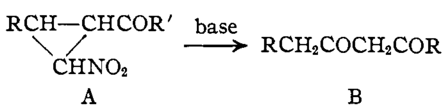
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Cyclopropanes. V.[1] Cyclopropyl Nitrocyclopropyl Ketones, and Their Behavior toward Alkaline Reagents

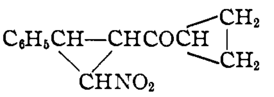
BY LEE IRVIN SMITH AND EDGAR R. ROGIER[2]

Two new types of nitrocyclopropyl ketones, I and VIII, each containing one substituted and one unsubstituted cyclopropane ring, have been synthesized. Each of the cyclopropanes was obtained in two racemic forms; each pair of stereoisomers could be partially interconverted. The behavior of the stereoisomers toward alkali was studied; the products were the same, and were obtained in substantially the same amounts, from each stereoisomer of a pair, and were the β-methoxy-α,β-unsaturated ketones V and XV from I and VIII, respectively. The structures of the enol ethers V and XV were proved by ozonolysis and by conversion into the respective 1,3-diketones VI and XVI, whose structures were also proved. Action of alkali upon these compounds thus involves attack upon the substituted cyclopropane ring only and is without effect upon the unsubstituted cyclopropane ring. The infrared absorption spectra of the four nitrocyclopropanes have been determined.

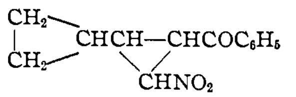
Previous reports in this series of investigations[3] have dealt with the action of alkali upon certain nitrocyclopropyl ketones (A) whereby these are converted into 1,3-diketones (B). In the second paper of the series[3b] a mechanism for this transformation was suggested. The work described here was undertaken in order to explore further this reaction, and in particular to determine whether or not a second cyclopropane ring, substituted for R or R′ in the nitrocyclopropyl ketone (A), would undergo ring cleavage during the rearrangement with alkali. For this purpose, the two nitrocyclopropyl ketones cyclopropyl 2-nitro-3-phenyl-1-cyclopropyl ketone I and 2-nitro-3-cyclo-propyl-1-benzoylcyclopropane VIII were prepared, and their behavior toward sodium methoxide was studied. The second of these is of special interest, for it is the first bicyclopropyl ketone to be prepared. Each of the ketones, I and VIII, was obtained in two racemic forms; this permitted a study of the action of alkali upon the pure (*dl*) stereoisomers. The only reports in the literature concerning the action of alkali upon stereoisomeric forms of nitrocyclopropyl ketones are those of Kohler and Engelbrecht[4] and of Kohler,[5] who reported that the three known racemic forms of A ($R = R' = C_6H_5$) melting at 95°, 88° and 144°, yielded the same 1,3-diketone B ($R = R' = C_6H_5$) in yields (as the copper enolate) of 70, 35 and 31%, respectively.



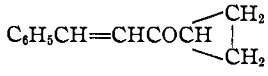
A B



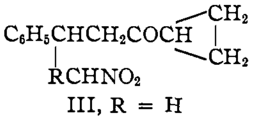
I



VIII



II

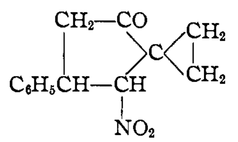


III, R = H
IV, R = Br

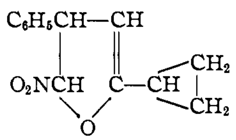
The synthesis of I followed the pattern developed by Kohler for the preparation of nitrocyclopropyl ketones. Styryl cyclopropyl ketone (II) was prepared in 88% yield by condensation of benzaldehyde with methyl cyclopropyl ketone in the presence of alcoholic sodium hydroxide. Addition of nitromethane to II produced the γ-nitroketone III; the yield of III was low (42–52%); however, no definite by-products could be isolated from the reaction mixture. Bromination of the sodium derivative of III at −5–0° produced the bromoketone IV (59%). The bromoketone, when refluxed in methanol for 48 hours with anhydrous potassium acetate, was converted into the nitrocyclopropyl ketone (I) in 60–63% yield. In large scale preparations, when IV was not purified but was used directly in the next step, the over-all yield of I from III was 87%.

The nitrocyclopropyl ketone I was first obtained as a liquid which did not crystallize until after it had stood in a refrigerator for several months. It then formed a solid melting at 35–53°, which was resolved into two of the four possible racemic forms of I by fractional crystallization from methanol. The least soluble form, white needles melting at 75°, crystallized first; from the mother liquor there was obtained the more soluble form, colorless prisms melting at 63°. Separation of the pure isomers of I was very tedious, and at best the yield of pure isomers was around 50% of the mixture.

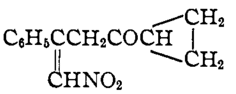
This route for the synthesis of the isomers of I, even though a conventional one, does not establish unequivocably the structures of these compounds. There are four other structures, C, D, E and F, possible for a substance derived from IV by elimination of the elements of hydrogen bromide.



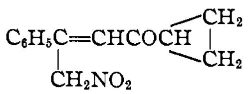
C



D



E



F

The substances $C_{13}H_{13}O_3N$ were inert to the action of potassium permanganate in acetone, and they did not react with a solution of bromine (5%) in carbon tetrachloride at 25°. Both isomers gave a precipitate (ferric hydroxide) by action of ferrous

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[1] Paper IV, Smith and Davis, *J. Org. Chem.*, **15**, 824 (1950).

[2] Abstracted from a thesis by Edgar R. Rogier, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, June, 1950. Allied Chemical and Dye Corporation Fellow, 1949–1950.

[3] Smith and Engelhardt, (a) THIS JOURNAL, **71**, 2671 (1949); (b) *ibid.*, **71**, 2676 (1949).

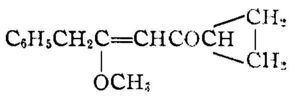
[4] Kohler and Engelbrecht, *ibid.*, **41**, 1379 (1919).

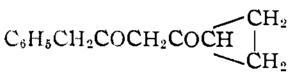
[5] Kohler, *ibid.*, **50**, 221 (1928).

sulfate and alkali, showing the presence of a nitro group.[6] The 63° isomer readily formed a semicarbazone and an oxime; the 75° isomer did not form a semicarbazone, and formed an oxime only with difficulty. When the 63° isomer was subjected to the action of saturated methanolic ammonia, a reagent previously found to be effective for interconversion of certain stereoisomeric nitrocyclopropyl ketones,[7] it was converted into the 75° isomer, which was unaffected by the reagent. These facts eliminate structures D, E and F as possibilities for the two isomers.

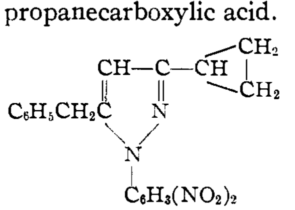
The absorption spectra in the infrared[8] of the two isomers are quite similar, differing only in a few regions. Thus the spectrum of the 63° isomer has bands at 1260 and 1305 cm.$^{-1}$ which are not present in that of the 75° isomer; on the other hand, the spectrum of the 75° isomer has a band at 840 cm.$^{-1}$ which is not present in that of the 63° isomer. The spectra of both isomers have very strong bands at 1700 cm.$^{-1}$ (unconjugated carbonyl), and at 1365 and 1550–1555 cm.$^{-1}$ (nitro group).

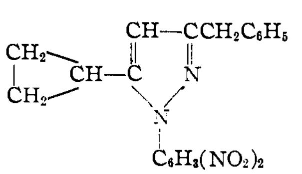
When a solution in methanol of either isomer of I was subjected to the action of sodium methoxide, heat was evolved, sodium nitrite was precipitated, and there resulted a neutral substance V.


V


VI

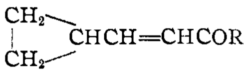
The substance V decolorized a solution of permanganate in acetone, and reacted rapidly with bromine in carbon tetrachloride with little evolution of hydrogen bromide. Ozonolysis of V led to methyl phenylacetate, thus locating the double bond in the α,β-position with reference to the carbonyl group. Action of methanolic hydrogen chloride converted V into the 1,3-diketone VI. Identity of VI was established by an independent synthesis from ethyl phenylacetate and methyl cyclopropyl ketone; the two specimens of the diketone gave the same copper derivative and the same pair of isomeric pyrazoles VIIa and VIIb. Action of hypobromite upon VI converted it into phenylacetic acid and cyclopropanecarboxylic acid.

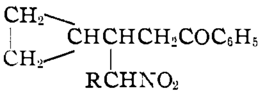

VIIa

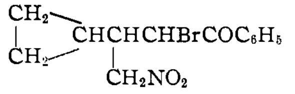

VIIb

These facts eliminate structure C, and show that the substances $C_{13}H_{13}O_3$ are racemic forms of the nitrocyclopropyl ketone I. Furthermore, the reactions of these compounds show that when the racemates of I are converted into a 1,3-diketone by action of alkali, the unsubstituted cyclopropyl group, α to the carbonyl group and δ to the nitro group, remains unchanged throughout. The same enol ether V results in substantially the same amounts from either stereoisomer of I.

The route to the nitrocyclopropyl ketone VIII involved steps similar to those followed in the synthesis of I. The α,β-unsaturated ketone IX was prepared by condensation of cyclopropanecarboxaldehyde with acetophenone. The analytical values for this compound were always somewhat low; the best value for carbon was about 0.5% low. The 2,4-dinitrophenylhydrazone gave the correct analytical values for a derivative of IX, but in order to be certain of the structure of this substance, IX was synthesized *via* an independent method. β-Cyclopropylacrylic acid (X) was synthesized from cyclopropanecarboxaldehyde and malonic acid; the acid X was converted into the acid chloride (XI), and the latter was converted into the ketone IX by action of diphenylcadmium. The α,β-unsaturated ketone IX obtained by the two methods melted at 23–24°, separately or when mixed, and both specimens gave the same 2,4-dinitrophenylhydrazone.


IX. R = C_6H_5
X, R = OH
XI, R = Cl


XII, R = H
XIII, R = Br


XIV

Addition of nitromethane to IX produced the γ-nitro ketone (XII) (71%). Bromination, in alkaline solution at −10°, converted XII into the bromo compound XIII. Isolation of the γ-bromo compound XIII in pure form was troublesome and was accomplished only in low (20%) yields, but it was found that the crude material, obtained by merely removing the solvent, was satisfactory for use in the preparation of VIII—the over-all yield of VIII from XII was then 70–73%. Conversion of XIII to VIII was accomplished by refluxing XIII in methanol with anhydrous potassium acetate; VIII was obtained as a liquid boiling at 164–170° (0.7 mm.). Bromination of XII in neutral medium gave a bromonitroketone XIV, different from XIII, and assigned the structure XIV of the α-bromoketone. When subjected to the action of potassium acetate in methanol, XIV was converted into the low (53°) melting isomer of VIII; the yield was low (33%) and the product was accompanied by a large amount of dark residue which could not be distilled.

The liquid nitrocyclopropane VIII solidified on standing overnight; fractional crystallization of this material yielded two of the racemic forms of VIII. One of these crystallized in white plates from methanol and melted at 77°; the other crystallized from methanol or petroleum ether in colorless prisms and melted at 53°. Both isomers were inert to the action of permanganate or bromine; both gave positive tests for the nitro group with al-

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(6) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 100.

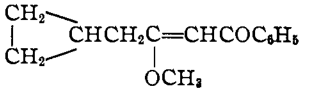
(7) Kohler and Smith, THIS JOURNAL, **44**, 624 (1922).

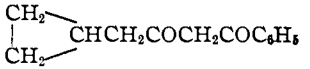
(8) We wish to express our thanks to Mr. John Lancaster and to Dr. Bryce L. Crawford, Jr., of this Laboratory, for the determination of these absorption spectra and for aid in the interpretation of the curves. The complete curves may be found in the Ph.D. thesis of E. R. Rogier (ref. 2).

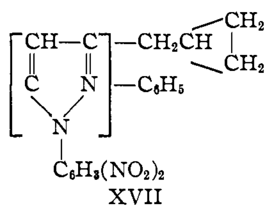
kaline ferrous sulfate. Action of methanolic ammonia upon the 53° isomer gave a mixture from which both isomers were isolated; this reagent was without action upon the 77° isomer. These facts eliminate the other three possible structures for VIII (*i.e.*, corresponding to D, E and F; a structure corresponding to C is not possible for a substance synthesized *via* the routes used for VIII).

The spectra of the two isomers of VIII in the infrared are quite similar,[8] differing only in a few regions. The spectrum of the 77° isomer has bands at 720 and 850 cm.$^{-1}$ which are not present in the spectrum of the 53° isomer. The spectra of both isomers have very strong bands at 1675–1680 cm.$^{-1}$ (singly conjugated carbonyl) and at 1365 and 1545 cm.$^{-1}$ (nitro group).

When either isomer of VIII, or a mixture of the isomers, reacted with sodium methoxide in methanol, there resulted a neutral substance XV; the yields of XV from the mixture, the 77 and 53° isomers were 53, 40 and 50%, respectively. Substance XV rapidly decolorized solutions of permanganate and of bromine and gave a red color, rapidly intensified on standing, with alcoholic ferric chloride. No copper derivative was found when XV was shaken with aqueous copper acetate. Ozonolysis of XV produced methyl cyclopropylacetate and benzoic acid, thus locating the double bond in the α,β-position with reference to the carbonyl group. Actions of methanolic hydrogen chloride upon XV converted it into the 1,3-diketone XVI. The diketone gave a dark red color with alcoholic ferric chloride, and formed a copper derivative. Action of 2,4-dinitrophenylhydrazine upon XVI converted it into one of the two possible isomeric pyrazoles (XVII). Cleavage of the diketone XVI by action of alkali gave all of the products possible by cleavage of a 1,3-diketone of structure XVI: acetophenone, cyclopropylacetone, cyclopropylacetic acid and benzoic acid. The reactions of these compounds serve to establish the structures of VIII, XV and XVI; moreover, these reactions show that when the stereoisomers of VIII are converted into a 1,3-diketone by action of alkali, the unsubstituted cyclopropyl group, β to the carbonyl group and to the nitro group, remains unchanged throughout. Thus in neither of the cyclopropanes I and VIII does there appear to be any conjugation of the unsubstituted cyclopropyl group with the substituted cyclopropyl group.


XV


XVI


XVII

Experimental Part[9]

Styryl Cyclopropyl Ketone (II).—A mixture of benzaldehyde (318 g., 3.0 moles) and methyl cyclopropyl ketone[10] (252 g., 3.0 moles) was maintained below 30° while ethanolic potassium hydroxide (150 cc., 10% in 95% ethanol) was slowly (one hour) added, with stirring. Stirring was continued for five hours longer, and then cold water (1.5 l.) was added to the mixture of solid and liquid. The solid was removed, washed thoroughly with cold water, dried in the air, and crystallized from methanol (450 cc.). The white platelets melted at 52–53° and weighed 436 g. A second crop, obtained by concentrating the mother liquor, weighed 11 g. (total 447 g., 88%). The analytical sample, recrystallized from methanol, melted at 53–53.5°.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.78; H, 7.12.

This substance, when distilled under reduced pressure, gave a light yellow-green distillate boiling at 130–134° (0.05 mm.) or 142–148° (0.15 mm.), which solidified when cooled to room temperature. It was important to use pure methyl cyclopropyl ketone, b.p. 110–111°, for this preparation, otherwise the yield of II was reduced considerably.

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate in long orange needles and small deep red prisms, and melted at 209–210°. When allowed to stand in contact with the solution at room temperature, the needles slowly disappeared and more prisms formed. After about two days, the material consisted entirely of the red prisms. Recrystallization of the red prisms yielded the two forms again.

Anal. Calcd. for $C_{18}H_{16}O_4N_4$: C, 61.36; H, 4.58. Found: C, 61.41; H, 4.55.

4-Nitro-3-phenyl-1-cyclopropyl-1-butanone (III).—A solution of the ketone II (447 g., 2.6 moles) and nitromethane (194 g., 3.18 moles, redistilled, b.p. 100–101°) in dry methanol (680 cc.) was stirred and maintained at 35–40° while a solution of sodium methoxide in methanol (from sodium, 78.2 g., 3.4 moles, and dry methanol, 680 cc.) was rapidly added (5–10 minutes, but not so rapidly that large amounts of sodium aci-nitromethane precipitated). Stirring was continued for 30 minutes longer (temp. 35–40°), and the mixture was then cooled (10–15°) and slowly acidified by addition of acetic acid (205 g.). Crystallization was started by seeding, and then the mixture was poured into a large volume of cold water. The solid was removed, washed thoroughly with water and then with cold methanol (500 cc.). and crystallized twice (two crops each time) from methanol (1 l. each time), when it weighed 316 g. (52%) and melted at 63.5–64.5°. An additional crystallization from methanol gave fine, white needles melting at 65–65.5°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48. Found: C, 66.72; H, 6.52.

The substance was inert toward permanganate in acetone, but gave a positive test for the nitro group with alkaline ferrous sulfate. The directions given above for preparation of III are quite critical; many variations in the amount of alkali, relative amounts of reagents, order of addition of reagents, etc., were tried but the yields were always much lower—even zero—unless the above directions were substantially followed. Even careful repetitions of these directions did not always result in the same yields; the yields varied from 42–52%, and no other pure product could be isolated from the reaction product.

4-Bromo-4-nitro-3-phenyl-1-cyclopropyl-1-butanone (IV).—A solution of sodium methoxide in methanol (from 2.5 g., 0.11 mole, of sodium and 40 cc. of dry methanol) was added to a stirred solution of the nitroketone III (23.2 g., 0.1 mole) in dry chloroform (30 cc.), at such a rate that the temperature could be maintained at −5–0° by external cooling. This cold solution of the aci-nitro salt was then added, with stirring, to a cooled (0–5°) solution of bromine (17.4 g., 0.11 mole) in dry chloroform (40 cc.). The cooling bath was removed, the mixture was stirred for 30 minutes and the solvent was removed under reduced pressure. The solid residue was washed with water, aqueous sodium bisulfite (5%) and again with water, and crystallized from ethanol, when it weighed 18.5 g. (59%) and melted at 108–109°.

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[9] Microanalyses by R. Amidon, J. Buckley, W. Cummings, W. Hunter, R. Kelly and H. Turner. All melting points and boiling points are uncorrected.

[10] Smith and Rogier, THIS JOURNAL, 73, 3837 (1951).

The analytical sample, crystallized again from ethanol, melted at 109–110°.

Anal. Calcd. for $C_{13}H_{14}O_3NBr$: C, 50.02; H, 4.52. Found: C, 49.98; H, 4.56.

The bromo compound was inert toward permanganate in acetone and toward alcoholic silver nitrate. In large scale preparations (248 g. of III) it was better not to purify the bromo compound, but to brominate at −15 to −10°, remove the solvent under reduced pressure, and use the dry, cream-colored product (319 g., 96%) directly in the next step.

Cyclopropyl 3-Phenyl-2-nitro-1-cyclopropyl Ketone (I).—A solution of the bromo compound IV (29.4 g., 0.1 mole) and potassium acetate (37 g., freshly fused) in dry methanol (600 cc.) was refluxed for 48 hours. Potassium bromide was removed and the solvent was removed under reduced pressure. The residual semi-solid was mixed with water and the mixture was extracted with ether. The extract was washed with water until neutral, dried (magnesium sulfate), the solvent was removed and the residue was distilled. The distillate formed a light yellow, viscous oil (13 g., 60%) boiling at 141–145° (0.01–0.1 mm.).

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.66. Found: C, 67.79; H, 5.83.

This product crystallized only after it had stood in a refrigerator for several months; once seed crystals were available, crystallization was readily induced. The crude bromo ketone (319 g., from the bromination described above) was dissolved in dry methanol (3.8 l.) and the solution was refluxed with potassium acetate (330 g.) for 41 hours and then processed as above. The crude, oily product (214 g., 91%) was not distilled, but was seeded and then separated into the pure isomers of I by fractional crystallization. This crude product, or the mixture after distillation (m.p. 35–53°), was taken up in slightly more than the minimum amount of warm methanol necessary for solution; the solution was cooled and seeded with a pure isomer, and the process was repeated on successive crops of crystals until no further separation was attained. In this way, 13.5 g. of the mixture was resolved into three fractions, A, B and C, the last an oil. A consisted largely of the higher melting isomer of I; it was resolved into 3.3 g. of I, m.p. 74–75°, and 0.3 g. of oil. B was resolved into 2.0 g. of I, m.p. 62–63°. C was resolved into 1.2 g. of I, m.p. 74–75°, and 6.2 g. of oil. The total recovery was 13.0 g., consisting of 4.5 g. of I, m.p. 74–75°; 2.0 g. of I, m.p. 62–63°; and 6.5 g. of oil which could not be separated further. The pure isomers, obtained by one or two additional recrystallizations from dry methanol, melted at 75–75.5° and 62.5–63°, respectively.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.66. Found: (75°) C, 67.60; H, 5.88. Found: (63°) C, 67.69; H, 5.81.

Both isomers were inert to permanganate in acetone, and to bromine (5%) in carbon tetrachloride. Both gave ferric hydroxide with ferrous sulfate and alkali.

Semicarbazone of the 63° Isomer of I.—This isomer readily formed a semicarbazone which crystallized from ethanol in white prisms melting at 176.5–177.5° (dec.). The 75° isomer of I was recovered unchanged after action of semicarbazide.

Anal. Calcd. for $C_{14}H_{16}O_3N_4$: C, 58.32; H, 5.60. Found: C, 58.21; H, 5.68.

Oxime of the 63° Isomer of I.—The ketone (2 g.) was refluxed for two hours with a solution of hydroxylamine hydrochloride (2 g.) in pyridine (10 cc.) and dry ethanol (10 cc.). The solvents were removed under reduced pressure, and the residue was recrystallized from aqueous methanol, when it formed light tan needles (1.6 g., 75%). Two additional recrystallizations (Norite) yielded long, white needles melting at 141–142°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73. Found: C, 63.36; H, 5.77.

Oxime of the 75° Isomer of I.—The ketone, when subjected to the conditions of the above experiment, was largely unchanged; 50% of it was recovered in pure form. A very small amount of the oxime was obtained; this, after crystallization from aqueous methanol, formed colorless prisms which melted at 128–129°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73. Found: C, 64.19; H, 6.00.

Interconversion of the Isomers of I.—Each of the isomers (0.5 g.) was dissolved in methanol (10 cc.) and the solutions were saturated with dry ammonia at 0° and allowed to stand overnight at room temperature in stoppered flasks. In this way there was obtained, from the 63° isomer, 0.27 g. of pure 75° isomer; from the 75° isomer, 0.29 g. of recovered material (m.p. 75°); none of the lower melting isomer could be isolated from this solution.

4-Phenyl-3-methoxy-1-cyclopropyl-2-buten-1-one (V).—A solution of sodium methoxide in methanol (from 0.8 g. of sodium and 9 cc. of methanol) was added, all at once, to a stirred solution of I (m.p. 63°) (2.5 g.) in dry methanol (5.5 cc.). The temperature rose to 55°, sodium nitrite separated, and the solution became deep red. The mixture was stirred for one hour, poured into ice-water (35 cc.), and extracted three times with ether. The combined ether extracts were washed with aqueous sodium bicarbonate (5%), then with water, dried (magnesium sulfate) and the solvent was removed. The residual solid was dissolved in methanol, the solution was decolorized with Norite, and the solvent was removed. The residue after crystallization from Skellysolve weighed 0.87 g. (37%) and melted at 70.5–71.5°. Another crystallization from petroleum ether (Norite) yielded white prisms which melted at 71.5–72.0°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.79; H, 7.68.

The 75° isomer of I (2.5 g.), subjected to the above conditions, gave 0.95 g. (41%) of V, melting at 71–72°, alone or when mixed with V prepared from the 63° isomer of I.

The methoxy ketone V decolorized a solution of permanganate in acetone, and reacted by addition with a solution of bromine (5%) in carbon tetrachloride at 25°.

Ozonolysis.—The methoxy ketone V (0.7 g.) was dissolved in ethyl bromide (50 cc.) and the solution was cooled (ice-hydrochloric acid) and subjected to the action of ozonized oxygen until ozone was detected in the exit gas (about five minutes). Most of the ethyl bromide was removed under reduced pressure, and the remaining solution was added dropwise to a boiling mixture of water (15 cc.) and zinc dust (0.25 g.) containing small amounts of hydroquinone and silver nitrate. The mixture was refluxed for 30 minutes, cooled, and extracted with ether. The extract was dried (magnesium sulfate) and the solvent was removed. The residue was warmed with aqueous sodium hydroxide (10%) for four hours, the solution was cooled, extracted with ether, the aqueous layer was decolorized (Norite), filtered and acidified with dilute sulfuric acid. The resulting solid melted at 76–77°, alone or when mixed with authentic phenylacetic acid.

4-Phenyl-1-cyclopropyl-1,3-butanedione (VI). A. From the Enol Ether V.—The methoxy compound V (0.3 g.) was refluxed with methanol (1.5 cc.) and hydrochloric acid (0.2 cc.) for 1.5 hours. The cooled solution was diluted with water and extracted with ether; the extract was washed with aqueous sodium bicarbonate (5%), then with water, and dried (magnesium sulfate). The solvent was removed and the residue, a light yellow liquid, weighed 0.24 g. after it was dried in a vacuum desiccator. The diketone formed a light blue copper compound which melted, after crystallization from methanol, at 187–187.5° (dec.), and was converted, by action of 2,4-dinitrophenylhydrazine, into a mixture of two isomeric 2,4-dinitrophenylpyrazoles, melting at 111–111.2° and 125.5–126°, respectively.

B.—The diketone VI (9.7 g., 24%) was prepared from methyl cyclopropyl ketone (16.8 g.), ethyl phenylacetate (65.7 g.) and lithium amide (9.2 g.) according to the general procedure of Zellars and Levine,[11] and was purified *via* the copper enolate. The diketone boiled at 130–133° (0.5 mm.) and had $n^{24.5}D$ 1.5621.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.98; H, 7.01.

The diketone gave an intense red color with ferric chloride, and it formed a copper enolate which, after crystallization from methanol, melted at 187–187.5° (dec.), alone or when mixed with the copper derivative of VI prepared from V.

Anal. Calcd. for $C_{26}H_{26}O_4Cu$: C, 67.00; H, 5.62. Found: C, 67.02; H, 6.04.

1-[2,4-Dinitrophenyl]-3-cyclopropyl-5-benzylpyrazole and 1-[2,4-Dinitrophenyl]-3-benzyl-5-cyclopropylpyrazole (VII).—The diketone VI (0.5 g.) was added to a solution of 2,4-

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[11] Zellars and Levine, *J. Org. Chem.*, **13**, 162 (1948).

dinitrophenylhydrazine (0.5 g.) in ethanol (15 cc.) containing sulfuric acid (1 cc.), and the mixture was allowed to stand overnight. The less soluble pyrazole separated; this, after crystallization from ethanol, formed pale yellow prisms which melted at 125.5–126°, alone or when mixed with the corresponding pyrazole prepared from V *via* VI.

Anal. Calcd. for $C_{19}H_{16}O_4N_4$: C, 62.63; H, 4.43. Found: C, 62.79; H, 4.64.

The mother liquor, when cooled, deposited the more soluble pyrazole; this, after crystallization from ethanol, formed long, pale yellow needles which melted at 111–111.2° alone, or when mixed with the corresponding pyrazole prepared from V *via* VI.

Anal. Calcd. for $C_{19}H_{16}O_4N_4$: C, 62.63; H, 4.43. Found: C, 62.36; H, 4.48.

No attempt was made to assign individual structures VIIa or VIIb to these two pyrazoles. On one occasion, a third compound was isolated along with the lower melting (111°) pyrazole; none of the higher melting (126°) pyrazole was formed in this experiment. This third compound—obtained only this one time—crystallized from ethanol in pale yellow prisms which melted at 113.5–114°; it also gave analytical values required by structure VII. It was not investigated further.

Anal. Calcd. for $C_{19}H_{16}O_4N_4$: C, 62.63; H, 4.43. Found: C, 62.54; H, 4.43.

Cleavage of the Diketone VI.—A solution of sodium hypobromite was prepared by addition of bromine (4.8 g.) to a solution of sodium hydroxide (3.3 g.) in water (28 cc.) at 5°. To this was added, with stirring, the diketone VI (2 g.). Dioxane (10 cc.) was added, and the solution was stirred at 5° until decolorization occurred (one hour). The solution was then stirred at room temperature for three hours. Bromoform was removed by distillation with steam; the residual solution was cooled (0°) and acidified with dilute sulfuric acid. The solid was removed; it melted at 75.5–76° alone or when mixed with authentic phenylacetic acid. The filtrate was extracted continuously with ether, the extract was dried (magnesium sulfate), the solvent was removed, and the residue, when distilled, yielded cyclopropanecarboxylic acid (0.44 g., 51%) boiling at 170–175°. The *p*-bromophenacyl ester, crystallized from aqueous ethanol, melted at 71.5–72°, alone or when mixed with a specimen (m.p., 72–72.5°) prepared from authentic cyclopropanecarboxylic acid. This derivative of cyclopropanecarboxylic acid is new.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92. Found: C, 51.10; H, 4.00.

β-Cyclopropylacrylic acid (X).—Cyclopropanecarboxaldehyde[12] (9.7 g.), malonic acid (15 g.) and dry pyridine (15 g.) were refluxed for four hours in an apparatus provided with a calcium chloride guard tube. The cooled mixture was acidified with dilute sulfuric acid, and the solid (11 g.) was removed and crystallized from Skellysolve B. It formed white needles which weighed 8.7 g. (56%) and melted at 66.5–67.5°. The analytical sample, crystallized twice more from petroleum ether and then sublimed at 65° (0.05 mm.), melted at 68.3–69°.

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.44; H, 7.33.

The anilide, prepared by way of the acid chloride, and crystallized from aqueous ethanol, melted at 100.5–101.5°.

Anal. Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00. Found: C, 76.80; H, 7.05.

β-Cyclopropylacryloyl Chloride (XI).—The acid X (11.2 g.) was added with stirring and in small portions over a period of 45 minutes to purified[13] thionyl chloride (15.9 g.) and the mixture was stirred at 40° for one hour. Excess thionyl chloride was removed under reduced pressure, and the residual oil was distilled through a short column (10 × 1.5 cm.) packed with glass helices. The product (10.6 g., 81%) formed a clear colorless liquid which boiled at 96° (30 mm.).

Anal. Calcd. for C_6H_7OCl: C, 55.18; H, 5.40. Found: C, 54.94; H, 5.62.

3-Cyclopropyl-1-phenyl-2-propene-1-one (IX). A.—A solution of diphenylcadmium in benzene (60 cc.) was prepared from bromobenzene (18.1 g.), magnesium (2.72 g.) and anhydrous cadmium chloride (10.8 g.) according to Cason.[14] To this solution at 10° was added slowly (six minutes) and with stirring, a solution of the acid chloride XI (9.8 g.) in benzene (20 cc.). The mixture was stirred at room temperature for 2.5 hours, and was then poured into iced dilute sulfuric acid. The benzene layer was removed, the aqueous layer was extracted with ether, the combined organic layers were dried (magnesium sulfate), and the solvents were removed. The residue (2.5 g., 20%) when distillled, boiled at 116–120° (0.5 mm.), and the distillate solidified when cooled. After crystallization from Skellysolve A the substance formed long white needles melting at 23–24°.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 82.90; H, 7.21.

The 2,4-dinitrophenylhydrazone, crystallized from ethanol, formed orange-red platelets melting at 168.5–169.5°.

Anal. Calcd. for $C_{18}H_{16}O_4N_4$: C, 61.36; H, 4.58. Found: C, 61.24; H, 4.71.

B.—Cyclopropanecarboxaldehyde (34.5 g.) was slowly (45 minutes) added to a well-stirred mixture of acetophenone (150 g.) and ethanolic potassium hydroxide (1 *N*, 25 cc.). Stirring was continued for three hours; the temperature was maintained below 40° throughout the reaction. Tartaric acid (4.4 g.) was added, and the mixture was extracted with ether (200 cc.). The extract was washed with saturated aqueous sodium bicarbonate, then twice with water, and dried (magnesium sulfate). Removal of the solvent left a colorless liquid (59.8–66.7 g., 71–79%) which boiled at 126–129° (0.7–0.8 mm.). The distillate, after crystallization from Skellysolve A, melted at 23–24°, alone or when mixed with IX prepared as in A above. The 2,4-dinitrophenylhydrazone melted at 168.5–169° alone or when mixed with the derivative from A above. The ketone decolorized a solution of bromine in carbon tetrachloride without evolution of hydrogen bromide.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.20; H, 7.08.

This reaction was very sensitive to changes in temperature, and it was important that the temperature not be allowed to exceed 40° at any time during the reaction. In one experiment in which double the quantities of materials were used, the temperature rose to 45°; this resulted in a lower yield (61%) of IX and formation of 63 g. of a product which boiled at 190–200° (0.1 mm.), and melted after crystallization from methanol at 49–49.5°. This product was analyzed, but otherwise was not investigated. It was inert toward permanganate in acetone, but reacted rapidly with bromine in carbon tetrachloride, with evolution of hydrogen bromide.

Anal. Found: C, 83.10, 83.00, 82.83; H, 7.19, 7.07, 7.39.

β-Cyclopropyl-γ-nitrobutyrophenone (XII).—A solution of sodium methoxide (from 18 g. of sodium and 185 cc. of dry methanol) was added rapidly (five minutes) and with stirring, to a solution of the ketone IX (103 g.) and nitromethane (44.6 g.) in dry methanol (185 cc.). The temperature was kept below 40° throughout; stirring was continued for 30 minutes. The mixture was cooled (−5°), stirred, and acetic acid (47.2 g.) was slowly (ten minutes) added. The mixture was seeded, and then the white solid was removed, washed thoroughly with cold water and crystallized from methanol (400 cc.). The product (99 g., 71%) formed white prisms which melted at 48.5–49.5°. The substance gave a dark greenish-brown precipitate with ferrous sulfate and alkali, and was inert toward permanganate in acetone.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48. Found: C, 66.96; H, 6.50.

β-Cyclopropyl-γ-bromo-γ-nitrobutyrophenone (XIII).—A solution of sodium methoxide (from 4.5 g. of sodium and 75 cc. of dry methanol) was added, with stirring and cooling (−10 to −15°), to a solution of the nitroketone XII (41.9 g.) in dry chloroform (75 cc.). This solution of the sodium derivative of XII was then added slowly, with stirring and cooling (−10°), to a solution of bromine (31.4 g.) in dry chloroform (75 cc.). The cooling bath was removed, stirring was continued for 30 minutes, and then the solution was washed successively with water, dilute aqueous sodium bisulfite, saturated aqueous sodium bicarbonate and water.

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[12] Smith and Rogier, THIS JOURNAL, **73**, this issue (1951).

[13] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Company, Boston, Mass., 1941, p. 381.

[14] Cason, THIS JOURNAL, **68**, 2078 (1946).

The solution was dried (magnesium sulfate), the solvent was removed, and the crude, oily product (59 g.) was dried under reduced pressure. After crystallization from dry ethanol, or from Skellysolve B, the substances formed fine white crystals melting at 54.5–55°, but recovery on crystallization was very low (20–30%) and it was better to use the crude, dried material directly in the next step.

Anal. Calcd. for $C_{13}H_{14}O_3NBr$: C, 50.02; H, 4.52. Found: C, 49.90; H, 4.54.

β-Cyclopropyl-α-bromo-γ-nitrobutyrophenone (XIV).—Bromine (12.3 g.) was added slowly (15 minutes) to a solution of the nitroketone XII (17.2 g.) in dry chloroform (55 cc.). The reaction was "primed" by addition of a drop of acetone and exposure to ultraviolet light. The mixture was allowed to stand for 4.5 hours, with occasional shaking. The solvent was removed under reduced pressure and the dark, gummy residue was crystallized from methanol. The light pink color of the product (19.3 g., 84%) was removed on crystallization, but the product (m.p. about 50°) was a mixture of stereoisomers and required several crystallizations before a pure isomer, melting at 69.5–70.5°, was obtained. This material was inert toward alcoholic silver nitrate.

Anal. Calcd. for $C_{13}H_{14}O_3NBr$: C, 50.02; H, 4.52. Found: C, 49.97; H, 4.66.

1-Benzoyl-2-nitro-3-cyclopropylcyclopropane (VIII). A. From the γ-Bromo Compound XIII.—The crude dried γ-bromo compound XIII (59 g., obtained as described above) was refluxed for 42 hours with potassium acetate (55 g., freshly fused) in dry methanol (850 cc.). The solvent was removed, water was added to the residue, and the mixture was extracted with ether. The extract was washed with saturated aqueous sodium bicarbonate and then with water until neutral, and dried (magnesium sulfate). The solvent was removed; the residue, when distilled under reduced pressure, boiled at 169–174° (1.0–1.5 mm.). The product (29 g., 70% based upon XII) solidified on standing in a refrigerator overnight. Fractional crystallization from methanol yielded the less soluble stereoisomer as colorless platelets melting at 76.3–77°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C. 67.52; H, 5.66. Found: C, 67.41; H, 5.82.

Concentration and cooling of the mother liquor yielded the more soluble isomer which melted at 47–53°; this isomer crystallized best from Skellysolve B, when it formed colorless prisms melting at 52–53°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.66. Found: C, 67.49; H, 6.00.

Both isomers were inert toward permanganate in acetone and toward bromine in carbon tetrachloride at 25°; both gave reddish-brown precipitates with ferrous sulfate and alkali.

Interconversion of the Isomers.—The 77° isomer (0.5 g.) was dissolved in dry methanol which had been saturated with ammonia at 0°, and the solution was allowed to stand overnight in a stoppered flask. The product (0.36 g.) was the unchanged 77° isomer; none of the 53° isomer could be isolated from the solution. The 53° isomer (0.5 g.) was subjected to the same treatment; from the solution there was recovered the 77° isomer (0.06 g.) and unchanged 53° isomer (0.26 g.). Neither isomer could be converted into a semicarbazone, and attempts to prepare oximes yielded only oils which could not be induced to crystallize.

B. **From the α-Bromo Compound XIV.**—The α-bromo ketone XIV (18.9 g.) was added to potassium acetate (23.5 g., freshly fused) in dry methanol (200 cc.). Heat was evolved, and potassium bromide separated within a few minutes. After two hours, the potassium bromide was removed and the filtrate was refluxed for 1.5 hours; no further precipitate formed. The solvent was removed under reduced pressure, water was added to the solid residue, and the mixture was extracted with ether. The extract was washed with saturated aqueous sodium bicarbonate and water, dried (magnesium sulfate), the solvent was removed, and the residue was distilled. The distillate, a light colored liquid (4.5 g., 33%) boiled at 155–177° (0.8–1.2 mm.). Considerable residue remained in the distilling flask; this decomposed when an attempt was made to distil it. The above distillate solidified when cooled, and then, after crystallization from methanol, the product melted at 53–54°, alone or when mixed with the 53° isomer prepared from the γ-bromo compound.

4-Cyclopropyl-3-methoxy-1-phenyl-2-butene-1-one (XV).—The nitrocyclopropane VIII (23.1 g., mixture of isomers) was added to a stirred solution of sodium methoxide (from 8 g. of sodium and 85 cc. of dry methanol). The temperature rose to 66°, the mixture became deep red, and sodium nitrite separated. Stirring was continued until the temperature fell to 30° (90 minutes). The mixture was poured into ice-water (550 cc.) and extracted with ether. The extract was washed with saturated aqueous sodium bicarbonate and water until neutral, dried (magnesium sulfate), the solvent was removed and the residue was distilled. The distillate, a pale yellow-green liquid (11.4 g., 53%), boiled at 143–146° (0.3 mm.). This material was essentially homogeneous, although it was difficult to obtain it analytically pure. It was fractionated repeatedly through a short (8 × 1 cm.) column packed with glass helices, yielding two fractions: A, 3.1 g., b.p. 127° (0.1 mm.), having $n^{24.3}$D 1.5585, and B, 4.7 g., b.p. 129–132° (0.1 mm.) having $n^{24.3}$D 1.5595.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found (fraction A): C, 76.80, 76.80, H, 7.58, 7.64. Found (fraction B): C, 77.01; H, 7.58.

Both fractions, with alcoholic ferric chloride, gave a red color which rapidly intensified on standing; both fractions decolorized permanganate in acetone and reacted with bromine in carbon tetrachloride with only slight evolution of hydrogen bromide. Neither fraction reacted with aqueous copper acetate.

Ozonolysis.—The methoxy ketone XV (2.23 g.) was dissolved in ethyl bromide (70 cc.) and cooled (ice–hydrochloric acid) while subjected to the action of a current of ozonized oxygen for 15 minutes. Most of the ethyl bromide was removed under reduced pressure, and the remaining solution was added dropwise to boiling water (50 cc.) containing zinc dust (0.8 g.), a trace of hydroquinone and a little silver nitrate. This mixture was distilled until 35 cc. of distillate was collected (residue A). The distillate was extracted with ether, the extract was dried (magnesium sulfate) and the solvent was removed. The residue, when distilled, yielded methyl cyclopropylacetate (0.46 g., 39%) boiling at 128–132° (748 mm.) and having n^{23}D 1.4195.[15] The ester was saponified, and the acid was converted into the *p*-bromophenacyl ester which, after crystallization from ethanol, melted at 85.5–86°, alone or when mixed with a specimen prepared in connection with the earlier work.[15] Residue A from above was filtered and the filtrate, when cooled, deposited benzoic acid (0.1 g.) melting at 121–122° alone or when mixed with an authentic sample.

Action of Sodium Methoxide upon the Stereoisomers of VIII. A.—The 77° isomer of VIII (5 g.) was added to sodium methoxide (from 1.73 g. of sodium and 18.4 cc. of methanol) and the reaction mixture was processed as described above for the mixture of isomers. Distillation of the final product gave 1.8 g. (43%) of XV boiling at 130–132° (0.4 mm.), and having $n^{23.5}$D 1.5590. A center cut ($n^{23.5}$D 1.5583) was analyzed.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.23; H, 7.82.

B.—The 53° isomer of VIII (5 g.) was subjected to the above reaction conditions. The product (2.15 g., 51%) boiled at 143° (0.8 mm.), and had $n^{24.3}$D 1.5603. A center cut ($n^{24.3}$D 1.5595) was analyzed.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 76.28; H, 7.62.

4-Cyclopropyl-1-phenyl-1,3-butanedione (XVI).—The enol ether XV (4.4 g.) was refluxed with methanol (11 cc.) and hydrochloric acid (2.2 cc.) for five minutes. The mixture was poured into ice-water and thoroughly extracted with ether, the extract was washed with water, the solvent was removed and an equal volume of methanol was added to the residual oil. This solution was poured into saturated aqueous copper acetate (1.3 g.) and cooled. The copper compound was removed and crystallized from methanol, when it formed fine, olive-green needles (3.94 g., 83%) melting at 158.5–159°.

Anal. Calcd. for $C_{26}H_{26}O_4Cu$: C, 67.00; H, 5.62. Found: C, 66.91; H, 5.77.

The above copper compound (3.94 g.), suspended in ether (50 cc.), was shaken with sulfuric acid (50 cc., 10%). The ether layer was washed with saturated aqueous sodium bicarbonate, then with water, dried (magnesium sulfate)

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(15) Smith and McKenzie, *J. Org. Chem.*, **15**, 74 (1950).

and the ether was removed. The residue, when fractionated repeatedly through a short (10 × 1 cm.) column packed with glass helices, gave a distillate (1.4 g., 41%) boiling at 119–119.5° (0.15 mm.), having $n^{20.5}_D$ 1.5866.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.07; H, 7.19.

1-[2,4-Dinitrophenyl]-3(or 5)-phenyl-5(or 3)-cyclopropylmethylpyrazole (XVII).—This derivative of XVI crystallized from methanol in pale yellow prisms, which melted at 108–108.5°.

Anal. Calcd. for $C_{19}H_{16}O_4N_4$: C, 62.63; H, 4.43. Found: C, 62.34; H, 4.24.

The diketone XVI (1 g.) was refluxed with aqueous sodium hydroxide (10 cc., 10%). The cooled solution was extracted with ether, the extract was washed with water, dried, and the solvent was removed. The residue was separated into two fractions by distillation: A, 0.17 g., b.p. 127–130°; B, 0.1 g., b.p. 180°. The 2,4-dinitrophenylhydrazone prepared from A, after several crystallizations from ethanol, formed orange platelets or needles melting at 152.5–153°, and analyzed for this derivative of cyclopropylacetone.

Anal. Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07. Found: C, 52.18; H, 5.43.

The 2,4-dinitrophenylhydrazone prepared from B crystallized from ethyl acetate in orange-red needles which melted at 239–241°, alone or when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of acetophenone.

The aqueous alkaline layer from the above extraction was acidified and the precipitate was removed and washed with cold water. This white solid melted at 121–122°, alone or when mixed with benzoic acid. The filtrate and washings from the benzoic acid were combined and extracted thoroughly with ether. The ether was evaporated, and the liquid residue, an acid, was converted into the *p*-bromophenacyl ester. This derivative crystallized from aqueous ethanol in white platelets which melted at 82°, alone or when mixed with the *p*-bromophenacyl ester prepared from authentic cyclopropylacetic acid.

MINNEAPOLIS 14, MINNESOTA

RECEIVED FEBRUARY 21, 1951

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

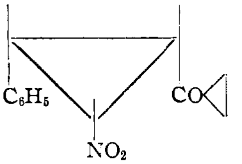
Cyclopropanes. VI.[1] The Configuration and Reduction of the Stereoisomers of Cyclopropyl 3-Phenyl-2-nitro-1-cyclopropyl Ketone

BY LEE IRVIN SMITH AND EDGAR R. ROGIER[2]

The two racemic forms, m.p. 63° and 75°, of the nitrocyclopropyl ketone I have been reduced, by the Meerwein–Ponndorf method, to cyclopropylcarbinols II. The 75° isomer of I gave a single carbinol, whereas the 63° isomer of I gave an unseparable mixture of two carbinols. The carbinols, in turn, were reduced over Raney nickel to aminocyclopropylcarbinols IV. It was not possible to convert either of the aminocyclopropylcarbinols IV into a crystalline cyclic derivative by a reaction involving the amino and hydroxyl groups, and thus fix the relative space relations of these two groups. Reduction of the nitrocyclopropyl ketones I over Raney nickel gave the same products from both stereoisomers of I. These products were the pyrroline V and the pyrrolidine VI.

Cyclopropyl 3-phenyl-2-nitro-1-cyclopropyl ketone (I) has been prepared in two racemic forms which melt at 63° and 75°, respectively.[1] The 63° form readily forms a semicarbazone and an oxime, whereas the 75° form does not react with semicarbazide and is converted into an oxime only with difficulty. The 63° form is converted into the 75° form by action of methanolic ammonia, but this reagent is without effect upon the 75° form.

There are four possible racemic forms of I: A, B, C and D.



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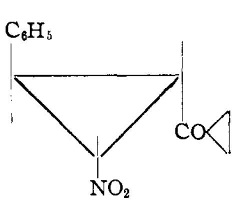

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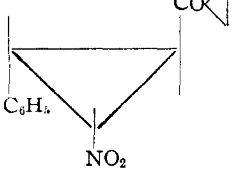

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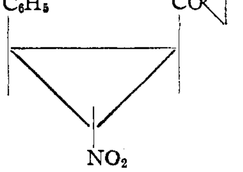

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From the fact that the 63° form readily forms carbonyl derivatives, whereas the 75° form does not, it follows with some certainty that the 63° form does not possess configuration A, with the most hindered carbonyl group, and that the 75° form does not possess configuration C, with the least hindered carbonyl group. It is also likely that the conversion of the 63° form to the 75° form involves a change in configuration in the direction of increased stability—*i.e.*, in the direction of a "more *trans*" configuration. These assumptions lead to the conclusion that the 63° form should be represented as B, C or D, and that the 75° form should be represented by B or D. In configurations B and D, there is a *cis–trans* relationship between the nitro group and the carbonyl group; consequently, if this relationship could be established, for the 75° form, the configuration of this isomer would follow with some certainty. If the nitro group and the carbonyl group of the two stereoisomeric forms of I could be reduced, the resulting aminoalcohol II, if the two groups are *cis* to each other, might be converted into the cyclic urethan III.

$C_6H_5CH—CHCHOHCH(CH_2)_2$; $CHNO_2$

II

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[1] Paper V, Smith and Rogier, THIS JOURNAL, **73**, 3831 (1951).

[2] Abstracted from a thesis by Edgar R. Rogier, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, June, 1950. Allied Chemical and Dye Corporation Fellow, 1949–1950.