

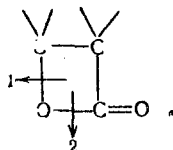
FLUORINE-CONTAINING β -LACTONES

COMMUNICATION 1. β,β -BISTRIFLUOROMETHYL- β -PROPIOLACTONE AND ITS PROPERTIES

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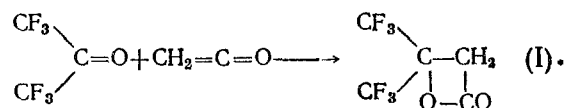
β -Lactones, which contain a strained four-membered ring, are unstable, extremely reactive compounds. They have properties determined by their ring-opening reactions; these may take two different courses: 1) with rupture of the bond between oxygen and carbon, and 2) with rupture of the bond between oxygen and the carbonyl group:



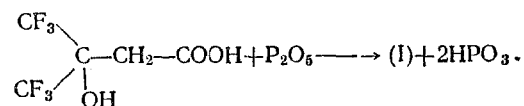
The course taken depends largely on the nature of the lactone, the character of the attacking reagent, and the reaction conditions. In this connection it was of interest to study the chemical properties of the previously unknown fluorine-containing β -lactones.

A study of the properties of β,β -bistrifluoromethyl- β -propiolactone [4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid β -lactone] formed the subject of the present investigation.

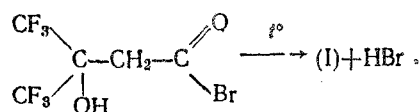
One of the most widely used methods for the preparation of β -lactones is the condensation of a ketene with a carbonyl compound [1]. It was found that perfluoroacetone reacts with ketene very much more readily than acetone does; reaction occurs under strong cooling in absence of catalyst, and it gives β,β -bistrifluoromethyl- β -propiolactone (I) in quantitative yield:



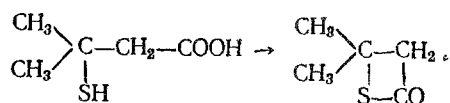
Quite unexpectedly, the lactone (I) was obtained also in the dehydration of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid with phosphoric oxide:



The lactonization of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyryl bromide occurs still more easily (simple distillation):

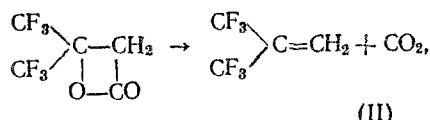


This unusual case of previously unknown ready lactonization of a β -hydroxy acid or its acid bromide* may be explained by the induction effect of two trifluoromethyl groups, which confers a certain mobility on the hydrogen atom of the hydroxy group (esters and amides of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid are soluble in dilute alkalis). The known analogous ready lactonization of 3-mercapto-3-methylbutyric acid into β,β -dimethyl- β -propiothiolactone is probably to be explained analogously by the high mobility of the hydrogen of the thiol group, as compared with that of hydrogen in hydroxyl [2]:

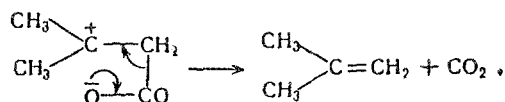


Lactonization is favored also by the fact that the trifluoromethyl groups greatly strengthen the link between the tertiary carbon and oxygen, which completely excludes the competing dehydration into the α,β -unsaturated compound that is of predominant significance in the case of nonfluorinated β -hydroxy acids [3].

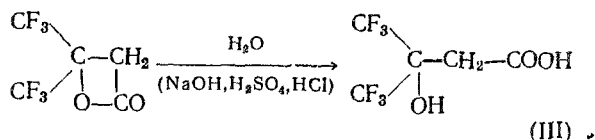
The lactone (I) undergoes thermal decomposition into carbon dioxide and 3,3,3-trifluoro-2-(trifluoromethyl) propene (II) only when heated to 340-350°



whereas β -isovalerolactone decomposes when heated to only 60° [9]. β -Isovalerolactone decomposes in the same way when dissolved in water at room temperature, evidently because the methyl groups screen the tertiary carbon atom to a certain extent and render the stabilization of the ion formed in a polar solvent by the elimination of carbon dioxide more probable than its stabilization by the addition of the elements of water:

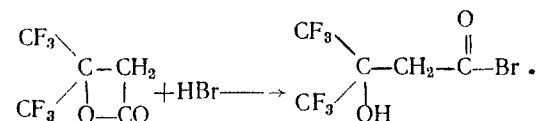


Unlike β -isovalerolactone, β,β -bistrifluoromethyl- β -propiolactone reacts with water only after prolonged heating, when it gives 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid (III). The same acid is obtained when the lactone is decyclized with alkali or concentrated sulfuric or hydrochloric acid:

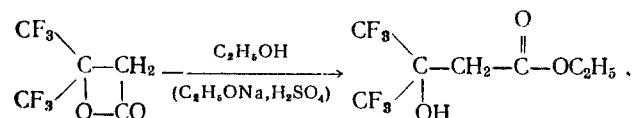


* Data in the literature on the cyclization of β -hydroxy α,α -dicarboxylic acids to lactones were rejected in the later work of Davidson and Bernhard [4] and Hurd and Hayao [5]. The suggestion of the intermediate formation of a β -lactone from β -hydroxy- β -t-butylhydrocinnamic acid [6] also appears to be improbable in view of modern views of the mechanism of the spontaneous decomposition of salts of β -halo acids [7, 8].

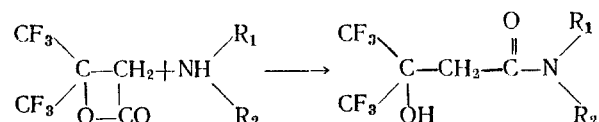
When treated with anhydrous hydrogen bromide, the lactone (I) gives 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyryl bromide (IV):



With alcohol the lactone (I), in absence of catalyst and also in presence of acids or alkalis, gives only one product, ethyl 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyrate (V):



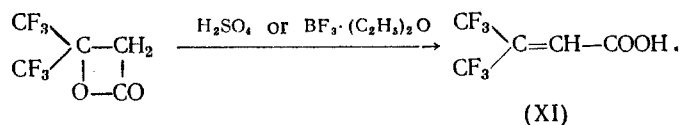
With ammonia or a primary or secondary amine, even under conditions that most favor the formation of amino acids, only the corresponding hydroxy amides (VI-X) are obtained:



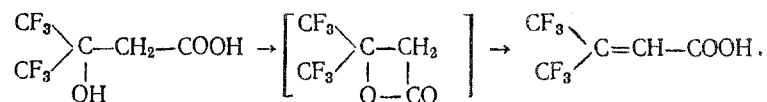
(VI) $\text{R}_1, \text{R}_2-\text{H}$; (VIII) R_1-H ; $\text{R}_2-\text{C}_2\text{H}_5$; (X) $\text{R}_1, \text{R}_2-(\text{CH}_2)_5-$
(VII) $\text{R}_1, \text{R}_2-\text{CH}_3$; (IX) R_1-H ; $\text{R}_2-\text{C}_6\text{H}_5$.

Hence, the outstanding feature of β, β -bistrifluoromethyl- β -propiolactone is the great strength of the bond between oxygen and tertiary carbon, which determines its exceptional stability and the fact that all decyclizations proceed in the direction of derivatives of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid.

Tertiary amines, and also sodium or traces of caustic alkali, cause the lactone to polymerize to a clear solid or semisolid polymer, which softens at 30-40° and is a 4,4,4-trifluoro-3-(trifluoromethyl) crotonic polyester of low molecular weight. Hydrolysis of the polyester with alkali leads to the acid (III), but treatment with anhydrous sulfuric acid or pyrolysis leads to 4,4,4-trifluoro-3-(trifluoromethyl) crotonic acid (XI). The acid (XI) is obtained in good yield by the isomerization of the lactone under the action of anhydrous sulfuric acid or the ether complex of boron trifluoride:



By the dehydration of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl)-butyric acid with concentrated sulfuric acid, 4,4,4-trifluoro-3-(trifluoromethyl) crotonic acid was again obtained. This was unexpected in view of the fact that we were unable to dehydrate the ethyl ester of this hydroxy acid even under severe conditions [10]. Consideration of these data in conjunction with the fact of the ready formation of the lactone (I) from 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid under the action of phosphoric oxide enables us to suggest that under the action of anhydrous sulfuric acid the first act is the formation of the β -lactone, which is not isolated because of its isomerization under these conditions to 4,4,4-trifluoro-3-(trifluoromethyl) crotonic acid:



EXPERIMENTAL

Anhydrous Perfluoroacetone

Perfluoroacetone hydrate forms very hygroscopic white crystals which melt at about 40°. However, the "hydrate" obtained by the oxidation of perfluoroisobutene by Morse's method [11] was a colorless liquid and, apart from perfluoroacetone and water, contained diethyl ether and 3,3,3-trifluoro-2-(trifluoromethyl) lactic acid [12]. The amount of ether can be determined after water has been bound with phosphoric oxide and gases have been driven off. The 3,3,3-trifluoro-2-(trifluoromethyl) lactic acid was titrated with Bromophenol Blue as indicator, and the amount of perfluoroacetone was calculated from the difference in the titrations to phenolphthalein and to Bromophenol Blue. In various experiments, 100 ml of the "hydrate" contained from 67 to 83 g of perfluoroacetone.

A three-necked flask fitted with stirrer, thermometer, and reflux condenser was charged with 300 ml of concentrated sulfuric acid and was cooled externally with ice water while 100 ml of "perfluoroacetone hydrate" (b.p. 90-126; containing 67.5 g of perfluoroacetone according to titration data) was added. When the vigorous reaction was complete, the solution was heated slowly until gas ceased to be liberated (110-120° in the liquid). The gas liberated was purified with sulfuric acid and anhydrous potassium fluoride, dried over phosphoric oxide, and condensed in a trap cooled in solid carbon dioxide. This gave 65.6 g (98%) of anhydrous perfluoroacetone, which was used immediately in the following experiment.

β,β -Bistrifluoromethyl- β -propiolactone (I)

Preparation from Perfluoroacetone and Ketene. A four-necked flask fitted with stirrer, reflux condenser, and two gas-inlet tubes which passed to the bottom of the flask was charged with 50 ml of ether and was cooled to -78° while, over a period of two hours, 123 g (0.74 mole) of perfluoroacetone and 40 g (1 mole) of ketene were passed in simultaneously and condensed. The flask was then warmed slowly up to room temperature, and 10 g of phosphoric oxide was added to the solution. On the next day the solution was decanted from the precipitate and fractionated through a column having a 400-mm filling. We obtained 129.6 g (96%) of the lactone (I); b.p. 94.5-95° (775 mm); n_D^{20} 1.3240; d_4^{20} 1.6561; found MR 26.75; calculated MR 26.04; λ_{max} : 5.29 μ ; 5.13 μ . Found: C 28.65; H 1.25; F 52.02%. $\text{C}_5\text{H}_2\text{F}_6\text{O}_2$. Calculated: C 28.8; H 0.94; F 54.8%.

Preparation from 4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyric Acid. A mixture of 15.69 g (0.0678 mole) of the hydroxy acid (III) and 15 g (0.118 mole) of phosphoric oxide was heated in a metal bath to 150°; at this temperature a colorless liquid, b.p. 95-106°, slowly distilled off. Redistillation through a column gave 10.5 g (73%) of the lactone (I), b.p. 94.8-95° (745.6 mm) and n_D^{20} 1.3240.

3,3,3-Trifluoro-2-(trifluoromethyl) propene (II)

The pyrolysis of the lactone (I) was carried out in an apparatus consisting of a scaled-down copy of a ketene lamp [13]. The lactone (11.72 g) was subjected to pyrolysis on a nichrome spiral at 340-352°. The temperature was measured with a thermocouple, the hot junction of which was soldered to the middle of the spiral. The gases, after passing through a wash bottle containing water and a calcium chloride column, were condensed in two traps cooled by a mixture of solid carbon dioxide and acetone. The uncondensed gas was collected in a gas holder. We obtained 1.1 liters of carbon dioxide and 5.9 g (68%) of (II) (on the amount of lactone that reacted); b.p. 13.0-13.1° Found: C 29.35; H 1.25; F 68.94%; M 162. $\text{C}_4\text{F}_6\text{H}_2$. Calculated: C 29.30; H 1.22; F 69.5%; M 164. The literature [14] gives b.p. 11-13°.

Distillation of the residue gave 0.8 g of the lactone (I), b.p. 94-100°, and 1.6 g (15%) of an acid of b.p. 152-158° and identical to (XI).

4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyric Acid (III)

A mixture of 1.87 g (0.009 mole) of the lactone (I) and 0.3 g (0.016 mole) of water was heated for six hours in a sealed glass tube. After the product had been dried we obtained 2.02 g (99%) of the hydroxy acid

(III), m.p. 89-89.5° (from carbon tetrachloride); λ_{\max} 5.81 μ . Found: C 26.35; H 1.73; F 50.31%. $C_5H_4F_6O_3$. Calculated: C 26.55; H 1.77; F 50.50%.

The lactone (I) (1.31 g) was mixed with 12 ml of concentrated sulfuric acid. When the exothermic reaction was complete, from the solution we distilled 1.36 g (96%) of crystals of m.p. 87-88° (from carbon tetrachloride), identical with (III). When concentrated hydrochloric acid was used instead of sulfuric acid, a short heating at 100° was required.

Dropwise addition of 35 ml of 2N NaOH was made to 10.16 g (0.049 mole) of the lactone (I). When the exothermic reaction was complete, the clear solution was decanted from the polymer formed and acidified. Extraction with ether gave 9.34 g (85%) of the hydroxy acid (III), m.p. 83-85°. After being washed with water and dried the polymer amounted to 1.34 g (13%).

The ester (V) (5.37 g) was boiled for one hour in 5 ml of anhydrous sulfuric acid, and from the reaction mixture we then distilled 4.58 g (96%) of (III), m.p. 87-88° (from carbon tetrachloride).

4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyryl Bromide (IV)

A mixture of 10.58 g (0.051 mole) of the lactone (I) and 5.25 g (0.65 mole) of anhydrous hydrogen bromide was heated for eight hours at 100° in a sealed quartz tube. Excess of hydrogen bromide was evaporated off, and fractional distillation of the residue gave 6 g (41%) of pure (IV); b.p. 43.5-43.8° (21 mm); d_4^{20} 1.860; n_D^{20} 1.3775; found MR 35.79; $C_5H_3F_6O_2Br$. Calculated MR 35.43; Found: C 20.64; H 1.00; F 37.59%. $C_5H_3F_6O_2Br$. Calculated: C 20.8; H 1.04; F 39.4%.

When (IV) (0.3 g) was left in air, it was quantitatively converted into the hydroxy acid (III), m.p. 87-88.5° (from carbon tetrachloride). During slow distillation through a column at atmospheric pressure, (IV) is decomposed with liberation of hydrogen bromide and formation of the lactone (I), b.p. 92-95° and n_D^{20} 1.3233, 0.45 g (0.0015 M) (IV). At a temperature of -78°, (IV) (0.45 g, 0.0015 mole) was mixed with piperidine (0.5 g, 0.0028 mole). When the vigorous reaction was complete, piperidine was washed out with dilute hydrochloric acid and the product was dried. It amounted to 0.32 g (70%) of crystals, m.p. 60-61.5° (from heptane) and identical with (X).

Ethyl 4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyrate (V)

A mixture of 10.7 g (0.051 mole) of the lactone (I) and 15 ml of absolute alcohol was boiled for six hours and then poured into water. Extraction with ether gave 10.000 g (77%) of the ester (V), b.p. 157-158° (756 mm) and n_D^{20} 1.3432, identical with the compound described in [10].

Analogous experiments, in which concentrated sulfuric acid or sodium ethoxide was used as catalyst, gave the ester (V) in 77% or 74% yield, respectively. On esterification of 10.0 g of the hydroxy acid (III) with 40 ml of absolute ethanol in presence of 1 ml of concentrated sulfuric acid we obtained 6.35 g (61%) of the ester (V), b.p. 154-156° (746.3 mm) and n_D^{20} 1.3432. In none of the experiments was the ethoxy acid isolated.

4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyramide (VI)

A mixture of 0.56 g of the ester (V) and 4.5 ml of concentrated aqueous ammonia was shaken until the whole of the ester dissolved. After evaporation of ammonia and drying, 0.31 g (63%) of the amide (VI), m.p. 83.5-84.5° (from dry benzene), was obtained. Found: C 27.25; H 2.44; F 51.55, N 6.23%. $C_5H_5F_6O_2N$. Calculated: C 26.65; H 2.46; F 50.06; N 6.23%.

The lactone (I) (0.99 g) was mixed with 10 ml of concentrated aqueous ammonia. When the exothermic reaction was complete we obtained 1.05 g (98%) of crystals of m.p. 84-84.5° (from benzene), identical with (VI).

4,4,4-Trifluoro-3-hydroxy-N,N-dimethyl-3-(trifluoromethyl) butyramide (VII)

Dry dimethylamine (6.1 g, 0.13 mole) was passed for one hour into a solution of 8.9 g (0.042 mole) of the lactone (I) in 15 ml of acetonitrile cooled to 0°. After evaporation of the excess of dimethylamine and acetonitrile we obtained 8.59 g of the amide (VII), m.p. 63-63.5° (from heptane). Found: C 33.26; H 3.67; F 44.44; N 5.70%. $C_7H_8F_6O_2N$. Calculated: C 33.3; H 3.18; F 45.3; N 5.56%.

Aqueous dimethylamine and the lactone (I) gave (VII) in quantitative yield. All the amides [(VII)-(X)] obtained are soluble in 10% potassium hydroxide solution and insoluble in dilute acids.

N-Ethyl-4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyramide (VIII)

By reaction of ethylamine with the lactone (I) at -78° we obtained the amide (VIII) in 84% yield; m.p. $47-47.5^{\circ}$ (from carbon tetrachloride). Found: C 32.93; H 3.58; F 44.44; N 5.77%. $C_7H_8F_6O_2N$. Calculated: C 33.3; H 3.18; F 45.3; N 5.56%.

4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyranilide (IX)

From 1.02 g (0.005 mole) of the lactone (I) and 0.5 g (0.0052 mole) of aniline we obtained 1.31 g (89%) of the amide (IX), m.p. $100-100.5^{\circ}$ (from carbon tetrachloride). Found: C 43.75; H 2.89; F 36.03; N 5.14%. $C_{11}H_8F_6O_2N$. Calculated: C 44.0; H 2.66; F 38.0; N 4.67%.

Piperidide of 4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyric Acid

This was prepared from the lactone (I) and piperidine in 92% yield; m.p. $62-62.5^{\circ}$ (from carbon tetrachloride). Found: C 40.97; H 4.40; F 39.72; N 4.78%. $C_{10}H_{13}F_6O_2N$. Calculated: C 41.0; H 4.44; F 38.95; N 4.78%.

4,4,4-Trifluoro-3-(trifluoromethyl) crotonic Acid

From β,β -Bistrifluoromethyl- β -propiolactone. The lactone (I) (3.12 g) was mixed with 2 ml of anhydrous sulfuric acid. When the exothermic reaction was complete, 2.92 g (94%) of colorless liquid, b.p. $157-163^{\circ}$, was distilled off; redistillation of this gave pure (XI); b.p. $158-158.5^{\circ}$ (762.1 mm); m.p. $28.5-29.5^{\circ}$; neutralization equivalent 205; calculated 208; λ_{max} 5.71μ . Found: C 28.85; H 0.94; F 52.89%. $C_5H_2F_6O_2$. Calculated: C 28.8; H 0.96; F 54.9%. The acid formed white needles which deliquesced in air; it formed a 58% solution with water. When the ether complex of boron trifluoride was used instead of sulfuric acid, boiling for several hours was necessary and the yield of the acid (XI) was then 82%.

From 4,4,4-Trifluoro-3-hydroxy-3-(trifluoromethyl) butyric Acid. A mixture of 1.65 g of the hydroxy acid (III) and 2 ml of anhydrous sulfuric acid was heated for 15 minutes at 100° , and distillation then gave 1.39 g (91%) of crystals of m.p. $28-29.5^{\circ}$ (from heptane), identical with (XI).

Polymerization of β,β -Bistrifluoromethyl- β -propiolactone

Addition of 0.01 g of sodium or traces of triethylamine to 13.32 g of the lactone (I) and keeping of the mixture at 20° for four days led to the formation of a thick colorless polymer which softened at $30-40^{\circ}$. Its molecular weight, determined cryoscopically, was 1310. The polymer (1.32 g) and anhydrous sulfuric acid (2 ml) were heated together until complete solution occurred (ten minutes), and from the mixture 1.14 g of the acid (XI), b.p. $157-159^{\circ}$ (742 mm) and m.p. $26-29^{\circ}$, was then distilled off. The polymer (1.31 g) was dissolved in 10 ml of 10% potassium hydroxide solution. Acidification and extraction with ether gave 0.96 g (73%) of the hydroxy acid (III), m.p. $87-89^{\circ}$ (from carbon tetrachloride). The polymer (8.2 g) was treated in ethereal solution with dilute hydrochloric acid. The solution was dried, solvent was distilled off, and pyrolysis of the residue at $160-180^{\circ}$ gave 5.84 g of the acid (XI).

SUMMARY

1. The reaction of perfluoroacetone with ketene was carried out and led to the formation of β,β -bistrifluoromethyl- β -propiolactone [4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid β -lactone].
2. It was shown that the β -hydroxy acid, i.e., 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid or its acid bromide, can be cyclized into the β -lactone.
3. The opening of the four-membered ring of β,β -bistrifluoromethyl- β -propiolactone, unlike that of β -isovalerolactone, proceeds exclusively in one direction with formation of derivatives of 4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butyric acid.

LITERATURE CITED

1. H.E. Zaugg, in: Organic Reactions [Russian translation] (IL, Moscow, 1956) Vol. 8, p. 569 (Vol. 8, p. 305 in American edition).
2. M.G. Lin'kova, O.V. Kil'disheva, and I.L. Knunyants, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk, 569 (1959).*

3. J. Houben, Die Methoden der organischen Chemie [Russian translation] (ONTI, 1955) Vol. 3, Part 2, p. 143.
4. D. Davidson and S.A. Bernhard, J. Am. Chem. Soc. 70, 3426 (1948).
5. C.D. Hurd and S. Hayao, J. Am. Chem. Soc. 76, 5563 (1954).
6. G.A. Tsatsas, Ann. chimie [12] 1, 342 (1946).
7. S.J. Cristol and W.P. Norris, J. Am. Chem. Soc. 75, 2645 (1953).
8. E. Grovenstein and D.E. Lee, J. Am. Chem. Soc. 75, 2639 (1953).
9. T.L. Grecham, I.E. Jansen, F.W. Shaver, W.L. Beeers, J. Am. Chem. Soc. 76, 486 (1954).
10. I.L. Knunyants, Ch'en Ch'ing-yun, and N.P. Gambaryan, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk, 686 (1960).*
11. A.T. Morse, P.B. Ayscough, and L.C. Leitch, Can. J. Chem. 33, 453 (1955).
12. I.L. Knunyants, E.M. Rokhlin, N.P. Gambaryan, Yu.A. Cheburkov, and Ch'en Ch'ing-yun, Khim. Nauka i Prom. 4, 802 (1959).
13. W.E. Hanford and J.C. Sauer, in: Organic Reactions [Russian translation] (IL, Moscow, 1951) Vol. 3, p. 129 (Vol. 3, p. 108 in American edition).
14. R.N. Haszeldine, J. Chem. Soc., 3565 (1953).

*Original Russian pagination. See C.B. translation.