CCA-33 547.447.5

Synthesis of Aminoalkylglyoxal Derivatives III. Aminoalkylglyoxal Derivatives of α-Aminobutyric Acid and Valine*

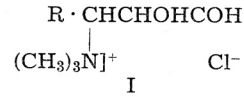
*K. Balenović, V. Škarić, and D. Dvornik***

Chemical Laboratory, Faculty of Science, University of Zagreb, Strossmayerov trg 14, Zagreb, Croatia, Yugoslavia, and Institute »Ruđer Bošković«, Department of Biochemistry

Received November 3, 1956

Starting from DL-α-aminobutyric acid and DL-valine the corresponding aminoalkylglyoxals VIIa and VIIb were prepared by Kröhnke's method, through the reaction stages II—VII. Further, a description is given of the preparation of DL-1-acetoxy-3-phthalimidopentan-2-one, and of the conversion of the glyoxal VIIa into the 1,1-diethylacetal VIIIa, the hydroxyacetal IXa, and the α-glycol Xa, which are useful intermediates for the synthesis of compounds of the type I. The aldehyde group of these glyoxals readily reacts with N,N-diphenyl-1,2-diaminoethane, affording condensation products XI. Quinoxaline and *bis*ethylenemercaptal derivatives of the glyoxals VII were also prepared. Improved preparations are described for DL-α-aminobutyric acid and the corresponding phthalimido derivative.

In connection with recent studies from this Laboratory on the stereospecificity of muscarinic activity[1] a description is now given of starting materials for compounds of the type I, this formula being proposed by Kögl[2] as an alternative one for muscarine.



I

Biological testing of similar compounds led several years ago[3] to the conclusion that Kögl's formulas for muscarine are not exactly correct, and this was the reason why the isolation and characterization of natural muscarine was undertaken in this Laboratory, using present-day techniques[4].

The preparation has been earlier given of aminomethylglyoxal derivatives[5,6] from α-amino acids, using Kröhnke's procedure, following the reaction scheme II—VII.

---

*) Communication No. 60 from this Laboratory.

**) Abstracted in part from a thesis presented by D. Dvornik to the Faculty of Science, University of Zagreb, in June 1954, for a Ph. D. degree, and from the Ph. D. thesis of V. Škarić (in preparation).

$C_6H_4(CO)_2NCH(R)COX$

II, X = Cl

III, X = CHN_2

IV, X = CH_2Br

V, X = $CH_2(Py)Br$

VI, X = $CH:NC_6H_4N(CH_3)_2$-p
↓
O

VII, $C_6H_4(CO)_2NCH(R)COCHO$

VIII, $C_6H_4(CO)_2NCH(R)COCH(OC_2H_5)_2$

IX, $C_6H_4(CO)_2NCH(R)CHOHCH(OC_2H_5)_2$

X, $C_6H_4(CO)_2NCH(R)CHOHCH_2OH$

XI, $C_6H_4(CO)_2NCH(R)COCH$ (with C_6H_5, N——CH_2, N——CH_2, C_6H_5)

a, R = CH_3CH_2

b, R = $(CH_3)_2CH$

The application of this synthesis to DL-α-aminobutyric acid (II—VII, R = CH_3CH_2 and DL-valine (II—VII, R = $(CH_3)_2CH$) is the subject of the present paper. Further, DL-1-acetoxy-3-phthalimidopentan-2-one was prepared from IIIa, and some new reactions of these glyoxals are also described.

Phthalimidoalkylglyoxals VII afforded, according to Claisen's procedure[7] with ethyl orthoformate, the diethylacetals VIII; catalytic hydrogenation of VIII with Adams' catalyst gave hydroxyacetals IX, which were useful intermediates for the preparation of compounds of the type I. α-Glycols X are also easily obtained by catalytic hydrogenation of glyoxals VII. The aldehyde group of these glyoxals reacted smoothly with N,N-diphenyl-1,2-diaminoethane[8] to the condensation products XI. This reagent was recently used for the isolation and characterization of N-phthaloyl aldehydes from oily reaction products[1].

The glyoxals VII were further characterized as quinoxaline and *bis*-thylenemercaptal derivatives.

Further, the improved preparation is given of DL-α-aminobutyric acid, DL-α-phtalimidobutyric acid, and the corresponding chloride IIa.

EXPERIMENTAL

All melting points are uncorrected unless otherwise stated.

Improved preparation of α-aminobutyric acid

α-Aminobutyric acid was obtained from DL-α-bromobutyric acid prepared according to Ahlberg[9], yield 95—96%. Freshly distilled DL-α-bromobutyric acid (75 g., 0.45 mole b. p. 106—108° / 12 mm.) was dissolved in 25% aqueous ammonia (1500 ml.) and allowed to stand at room temperature for 30 hours following the procedure of Tobie and Ayres[10]. After evaporating the reaction mixture to dryness the

ammonium bromide was continuously extracted from the reaction mixture with absolute methanol. The remaining *α-aminobutyric acid* (yield 33,5—34,5 g., 72—73,5%) had the m. p. 283—285° (decomp.)

Improved preparation of DL-*α-phthalimidobutyric acid*

Equimolar quantities of DL-α-aminobutyric acid (37,5 g., 0,363 mole) and phthalic anhydride (54,6 g., 0,37 mole) were thoroughly mixed and heated on an oil bath (bath temp. 150—160°) for one hour. After treating the reaction mixture with benzene (400 ml.), crystallization of DL-*α-phthalimidobutyric acid* occurred, yield 83—85 g. (96—99%), m. p. 94—96°. Earlier similar preparations with the same starting materials[11] describe this compound as an oil. Recrystallization from benzene yielded colourless needles of the pure compound, m. p. 96,5—98°.

Anal. 11,67 mg. subst.: 26,38 mg. CO_2, 4,91 mg. H_2O
$C_{12}H_{11}O_4N$ (233,22) calc'd.: C 61.79; H 4.75%
found: C 61.71; H 4.71%

Improved preparation of DL-*α-phthalimidobutyryl chloride* (IIa)

DL-α-phthalimidobutyric acid (32 g., 0.137 mole) and thionyl chloride (40 ml.) were refluxed for one hour on an oil bath (bath temp. 90—95°). The excess of thionyl chloride was removed under reduced pressure and DL-*α-phthalimidobutyryl chloride* remained, which distilled at 181—185°/12 mm. as a pale yellow oil; after standing, crystallization occurred, yield 27—28 g. (78—81%), m. p. 52—53°. Several recrystallizations from petroleum ether afforded white prisms, m. p. 63°. A sublimate obtained at 70—75°/0.01 mm. had the same m. p.

Anal. 10.02 mg. subst.: 21.06 mg. CO_2, 3.49 mg. H_2O
$C_{12}H_{10}O_3NCl$ (251.67) calc'd.: C 57.27; H 4.01%
found: C 57.35; H 3.90%

This compound has been described earlier[11] but without analytical data.

DL-*1-Diazo-3-phthalimidopentan-2-one* (IIIa)

Distilled DL-α-phthalimidobutyryl chloride (20 g., 0.08 mole, m. p. 54°) was added in small portions to an ethereal solution of 500 ml. of diazomethane (prepared from 35 g. of nitrosomethylurea). After standing overnight the precipitated yellow crystals of DL-*1-diazo-3-phthalimidopentan-2-one* were collected, yield 16 g. (78%), m. p. 115—117° (decomp.). After recrystallization from ethyl acetate yellow needles of the pure compound were obtained, with the constant m. p. 117—118.5° (decomp.).

Anal. 10.70 mg. subst.: 23.84 mg. CO_2, 4.16 mg. H_2O
$C_{13}H_{11}O_3N_3$ (257.24) calc'd.: C 60.69; H 4.31%
found: C 60.80; H 4.35%

DL-*1-Acetoxy-3-phthalimidopentan-2-one*

DL-1-Diazo-3-phthalimidopentan-2-one (IIIa, 1.0 g., 0.004 mole) was gradually added to glacial acetic acid (20 ml.) and the solution heated under reflux for 2 hours. After evaporating to dryness under reduced pressure DL-*1-acetoxy-3-phthalimidopentan-2-one* remained as a pale green oil in a quantitative yield. Distillation at 125°/0.01 mm. afforded the pure compound as a colourless oil.

Anal. 9.75 mg. subst.: 22.27 mg. CO_2, 4.56 mg. H_2O
$C_{15}H_{15}O_5N$ (289.28) calc'd.: C 62.27; H 5.23%
found: C 62.31; H 5.24%

DL-*1-Bromo-3-phthalimidopentan-2-one* (IVa)

To a suspension of DL-1-diazo-3-phthalimidopentan-2-one (IIIa, 16.7 g., 0.065 mole) in glacial acetic acid (60 ml.), 48% hydrobromic acid (18 ml.) was added dropwise, with stirring. The reaction mixture was left standing for one hour when the reaction was complete. Water was added (700 ml.), and after standing overnight,

the separated colourless crystals of DL-*1-bromo-3-phthalimidopentan-2-one* were collected. Yield 20 g. (99%), m. p. 114—116°. Several recrystallizations from acetone — water gave colourless needles, m. p. 118.5°.

Anal. 13.12 mg. subst.: 24.33 mg. CO_2, 4.51 mg. H_2O
$C_{13}H_{12}O_3NBr$ (310.15) calc'd.: C 50.34; H 3.90%
found: C 50.62; H 3.84%

N-[2-*Oxo*-DL-*3-phthalimidopentyl)-(1)]pyridinium bromide* (Va)

DL-1-Bromo-3-phthalimidopentan-2-one (IVa, 21 g., 0.068 mole) in dry pyridine (90 ml.) was refluxed for 15 minutes. After cooling, the separated crystals of N-[*2-oxo*-DL-*3-phthalimidopentyl)-(1)]pyridinium bromide* were filtered off, and washed with petroleum ether, yield 25 g. (94%), m. p. 220°. Recrystallization from absolute ethanol gave colourless clusters of needles, m. p. 221°.

Anal. 11.24 mg. subst.: 22.87 mg. CO_2, 4.26 mg H_2O
$C_{18}H_{17}O_3N_2Br$ (389.25) calc'd.: C 55.54; H 4.40%
found: C 55.54; H 4,24%

α(*2-*DL-*Phthalimidobutyryl)*-N-(p-*dimethylaminophenyl)nitrone* (VIa)

A mixture of a solution of *N*-[2-oxo-DL-3-phthalimidopentyl-(1)]pyridinium bromide (Va, 16.3 g., 0.042 mole) in water (42 ml.) and ethanol (12 ml.), and of *p*-nitrosodimethylaniline (6.30 g., 0.042 mole) in ethanol (200 ml.) was cooled to —5°. To this mixture *N* sodium hydroxide (21 ml., 0.042 mole) was gradually added, with stirring, during 15 minutes. The separation of the yellow α-(2-DL-*phthalimidobutyryl*-N-(p-*dimethylaminophenyl)nitrone* was complete after 30 minutes. The precipitate was collected, and washed with cold aqueous ethanol (2:5), yield 13.2 g. (88.5%), m. p. 128—129.5°. Recrystallization from ethanol gave orange-yellow leaflets, m. p. 132—133°.

Anal.: 9.68 mg. subst.: 23.62 mg. CO_2, 4.86 mg. H_2O
$C_{21}H_{21}O_4N_3$ (379.40) calc'd.: C 66.48; H 5.58%
found: C 66.58; H 5.62%

DL-(α-*Phthalimidopropyl)glyoxal* (VIIa)

To a suspension of powdered α-(2-DL-phthalimidobutyryl)-*N*-(*p*-dimethylaminophenyl)-nitrone (VIa, 5.7 g., 0.015 mole) in water (12 ml.) in a separatory funnel, 5 *N* sulphuric ocid (45 ml.) and pure ether (45 ml.) were added. This mixture was thoroughly shaken until the nitrone dissolved. The aqueous layer was extracted 6 times with ether, and the combined ethereal extracts washed twice with 5 *N* sulphuric acid and then with water. They were filtered and evaporated at 25° under reduced pressure. DL-(α-*Phthalimidopropyl)glyoxal* remained as a yellow oil, yield 2.7—3 g (71—83%). The analytical sample distilled at 110°/0.01 mm., and was a greenish-yellow oil.

Anal. 8.76 mg. subst.: 20.40 mg. CO_2, 3.62 mg. H_2O
$C_{13}H_{11}O_4N$ (245.23) calc'd.: C 63.67; H 4.52%
found: C 63.53; H 4.62%

DL-(α-*Phthalimidopropyl)glyoxal-1,1-diethyl acetal* (VIIIa)

A mixture of ethyl orthoformate (1.5 g.) anhydrous ammonium chloride (50 mg.), DL-(α-phthalimidopropyl)glyoxal (VIIa, 1.2 g.), absolute ethanol (4 ml.) was left at room temperature according to Claisen's method[7]. After standing for a week, the phthalimidoglyoxal dissolved, and the clear liquid was diluted with water (20 ml.), to which one drop of 25% ammonia had been previously added. The reaction mixture was extracted with three 20 ml. portions of ether, washed with water, and dried (Na_2SO_4). After tvaporating the ether 1.1 g. (70%) of oily *1,1-diethyl acetal of* DL-(α-*phthalimidopropyl)glyoxal* remained. Precipitation from dichloromethane-

petroleum ether, and chromatography from benzene on alumina (1:10, activity IV according to Brockmann), and subsequent distillation at 100°/0.01 mm. gave a pale yellow oil.

Anal.: 9.09 mg. subst.: 21.25 mg. CO_2, 5.37 mg. H_2O
$C_{17}H_{21}O_5N$ (319.35) calc'd.: C 63.93; H 6,63%
found: C 63.80; H 6,61%

2-(α-Phthalimidopropyl)quinoxaline

A mixture of DL(α-phthalimidopropyl)glyoxal (VIIa, 0.45 g.), acetic acid (5 ml.) and an equimolar amount of *o*-phenylenediamine was refluxed during 2 hours, and then cooled. After addition of water, the crude *2-(α-phthalimidopropyl)quinoxaline* (0.31 g., 68%), m. p. 95—97° separated. This was recrystallized from ethanol, m. p. 99—100°.

Anal.: 6.07 mg. subst.: 15.97 mg. CO_2, 2.51 mg. H_2O
$C_{19}H_{15}O_2N_3$ (317.34) calc'd.: C 71.91; H 4.76%
found: C 71.81; H 4.63%

Bisethylenemercaptal of DL-*(α-phthalimidopropyl)glyoxal*

DL-(α-Phthalimidopropyl)glyoxal (VIIa, 1.0 g., 0.0041 mole) and ethanedithiol (1 ml.) were dissolved in a 3% solution of anhydrous hydrochloric acid in dioxane (13.5 ml.). After standing at room temperature for 4 days, the reaction mixture was evaporated to dryness *in vacuo*. *Bisethylenemercaptal of* DL-*(α-phthalimidopropyl) glyoxal* was obtained as a yellow oil, which crystallized on addition of benzene; yield 1.3 g., (80.6%), m. p. 150—154°. The analytical sample was recrystallized from dichloromethane-petroleum ether, and orange-coloured clusters of needles were obtained, m. p. 156—157°.

Anal.: 9,97 mg. subst.: 18.71 mg. CO_2, 4,31 mg. H_2O
$C_{17}H_{19}O_2NS_4$ (397.57) calc'd.: C 51.35; H 4.82%
found: C 51.20; H 4.84%

DL-*1,3-Diphenyl-2-(α-phthalimidobutyroyl)tetrahydroimidazole* (XIa)

To a solution of DL-(α-phthalimidopropyl)glyoxal (VIIa, 0.5 g., 0.002 mole) in methanol (2 ml.) an equimolar amount of 1,2-dianilinoethane solution (prepared from 5.3 g. of 1,2 dianilinoethane in 100 ml. of methanol and 2 ml. of 50% acetic acid)[8] was added. The mixture was heated at 60° for five minutes and left at room temperature overnight. The separated crystals of DL-*1,3-diphenyl-2-(α-phthalimidobutyroyl)-tetrahydroimidazole* were collected, yield 0.5 g. (56%), m. p. 133—135°. In preparations where solid 1,2-dianilinoethane was used instead of the solution, much higher yields were obtained. The analytical sample was recrystallized from ethanol, and clusters of yellow needles were obtained, m. p. 135.5—137°.

Anal. 9.42 mg. subst.: 25.40 mg. CO_2, 4.83 mg. H_2O
$C_{27}H_{25}O_3N_3$ (439.49) calc'd.: C 73.78; H 5.73%
found: C 73.58; H 5.74%

DL-*3-Phthalimido-2-hydroxypentanal-1,1-diethyl acetal* (IXa)

Hydrogenation over previously reduced atmospheric pressure and at 23° with a solution of DL-(3-phthalimidopropyl)glyoxal-1,1-diethylacetal (310 mg., 0.001 mole) in ethanol (20 ml.). [The DL-(3-phthalimidopropylglyoxal-1,1-diethyl acetal was previously purified by filtration through a column of alumina, activity IV.] In eight hours 24.8 ml. (1 mole) of hydrogen was absorbed. The catalyst was filtered off, and from the filtrate DL-*3-phthalimido-2-hydroxypentanal-1,1-diethylacetal* was obtained by evaporation under reduced pressure in a quantitative yield. The analytical sample distilled at 105—110°/0.01 mm., as a pale yellow oil.

Anal. 8.38 mg. subst.: 19.58 mg. CO_2, 5.22 mg. H_2O
$C_{17}H_{23}O_5N$ (321.36) calc'd.: C 63.53; H 7.21%
found: C 63.78; H 6.97%

DL-*3-Phthalimido-1,2-dihydroxypentane* (Xa)

Hydrogenation over previously reduced Adams' PtO_2 catalyst (144 mg.) was carried out at atmospheric pressure and at 22° with a solution of DL-(α-phthalimidopropyl)glyoxal (VIIa, 4 g., 0.016 mole) in ethanol (40 ml.). The DL-α-phthalimidopropyl)glyoxal was distilled before hydrogenation at 110°/0.02 mm. After two moles of hydrogen were absorbed, the catalyst was filtered off, and from the filtrate DL-*3-phthalimido-1,2-dihydroxypentane* was obtained by evaporation under reduced pressure, in a quantitative yield. The analytical sample was dissolved in ethanol, filtered through a column of alumina (1:5, activity IV) and evaporated to dryness. Purification from dichloromethane-petroleum ether yielded a colourless oil.

Anal. 10.63 mg.: 24.31 mg. CO_2, 5.97 mg. H_2O
$C_{13}H_{15}O_4N$ (249.26 calc'd.: C 62.64; H 6.07%
found: C 62.42; H 6.28%

DL-*1-Bromo-3-phthalimido-4-methylpentan-2-one* (IVb)

To a solution of DL-diazo-3-phthalimido-4-methylpentan-2-one (IIIb, 15.3 g., 0.057 mole) prepared according to Dvornik[12]) in glacial acetic acid (75 ml), 48% hydrobromic acid (14.5 ml.) was dropwise added, with stirring and cooling. The reaction mixture was stirred for one hour at room temperature, and water added (820 ml.). An oil separated, which soon solidified, and this solid was filtered off and thoroughly washed with water. The crude DL-*1-bromo-3-phthalimido-4-methylpentan-2-one* (15.4 g., 84.1%, m. p. 79—81°) was recrystallized from carbon tetrachloride-petroleum ether, and the pure bromoketone was obtained, 13.2 g. (72%), m. p. 84—87°. The analytical sample was repeatedly recrystallized from the same solvents, m. p. 83—86° (c

stallized from absolute ethanol-petroleum ether. Orange-coloured prisms with the m. p. 145—153° (decomp.) (corr.) were obtained.

Anal. 9.21 mg. subst.: 22.80 mg. CO_2, 4.91 mg. H_2O
$C_{22}H_{23}O_4N_3$ (393.42) calc'd.: C 67.17; H 5.89%
found: C 67.54; H 5.9%

DL-(*α-Phthalimido-β-methylpropyl) glyoxal* (VIIb)

A mixture of α-(phthalimido-DL-valinoyl)-*N*-(*p*-dimethylaminophenyl) nitrone (VIb, 1.5 g., 0.039 mole), water (3.5 ml.) and 25% sulphuric acid (15 ml.) was shaken in a separating funnel until clear. The aqueous layer was extracted with ether (6 × 15 ml.), dried (anhydrous Na_2SO_4) and evaporated *in vacuo* to dryness. The remaining light yellow oil of crude DL-(*α-phthalimido-β-methylpropyl) glyoxal* (0.90 g., 88.6%) was dissolved in benzene (25 ml.) and passed through a column of alumina (3 g., activity IV according to Brockmann). The column was washed with benzene (25 ml.), and the combined benzene filtrates evaporated to dryness *in vacuo*. The pure glyoxal remained as a clear light yellow oil, which distilled at 150—170°/0.04 mm.

Anal. 15.78 mg. subst.: 37.58 mg. CO_2, 7.34 mg. H_2O
$C_{14}H_{13}O_4N$ (259.25) calc'd.: C 64.86; H 5.05%
found: C 65.01; H 5.21%

2-(α-Phthalimido-β-methylpropyl) quinoxaline

A mixture of DL-(α-phthalimido-β-methylpropyl) glyoxal (VIIb, 0.19 g., 0.73 mole), glacial acetic acid (2 ml.), and an equimolar amount of *o*-phenylenediamine was heated under reflux for 1.5 hours. After addition of water (20 ml.) a sticky brown precipitate separated. From the aqueous layer a further amount of precipitate was obtained by addition of water and standing overnight. Both precipitates were combined and dissolved in acetone (10 ml.), treated with charcoal and the acetone removed by evaporation. The residual oil (0.18 g., 74.1%) was dissolved in absolute ethanol, and evaporation of the solvent left crystals of 2-(*α-phthalimido-β-methylpropyl) quinoxaline*, with the m. p. 85—87° (corr.). The analytical sample was sublimed at 150—170°/0.04 mm. and was a glassy pale green substance.

Anal. 4.43 mg. subst.: 0.51 ml. N_2 (23°, 746 mm.)
$C_{20}H_{17}O_2N_3$ (331.36) calc'd.: N 12.69%
found: N 12.77%

REFERENCES

1. K. Balenović, N. Bregant, T. Galijan, Z. Štefanac, and V. Škarić, *J. Org. Chem.* **21** (1956) 115.
2. F. Kögl, H. Duisberg, and H. Erxleben, *Ann.* **489** (1931) 156.
3. cf. K. Balenović, N. Bregant, and T. Galijan, *Arhiv kem.* **26** (1954) 223.
4. K. Balenović, D. Cerar, B. Gašpert, and T. Galijan, *Arhiv kem.* **27** (1955) 107.
5. K. Balenović and N. Bregant, *J. Org. Chem,* **17** (1952) 1328.
6. K. Balenović, D. Cerar, and L. Filipović, *J. Org. Chem.* **18** (1953) 868.
7. L. Claisen, *Ber.* **47** (1914) 317.
8. H. Wanzlick and W. Löchel, *Chem. Ber.* **86** (1953) 1463; cit. from J. H. Billman, Ju Yu Chen Ho, and L. R. Caswell, *J. Org. Chem.* **17** (1952) 1375.
9. R. Ahlberg, *J. prakt. Chem.* **135** (1932) 282.
10. W. C. Tobie and G. B. Ayres, *J. Am. Chem. Soc.* **64** (1942) 725.
11. A. Hildesheimer, *Ber.* **43** (1910) 2796.
12. D. Dvornik, *Arhiv kem.* **26** (1954) 211.

IZVOD

Aminoalkilglioksali III.
Aminoalkilglioksalni derivati α-aminomaslačne kiseline i valina

K. Balenović, V. Škarić i D. Dvornik

Polazeći od DL-α-aminomaslačne kiseline i DL-valina priređeni su Kröhnkeovom metodom, putem međuprodukata II—VII, odgovarajući aminoalkilglioksali VIIa i VIIb. Opisana je osim toga priprava DL-1-acetoksi-3-ftalimidopentan-2-ona, te transformacije glioksala VIIa u 1,1-dietilacetal VIIIa, hidroksiacetal IXa, i α-glikol Xa, koji su korisni međuprodukti za sintezu spojeva tipa I. Aldehidna grupa tih glioksala lagano reagira s *N,N*-difenil-1,2-diaminoetanom stvarajući kondenzacione produkte XI. Priređeni su kinoksalinski i *bis*etilenmerkaptalski derivati istih glioksala. Poboljšana je preparacija DL-α-aminomaslačne kiseline i odgovarajućeg ftalimido derivata.

KEMIJSKI INSTITUT
PRIRODOSLOVNO-MATEMATSKI FAKULTET
I
I. BIOKEMIJSKA GRUPA
INSTITUT »RUĐER BOŠKOVIĆ«
ZAGREB

Primljeno 3. studenog 1956.