[CONTRIBUTION FROM THE CHEMICAL INSTITUTE, FACULTY OF SCIENCE,
UNIVERSITY OF ZAGREB]

SYNTHESIS OF AMINOMETHYLGLYOXAL DERIVATIVES

K. BALENOVIĆ AND N. BREGANT

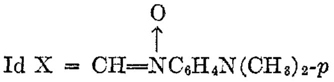
Received March 20, 1952

On account of their properties, aminoalkylglyoxals are expected to be interesting compounds for different further syntheses. With glycine as starting material, we have prepared aminomethylglyoxal, the simplest compound of this series, in the form of several crystalline derivatives.

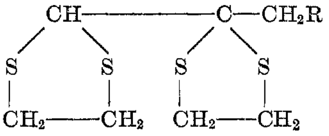
1-Diazo-3-phthalimidopropanone (1) (Ia) was converted to 1-bromo-3-phthalimidopropanone (Ib) from which, following the method of Kröhnke and Börner (2), phthalimidomethylglyoxal (Ie) was prepared through the reaction stages Ic–d. The compound Ie crystallizes from diethyl ether as a hemihydrate, and with one molecule of solvent. Recrystallization from a mixture of dichloromethane and petroleum ether leaves this molecular compound unchanged; by vacuum distillation the anhydrous, solvent-free product was obtained. From Ie the 1,1-diethylacetal (If), the bisethylenemercaptal (IIa), and the quinoxaline derivative were prepared.

$C_6H_4(CO)_2NCH_2COX$
I

Ia X = CHN_2
Ib X = CH_2Br
Ic X = $CH_2(Py)Br$



Id X = $CH{=}\overset{\overset{O}{\uparrow}}{N}C_6H_4N(CH_3)_2\text{-}p$
Ie X = CHO
If X = $CH(OC_2H_5)_2$



II

IIa R = $C_6H_4(CO)_2N$
IIb R = NH_2

The splitting off of the phthaloyl group was carried out by the method of Ing and Manske (3), and the bisethylenemercaptal of aminomethylglyoxal (IIb) was thus obtained.

Acknowledgment. We are indebted to the Rockefeller Foundation for financial assistance.

EXPERIMENTAL

All melting points are uncorrected.

Microanalyses have been carried out by Dr. L. Filipović in our laboratory.

1-Bromo-3-phthalimidopropanone (Ib). A suspension of 4.6 g. (0.02 mole) of 1-diazo-3-phthalimidopropanone in 25 ml. of glacial acetic acid was treated with 5 ml. of 48% hydrobromic acid. On stirring the reaction mixture, nitrogen evolution took place. After standing for one hour at room temperature the reaction was complete. The mixture was then diluted with 200 ml. of water and the crystals collected. Yield 5.15 g. (92%), m.p. 147°; recrystallized from benzene, m.p. unchanged. Gabriel (4) gives m.p. 147–148°.

Anal. Calc'd for $C_{11}H_8BrNO_3$: N, 4.97. Found: N, 5.05.

3-(1-Phthalimidoacetonyl)pyridinium bromide (Ic). The compound Ib (9.6 g., 0.034 mole) and 40 ml. of anhydrous pyridine were refluxed for 15 minutes, protected with a calcium chloride tube. After cooling, the crystals were collected and washed with petroleum ether. Yield 12.15 g. (100%), m.p. 210° (decomp.) of hygroscopic needles. Recrystallization from absolute ethanol does not change the m.p.

Anal. Calc'd for $C_{16}H_{13}BrN_2O_3$: C, 53.20; H, 3.63.
Found: C, 52.96; H, 3.95.

α-(Phthalimidoglycyl)-N-(p-dimethylaminophenyl)nitrone (Id). A mixture of a solution of Ic (7.7 g., 0.021 mole) in 21 ml. of water and 6 ml. of ethanol, and of 3.15 g. (0.021 mole) of *p*-nitrosodimethylaniline in 100 ml. of ethanol was cooled to −5°. To this mixture 0.021 mole of *N* NaOH was gradually added during 15 minutes with occasional stirring. The orange-yellow nitrone was left at the same temperature for another 15 minutes and then washed with a cold mixture of ethanol and water (2:5). Yield 4.9 g. (67.2%). Recrystallized from dioxane-water, m.p. 188°.

Anal. Calc'd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88.
Found: C, 64.92; H, 5.07.

Phthalimidomethylglyoxal (Ie). To a suspension of the powdered nitrone (Id, 3.5 g., 0.01 mole) in 8 ml. of water in a separatory funnel, 30 ml. of 5 *N* H_2SO_4 and 30 ml. of pure ether were added. This mixture was thoroughly shaken until the nitrone dissolved. The water layer was extracted six times with ether and the combined ethereal extracts were washed twice with 5 *N* H_2SO_4, and then with water. They were filtered and evaporated at 25° under reduced pressure. When the wet crystalline residue was washed with 25 ml. of ether, 1.38 g. (60%) of crystals remained, m.p. 112°. These were dissolved in dichloromethane and precipitated with petroleum ether (3:1); the m.p. remained unchanged. The analytical results show that the product obtained is phthalimidomethylglyoxal-hemihydrate, crystallized with one molecule of diethyl ether.

Anal. Calc'd for $C_{26}H_{26}N_2O_{10}$: C, 59.31; H, 4.98; N, 5.32; OC_2H_5, 17.10.
Found: C, 59.07; H, 4.96; N, 5.47; OC_2H_5, 18.12.

This compound reduces a cold Fehling solution as well as a cold ammoniacal silver nitrate solution. Distillation at 140–150°/0.036 mm. yields hygroscopic yellow needles of anhydrous, solvent-free *phthalimidomethylglyoxal* (Ie), m.p. 95°.

Anal. Calc'd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25.
Found: C, 60.30; H, 3.58.

The 1,1-diethylacetal of phthalimidomethylglyoxal (If) was prepared according to Claisen's method (5). Ethyl orthoformate (1.48 g.) and 50 mg. of anhydrous ammonium chloride were added to a suspension of 1 g. of phthalimidomethylglyoxal (m.p. 112°) in 4 ml. of absolute ethanol. After standing for a week at room temperature, the phthalimidoglyoxal dissolved. The clear liquid was diluted with 20 ml. of water to which one drop of 25% ammonia had been previously added, extracted with three 20-ml. portions of ether, washed with water, and dried (Na_2SO_4). After evaporating the ether, 0.82 g. (74%) of white prisms separated, m.p. 56–62°. The crystals were repeatedly dissolved in dichloromethane and precipitated with petroleum ether to the constant m.p. 65°.

Anal. Calc'd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88.
Found: C, 61.67; H, 5.82.

2-Phthalimidomethylquinoxaline. The phthalimidomethylglyoxal of the m.p. 112° (340 mg.), 5 ml. of acetic acid, and an equimolar amount of *o*-phenylenediamine were refluxed during 2 hours and then cooled. After addition of water, 250 mg. of the crude quinoxaline derivative separated. This was recrystallized from ethanol and sublimed at 160°/0.036 mm., m.p. 226°.

Anal. Calc'd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83.
Found: C, 70.65; H, 3.98.

Bisethylenemercaptal of phthalimidomethylglyoxal (IIa). Phthalimidomethylglyoxal (Ie, m.p. 112°, 0.65 g., 0.003 mole) and ethanedithiol (0.7 ml., 0.007 mole) were dissolved in a 3% solution of anhydrous HCl in dioxane (10 ml.). After standing at room temperature for four days, the solution was evaporated to dryness under reduced pressure. The yellow oily residue crystallized after the addition of a small amount of benzene. Yield, 0.75 g. (82%). Recrystallized from benzene, it formed white prisms, m.p. 175°.

Anal. Calc'd for $C_{15}H_{15}NO_2S_4$: C, 48.75; H, 4.09.
Found: C, 49.07; H, 3.99.

Bisethylenemercaptal of aminomethylglyoxal (IIb). The mercaptal (IIa, 1.84 g., 0.005 mole), 5 ml. of a molar solution of hydrazine hydrate in ethanol, and 40 ml. of ethanol were refluxed for ten hours. The reaction mixture was evaporated under reduced pressure to dryness and 30 ml. of *N* HCl was added to the residue. After heating this mixture at 50° for 5 minutes, the phthalylhydrazide was filtered off (750 mg., 93%), the filtrate was made alkaline with concentrated ammonia and then extracted with three 50-ml. portions of ether. The extracts were dried (Na_2SO_4); evaporation of the ethereal extracts yielded 597 mg. (50%) of crude bisethylenemercaptal (IIb). Crystallization occurred overnight; recrystallization from ether-petroleum ether gave a product, m.p. 45°. This substance was distilled at 120–130°/0.025 mm.; m.p. unchanged.

Anal. Calc'd for $C_7H_{13}NS_4$: C, 35.23; H, 5.46.
Found: C, 35.31; H, 5.31.

SUMMARY

A description is given of the preparation of phthalimidomethylglyoxal (Ie) from glycine, through the reaction stages Ia–d. The following derivatives have been also prepared: the 1,1-diethylacetal (If), the bisethylenemercaptal (IIa), and the quinoxaline derivative. The bisethylenemercaptal of aminomethylglyoxal (IIb) has also been obtained.

STROSMAYEROV TRG 14
ZAGREB, YUGOSLAVIA

REFERENCES

(1) BALENOVIĆ, BREGANT, CERAR, AND TKALČIĆ, *J. Org. Chem.*, **16**, 1308 (1951).
(2) KRÖHNKE AND BÖRNER, *Ber.*, **69**, 2006 (1936).
(3) ING AND MANSKE, *J. Chem. Soc.*, 2348 (1926).
(4) GABRIEL, *Ber.*, **44**, 1906 (1911).
(5) CLAISEN, *Ber.*, **47**, 317 (1914).