SYNTHESIS OF N-(2-CARBOXY-4-NITROARYL)-β-ALANINES AND THEIR CYCLIZATION TO QUINOLINE DERIVATIVES

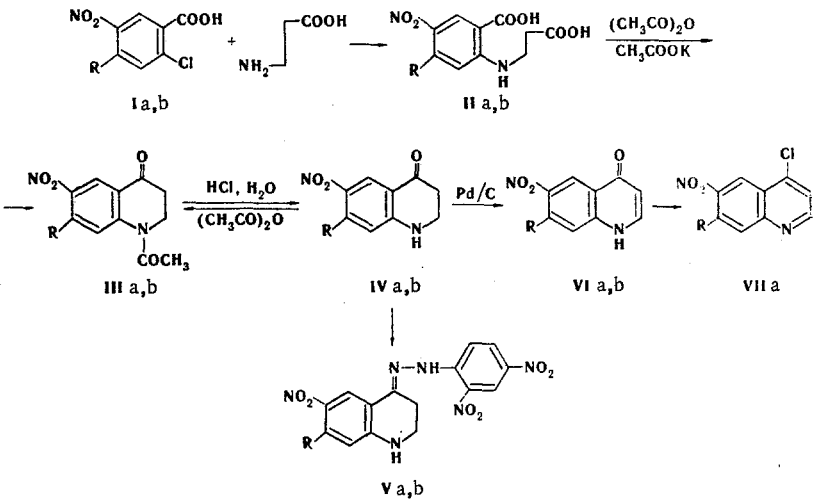
A. F. Bekhli and L. A. Bolotina

UDC 547.831.4.6'432.5.07

N-(2-Carboxy-4-nitroaryl)-β-alanines were obtained by reaction of 2-chloro-5-nitrobenzoic acids with β-alanine. The products were converted to the corresponding 1,2,3,4-tetrahydro-4-oxo-6-nitroquinolines by cyclization.

Previously in our laboratory we synthesized N-(2-carboxyaryl)-β-alanines by cyanoethylation of o-aminobenzoic [1] and 2,3-aminonaphthoic [2] acids with subsequent saponification of the reaction products to the corresponding dicarboxylic acids. This method cannot be used to prepare N-(2-carboxy-4-nitroaryl)-β-alanines (IIa, b), apparently because of the lower basicity of the amino group in nitroanthralic acids. We therefore investigated the possibility of nucleophilic substitution of the halogen in 2-chloro-5-nitrobenzoic acids (Ia, b) by β-alanine.

The reaction of acids Ia, b with β-alanine should be carried out in an anhydrous medium, inasmuch as dicarboxylic acids IIa, b are formed in low yields when water is present because of simultaneous replacement of the halogen by the hydroxyl group. The reaction is successfully accomplished in butyl or isoamyl alcohols in the presence of potassium carbonate, sodium acetate, and copper acetate.



β-Alanines IIa, b were cyclized in acetic anhydride in the presence of potassium acetate by the method in [3]. It should be noted that, in contrast to the previously studied N-β-arylalanines without a nitro group [4, 5], this cyclization is accomplished at higher temperatures. The resulting N-acetyl-tetrahydro-4-oxoquinolines (IIIa, b) are hydrolized in acidic media to quinolones IVa, b, which on heating with acetic anhydride and potassium acetate can be reconverted to quinolones IIIa, b. Quinolones VIa, b were obtained by dehydrogenation of IVa, b with palladium on carbon. Their structure is confirmed by the agreement

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1118-1120, August, 1975. Original article submitted July 31, 1974.

TABLE 1. UV Spectra of Quinolones

Compound	λ_{max}, nm	lg ε
IIIa	325; 232; 213	3,98; 4,74; 4,09
IIIb	300; 244	3.81; 4,23
IVa	360; 244; 231	4,17; 3,97; 4.14
IVb	363; 256; 237	4,02; 4,07; 4.27
VIa	354; 323; 265; 222	3,46; 3,55; 3,82; (4,02)
VIb	336; 272; 234; 211	3,8; 3.9; 4.32; 4,13

between the physical constants of quinolone VIa and the identical quinolone obtained by a different method [6] and also by its conversion to the known 4-chloro-6-nitroquinoline [6].

The IR spectra of IIIa, b contain absorption bands at 1665 and 1620-1625 cm^{-1}, which are related to the stretching vibrations of keto and amide groups. A band at 3360 cm^{-1} (NH) is also observed in the spectra of quinolones IVa, b. All of the quinolones obtained have $C-NO_2$ bands at 1530-1570 and 1320-1330 cm^{-1}.

The UV spectra of quinolones III and IVa, b have three maxima corresponding to the spectra of analogous systems [7]. The UV spectrum of quinolone VIa is identical to the spectrum presented in [8]. The introduction of an acetyl group relative to the ring nitrogen atom of IIIa, b, which decreases the nitrogen–carbonyl interaction, leads to a hypsochromic shift of the absorption maxima [9] (Table 1).

EXPERIMENTAL METHOD

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer.

N-(2-Carboxy-4-nitrophenyl)-β-alanine (IIa). A mixture of 94.4 g (0.4 mole) of Ia, 39.2 g (0.44 mole) of β-alanine, 88 g(0.638 mole) of potassium carbonate, 59.7 g (0.44 mole) of sodium acetate, 8 g of copper acetate, and 600 ml of isoamyl alcohol was refluxed and stirred for 8 h, after which it was cooled and filtered, and the filtrate was washed with acetone. The resulting salt was dissolved in dilute sodium hydroxide by heating, and the solution was treated with charcoal, filtered, and cooled, The filtrate was acidified to pH 3-4 with hydrochloric acid, and the resulting precipitate was removed by filtration and dried to give 93 g (91.3%) of yellow crystals with mp 216-217° (from water). The product was soluble in water, alcohol, and acetone, only slightly soluble in nonpolar solvents, and had R_f 0.73 [silicic acid, benzene–alcohol (1 :2)]. Found: C 47.2; H 4.0; N 11,0%. $C_{10}H_{10}N_2O_6$. Calculated: C 47.2; H 3.9; N 11.0%.

N-(2-Carboxy-4-nitro-5-chlorophenyl)-β-alanine (IIb). This compound was similarly obtained as yellow crystals with mp 185-187° (from water) and R_f 0.55 [silicic acid, benzene–alcohol (1 :2)] in 93.5% yield from Ib in butyl alcohol. Found: C 41.6; H 3.7; Cl 12.0; N 9.8%. $C_{10}H_9ClN_2O_6$. Calculated: C 41.6; H 3.1; Cl 12.3; N 9.7%.

N-Acetyl-1,2,3,4-tetrahydro-4-oxoquinoline (IIIa). A) A mixture of 25.4 g (0.1 mole) of IIa, 19.6 g (0.2 mole) of potassium acetate, and 100 ml of acetic anhydride was stirred at 110-115° for 2 h and at 125° for 30 min until carbon dioxide evolution ceased. The acetic anhydride was removed by distillation, and the residue was treated with water. The product was extracted with chloroform, and the chloroform extract was washed with water, dried with calcium chloride, and evaporated to give 23.2 g (93.7%) of quinolone IIIa. Crystallization from alcohol gave yellow crystals with mp 108-110°. The product was quite soluble in alcohol, acetone, chloroform, and benzene, was insoluble in water, ether, and hexane, and had R_f 0.73 [Al_2O_3, benzene–alcohol (9 :1)]. Found: C 56.1; H 4.8; N 11.9%. $C_{11}H_{10}N_2O_4$. Calculated: C 56.4; H 4.6; N 11.9%.

B) A mixture of 0.77 g (0.004 mole) of IVa, 0.2 g (0.002 mole) of potassium acetate, and 5 ml of acetic anhydride was heated at 100° with stirring for 3 h, after which the acetic anhydride was removed by distillation, water was added to the residue, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.45 g (60%) of quinolone IIIa with mp 108-110° (from alcohol). No melting-point depression was observed for a mixture of this product with IIIa obtained by the method presented above.

N-Acetyl-1,2,3,4-tetrahydro-4-oxo-6-nitro-7-chloroquinoline (IIIb). A) This compound was similarly obtained from IIb in 69.5% yield as yellowish-orange crystals with mp 174-176° (from alcohol) and R_f 0.75 [Al_2O_3, benzene–alcohol (9 :1)]. Found: C 49.4; H 4.1; Cl 13.0; N 10.5%. $C_{11}H_9ClN_2O_4$. Calculated: C 49.2; H 4.3; Cl 13.2; N 10.4%.

B) This compound was similarly obtained by method B from IVb in 63% yield and had mp 175-176° (from alcohol). No melting-point depression was observed for a mixture of this product with the IIIb obtained by method A.

1,2,3,4-Tetrahydro-4-oxo-6-nitroquinoline (IVa). A mixture of 21.1 g (0.09 mole) of crude quinolone IIIa, 103.5 ml of concentrated HCl, 16.5 ml of glacial acetic acid, and 11 ml of water was stirred at 75-80° for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with water, and dried to give 12 g (69.8%) of yellow crystals of quinolone IVa with mp 232-234° (from alcohol) and R_f 0.52 [Al_2O_3, benzene–alcohol (9 :1)]. The product was quite soluble in alcohol, benzene, and chloroform but insoluble in water and ether. Found: C 56.3; H 4.3; N 14.4%; $C_9H_8N_2O_3$. Calculated: C 56.2; H 4.2; N 14.6%.

1,2,3,4-Tetrahydro-4-oxo-6-nitro-7-chloroquinoline (IVb). This compound, with mp 154-156° (from alcohol) and R_f 0.59 [Al_2O_3, benzene–alcohol (9 :1)], was obtained as yellow crystals in 63.4% yield from IIIb by the method used to obtain IVa. Found: C 47.5; H 3.7; Cl 15.8; N 12.2%. $C_9H_7ClN_2O_3$. Calculated: C 47.6; H 3.1; Cl 15.6; N 12.4%.

1,2,3,4-Tetrahydro-4-oxo-6-nitroquinoline 2,4-Dinitrophenylhydrazone (Va). This compound was obtained from quinolone IVa and 2,4-dinitrophenylhydrazine in ethanol in the presence of sulfuric acid at room temperature. The yield of red crystals with mp 327-329° (from alcohol) was 82.7%. Found: C 48.2; H 3.4; N 22.8%. $C_{15}H_{12}N_6O_6$. Calculated: C 48.4; H 3.3; N 22.6%.

1,2,3,4-Tetrahydro-4-oxo-6-nitro-7-chloroquinoline 2,4-Dinitrophenylhydrazone (Vb). This compound was obtained as raspberry-red crystals with mp 345-346° (from alcohol) in 77.8% yield from quinolone IVb by the method used to obtain hydrazone Va. Found: C 44.2; H 3.1; Cl 8.6; N 20.8%. $C_{15}H_{11}ClN_6O_6$. Calculated: C 44.3; H 2.8; Cl 8.8; N 20.6.

6-Nitroquinoline-4[1H]-one (VIa). A mixture of 1 g of IVa, 1 g of 20% palladium on carbon, and 20 ml of xylene was refluxed for 24 h, after which the catalyst was removed by filtration and treated with methanol (with heating). The solvents were then removed by distillation, and the residue was crystallized from alcohol to give 0.4 g (40.5%) of cream-colored crystals with mp 310-312° (mp 310-315° [6]) and R_f 0.42 [Al_2O_3, benzene–alcohol (9 :2)]. The product was quite soluble in alcohol, acetone, benzene, and hot dilute alkalis but only slightly soluble in water and ether. Found: C 56.6; H 3.4; N 14.8%. $C_9H_6N_2O_3$. Calculated: C 56.8; H 3.2; N 14.8%.

4-Chloro-6-nitroquinoline VIIa, with mp 142-143° (mp 142-5-143° [6]), was obtained from VIa.

6-Nitro-7-chloroquinolin-4[1H]-one (VIb). This compound was obtained as cream-colored crystals with mp 292-294° (from alcohol) in 35.4% yield by the method used to obtain IVb. The solubility of the product was similar to the solubility of VIa. The product had R_f 0.26 [Al_2O_3, benzene–alcohol (9 :2)]. Found: C 48.6; H 2.4; Cl 15.6; N 12.4%. $C_9H_5ClN_2O_3$. Calculated: C 48.2; H 2.2; Cl 15.8; N 12.5%.

LITERATURE CITED

1. A. F. Bekhli, Zh. Obshch. Khim., 27, 698 (1957).
2. A. F. Bekhli and N. P. Kozyreva, Khim. Geterotsikl. Soedin., No. 1, 296 (1967).
3. A. F. Bekhli, Dokl. Akad. Nauk SSSR, 101, 679 (1955).
4. A. F. Bekhli, F. S. Mikhailitsyn, and I. V. Persianova, Zh. Organ. Khim., 2255 (1968).
5. A. F. Bekhli and F. S. Mikhailitsyn, Khim. Geterotsikl. Soedin., 235 (1971).
6. A. Adams and D. H. Heu, J. Chem. Soc., 255 (1949).
7. J. Allison, J. Braunholtz, and F. Mann, J. Chem. Soc., 403 (1954).
8. J. Hearn, R. Morton, and J. Simpson, J. Chem. Soc., 3318 (1951).
9. J. Braunholtz and F. Mann, J. Chem. Soc., 4166 (1957).