# On the Reaction of α-Phthalimidoacid Chlorides with Substituted Sodiomalonates. A Method for the Preparation of α-Amino Ketones and Related Compounds

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The Bowman ketone synthesis was successfully applied to N-phthalylaminoacid chlorides. In this manner 1-phthalimido-4-phenyl-2-butanone [V] as well as 1-phthalimido-2-octadecanone [IV] were formed in the reaction of N-phthalylglycyl chloride with corresponding substituted dibenzyl or ditetrahydropyranyl sodiomalonates. The optically active 2-phthalimido-5-phenyl-3-pentanone [X] was obtained with N-phthalylalanyl chloride. From 1-phthalimido-4-phenyl-2-butanone [V] we prepared 1-benzamido-4-phenyl-2-butanone [VII] and 1-amino-4-phenylbutane [IX] so that the reaction represents a method for the preparation of α-amino ketones and related compounds.

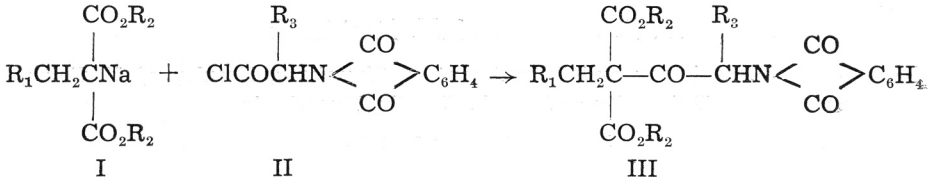
The acylation of diethyl sodiomalonates with N-phthalylaminoacid chlorides was extensively investigated by Gabriel et al.[1], and Immendörfer[2]. Pascual and Rebollo[3] prepared the diethyl phthalylglycyl-benzylmalonate[4] from phthalylglycyl chloride and sodiobenzylmalonate, but their attempts to hydrolize this compound to 1-amino-4-phenyl-2-butanone failed. The reaction was also applied by Baker, Querry, Schaub, and Williams[5] in their work on an antimalarial alkaloid from Ch'ang Shan roots.

A general method for the preparation of ketones by acylation of substituted malonic esters was described recently in a series of papers by Bowman and Fordham[6] and by Fonken and Johnson[7]. These authors made use of dibenzyl, ditetrahydropyranyl and di-tert. butyl malonates which could be easily hydrolyzed and decarboxylated, and the corresponding ketones were obtained in high yields. The method was shown to be of great value in the preparation of long-chain aliphatic compounds.

In our work on long-chain amino alcohols of the sphingosine type we have been interested in investigating the possibility of preparing some α-aminoketones as model compounds using natural α-aminoacids as starting material. The reaction of N-phthalylaminoacid chlorides [II] with substituted dibenzyl and ditetrahydropyranyl-malonates [I] was investigated. The formation of phthalimido ketones has been effected and so a further evidence of the generality of the reaction has been given. When using L-alanine as the amino acid component, an optically active product was obtained. Since the asymmetric centre is not attacked during the reaction, an inversion in configuration is not expected, and the described method seems to be of importance for stereochemical studies. The described reaction offers very likely a new possibility

for the determination of the absolute configuration of some natural amino compounds. This possibility is under investigation in our laboratories.

In this paper we describe the acylation of sodiobenzyl malonate and sodiopentadecyl malonate with N-phthalylglycyl chloride. The method used is essentially that of Bowman which was applied to the corresponding ditetrahydropyranyl malonates. In one case the dibenzyl benzylmalonate was used.

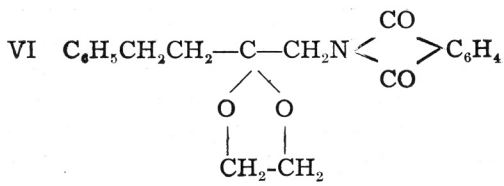


I II III

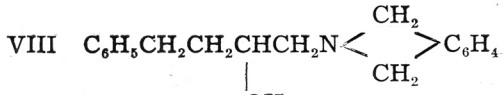
a) $R_2$ = benzyl
b) $R_2$ = tetrahydropyranyl

IV

V



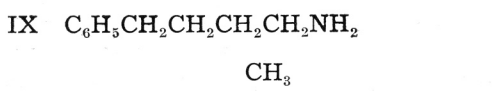
VI



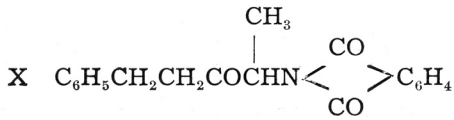
VII



VIII



IX



X

and the intermediary crystalline 1-phthalimido-3,3-dicarbobenzyloxy-4-phenyl-2-butanone [IIIa, $R_3$=H] was debenzylated catalytically. Decarboxylation yielded the desired 1-phthalimido-4-phenyl-2-butanone [V]. This compound was first prepared from 1-chloro-4-phenyl-2-butanone and potassium phthalimide by Henze and Shown[8]. Starting from [V] a series of related compounds was prepared. For further studies it became necessary to devise a method for

removing the phthalimido group. Henze and Shown eliminated it by hydrolysis of the intermediary formed phthalamic acid. We tried to remove the phthalyl group by direct hydrolysis with hydrochloric acid as well as by hydrazinolysis of the corresponding ketal [VI], but in both cases undefined products were obtained. Finally, the phthalyl group was removed by heating the ketone [V] with hydriodic acid in glacial acetic acid. The crystalline hydriodide thus obtained was converted without further characterization into the benzoyl derivative [VII] according to the method of Gabriel[9]. These reactions offer the possibility of preparing the corresponding α-amino alcohol and the α, β-diamine by lithium aluminum hydride reduction of [VII] or of its oxime and subsequent hydrogenolysis of the benzyl group.

The reduction of [V] with lithium aluminum hydride yielded, as expected[10], 1-(N-isoindolinyl-)-4-phenyl-2-butanol [VIII], a viscous semicrystalline oil, which was identified by converting it into the crystalline oxalate. An attempt was made to split off the o-xylene from this compound hydrogenolytically. Only a minute amount of an oxalate with a nitrogen content between the values for neutral and acid oxalate of 1-amino-4-phenyl-2-butanol was obtained. The reaction was not further investigated, since the benzoylamino ketone [VII] seemed to be a more suitable starting material for the preparation of amino alcohols and diamines.

In the Huang-Minlon modification of the Wolf-Kishner reaction the ketone [V] was reduced — with simultaneous elimination of the phthalyl group — to the already described 1-amino-4-phenylbutane [IX][11].

In order to check the suitability of this synthesis in the long-chain series, the reaction was extended to pentadecyl malonic acid yielding 1-phthalimido--2-octadecanone [IV].

Finally, the synthesis of phthalimido ketones from optically active amino acids has been attempted. N-Phthalyl-L-alanyl chloride [II, $R_3 = CH_3$] was brought into reaction with ditetrahydropyranyl sodiobenzylmalonate. The isolation of the reaction product presented more difficulty and the ketone fraction was separated by means of the Girard reagent. Chromatography of the crude fraction led to an oily substance, which was oximated giving 2--phthalimido-5-phenyl-3-pentanone oxime ($[\alpha]_D = +5.31^0$).

We wish to point out that the yields of the phthalimido ketones prepared in this way were rather low and in some instances a part of the material was lost in trying to find out the best method for isolating the products. No attempt has been made to improve the yields since the general application of the reaction was the first aim and most of the experiments were not repeated in the course of this work.

## EXPERIMENTAL*

The phthalimido acid chlorides were prepared in the usual manner from the corresponding acids, i. e. phthalylglycine and phthalyl-L-alanine, using thionyl chloride. The crude chlorides were purified by distillation in vacuo.**

* The melting points are uncorrected.

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*1-Phthalimido-3,3-dicarbobenzyloxy-4-phenyl-2-butanone* [IIIa, $R_3$ = H]

A solution of diethyl benzylmalonate (5 g., 0,02 mole) in benzene (30 ml.) was added to dry sodium ethoxide (prepared according to Bowman[6] from 0,46 g. of sodium). Formation of the sodium enolate was immediate; when the dissolution was completed, benzyl alcohol (4,32 g.) was added, and the mixture distilled through an efficient fractionating column until all benzene-ethanol azeotrope was removed. Phthalylglycyl chloride (4,48 g., 0,02 mole) in benzene was then added to the residual benzene solution of dibenzyl sodiobenzylmalonate and the mixture refluxed for 30 minutes. The cooled solution was poured into ice-water (100 ml.) containing a trace of sulfuric acid, and the organic layer separated. The aqueous layer was extracted with benzene, and the combined extracts washed with water, dried with anhydrous sodium sulphate, and the solvent evaporated in vacuo. The remaining yellow oil was dissolved in dioxane (25 ml.). On addition of 200 ml. of 95% ethanol and scratching with a glass rod, the product crystallized in colorless prisms (2,4 g., 21,4%, m. p. 100°). For analysis the product was crystallized twice from dioxane-ethanol, m. p. 101—102°.

*Anal.* 10,120 mg. subst.: 0,250 ml. $N_2$ (23°, 750 mm.)
$C_{34}H_{27}O_7N$ (561,56) calc'd N 2,50%
found N 2,83%

*1-Phthalimido-4-phenyl-2-butanone* [V]

Method A: Benzylmalonic acid (19,43 g.) was added in portions with stirring to a solution of dihydropyrane (25,2 g.) in benzene (100 ml.) containing one drop of sulfuric acid. Stirring was continued for 30 minutes. Anhydrous potassium carbonate (4 g.) was added to the clear solution, and the stirring continued for additional 30 minutes. The solution was decanted from inorganic material and the solvent and excess of dihydropyrane removed by evaporation in vacuo below 30°. The residual oil was dissolved in benzene (100 ml.) and added to a stirred suspension of sodium powder (2,3 g.) in benzene (200 ml.). Stirring was continued until the metal was dissolved, and a solution of phthalylglycyl chloride (21 g.) in benzene (100 ml.) was then slowly added at room temperature. After standing for one hour, the mixture was acidified with acetic acid (10 ml.) and refluxed for 150 minutes. Carbon dioxide escaped and the yellow solution became colorless. The cooled mixture was washed with water, and a small amount of undissolved phthalylglycine was recovered. After evaporating the benzene solution the residual oil (44 g.) was dissolved in 95% ethanol (60 ml.). After standing in the refrigerator, the separated crystals were filtered, washed with ethanol and dried, m. p. 109—110° (10 g., 36,4% based on phthalylglycyl chloride). For analysis the product was recrystallized from 95% ethanol m. p. 110,5° (recorded m. p. 106—107°)[8].

*Anal.* 5,705 mg. subst.: 15,50 mg $CO_2$ 2,50 mg. $H_2O$
7,815 mg. subst.: 0,333 ml. $N_2$ (22,5°, 753 mm.)
$C_{18}H_{15}O_3N$ (293,31) calc'd: C 73,70; H 5,15; N 4,78%
found: C 74,14; H 4,90; N 4,88%

Method B: The keto ester [IIIa, $R_3$=H], (1,0 g., 1,78 m Mole), dissolved in ethyl acetate (30 ml.) was catalytically reduced with 10% palladium on baryum sulphate catalyst (1,0 g.) at ordinary pressure and room temperature. After 10 hours the hydrogenolysis was completed, the catalyst filtered off and the solvent evaporated to dryness on the water bath. The residual oil was heated for 0,5 hour at 100°. On cooling the product solidifies (515 mg., 98,6%). Two recrystallizations from 95% ethanol gave colorless needles, m. p. 110,5°, indentical with the product obtained by method A.

Oxime. Obtained from [V] and hydroxylamine acetate (100% excess) in absolute ethanol on the steam bath for one hour. On cooling the oxime crystallizes in

colorless needles, m. p. 139—141°. After two crystallizations from 95% ethanol the oxime melted at 140—141°.

*Anal.* 9,100 mg. subst.: 23,30 mg. $CO_2$, 4,10 mg. $H_2O$
6,915 mg. subst.: 0,568 ml. $N_2$ (24°, 750 mm.)
$C_{18}H_{16}O_3N_2$ (308,32) calc'd: C 70,12; H 5,23; N 9,09%
found: C 69,88; H 5,04; N 9,32%

*Pentadecylmalonic Acid*

To a solution of diethyl sodiomalonate, prepared from diethylmalonate (8 g., 0,05 mole) and sodium ethoxide (from 1,15 g. sodium) in benzene (50 ml.), pentadecylbromide (14,55 g., 0,05 mole) in benzene (50 ml.) was added. The mixture was refluxed for 12 hours. During the reaction sodium bromide separated. Water (100 ml.) was added, the mixture acidified with dilute hydrochloric acid, and the organic layer separated. After drying, the solution was distilled in vacuo. A small forerun (b. p. up to 130°/0,3 mm.) was collected. The residue in the distilling flask was hydrolysed by shaking it with a solution of potassium hydroxide (15 g.) in water (12 ml.). After the hydrolysis was completed, water (100 ml.) was added, and the clear solution acidified with 5 *N* hydrochloric acid. The precipitated acid was extracted with ether, the solvent distilled off, and the crude product crystallized from benzene. Yield 8,9 g. (83%), colorless needles, m. p. 114—115°.

*Anal.* 10,320 mg. subst.: 26,04 mg. $CO_2$, 10,165 mg. $H_2O$
$C_{18}H_{34}O_4$ (314,45) calc'd: C 68,75; H 10,90%
found: C 68,86; H 11,02%

*1-Phthalimido-2-octadecanone* [IV]

A solution of ditetrahydropyranyl pentadecylmalonate (from 8,56 g., 0,04 mole of pentadecylmalonic acid, prepared in the same manner as described for the benzylmalonate) was added to dry sodium ethoxide (from 0,92 g., 0,04 g-atom of sodium) at room temperature. Phthalylglycyl chloride (8,96 g., 0,04 mole) in dry benzene (30 ml.) was then added. After standing at room temperature (2 hours), 4 drops of acetic acid were added and the mixture refluxed for 2 hours. The cooled benzene solution was washed with water, and the solvent evaporated. The residual oil was induced to crystallisation by addition of 95% ethanol (30 ml.). Thus, 3,9 g. of a colorless crystalline product, m. p. 80—82° was obtained. Two crystallizations from ethanol gave 1,8 g. (10,87%) of colorless, glistening plates, m. p. 89—90°.

*Anal.* 9,010 mg. subst.: 25,09 mg. $CO_2$, 7,70 mg. $H_2O$
7,095 mg. subst.: 0,216 ml. $N_2$ (19,4°, 748 mm.)
$C_{26}H_{39}O_3N$ (413,58) calc'd: C 75,50; H 9,51; N 3,39%
found: C 75,99; H 9,56; N 3,50%

Oxime. A solution of the ketone [IV] and hydroxylamine acetate in absolute ethanol was refluxed for 1 hour. From the concentrated reaction mixture colorless needles separated, which were crystallized three times from 95% ethanol, m. p. 108—110°.

*Anal.* 6,900 mg. subst.: 0,375 ml. $N_2$ (20,5°, 748 mm.)
$C_{26}H_{40}O_3N_2$ (428,60) calc'd: N 6,54%
found: N 6,22%

*1-Phthalimido-4-phenyl-2-butanone ketal* [VI]

A mixture of [V] (500 mg.), ethylene glycol (4 ml.), p-toluenesulphonic acid (20 mg.) in toluene (30 ml.) was slowly distilled from a flask provided with a total condensation take-off adapter. During 4 hours 10 ml. of distillate was collected. The mixture was cooled, washed successively with 2 *N* sodium hydrogen carbonate solution and water, the toluene layer dried with anhydrous sodium sulphate and

evaporated to dryness in vacuo. A colorless oil which crystallizes on standing was obtained (540 mg., m. p. 114—118°). The product was recrystallized three times from 95% ethanol. Colorless crystals, m. p. 125—125,5° (380 mg.).

*Anal.* 9,790 mg. subst.: 25,50 mg. $CO_2$, 5,295 mg. $H_2O$
6,700 mg. subst.: 0,250 ml. $N_2$ (21°, 748 mm.)
$C_{20}H_{19}O_4N$ (337,36) calc'd: C 71,20; H 5,68; N 4,15%
found: C 71,08; H 6,05; N 4,27%

*1-Benzamido-4-phenyl-2-butanone* [VII]

To a solution of [V] (1,0 g.) in acetic acid (10 ml.) 3 ml. of hydriodic acid (d. 1,96) was added, and the mixture heated on a steam bath for 10 hours. The solution was evaporated to dryness in vacuo, the dark residue dissolved in water and exhaustively extracted with chloroform, which removed the iodine. The aqueous solution was concentrated in vacuo to a small volume, cooled and filtered from the insoluble material. The filtrate was evaporated in vacuo, the yellow solid residue dissolved in a small volume of absolute ethanol, and the product precipitated with ether. The solvent was decanted, and the crystalline precipitate purified by repeating this process two times. After crystallization from absolute ethanol-petroleum ether, 320 mg. of colorless needles m. p. 120—123°, were obtained. Without further purification the hydriodide was benzoylated according to Gabriel[9]. It was dissolved in warm acetic acid (1,5 ml.), the solution cooled to 20°, anhydrous sodium acetate (320 mg.) added, and the mixture treated with benzoyl chloride (0,4 ml.). After heating for 10 minutes on the steam bath, the cooled mixture was diluted with water (15 ml.). A pink colored oil separated, which solidifies upon standing (290 mg.). Two crystallizations from ethanol-water (3 : 1) with addition of charcoal gave colorless leaflets, m. p. 86,5—87,5°.

*Anal.* 10,005 mg. subst.: 28,035 mg. $CO_2$, 5,785 mg. $H_2O$
7,059 mg. subst.: 0,341 ml. $N_2$ (21°, 748 mm.)
$C_{17}H_{17}O_2N$ (267,31) calc'd: C 76,38; H 6,41; N 5,24%
found: C 76,47; H 6,47; N 5,27%

O x i m e. Prepared in the usual manner with alcoholic hydroxylamine acetate solution. After two recrystallizations from benzene it separated in colorless leaflets, m. p. 151—152°.

*Anal.* 5,900 mg. subst.: 0,501 ml. $N_2$ (21°, 747 mm.)
$C_{17}N_{18}O_2N_2$ (282,33) calc'd: N 9,92%
found: N 9,69%

*1-(N-Isoindolinyl)-4-phenyl-2-butanol* [VIII]

The reaction was carried out in a Soxhlet extractor. In the thimble 3 g. (10,22 mMole) of [V] was placed, and a solution of lithium aluminium hydride (1,5 g.) in ether (300 ml.) maintained at a moderate rate of boiling until all the ketone has been dissolved. The excess of hydride was destroyed by cautious addition of water, the ether solution decanted, and the solvent evaporated. Thus, 2,82 g. of a thick, brown oil, which partly crystallizes on standing, was obtained. It was dissolved in absolute ethanol (15 ml.) and added to solution of oxalic acid (1,5 g.) in ethanol (30 ml.). After few minutes a crystalline o x a l a t e was formed. The salt was recrystallized three times from ethanol with addition of charcoal. Colorless needles, m. p. 158° (decomp.).

*Anal.* 10,495 mg. subst.: 25,860 mg. $CO_2$, 5,770 mg. $H_2O$
6,405 mg. subst.: 0,216 ml. $N_2$ (20°, 748 mm.)
found: C 67,24; H 6,15; N 3,87 %
$C_{20}H_{23}O_5N$ (357,4) calc'd: C 67,21; H 6,49; N 3,92 %

*1-Amino-4-phenylbutane* [IX]

Diethylene glycol (10 ml.), V (1,5 g., 5,12 mMole), hydrazine hydrate (2,5 ml.) and potassium hydroxide (2 g.) were heated by means of an oil bath in a flask equipped with a reflux condenser at 140° for 1,5 hour. The temperature was then raised to 200—240° and maintained there for two hours. After cooling, the solid, yellow residue in the flask was dissolved in warm water and distilled with steam. The turbid, strongly alcaline distillate (60 ml.) was saturated with anhydrous potassium carbonate and extracted with ether. The combined extracts were dried with anhydrous potassium carbonate, and the solvent evaporated. There remained 500 mg. of a colorless oil which was dissolved in absolute ethanol and treated with an alcoholic solution of oxalic acid. The precipitated salt was recrystallized several times from 95% ethanol. Colorless needles of *1-amino-4-phenylbutane* oxalate, m. p. 142—145° (decomp.) were obtained.

*Anal:* 5,590 mg. subst.: 0,272 ml. $N_2$ (19,5°, 749 mm.)
$C_{12}H_{17}O_4N$ (239,27) calc'd: N 5,85%
found: N 5,60%

Picrate. From the oxalate with sodium picrate in water. Recrystallized from aqueous ethanol and then from benzene containing a trace of ethanol it separated in yellow needles, m. p. 125—126° (recorded m. p. 125°).[11]

*Anal.* 5,405 mg. subst.: 0,694 ml. $N_2$ (23°, 749 mm.)
$C_{16}H_{18}O_7N_4$ (378,34) calc'd: N 14,81%
found: N 14,60%

*2-Phthalimido-5-phenyl-3-pentanone* [X]

A solution of ditetrahydropyranyl benzylmalonate (prepared from 7,77 g., 0,04 mole of benzylmalonic acid by the method described above) in benzene (40 ml.) was added to dry sodium ethoxide (from 920 mg. of sodium). The mixture was shaken until complete dissolution was effected. N-Phthalyl-L-alanyl chloride[12] (9,5 g.) in benzene (40 ml.) was slowly added. During the addition the temperature was held below 30°. After standing at room temperature for 6 hours, the mixture was refluxed for additional 15 hours, cooled, washed with water, and the solvent removed in vacuo. Thus, 16,2 g. of a yellow oil was obtained. It could not be induced to crystallization.

A part of this product (13,38 g.) was refluxed with Girard T reagent (10 g.) and acetic acid (15 g.) in absolute ethanol (135 ml.) for one hour. The solution was cooled and added to an ice-cold solution of sodium hydroxide (9 g.) in water (1 l.). The non-ketonic fractions (6,65 g., 50%) were removed by extraction with ether, and the aqueous layer acidified with 12 N hydrochloric acid (100 ml.). After standing for one hour it was extracted with ether, the combined extracts dried with calcium chloride and evaporated to dryness. Thus, 5,22 g. (39%) of crude ketonic fractions were obtained.

For further purification 2,22 g. of this oil was dissolved in benzene (20 ml.) and purified by chromatography through an alumina column (20 g.). The product was eluated with 10 ml. portions of benzene. Fractions 5—16 were combined (500 mg., pale yellow oil), and oximated with an alcoholic solution of hydroxylamine acetate. After recrystallization from ethanol-petroleum ether *2-phthalimido-5-phenyl-3-pentanone* oxime was obtained. Colorless needles, m. p. 170-172°, $[\alpha]_D^{19} = +5{,}31°$ (c = 1,32 in chloroform).

*Anal.* 9,300 mg. subst.: 24,10 mg. $CO_2$, 4,60 mg. $H_2O$
6,605 mg. subst.: 0,487 ml. $N_2$ (24°, 756 mm.)
$C_{19}H_{18}O_3N_2$ (322,35) calc'd: C 70,79; H 5,89; N 8,68%
found: C 70,72; H 5,54; N 3,43%

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REFERENCES

1. S. Gabriel and J. Colman, *Ber.* **42** (1909) 1243; S. Gabriel, *Ber.* **42** (1909) 1238, 1249, 4050; **44** (1911) 57; **46** (1913) 1319; **47** (1914) 2119, 2922; S. Gabriel and B. Löwenberg, *Ber.* **51** (1918) 1493.
2. E. Immendörfer, *Ber.* **48** (1915) 605.
3. J. Pascual and R. R. Rebollo, *Anales soc. espan. fis y quim.* **32** (1934) 374.
4. E. Pfaehler, *Ber.* **46** (1913) 1702.
5. B. R. Baker, M. V. Querry, R. E. Schaub, and J. H. Williams, *J. Org. Chem.* **17** (1952) 58, 77.
6. R. E. Bowman, *J. Chem. Soc.* **1950** 325; R. E. Bowman and W. D. Fordham, *J. Chem. Soc.* **1952** 3945.
7. G. S. Fonken and W. S. Johnson, *J. Am. Chem. Soc.* **74** (1952) 831.
8. H. R. Henze and J. H. Shown, *J. Am. Chem. Soc.* **69** (1947) 1662.
9. S. Gabriel, *Ber.* **43** (1910) 134.
10. A. Uffer and E. Schlittler, *Helv. Chim. Acta* **31** (1948) 1397.
11. J. v. Braun, *Ber.* **43** (1910) 2837.
12. K. Balenović, D. Cerar, and Z. Fuks, *J. Chem. Soc.* **1952** 3316.

## IZVOD

**O reakciji klorida α-ftalimido kiselina sa supstituiranim natrijevim malon-esterima.**

**Metoda za pripremanje α-amino ketona i srodnih spojeva**

*D. Sunko i M. Proštenik*

1. Bowmanova ketonska sinteza s uspjehom je proširena na kloride N- ftalil-α-amino kiselina.

2. Na taj su način priređeni 1-ftalimido-4-fenil-2-butanon [V], 1-ftalimido-2-oktadekanon [IV] i optički aktivni 2-ftalimido-5-fenil-3-pentanon [X].

3. Iz 1-ftalimido-4-fenil-2-butanona [V] pripremljen je 1-benzamido-4-fenil-2-butanon [VII] i 1-amino-4-fenilbutan [IX], te prema tome opisana reakcija predstavlja jednu metodu za dobivanje α-amino ketona i srodnih spojeva.

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