TABLE I

HYDROXYL AND CARBONYL FREQUENCIES OF SOME NATURALLY OCCURRING FLAVONOIDS

Compound	Hydroxyl, Cm.$^{-1}$	Carbonyl, Cm.$^{-1}$	Flavone-Flavonoid, Δ Cm.$^{-1}$
	Flavones		
Flavone	...	1660	0
Apigenin-7-rhamnoglucoside	3330	1658	2
Apiin	3240	1660	0
Luteolin	3220	1655	5
Luteolin-7-glucoside	3160	1658	2
Pectolinarin	3320	1658	2
	Flavonols		
Chrysosplenetin	3320	1658	2
Chrysosplenin	3300	1658	2
Dactylin	3220	1655	5
Isorhamnetin	3160	1655	5
Quercetin	3340	1655	5
Quercitrin	3280	1655	5
Reynoutrin	3140	1652	8
Robinin	3240	1655	5
Rutin	3300	1655	5
	Flavanones		
Flavanone	...	1680	0[a]
Hesperidin	3340	1639	41[a]
Naringin	3360	1639	41[a]

[a] Flavanone-flavonoid values.

noutrin, robinin, and rutin, have carbonyl absorption bands between 1652 cm.$^{-1}$ and 1658 cm.$^{-1}$ as shown in the table. The difference (Δ cm.$^{-1}$) of the parent flavone minus the flavonoid is very small for the flavones and considered to be within the experimental error of the parent flavone carbonyl frequency. The flavones listed in Table I have hydroxyl group at the C—5 position adjacent to the carbonyl group with the exception of the parent compound, flavone. The lack of difference of the naturally occurring flavone carbonyl frequencies from the parent flavone would suggest the lack of hydrogen bonding in these substances. This does not seem reasonable, nor can it be rationalized on the basis of the shifts observed for hydrogen bonding for similar substituted substances.[9-11] The interpretation of these anomalies by Hergert and Kurth appears to be sufficient.

The flavonols differ from the flavones by having a hydroxyl or glycosidic linkage at the C-3 position. This added opportunity for hydrogen bonding of the C-3 hydroxyl group with the carbonyl for the flavonoids, isorhamnetin, quercetin, and chrysosplenetin, did not make itself apparent. Likewise the C-5 hydroxyl containing flavonols do not reveal an appreciable difference (Δ cm.$^{-1}$) between the flavonol carbonyl frequency and the parent flavone.

(9) M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948).
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The flavanone carbonyl absorption frequencies are in sharp contrast to the flavones as also noted by Hergert and Kurth. The parent flavanone has a carbonyl absorption band at 1680 cm.$^{-1}$ and the substituted flavanones, hesperidin, and naringin, have carbonyl absorption bands at 1639 cm.$^{-1}$ This shift of 41 wave numbers to the longer wave length is evidence of hydrogen bonding in these flavonoids.

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Syntheses of DL-β-Aminobutyric Acid and Its *N*-Alkyl Derivatives

ALBERT ZILKHA AND JOSEPH RIVLIN

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Only a few *N*-alkyl derivatives of β-aminobutyric acid are reported in the literature.[1,2] They were usually prepared in low yield by reduction of the intermediate imino derivative obtained by the reaction of the appropriate amine with ethyl acetoacetate.[1,2] Some esters of these compounds were prepared by the reaction between amines and ethyl crotonate,[3] which requires a long reaction time and usually gives low yields.

In this paper is given a simple synthesis of these compounds based on the direct addition of amines to crotonic acid. It was found that the addition of amines to the double bond in neutral solvents such as dioxane or benzene did not take place and only the amine salts of crotonic acid were formed. However, under the influence of basic solvents such as pyridine or α-picoline, the addition of primary aliphatic amines readily took place; the less reactive secondary amines and aromatic amines did not interact with the double bond.

The reaction was carried out by heating one mole of crotonic acid with one mole of amine in pyridine at 120–130° for 1–2 hours, and proceeded according to the following scheme:

$$CH_3CH{=}CHCOOH + RNH_2 \longrightarrow CH_3\underset{\displaystyle NHR}{\underset{|}{C}}HCH_2COOH$$

The *N*-alkyl derivatives of DL-β-aminobutyric acid usually crystallized out directly on cooling; otherwise the pyridine solution was evaporated to dryness *in vacuo* and the oily residue crystallized from hot acetone.

(1) C. A. Skita and C. Wulff, *Ann.*, **453**, 190 (1927).
(2) J. Décombe, *Ann. Chim.*, **18**, 81 (1932).
(3) K. Morsch, *Monatsh.*, **60**, 50 (1932).

TABLE I

PREPARATION OF *N*-ALKYL DERIVATIVES OF DL-β-AMINOBUTYRIC ACID

N-Alkyl Substituent	M.P.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Isopropyl	170	77	$C_7H_{15}NO_2$	57.9	57.9	10.3	10.4	9.6	9.4
Isobutyl	182	75	$C_8H_{17}NO_2$	60.4	60.2	10.7	10.5	8.8	8.8
2-Hydroxy-*n*-propyl	178	95	$C_7H_{15}NO_3$	52.2	52.2	9.3	9.3	8.7	8.6
2-Hydroxyethyl	181	86	$C_6H_{13}NO_3$	49.0	49.0	8.8	8.7	9.5	9.5
n-Hexyl	158	70	$C_{10}H_{21}NO_2$	64.2	65.1	11.2	11.3	7.5	7.3
Cyclohexyl	167	65	$C_{10}H_{19}NO_2$	64.8	64.2	10.2	10.0	7.6	7.6

[a] Substances were recrystallized from water-acetone or ethanol-acetone.

The compounds obtained were soluble in water and ethanol and insoluble in cold acetone. They gave negative reaction with copper carbonate when this was added to their boiling aqueous solution, as is compatible with *N*-alkyls of β-amino acids.[4] Their reactions with aqueous potassium permanganate and ninhydrin were negative indicating the absence of double bonds and of amine salts. However, it is interesting to note that their chromatograms gave positive reaction (purple color) when sprayed with ninhydrin solution in butanol. Their R_f values on paper chromatograms using 80% aqueous phenol were around 0.95.

DL-β-Aminobutyric acid was obtained by catalytic hydrogenolysis of *N*-benzyl-DL-β-aminobutyric acid. The present synthesis is much simpler than the methods used in previous preparations; *e.g.*, from crotonic acid and ammonia under pressure,[5,6] from acetoacetic ester phenylhydrazone,[7] or from malonic acid, acetaldehyde, and ammonia.[8]

Passing phosgene into a suspension of *N*-benzyl-DL-β-aminobutyric acid at 60° gave the mixed anhydride of *N*-benzyl-DL-β-aminobutyric acid with chloroformic acid.[9] This interacted with ammonia with evolution of carbon dioxide to give the amide according to the following scheme:

$$CH_3CHCH_2COOH + COCl_2 \longrightarrow CH_3CHCH_2COOCOCl + HCl$$
$$\quad NHCH_2C_6H_5 \qquad\qquad\qquad NHCH_2C_6H_5$$

$$NH_3 \xrightarrow[-HCl]{-CO_2} CH_3CHCH_2CONH_2$$
$$\qquad\qquad\qquad\qquad\quad NHCH_2C_6H_5$$

In this way amides and peptides of DL-β-aminobutyric acid could be readily synthesized, the *N*-benzyl protecting group being easily removed catalytically.

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(6) C. Engel, *Bull. soc. chim. France*, **50**, 102 (1888).
(7) E. Fischer and A. Groh, *Ann.*, **383**, 365 (1911).
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(9) Y. Liwschitz and A. Zilkha, *J. Am. Chem. Soc.*, **76**, 3698 (1954).

EXPERIMENTAL

Micro combustion analyses were carried out by Drs. Weiler and Strauss. Melting points were determined in a Fisher-Johns apparatus.

A procedure for one typical example for the preparation of *N*-alkyl-β-aminobutyric acids is given below, the rest summarized in Table I.

*N-Benzyl-*DL-*β-aminobutyric acid.* To a solution of 43 g. (0.5 mole) crotonic acid in 150 ml. pyridine was added 53.5 g. (0.5 mole) of benzylamine. The solution was heated in an oil bath at 120–130° for 1.5 hr. On cooling, the *N*-benzyl-DL-β-aminobutyric acid crystallized out. It was filtered and washed with acetone; yield 83 g. (86%) m.p. 186–187°. The substance gave weakly positive permanganate and ninhydrin reactions. Recrystallization from hot water–acetone, gave 75 g. (90% recovery) of the pure substance m.p. 189°, giving negative permanganate and ninhydrin reactions.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.7; H, 7.8; N, 7.2. Found: C, 68.4; H, 7.7; N, 7.0.

DL-*β-Aminobutyric acid.* *N*-Benzyl-DL-β-aminobutyric acid (8 g.) was dissolved in 80 ml. of glacial acetic acid and 0.3 g. of 30% palladium chloride on charcoal was added. The hydrogenolysis was carried out in a Parr low pressure apparatus for 6 hr. at 50–60°. After separation of the catalyst the solvent was removed *in vacuo*, and the residue was dissolved in absolute ethanol and evaporated once more *in vacuo* to complete dryness to remove the last traces of acetic acid. The remaining oily residue was dissolved in alcohol and precipitated by the addition of acetone. The DL-β-aminobutyric acid was filtered and washed with acetone; yield 4 g. (95%) m.p. 190–192°. On recrystallization, with 90% recovery, from hot slightly diluted ethanol, and addition of acetone the melting point was raised to 194–195°. Chromatography on paper using 80% aqueous phenol gave a purple spot, R_f 0.89, compared to R_f 0.74 for α-aminobutyric acid.

Anal. Calcd. for $C_4H_9NO_2$: C, 46.6; H, 8.7; N, 13.6; N (Van Slyke), 13.6. Found: C, 46.9; H, 8.8; N, 13.3; N (Van Slyke), 13.3.

*N-*DL-*β-benzylaminobutyramide.* *N*-Benzyl-β-DL-aminobutyric acid (6 g.), which had been dried before in a vacuum desiccator over concentrated sulfuric acid, was suspended in 100 ml. dry dioxane in a 3-necked flask equipped with a gas leading tube, reflux condenser connected to a calcium chloride tube, and a mechanical stirrer. Phosgene was bubbled in with stirring for 40 min. and the temperature maintained at 60°. Excess phosgene and solvent were removed *in vacuo* at a temperature not exceeding 40°. The residue was dissolved in 50 ml. dry dioxane and dry ammonia gas passed in with stirring and cooling for 15 min. After leaving overnight the solution was filtered from ammonium chloride and evaporated to dryness *in vacuo*. The oily residue was recrystallized from ethyl acetate–petroleum ether with cooling in ice salt mixture, giving 4.2 g. (70%) of *N*-benzyl-DL-β-aminobutyramide, m.p. 48–50°. On second recrystallization, with 80% recovery, from the same solvents, the melt-

ing point was raised to 55–56°. It is also soluble in water, ethanol, and acetone.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.3; N, 14.6. Found: C, 68.3; H, 8.3; N, 14.7.

DEPARTMENT OF ORGANIC CHEMISTRY,
THE HEBREW UNIVERSITY,
JERUSALEM, ISRAEL

α-Alkyloximino Acids in Azlactone Reactions[1]

LEE M. C. SHEN[2] AND WALTER H. HARTUNG[3]

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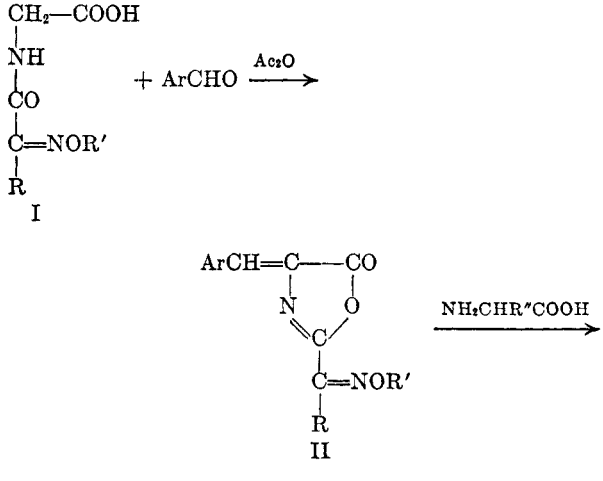
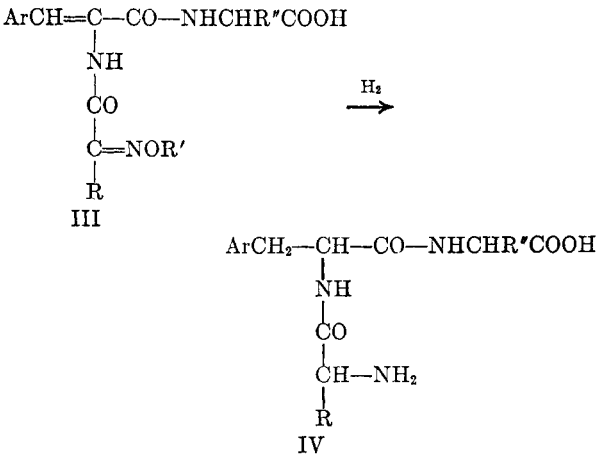
The azlactone procedure for the synthesis of α-amino acids and acyl dipeptides, RCO-NHCHR'-CO-NHCHR"COOH, has been reviewed by Carter.[4] Proper selection of the acyl group in these amides would be expected, on suitable conversion, to lead to the corresponding aminoacyl derivative, that is, a tripeptide. Previous studies with α-alkyloximino acids[5] show that the arrangement R-C(=NOR')-CO- lends itself well for transformation into the corresponding aminoacyl, R-CH(NH_2)-CO, for the synthesis of various amides. Their value for the synthesis of a tripeptide by way of the azlactone route would then be comprehended according to the scheme:





We now report the synthesis, by this procedure, of phenylalanylphenylalanylglycine, IV in which R = $C_6H_5CH_2$-, Ar = C_6H_5, and R" = H, as a successful application. In view of the large number of α-alkyloximino acids which may be prepared and the fact that many aldehydes may be employed in the step from I to II, the number of prospective azlactones of type II becomes impressive. Nor is it anticipated that the conversion of II to III is limited to the reaction with glycine. The hydrogenation of III to IV appears to offer no difficulty.

For some reason which does not now appear the azlactones prepared from benzyloximino intermediates, compounds of structure II in which R' = $C_6H_5CH_2$-, while seemingly pure crystalline products, do not give satisfactory analyses; yet when allowed to react further, the intermediate III and the tripeptide IV are acceptable. No such difficulty was experienced with the methyloximino intermediate, type II in which R' = CH_3-.

EXPERIMENTAL

The synthesis of *β-phenyl-α-benzyloximinopropionylglycine* has been described.[5b] *β-Phenyl-α-methyloximinopropionylglycine*, was prepared from glycine and β-phenyl-α-methyloximinopropionic acid in a similar manner; recrystallized from benzene it melts 104.5–105°.

Anal. Calcd. for $C_{12}H_{14}N_1O_4$: N, 11.20. Found: N, 11.13.

2-(1-Methyloximino-2-phenylethyl)-4-benzaloxazolone. In a 100-ml. Erlenmeyer flask was placed a mixture of 1.0 g. (0.0095 mole) benzaldehyde, 2.67 g. (0.0113 mole) of powdered β-phenyl-α-methyloximinopropionylglycine, 0.8 g. of freshly fused and powdered sodium acetate, and 2.5 ml. acetic anhydride. The flask was heated gently with constant shaking over a low flame until the contents liquefied, turning yellow; it was then heated on a steam bath for an hour, when yellow crystals formed on the walls of the flask. The reaction mixture was then treated with 4 ml. alcohol and allowed to stand overnight in the refrigerator. The yellow crystalline product was removed by suction, washed with a small amount of alcohol, then with 1 ml. water. The crude product weighed 2.0 g., m.p. 156–158°; recrystallized first from ligroin and then from acetone, m.p. 158–159° (uncorr.).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.03; N, 8.74. Found:[6] C, 71.93; H, 5.51; N, 8.85.

(1) No. 16 in amino acid series; for No. 15 see G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, 79, 5203 (1957). This investigation was supported by Grant G-3594, National Institutes of Health, for which the authors express their thanks and appreciation.

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(6) Analyses by G. Weiler and F. B. Strauss, Oxford, England.