. Goth, *Ber.*, **58**, 447 (1925).
(14) S. C. Sen Gupta, *J. Indian Chem. Soc.*, **17**, 183 (1940).

tallized from 95% ethanol; yield, 6.5 g. (69%); m.p. 75–76°.

Anal. Calcd. for $C_8H_{10}O_3N_4$: C, 45.7; H, 4.8; N, 26.7. Found: C, 45.5; H, 4.6; N, 27.0.

Dianilide of 1-Cyclopentene-1,2-dicarboxylic Acid.—The acid chloride, prepared as described above from the diacid (VIII) (540 mg.), was dissolved in ether (5 ml.) and the solution added to a solution of freshly distilled aniline (1.3 g.) in ether (5 ml.). The anilide was isolated in the usual manner and recrystallized from 95% ethanol; yield, 700 mg. (66%); m.p. 195–196°.

Anal. Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.5; H, 5.9; N, 9.1. Found: C, 74.6; H, 5.7; N, 9.3.

Azide of 2-Phenylureido-1-cyclopentenecarboxylic Acid.—To an ether solution of the diazide (XV), prepared from 1 g. of the diacid (VIII) as described above, a solution of aniline (0.6 g.) in dry benzene (5 ml.) was added, the mixture slowly heated at 65–70° and the ether removed by distillation. The remaining benzene solution was then kept at 70° for an additional fifteen minutes and was evaporated to dryness *in vacuo*. The material was recrystallized from 95% ethanol; yield, 900 mg. (52%); dec. 128–129°.

Anal. Calcd. for $C_{13}H_{13}O_2N_5$: C, 57.6; H, 4.8; N, 25.8. Found: C, 57.5; H, 4.5; N, 25.9.

Amide of 2-Carbomethoxyamino-1-cyclopentenecarboxylic Acid. A. By Catalytic Hydrogenation of (XVI).—The azide urethan (XVI) (3.3 g.) was dissolved in methanol (90 ml.) and hydrogenated over a palladium-on-charcoal catalyst[15] (2.8 g.) for a period of three hours. No uptake of hydrogen was noted since the volume of hydrogen absorbed is equivalent to the volume of nitrogen liberated during the reaction. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. Recrystallization of the residue from methanol yielded 1.2 g. (42%) of the amide, melting at 181–182°. A sample for analysis was sublimed at 150°, 0.01 mm.

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.2; H, 6.6; N, 15.2. Found: C, 52.3; H, 6.4; N, 15.4.

B. By Treatment of (XVI) with Ammonia.—The azide urethan (XVI) (500 mg.) was dissolved in methanol (7.5 ml.) and a saturated solution of ammonia in methanol (7.5 ml.) was added. The mixture was kept at room temperature for 20 hours and then evaporated to dryness *in vacuo*. Several recrystallizations from methanol gave 145 mg. (33%) of the amide urethan, melting at 182–184°. This was identified, by mixed melting point, with the compound described above under A.

Amides of *cis*- and *trans*-2-Carbomethoxyaminocyclopentanecarboxylic Acids (XVII and XVIII).—A solution of (XVI) (6.0 g.) in glacial acetic acid (100 ml.) was hydrogenated over a platinum-oxide catalyst (6.0 g.) for 50 minutes; no uptake of hydrogen was noted (conversion of the azide to the amide). The mixture of nitrogen and hydrogen was then displaced by fresh hydrogen and the hydrogenation continued for seventy minutes. During this time an amount of hydrogen equivalent to one mole was absorbed. The catalyst was removed and the solvent evaporated *in vacuo*. The residue was dissolved in hot water (100 ml.) and the solution kept at room temperature for 20 hours. The resulting solid was recrystallized from 95% ethanol. The *trans* isomer (XVIII) melted at 198–199°; yield, 1.8 g. (34%). A sample for analysis was sublimed at 150°, 0.01 mm.

Anal. Calcd. for $C_8H_{14}O_3N_2$: C, 51.6; H, 7.6; N, 15.1. Found: C, 51.9; H, 7.8; N, 15.2.

When concentrated to a small volume *in vacuo*, the mother liquors from the preparation of the *trans* isomer yielded 2.7 g. of crystals which melted at 138–146°. Recrystallization from dilute ethanol gave the *cis* compound (XVII); yield, 2.1 g. (40%); m.p. 148–149°.

Anal. Calcd. for $C_8H_{14}O_3N_2$: C, 51.6; H, 7.6; N, 15.1. Found: C, 51.8; H, 7.2; N, 15.2.

N-Carbomethoxy-1,2-ureylenecyclopentane (XIII). A. By Hofmann Degradation of (XVII).—To a cooled solution of (XVII) (400 mg.) in dry methanol (10 ml.) was added a sodium methoxide solution (1.73 ml.) (1 g. sodium in 20 ml. methanol), followed by bromine (0.2 ml.). The mixture was refluxed for thirty minutes and then evaporated to dryness *in vacuo*. The residue was extracted with several portions of hot ethyl acetate and the ethyl acetate-soluble fraction recrystallized from dilute methanol; yield, 88 mg. (22%); m.p. 156–157°. A sample for analysis was sublimed at 120°, 0.01 mm.

Anal. Calcd. for $C_5H_{12}O_3N_2$: C, 52.2; H, 6.6; N, 15.2. Found: C, 52.3; H, 6.4; N, 15.3.

B. By Curtius Degradation of (XI).—A solution of the *cis* dihydrazide (XI) (700 mg.) in 2 *N* hydrochloric acid (16 ml.) was cooled to 0° in an ice-bath, and a solution of sodium nitrite (1.04 g.) in water (2.5 ml.) was added dropwise with stirring. After ten minutes further stirring, the azide was extracted with three 60-ml. portions of ice-cold ether. The combined ether solutions were washed with sodium bicarbonate and water, dried over sodium sulfate, and the ether evaporated at room temperature. Methanol (10 ml.) was added to the residue and the solution refluxed for two hours. Evaporation gave an oil which soon solidified. Recrystallization from methanol gave 215 mg. (31%) of needle-like crystals which melted at 154–155°. The material was identified, by mixed melting point, with the substance obtained according to Method A above.

1,2-Ureylenecyclopentane (I). A. By Hydrolysis of (XIII).—A solution of (XIII) (88 mg.) in 10% barium hydroxide (6 ml.) was heated on a steam-bath for two and a half hours. Carbon dioxide was passed into the solution and the barium carbonate removed by filtration. The precipitate was washed repeatedly with hot water and the combined filtrate and washings acidified to congo red with 2 *N* sulfuric acid. The solution was filtered and the clear filtrate concentrated to dryness *in vacuo*. Sublimation of the residue at 150–170° at 15 mm. gave 52 mg. (87%) of the desired cyclic urea derivative. Following recrystallization from 95% ethanol and resublimation, the compound melted at 205–206°.

Anal. Calcd. for $C_6H_{10}ON_2$: C, 57.1; H, 8.0; N, 22.2. Found: C, 56.9; H, 7.7; N, 22.4.

B. By K. F. Schmidt Degradation of (IX).—To a solution of the diacid (IX) (2.55 g.) in concentrated sulfuric acid (17 ml.), 1.45 *N* hydrazoic acid in chloroform[16] (33.5 ml.) was added dropwise during half an hour. The mixture was stirred vigorously for 14 hours at a temperature of 42–45°. An additional 30 ml. of the hydrazoic acid solution was added and stirring continued for 4 hours. The mixture was poured on cracked ice, the chloroform layer separated, the aqueous phase made alkaline by the addition of strong potassium hydroxide, and steam distilled until the distillate became neutral. The distillate was acidified to congo red with 5 *N* hydrochloric acid and evaporated to dryness *in vacuo*, leaving 1.35 g. (47%) of the crude dihydrochloride of (VII). Treatment of this dihydrochloride with a solution of phosgene in toluene in 5 *N* potassium hydroxide in the usual manner gave the cyclic urea derivative, which was purified by sublimation at 100°, 0.1 mm., and recrystallization from a mixture of 95% ethanol and ether; yield, 385 mg. (19% based on (IX)); m.p. 204–205°. The compound was, by mixed-melting point, identified with the substance described under A above.

Anal. Calcd. for $C_6H_{10}ON_2$: C, 57.1; H, 8.0; N, 22.2. Found: C, 57.4; H, 7.6; N, 22.3.

C. By Hydrolysis of (XIII-A).—Barium hydroxide (10%) (16 ml.) was added to a solution of (XIII-A) (230 mg.) in methanol (10 ml.) and the mixture refluxed for 3 hours. The barium ions were removed in the usual manner and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with hot absolute ethanol, the filtered alcoholic extracts evaporated and the residue sublimed at 100°, 0.01 mm.; yield, 59 mg. (47%); m.p. 205–206°. The material was identical with the compound prepared according to procedures A and B.

Anal. Calcd. for $C_6H_{10}ON_2$: C, 57.1; H, 8.0; N, 22.2. Found: C, 57.3; H, 8.0; N, 22.3.

***trans*-1,2-Dicarbomethoxyaminocyclopentane (XIV). A. By Hofmann Degradation of (XVIII).**—The amide (XVIII) (1.12 g.) was converted into (XIV) essentially according to the procedure used in the conversion of (XVII) into (XIII). The crude *trans* urethan, 680 mg. (52%), was recrystallized from a mixture of methanol and ether (2:1); m.p. 140–141°.

(15) Obtained from the American Platinum Works, Newark, New Jersey.

(16) J. von Braun, *Ann.*, **490**, 125 (1931).

Anal. Calcd. for $C_9H_{16}O_4N_2$: C, 50.0; H, 7.5; N, 12.9. Found: C, 50.2; H, 7.4; N, 12.8.

B. By Curtius Degradation of (XII).—The *trans* dihydrazide (XII) (745 mg.) was transformed into the *trans* diurethan (XIV) essentially according to the procedure used in the conversion of (XI) to (XIII). The resulting crude material, 340 mg. (39%), was recrystallized from a mixture of methanol and ether (2:1). The purified compound melted at 142–143° and was, by mixed melting point, identified with the material prepared according to A above.

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Studies on the Chemistry of Limonin

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Reinvestigation of the catalytic hydrogenation of limonin yielded two products, hydrolimoninic acid and tetrahydrolimonin, thus extending the earlier work of Koller and Czerny. A new degradation product, decarboxyhydrolimonin, has been isolated and characterized. The stepwise removal of one of the lactone groups of limonin has been achieved. The infrared absorption curves of limonin and two of its degradation products are presented.

Although the chemistry of limonin, one of the bitter principles of citrus plants, has been studied by numerous investigators, little information is as yet available on the chemical structure of this compound. Pertinent aspects of its chemistry have been summarized by Geissman and Tulagin[2] and by Emerson.[3] Limonin represents a neutral compound of the composition $C_{26}H_{30}O_8$, which is insoluble in sodium bicarbonate but readily dissolves in dilute sodium hydroxide solution. Acidification of such solutions results in a quantitative recovery of the bitter principle. Saponification studies indicate the presence of two lactone groups, while the formation of a crystalline monoxime[3] points to the presence of a carbonyl function. Thus, of the eight oxygen atoms of limonin, five are accounted for in the form of the ketodilactone functions, while the nature of the remaining three oxygens is still unknown. It is generally assumed that they are present as ether linkages.

The present investigation was undertaken to: (1) re-examine the behavior of limonin toward catalytic hydrogenation; (2) further characterize the lactone functions, and (3) obtain some insight into its basic ring skeleton.

Koller and Czerny[4] reduced limonin over a palladium-on-charcoal catalyst in absolute ethanol and observed a slow uptake of three moles of hydrogen per mole of bitter principle. The resulting amorphous reduction product readily crystallized when brought into contact with water and was shown to represent a monocarboxylic acid. The formation of this "hexahydrolimoninic" acid was postulated as involving the addition of three molecules of hydrogen and one molecule of water to the bitter principle. The acid decomposed at 175–178° and reacted with diazomethane to form an amorphous monomethyl ester. In addition to hexahydrolimoninic acid, a small amount of a neutral hydrogenation product, tetrahydrolimonin, was isolated. Similar results were obtained by Feist and Schulte-Overberg.[5] Schechter and Haller[6] also studied the hydrogenation of limonin; however, their results did not substantiate those of the previous workers. They observed a slow hydrogen uptake with the formation of a mixture of products which were not characterized. This situation prompted us to reinvestigate the hydrogenation of limonin.

Highly purified limonin, which was recrystallized from glacial acetic acid and consequently contained acetic acid of crystallization, served as the starting material. Hydrogenation of this material, over a palladium-on-charcoal catalyst with ethanol as the solvent, resulted in a rapid uptake of three moles of hydrogen per mole of bitter principle. Several hydrogenations of limonin were carried out with essentially similar results. Evaporation of the solvent gave an amorphous material which crystallized on the addition of water. Recrystallization from dilute ethanol afforded a monocarboxylic acid melting with decomposition at 163–165°. Neutral equivalent determinations and elementary analyses pointed to a formula of $C_{26}H_{36-38}O_9$ for this compound. A crystalline substance with properties identical to those reported for tetrahydrolimonin was isolated from the neutral hydrogenation products.

The properties of our acidic hydrogenation product are similar to those reported for hexahydrolimoninic acid[4]; however, certain differences are noteworthy. The decomposition point of hexahydrolimoninic acid is given as 175–178°; in contrast, our acid decomposed consistently at 163–165°. Also, the analytical figures and neutral equivalents obtained in our laboratory differ somewhat from those previously reported (see Experimental). Although no explanation can be offered for these differences, it seems reasonable to assume the identity of the products; their similar behavior on heating, as discussed below, also supports this conclusion. Limonin absorbs three moles of hydrogen under the experimental conditions employed; however, the acidic reduction product was obtained in only 40–50% yields. Consequently, we cannot exclude the possibility of competing reactions simulating an over-all uptake of three moles of hydrogen and leading to more highly hydrogenated amor-

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