12. L. V. Volodarskii and T. K. Sevast'yanova, Zh. Org. Khim., 7, 1687 (1971).
13. T. K. Sevast'yanova and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2339 (1972).

SYNTHESIS OF 1-ALKYL(ARALKYL)-4-ACYL-2-PIPERAZINONES

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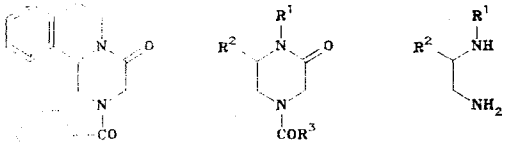
1-Alkyl(aralkyl)-4-acyl-2-piperazinones are formed in high yields during selective acylation of N-monosubstituted ethylenediamines by benzoyl and cyclohexylcarbonyl chlorides in the presence of pyridine hydrochloride and treatment of the reaction products with chloroacetyl chloride in the presence of potassium tert-butylate.

Among 2-piperazinones, having different biological activities [1-3], the little investigated 4-acyl derivatives are of special interest, since the 4-acyl-2-piperazinone fragment is included in the structure of a new anthelmintic prasiquantel (I) [4] with a broad spectrum of activity. The aim of the present work was to find suitable method for the synthesis of 1-alkyl(aralkyl)-4-acyl-2-piperazinones (IIa-g). Compounds IIa-g were selected as the object products, since they contain the same functional groups as prasiquantel, and have a similar lyophilicity.

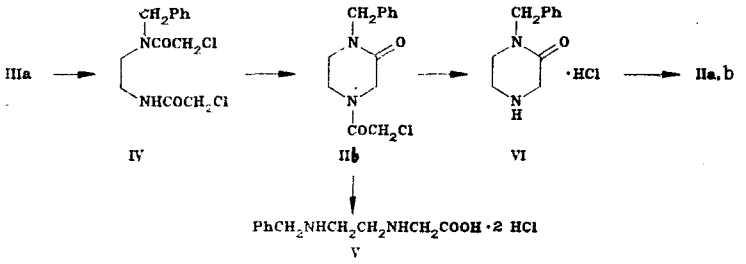
In the course of the investigation, we studied schemes of synthesis of compound IIa-g, based on the use of available N-monosubstituted ethylenediamines IIIa-c.



I IIa-h IIIa-c

IIa-c,f IIIa R^1=$PhCH_2$, IId,e IIIb R^1=$PhCH_2CH_2$, IIfg, IIIc R^1=Et; IIa-e,h IIIa,b R^2=H, IIf,g IIIc R^2=Ph; IIa,d,f R^3=Ph, b R^3=4-$NO_2C_6H_4$, c,e,g R^3=cyclohexyl h R^3=$ClCH_2$

Taking compound IIIa as an example, we first studied the variant of the synthesis of 2-piperazinones, which gives the formation of a hetero ring by the cyclization of the bis-chloroacetyl derivative IV by the action of a strong base, and the subsequent elimination of the chloroacetyl group.



IIIa → IV → IIb → VI ·HCl → IIa,b

IIb → $PhCH_2NHCH_2CH_2NHCH_2COOH \cdot 2\,HCl$ V

During the acylation of compound IIIa by chloroacetyl chloride, the derivative IV is obtained in high yield. By the action of potassium tert-butylate, this converts into piperazinone IIh in a yield of 37% only. Even mild acidic hydrolysis of compound IIh results not

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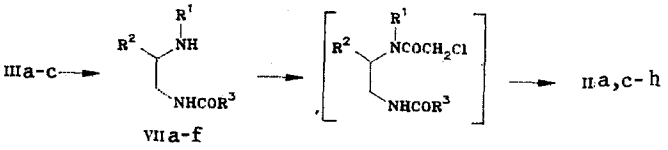
only in splitting of the chloroacetyl group, but also in opening of the piperazine ring. As the result, amino acid V is formed, which has been previously obtained by another method [5]. Because of this, specific methods were used for the removal of the chloroacetyl group: action of o-phenylenediamine [6] or thiourea [7] on compound IIh. In both cases pyrazinone VI was obtained from compound IIh in a yield not higher than 55-60%, since the isolation of the reaction products is difficult, due to the presence of difficultly separable impurities. The acylation of compound IIh by benzoyl of 4-nitrobenzoyl chloride leads to compounds IIa,b.

Better results were obtained by the alternative route also based on the use of substituted ethylenediamines IIIa-c. The latter contain both a primary and secondary amino group, differing in the degree of steric hindrance. It could be assumed that the less hindered primary amino group will be preferentially acylated. However, only in the case of compound IIIc, where the differences in the environment of the amino groups are in particular considerable, it is possible under normal conditions (see the Experimental section) to acylate selectively the primary group and to obtain compounds VIIa,b. N-Benzyl-N,N'-dibenzoylethylenediamine (VIII) is formed under these conditions from equimolar amounts of ethylene-diamine IIIa and benzoyl chloride, and ~50% of the initial compound IIIa, which does not enter the reaction, is left. Monoaceylation of compounds IIIa,b could be accomplished using a method previously proposed for 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline [8]. The reaction of ethylenediamines IIIa,b with benzoyl or cyclohexylcarbonyl chloride in acetonitrile in the presence of pyridine hydrochloride leads to compounds VIIc-f in high yields



VIIIa,b R^1=Et, c,d R^1=$PhCH_2$, e,f R^1=$PhCH_2CH_2$; a,b R^2=Ph, c-f R^2=H; a,d,e R^3=Ph, b,c,f R^3=cyclohexyl

The secondary amino group becomes acylated by the action of chloroacetyl chloride on acetylethylenediamines VIIa-f in the presence of potassium tert-butylate, and this is followed by cyclization to give piperazinones IIa,c-g. The 4-acyl-2-piperazinones IIa-g thus synthesized are colorless crystalline substances, an exception being compound IIh, which is a viscous liquid. The structure of the compounds was confirmed by elemental analysis and IR spectroscopy (Table 1).

Thus, the selective acylation of N-monosubstituted ethylenediamines and subsequent reaction with chloroacetyl chloride in the presence of potassium tert-butylate represents a convenient general method for the synthesis of 4-acyl-2-piperazinones.

EXPERIMENTAL

The IR spectra of the compounds synthesized were run on a UR-20 spectrophotometer in KBr tablets. The course of the reactions and the purity of the products obtained controlled by TLC on Silufol plates in 3:1 ether–acetone system.

Compounds IIIa,b were obtained from ethylenediamine and the corresponding aralkyl chloride by the method in [9], and compound IIIc by reducing α-ethylaminobenzyl cyanide with lithium aluminum hydride according to a method described in [10].

N-Benzyl-N,N'-bis(chloroacetyl)ethylenediamine (IV). A solution of 15.5 ml (200 mmoles) of chloroacetyl chloride in 10 ml of methylene chloride is added in the course of 20 min, at 0°C to a mixture of 13.5 g (90 mmoles) of compound IIIa and 30 g (280 mmoles) of Na_2CO_3 in 100 ml of anhydrous methylene chloride. The mixture is stirred for another 40 min, the precipitate is filtered, and washed with 100 ml of methylene chloride. The filtrates are combined and evaporated *in vacuo*. Yield, 25.2 g (92%) of compound IV in the form of a pale-yellow oil. IR spectrum: 3330 (NH), 1665 (CO), 1645 cm^{-1} (sh, CO). Compound IV is used in the following stage without additional purification.

1-Benzyl-4-chloroacetyl-2-piperazinone (IIh). A solution of potassium tert-butylate, prepared from 0.274 (7 mmoles) of potassium and 10 ml of tert-butanol, is added in the course of 20 min to a solution of 2.02 g (7 mmoles) of compound IV in 20 ml of anhydrous tert-butanol. The mixture is stirred for another 20 min, 100 ml of water are added, and the mixture is ex-

TABLE 1. 1-Alkyl(aralkyl)-4-acyl-2-piperazinones

Compound	mp,* °C	IR spectrum, cm^{-1}, ν_{CO}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N(Cl)		C	H	N(Cl)	
IIa	101—102	1624, 1660	73,2	6,0	9,7	$C_{18}H_{18}N_2O_2$	73,5	6,2	9,5	71 (82)†
IIb	113—114	1640, 1660	63,7	5,1	12,2	$C_{18}H_{18}N_3O_4$	63,5	5,3	12,4	87
IIc	87—88	1632	71,5	7,6	9,0	$C_{18}H_{24}N_2O_2$	72,0	8,1	9,3	65
IId	80—82	1638, 1650 sh	74,1	7,0	8,9	$C_{19}H_{20}N_2O_2$	74,0	6,6	9,1	62
IIe	116—118	1630, 1642 sh	72,2	8,1	9,3	$C_{19}H_{26}N_2O_2$	72,6	8,3	8,9	67
IIf	72—74	1635, 1660	74,2	6,9	9,0	$C_{19}H_{20}N_2O_2$	74,0	6,6	9,1	66
IIg	152—154	1630, 1655 br	72,3	8,2	9,0	$C_{19}H_{26}N_2O_2$	72,6	8,3	8,9	64
IIh	—	1662			(13,7)	$C_{13}H_{15}ClN_2O_2$			(13,3)	35

*Compounds IIa,c were recrystallized from an acetone—petroleum ether mixture, IIb from alcohol, IId-g from an ethyl acetate—hexane mixture.

†Prepared from compound VI and benzoyl chloride.

tracted by chloroform. The organic layer is separated, washed with water, 5% HCl, and water again, and dried over $MgSO_4$. The solvent is distilled off, and the residue is chromatographed on a column with silica gel (eluent, chloroform) to yield 0.65 g (35%) of compound IIh.

N-(2-Benzylaminoethyl)glycine Dihydrochloride (V). A 1.03 g portion (3.9 mmoles) of compound IIh is boiled for 1 h in 10 ml of dilute hydrochloric acid (1:1). The mixture is then cooled and the precipitate filtered to yield 1.0 g (92%) of compound V. Colorless crystals, mp 215-216°C [5].

1-Benzyl-2-piperazinone hydrochloride (VI). A. A mixture of 4.08 g (15.3 mmoles) of compound IIh and 1.16 g (15.3 mmoles) of thiourea in 30 ml of alcohol is heated for 1 h at 60-65°C, and then boiled for 15 min. The solvent is distilled *in vacuo*, and 20 ml of water are added to the residue. The mixture is boiled for 1.5 min, then cooled and the precipitate is filtered. The filtrate is evaporated *in vacuo*, the residue is ground with acetone, and compound VI is filtered. Yield, 1.91 g (55%), colorless crystals, mp 106-107.5°C (alcohol—ether). IR spectrum: 3300-3400 (br, NH), 1640 cm^{-1} (CO). Found Cl 15.8 N 12.1%. $C_{11}H_{15}ClN_2O$. Calculated Cl 15.6 N 12.4%.

B. A 9.87 g (37 mmoles) of compound IIh and 4.32 g (40 mmoles) of o-phenylenediamine are boiled in a mixture of 20 ml of alcohol and 30 ml of water for 2 h. The solution is evaporated *in vacuo* to 1/3 its volume, 50 ml of water are added, and the precipitate is filtered. The precipitate is washed with 15 ml of water, and the filtrates are combined. The aqueous solution is evaporated *in vacuo*, the residue is ground with acetone and 5.0 g (60%) of compound VI are filtered, and found to be identical with the product by method A.

4-Benzoyl- and 4-(4-Nitrobenzoyl)-1-benzyl-2-piperazinones (IIa,b). A 23 mmole portion of the acyl chloride is added gradually at a temperature not higher than 20°C to a stirred solution of 22 mmoles of compound VI and 44 mmoles of triethylamine in 50 ml of chloroform. The mixture is stirred for 1 h, then washed with water, 5% hydrochloric acid, and water again, and dried over $MgSO_4$. The solvent is distilled off, and the residue is crystallized to yield IIa,b.

1-Phenyl-N^1-ethyl-N^2-benzoyl(cyclohexylcarbonyl)ethylenediamines (VIIa,b). A 16 mmole portion of Na_2CO_3 is added to a solution of 15 mmoles of compound IIIc in 25 ml of methylene chloride, and then with stirring, a solution of 15 mmoles of acyl chloride in 10 ml of anhydrous methylene chloride is added gradually at a temperature not higher than 20°C. At the end of the addition, the mixture is stirred for another 30 min, and the precipitate is filtered. The precipitate is washed with 25 ml of methylene chloride. The filtrates are combined and evaporated *in vacuo* to yield compound VIIa [colorless crystals, mp 63-64°C (hexane). Found: C 76.4; H 7.6; N 10.5%. $C_{17}H_{20}N_2O$. Calculated: C 76.1; H 7.5; N 10.4%] and VIIb [colorless crystals, mp 103-104°C (ethyl acetate—hexane). Found: C 74.3; H 9.2; N 10.3%. $C_{17}H_{26}N_2O$. Calculated: C 74.4; H 9.6; N 10.2%].

N-Benzyl-N,N'-dibenzoylethylenediamine (VIII) was obtained from ethylenediamine IIIa and benzoyl chloride in a similar way as compounds VIIa,b. Yield 45%. Colorless crystals, mp 182-184°C (alcohol). IR spectrum: 3330 (NH), 1658 (CO), 1620 cm^{-1} (CO). Found: C 77.2; H 6.0; N 8.2%. $C_{23}H_{22}N_2O_2$. Calculated: C 77.1; H 6.2; N 7.8%.

N-Benzyl-N'-cyclohexylcarbonylethylenediamine (VIIc). A solution of 4.4 ml (33 mmoles) of cyclohexylcarbonyl chloride in 20 ml of anhydrous acetonitrile is added in the course of 1 h to a solution of 4.5 g (30 mmoles) of compound IIIa in a mixture of 60 ml of acetonitrile, 2.66 ml (33 mmoles) of pyridine and 15 ml of 2 N HCl. At the end of the addition, the reaction mixture is stirred for another 2 h, the solvent is distilled off in vacuo, and to the residue 200 ml of ether are added, and the mixture is extracted with 60 ml of 1 N HCl. The acid extract is made alkaline with 30% NaOH to pH 10, and extracted by chloroform. The chloroform solution is dried over Na_2SO_4, the solvent is distilled off, and the residue is crystallized from an acetone–petroleum ether mixture. Yield, 6.2 g (79.5%) of colorless crystals, mp 56-58°C. IR spectrum: 3325 (NH), 1640 cm^{-1} (CO). Found: N 10.8%. $C_{16}H_{24}N_2O$. Calculated: N 10.8%.

Hydrochlorides of N-Benzyl(phenylethyl)-N'-benzoyl(cyclohexylcarbonyl)ethylenediamines (VIId-f) are obtained in a similar way as compound VIIc with the difference that at the end of the reaction, 200 ml of ether is added to the mixture and the precipitates of hydrochlorides of compounds VIId-f are separate are filtered. [As in Russian original; there's probably some HCl in the final ether solution – Editor.]

Hydrochloride of Compound VIId. Colorless crystals, mp 194-195°C (alcohol–ether). Found: Cl 12.5; N 10.0%. $C_{16}H_{17}ClN_2O$. Calculated: Cl 12.3; N 9.7%.

Hydrochloride of Compound VIIe. Colorless crystals, mp 198-199°C (water). Found: Cl 11.6; N 9.2%. $C_{17}H_{21}ClN_2O$. Calculated: Cl 11.2; N 9.5%.

Hydrochloride of Compound VIIf. Colorless crystals, mp 230-231.5°C (alcohol–ether). Found: C 65.9; H 8.8; Cl 11.1; N 9.4%. $C_{17}H_{27}ClN_2O$. Calculated: C 65.7; H 8.8; Cl 11.4; N 9.0%.

4-Acyl-2-piperazinones (IIa,c-g). A solution of 0.75 ml (10 mmoles) of chloroacetyl chloride in 12 ml of benzene is added at 20°C to a solution of 10 mmoles of compounds VIIa-f (the compounds VIId-f were isolated from the corresponding hydrochlorides) in 30 ml of anhydrous benzene, and then a solution of potassium tert-butylate (prepared from 20 mmoles of potassium and 30 ml of anhydrous tert-butanol), is added. The reaction mixture is stirred for 1 h, boiled for 3 h, cooled and poured into 100 ml of water. The organic layer is separated, and the aqueous layer is extracted by chloroform. The extracts are combined, washed with water, 5% HCl, and water again, and dried over Na_2SO_4. The solvent is distilled off in vacuo, and the residue is crystallized to yield compound IIa,c-g.

LITERATURE CITED

1. H. Zellner, US Patent No. 3935214; Chem. Abstr., 85, 214956 (1976).
2. Japanese Patent No. 80136280; Chem. Abstr., 94, 156968 (1981).
3. W. Zumma, et al., US Patent No. 4163849; Chem. Abstr., 92, 41986 (1980).
4. J. Seubert, R. Pohlke, and F. Loeblich, Experientia, 33, 1036 (1977).
5. G. Struve, C. Gazzola, and G. Kenyon, J. Org. Chem., 42, 3069 (1977).
6. R. Hollev and A. Hollev, J. Amer. Chem. Soc., 74, 3069 (1952).
7. M. Masaki, J. Amer. Chem. Soc., 90, 4508 (1968).
8. J. Seubert, German (West) Patent No. 2504250; Chem. Abstr., 85, 142999 (1976).
9. A. Frost and A. Carlson, J. Org. Chem., 24, 1581 (1959).
10. A. P. Roszkowski, et al., German (West) Patent No. 2733698; Chem. Abstr., 88, 170144 (1978).