A NEW SYNTHESIS 2-ACYL-1,2,3,6,7,11*b*-HEXAHYDROPYRAZINO[2,1-*a*]ISOQUINOLIN-4-ONES BASED ON N-CYANOMETHYL DERIVATIVES OF 2-PHENYL-ETHYLAMIDES OF ACYLGLYCINES

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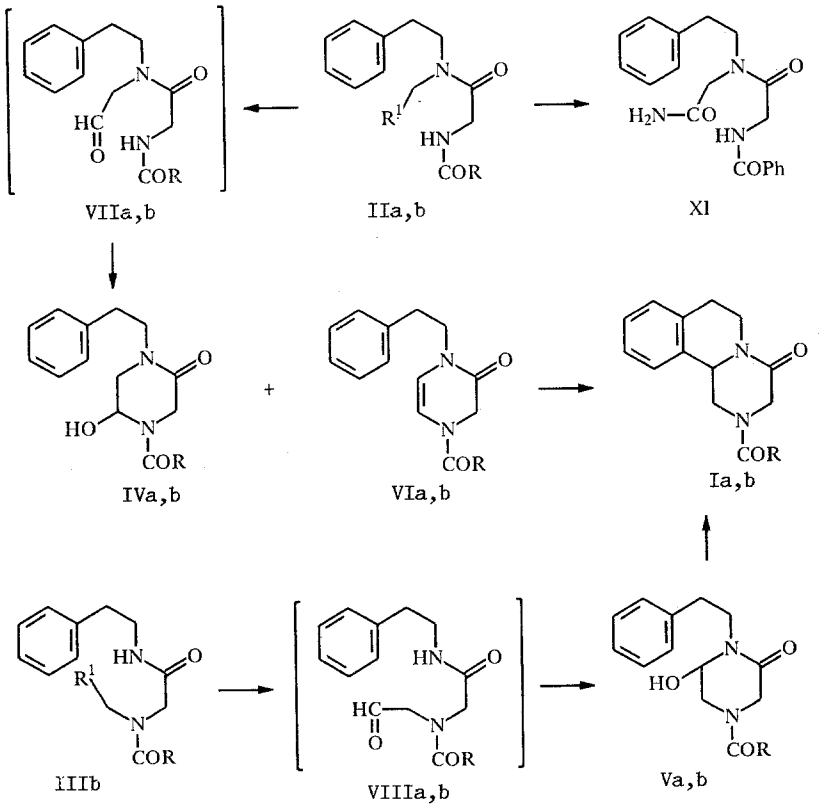
A new route for the synthesis of 2-acyl-1,2,3,6,7,11b-hexahydropyrazino[2,1-a]isoquinolin-4-ones has been studied which includes a stage in which substituted piperazinones are obtained by reductive cyclization of N-cyanomethyl derivatives of 2-phenylethylamides of acylglycines under influence of Raney alloy in formic acid.

In recent years a variety of methods have been developed for the synthesis of the highly effective antihelminthic praziquantel (Ia) which is a derivative of pyrazino[2,1-*a*]isoquinoline [1]. The most important schemes are based on the cyclization of hydroxypiperazinones or their equivalents, particularly acetals of types II and III, where R = C_6H_5 or C_6H_{11} and R^1 = $CH(OAlk)_2$ or $CH(OCOAlk)_2$. which unfortunately are hard to come by. Conversion of the acetals and acylals into the corresponding pyrazinoisoquinilines Ia and Ib occurs under the influence of acid via formation of the hydroxypiperazinones



I—VIII a R = C_6H_{11}, b R = C_6H_5; II, III R^1 = CN

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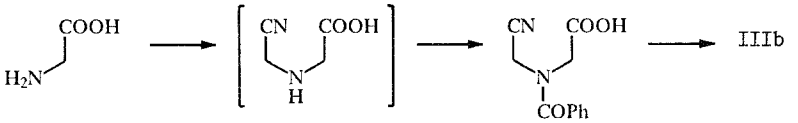
TABLE 1. Reductive Cyclization of Compounds IIa, b and IIIb

Experiment	Starting material	Exptl. conditions		Yield, %			
		HCOOH concentration %	time, h	IV	V	VI	IX
1	IIa	50	1	3	—	53	—
2	IIb	75	1	—	—	45	29
3	IIb	50	1	1	—	63	7
4	IIb	25	2	32	—	39	—
5	IIIb	50	2	—	23	45	—
6	IIIb	25	3	—	26	40	—

(IVa,b), (Va,b) and dehydropiperazinones (VIa,b) [2,3]. A new route to the synthesis of the pyrazinoisoquinolines Ia,b is studied starting from the synthons (IIa,b) and (IIIb) containing a nitrile group in place of the protected aldehyde group. The choice of these N-cyanomethyl derivatives is because they can be converted into the pyrazinoisoquinolines Ia,b after reduction to the corresponding aldehydes in the same way as the acetals and acylals of types II and III.

Compounds IIa,b are obtained by the carbodiimide method from 2-phenylethylaminoacetonitrile [4] and hippuric acids or the cyclohexylcarbonylglycine respectively. The isomeric diamide IIIb is made analogously from 2-phenylethylamine and N-cyanomethyl hippuric acid (IX). The later is prepared from glycine by the reaction of formaldehyde and potassium cyanide with subsequent acylation without isolation of the intermediate N-cyanomethylglycine (X, cf. [5]).



X IX

Of the known methods for the conversion of nitriles into aldehydes we chose a method based on the reduction of the nitrile with Raney alloy in formic acid [6]. It was expected that in the presence of an acid as strong as formic acid , the aldehydes VIIa,b and VIIIb formed would cyclize into piperazinones in the same way as the acetals and acylals of types II and III [2,3]. In fact, when nitrile IIb was heated with Raney alloy in formic acid the hydroxypiperazinone IVb and the 2,3-dehydropiperazinone Vb were formed along with the triamide XI. The latter is formed by concurrent hydrolysis of the nitrile group.

The structures of compounds XI, IVb, and VIb, which were isolated by column chromatography, were confirmed by elemental analysis, IR and mass spectrometry. The reaction product ratio depends on the formic acid concentration. Two processes were observed when the concentration was lowered: a decrease in content of the hydrolysis product XI and an increase in the content of the hydroxypiperazinone IVb. The reason for the former is obvious, and the second is easily explained since the primary product of cyclization of aldehyde VIIb, compound IVb, is dehydrated to VIb the faster the higher the acid concentration. The process was not optimized, but the general tendency is clearly seen from experiments 2-4 (Table 1) in which 75%, 50%, and 25% formic acid were used.

The previously described [2] 2,3-dehydropiperazinone VIa, containing a small amount of IVa as impurity [2] (Table 1, experiment 1) was obtained similarly by reductive cyclization of compound IIa in 50% formic acid.

Thus on reduction of the cyanomethyl derivatives IIa,b with Raney alloy in 50% formic acid the aldehydes VIIa,b are formed which are cyclized rapidly into the hydroxypiperazines IVa,b, which in turn may lose water to give the dehydropiperazinones VIa,b the more readily the more concentrated the acid.

Under reductive cyclization conditions the cyanomethyl derivative IIIb is converted to a mixture of piperazinones Vb and VIb. The structure of the former was confirmed by comparison with an authentic sample synthesized by an independent method. The ratio of the products (Vb:VIb) also depends on the acid concentration and the reaction time (Table 1, experiments 5 and 6). However the reductive cyclization of nitrile IIIb is slower than that of IIb: some starting material remained, according to TLC analysis, after the reaction mixture had been heated for one hour.

The synthesized dehydropiperazinones VIa,b gave the corresponding pyrazinoisoquinolines Ia,b on treatment with conc. H_2SO_4. Since cyclization of the hydroxypiperazinones IVa,b and Va,b occurs under the same conditions [2,3], the mixtures

of compounds IVb and VIb or Vb and VIb formed in experiments 3 and 5 (Table 1) were directly converted into the pyrazinoisoquinoline Ib which avoided the need for chromatographic separation.

Thus the N-cyanomethyl derivatives II and III were converted in two steps in satisfactory yields to the pyrazinoisoquinolines Ia and Ib. This new synthetic route to praziquantel and its analogues is of interest because of the suitable methods for preparing the starting materials II or III. Moreover the method proposed provides for the preparation of the difficult to obtain 2(3)-hydroxy and 2,3-dehydro-4-acylpiperazin-6-ones.

EXPERIMENTAL

IR spectra were recorded as KBr discs with a UR-20 spectrometer and mass spectra with a Varian MAT-112 with direct insertion of samples into the ion source, ionization energy 70eV, ionization chamber temperature 180 °C. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 strips with 1:1 benzene–acetone as eluent and development by UV light or iodine vapor. Silica gel L 100/250 was used for column chromatography with chloroform as eluent.

C, H, N elemental analyses for the synthesized compounds corresponded to the calculated values.

N-(2-Phenylethyl)-N-(cyanomethyl)amide of Hippuric Acid (IIb, $C_{19}H_{19}N_3O_2$). Dicyclohexylcarbodiimide (0.83 g, 4 mmol) was added to a suspension of hippuric acid (0.72 g, 4 mmol) in dry chloroform (20 ml), the mixture was stirred for 30 min at 20 °C, and 2-phenylethylaminoacetonitrile (0.64 g, 4 mmol) was added. The mixture was stirred for 6 h and stood for 70 h at 20 °C. At the end of the reaction, product IIb and dicyclohexylurea were filtered off and washed with chloroform (5 ml), dried in vacuum and treated with benzene (20 ml). The insoluble dicyclohexylurea was filtered off and the benzene solution was washed with 5% HCl (2 x 6 ml) and water, and was dried over Na_2SO_4. After removal of the benzene in vacuum, the residue was stirred with ether (30 ml) and the residue was filtered off to give product IIb (1.01 g, 78%), m.p. 69-71 °C (1:1 ethyl acetate–hexane). IR spectrum: 3350 (NH), 2260 (C≡N), 1660, 1640 cm^{-1} (C=O).

N-(2-Phenylethyl)-N-(cyanomethyl)amide of Cyclohexylcarbonylglycine (IIa, $C_{19}H_{25}N_3O_2$). Amide IIa was obtained analogously to IIb from cyclohexylcarbonylglycine and 2-phenylethylaminoacetonitrile as an oil in 77% yield which was used without further purification in the next reaction. An analytical sample of IIa was isolated by column chromatography. TLC R_f 0.65. IR spectrum: 3400-3340 (NH), 2260 (C≡N), 1670, 1640 cm^{-1} (C=O).

N-Cyanomethylhippuric Acid (IX, $C_{11}H_{10}N_2O_3$). Formalin (3.8 ml, 34%; 1.4 g, 47 mmol) was added dropwise with stirring over 5 min to a solution of glycine (3.3 g, 44 mol) and potassium cyanide (3.1 g, 47 mmol) in water (15 ml). Sodium hydrogen carbonate (4.2 g, 50 mmol) was added to the stirred solution over 25 min at 20 °C. The solution was then cooled in ice and benzoyl chloride (6.0 ml, 52 mmol) was added over 10 min. Sodium hydrogen carbonate (0.8 g portions) was added to the stirred solution at 20 °C at 10, 30, and 50 minutes and after a total of 1.5 h the mixture was acidified by addition of conc. HCl dropwise over 15 min to a pH of 2-3, and the solution was then extracted with ethyl acetate (4 x 40 ml). The extract was washed with water (2 x 20 ml) and dried over Na_2SO_4. After removal of the solvent in vacuum the residue was recrystallized from 1:1 ethyl acetate–acetone to give compound IX (6.6 g, 67%), m.p. 133-135 °C. IR spectrum: 3300-2800 (OH), 2260 (C≡N), 1740, 1610 cm^{-1} (C=O).

2-Phenylethylamide of N-cyanomethylhippuric Acid (IIIb, $C_{19}H_{19}N_3O_2$). Amide IIIb was prepared in 62% yield analogously to IIb from acid IX and 2-phenylethylamine in dry acetonitrile. After standing the reaction mixture at 20 °C for 24 h, the reaction mixture was worked up as described for IIb and the product was used in the next stage without further purification. An analytical sample was obtained by column chromatography. TLC R_f 0.5. IR spectrum: 3325 (NH), 2270 (C≡N), 1660 cm^{-1} (C=O).

Reductive Cyclization of Amides IIa, IIb, and IIIb (general method). Finely divided Raney nickel (2 g) was added to a suspension of amide (3 mmol) in formic acid (20 ml) and the mixture was refluxed for 1-3 h (Table 1). The alloy was filtered off after cooling and was washed on the filter with chloroform (20 ml). The filtrate was diluted with water (40 ml), the organic layer was removed, and the aqueous layer was extracted with chloroform (3 x 10 ml). The combined chloroform extracts were washed with water (3 x 10 ml), 5% $NaHCO_3$ solution (2 x 10 ml), and water (10 ml), and dried over Na_2SO_4. The product mixture obtained after evaporation of the chloroform in vacuum was separated by column chromatography. The reaction conditions and the composition of the product mixture are given in Table 1 while characteristics of individual compounds are given below.

N-(2-Phenylethyl)-N-(carbomylmethyl)amide of Hippuric Acid (XI, $C_{19}H_{21}N_3O_3$). M.p. 104-106 °C. R_f 0.2. IR spectrum: 3400-3300, 3220 (NH), 1690, 1660, 1630 cm^{-1} (C=O), Found : M^+ 339. Calculated M 339.

1-(2-Phenylethyl)--3-hydroxy-4-benzoyl-2,3-dehydropiperazin-6-one (IVb, $C_{19}H_{20}N_2O_3$). M.p. 100-103 °C. R_f 0.4. IR spectrum: 3500-3200 (OH), 1680, 1660 cm^{-1} (C=O). Found: M^+ 324. Calculated: M 324.

1-(2-Phenylethyl)-4-benzoyl-2,3-dehydropiperazin-6-one (VIb, $C_{19}H_{18}N_2O_2$). M.p. 62-65 °C. R_f 0.8. IR spectrum: 1680, 1650 cm^{-1} (C=O). Found: M^+ 306. Calculated: M 306. **1-(2-Phenylethyl)-4-cyclohexylcarbonyl-2,3-dehydropiperazin-6-one (VIa, $C_{19}H_{24}N_2O_2$).** M.p. 128-130 °C. R_f 0.75. IR spectrum: 1670, 1650 cm^{-1} (C=O). M.p. < 129-131 °C [2].

1-(2-Phenylethyl)-4-benzoyl-2-hydroxypiperazin-6-one (Vb, $C_{19}H_{20}N_2O_2$). M.p. 40-42 °C. R_f 0.35. IR spectrum: 3500-3100 (OH), 1643 cm^{-1} (C=O). The compound was identical to a sample synthesized by Schotten-Bauman acylation of 1-(2-phenylethyl)-2-hydroxypiperazin-6-one [3] with benzoyl chloride ion $NaHCO_3$ solution.

2-Benzoyl-1,2,3,6,7,11*b*-hexahydro-4H-pyrazino[2,1-*a*]isoquinolin-4-one (Ib, $C_{19}H_{18}N_2O_2$). A. A mixture of compound VIb (0.31 g, 1 mmol) and conc. H_2SO_4 (2.0 ml) was stirred for 3 h at 20 °C. The solution was treated with ground ice (20 g) and extracted with chloroform (3 x 10 ml); the organic layer was separated, washed with water (3 x 5 ml), 5% $NaHCO_3$ solution (2 x 5 ml), and water (5 ml) and dried over Na_2SO_4. The solvent was evaporated in vacuum to give Ib (0.25 g, 83%), m.p. 159-161 °C (ethyl acetate). R_f 0.6. The substance was identical to a sample prepared by a known method [7].

B. Compound Ib was synthesized in 72% yield as described in A by the reaction of conc. H_2SO_4 on a mixture of IVb and VIb made in experiment 4 (Table 1), m.p. 158-160 °C.

C. Compound Ib was synthesized as described in A by the reaction of conc. H_2SO_4 on a mixture of VIb and Vb made in experiment 5 (Table 1). Yield 68%. M.p. 158-160 °C.

2-Cyclohexylcarbonyl-1,2,3,6,7,11*b*-hexahydro-4H-pyrazino[2,1-*a*]isoquinolin-4-one(Ia,$C_{19}H_{24}N_2O_2$). Praziquatel Ia was obtained analogously to Ib (method A) from VIa by reaction with conc. H_2SO_4. Yield 70%, m.p. 132-134 °C (1:2 ethyl acetate–hexane). R_f 0.55. The substance was identical to a sample prepared by a different method [7].

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