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Synthesis of 4-[(*p*-Alkylanilino-*p*-alkylphenyl)methyl]-4-butyl-1,2-diphenylpyrazolidine-3,5-diones

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Abstract — 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione derivatives were prepared by its condensation with Schiff bases formed from *p*-aminobenzoic acid and its methyl and ethyl esters as amine components and substituted aromatic aldehydes.
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Azomethines containing a readily polarizable C=N bond add to organic compounds containing labile hydrogen atoms [1–3]. 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone) as a CH acid is among such compounds.

Reactions of azomethines with phenylbutazone are of not only basic but also applied importance, as their products may exhibit biological activity, taking into account the fact that phenylbutazone is a structural analog of amidopyrine, an analgetic, antipyretic, and antiphlogistic. Phenylbutazone considerably surpasses amidopyrine in the antiphlogistic activity and is therefore considered as a nonsteroid antiphlogistic [4, 5].

In this study we performed condensation of phenylbutazone **IV** with Schiff bases **III** derived from benzaldehyde derivatives **IIa**–**IIf** and amines containing pharmacophore groups: *p*-aminobenzoic acid **Ia** and its methyl (**Ib**) and ethyl (**Ic**) esters. It is known that *p*-aminobenzoic acid is a microbial growth factor [6], and ethyl *p*-aminobenzoate hydrochloride (Anesthesin) exhibits an anesthetic effect and is used for local anesthesia as cocaine substitute [7].

The reactions were performed by refluxing the reactants in alcohol for 15–40 min.

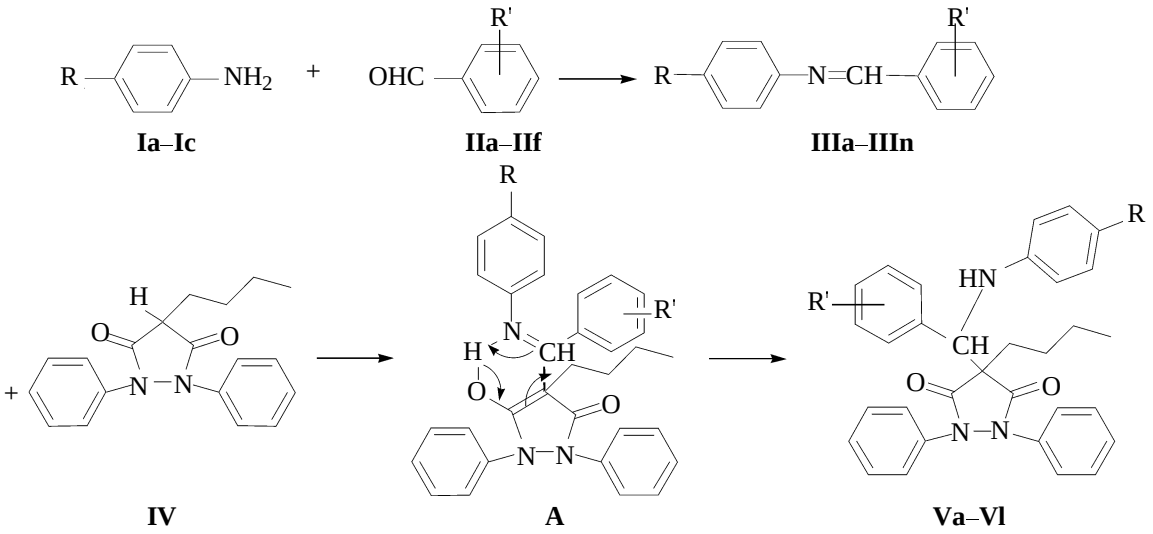
Phenylbutazone **IV** is a pyrazolidine derivative. It exists in solution as a mixture of the enol and dicarbonyl tautomers [8].

The mechanism of reactions of phenylbutazone **IV** with Schiff bases **III** presumably involves formation of complex **A** between the enol form of **IV** and azomethine, followed by the electron redistribution. The reaction is favored by the polarizability of the C=N bond in Schiff bases and formation of a chelate bond of the enol hydrogen atom with the azomethine nitrogen atom.

The polarizability of the azomethine bond in Schiff bases is influenced by the nature and location of substituents in the benzene rings of the aniline and benzaldehyde fragments. The electron-withdrawing substituents in the *p*-position enhance the polarization of the azomethine bond, and condensation with Schiff bases containing these substituents occurs under milder conditions without additional heating, with high yields of the final products. In particular, 4-butyl-1,2-diphenyl-4-[(*p*-ethoxyanilino-*p*-bromophenyl)methyl]pyrazolidine-3,5-dione **Vj** is formed within 15 min in 80% yield, and 4-butyl-1,2-diphenyl-4-[(*p*-ethoxyanilino-*p*-hydroxyphenyl)methyl]pyrazolidine-3,5-dione **Vl**, in 32% yield after refluxing the reactants (**IIIl**, **IV**) for no less than 40 min. If the benzaldehyde fragment of the azomethine contains substituents (both donor and acceptor) in the *o*-position (**IIIm**, **IIIn**), chelate **A** is not formed, and addition of phenylbutazone **IV** does not occur at all, apparently because of the steric effect of the substituent.

The yields, melting points, and elemental analyses of 4-butyl-1,2-diphenylpyrazolidine-3,5-dione derivatives **Va**–**Vl** are listed in Table 1.

The structures of **Va**–**Vl** were confirmed by ^{1}H NMR and IR spectroscopy and by mass spectrometry. The IR spectra contained bands characteristic of the carbonyl groups of the diketone moiety (a band at



Ia–Ic **IIa–IIf** **IIIa–IIIn**

IV **A** **Va–Vl**

R = 4-COOH (**a**), 4-CH_3OCO (**Ib**), 4-C_2H_5OCO (**Ic**); R' = H (**IIa**), 4-Br (**IIb**), 4-NO_2 (**IIc**), 4-OH (**IId**), 2-Cl (**IIe**), 2-OH (**IIf**); R = 4-COOH, R' = H (**IIIa, Va**), 4-Br (**IIIb, Vb**), 4-NO_2 (**IIIc, Vc**), 4-OH (**IIId, Vd**), 2-Cl (**IIIm**), 2-OH (**IIIn**); R = 4-CH_3OCO, R' = H (**IIIe, Ve**), 4-Br (**IIIf, Vf**), 4-NO_2 (**IIIg, Vg**), 4-OH (**IIIh, Vh**); R = 4-C_2H_5OCO, R' = H (**IIIi, Vi**), 4-Br (**IIIj, Vj**), 4-NO_2 (**IIIk, Vk**), 4-OH (**IIIl, Vl**).

1703–1710 cm^{-1}) and of the ester fragment (a band at 1726–1748 cm^{-1} in the spectra of **Ve**–**Vl**). The carbonyl group of the carboxylate ion $[C_6H_5CO_2]^-$ in **Va**–**Vd** absorbs at 1605–1603 cm^{-1}. The spectra of **Ve**–**Vl** contain a band at 1280–1270 cm^{-1} characteristic of the C–O–C stretching vibrations. The presence of the secondary amino group in all the compounds **Va**–**Vl** is confirmed by a band at 3390–3360 cm^{-1}. The bands at 2950–2930 and 2870–2850 cm^{-1} belong to the antisymmetric and symmetric vibrations of the CH_2 groups in the butyl substituent, respectively. The spectra of **Vb**, **Vf**, and **Vj** also contain a strong band at 570–550 cm^{-1} assignable to the C–Br stretching vibrations, and the spectra of **Vc**, **Vg**, and **Vk**, bands at 1350 and 1520 cm^{-1} belonging to the symmetric and antisymmetric vibrations of the N–O bonds, respectively.

The mass spectra of **Va**–**Vl** contain no molecular peak (M^+). The strongest (100%) fragment peak, *m/z*

Table 1. Yields, melting points, and elemental analyses of 4-[(R-anilino-R'-phenyl)methyl]-4-butyl-1,2-diphenylpyrazolidine-3,5-diones **Va**–**Vl**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N (Hlg)		C	H	N (Hlg)
Va	77	177 [a]	74.24	5.83	7.88	$C_{33}H_{31}N_3O_4$	74.28	5.82	7.87
Vb	80	229–230	64.52	4.91	6.89 (13.00)	$C_{33}H_{30}BrN_3O_4$	64.71	4.94	6.86 (13.05)
Vc	52	247	68.53	5.20	9.61	$C_{33}H_{30}N_4O_6$	68.50	5.23	9.68
Vd	45	136	72.10	5.70	7.63	$C_{33}H_{31}N_3O_5$	72.11	5.68	7.65
Ve	70	131 [a]	74.62	6.06	7.71	$C_{34}H_{33}N_3O_4$	74.57	6.07	7.67
Vf	76	138 [a]	65.21	5.09	6.70 (12.78)	$C_{34}H_{32}BrN_3O_4$	65.18	5.15	6.71 (12.75)
Vg	60	158	68.90	5.38	9.42	$C_{34}H_{32}N_4O_6$	68.91	5.44	9.45
Vh	40	172	72.49	5.90	7.48	$C_{34}H_{33}N_3O_5$	72.45	5.90	7.45
Vi	60	121 [a]	74.85	6.27	7.53	$C_{35}H_{35}N_3O_4$	74.84	6.28	7.48
Vj	80	138 [a]	65.64	5.39	6.60 (12.28)	$C_{35}H_{34}BrN_3O_4$	65.63	5.35	6.56 (12.47)
Vk	50	123	69.34	5.59	9.27	$C_{35}H_{34}N_4O_6$	69.29	5.65	9.24
Vl	32	138	72.85	6.15	7.28	$C_{35}H_{35}N_3O_5$	72.77	6.11	7.27

[a] The melting points agree with the published data for **Va** [9] and **Ve, Vf, Vj** [10].

Table 2. ^{1}H NMR spectra of 4-[(R-anilino-R'-phenyl)methyl]-4-butyl-1,2-diphenylpyrazolidine-3,5-diones **Va**–**Vl**, δ, ppm (*J*, Hz) (2–5% solutions in DMSO-d_6)

Comp. no.	CH, d (^3J)	CH_2, m	CH_2CH_2, m	CH_3, t	OCH_3, s	Aromatic protons, protons of R and R', and NH protons
Va	5.00 (6.0)	1.95	1.25–1.49	0.90	–	6.50–6.55 m, 6.75 d (9.0), 6.85 d (8.0), 6.90 d (8.8), 7.10–7.40 m, 7.50–7.70 m, 7.90–8.00 m, 10.00 s (1H, NH), 12.00 br.s (1H, COOH)
Vb	4.75 (6.3)	1.85–1.95	1.18–1.35	0.88	–	5.90 d (8.7), 6.29 d (8.5), 6.50 d (9.0), 6.60 d (9.2), 6.84–7.00 m, 7.06–7.10 m, 7.48–7.55 m, 8.20 s (1H, NH), 9.70 (1H, COOH)
Vc	5.15 (6.0)	1.95	1.20–1.25	0.95	–	6.50 d (8.0), 6.60 d (9.0), 6.90 d (8.0), 7.00 d (10.0), 7.05–7.20 m, 7.65 m, 8.05 m, 8.10–8.20 m, 8.30 d (9.0), 8.40 d (7.6), 10.20 s (1H, NH), 11.50 br.s (1H, COOH)
Vd	4.90 (5.9)	1.95–2.10	1.25–1.50	0.93	–	6.30–6.50 m, 6.70 d (9.0), 6.85 d (8.9), 6.93 d (8.5), 7.00–7.30 m, 7.60–7.80 m, 7.95–8.10 m, 10.10 s (1H, NH), 12.20 s (1H, OH), 12.80 s (1H, COOH)
Ve	4.95 (6.0)	1.90–2.05	1.15–1.20	0.96	3.70	6.20–6.40 m, 6.50 d (8.5), 6.65 d (9.3), 6.79 d (9.0), 7.65 d (9.0), 7.80–8.00 m, 10.00 s (1H, NH)
Vf	4.85 (6.2)	1.90–2.10	1.20–1.30	0.87	3.68	6.10 d (8.9), 6.48 d (8.5), 6.70 d (9.0), 6.79 d (9.2), 7.00–7.25 m, 7.69 d (6.9), 9.90 s (1H, NH)
Vg	5.10 (5.9)	1.90–2.00	1.32–1.50	0.98	3.72	6.55 d (8.5), 6.70 d (8.9), 6.90 d (9.0), 7.10–7.30 m, 7.60–7.70 m, 8.05–8.25 m, 8.35–8.40 m, 10.18 s (1H, NH)
Vh	5.00 (6.1)	1.95–2.10	1.15–1.35	1.05	3.62	6.20 d (8.0), 6.30 d (8.7), 6.80 d (8.9), 7.05–7.20 m, 7.40–7.50 m, 7.90–8.00 m, 10.50 s (1H, NH), 11.60 s (1H, OH)
Vi[a]	4.80 (6.0)	1.80–2.00	1.25–1.26	0.95	–	6.40 d (9.0), 6.56 d (8.9), 6.67 d (9.3), 6.76 d (8.6), 6.85 d (8.3), 7.10–7.30 m, 7.40–7.50 m, 7.70 d (8.9), 7.90 d (8.3), 8.10 d (10.2), 8.50 s, 10.00 s (1H, NH)
Vj[b]	4.90 (6.8)	1.90–2.10	1.26–1.40	0.80	–	6.40 d (10.0), 6.65 d (9.0), 6.80 d (9.2), 6.90 d (9.6), 7.15–7.30 m, 7.65 d (9.2), 7.90 d (9.0), 8.00 d (9.3), 9.80 s (1H, NH)
Vk[c]	5.16 (6.4)	1.90	1.15–1.20	0.90	–	6.50 d (10.0), 6.55 d (10.4), 6.70 d (10.0), 6.90 d (9.7), 7.00 d (10.5) 7.05–7.20 m, 7.30–7.35 m, 8.00 m, 8.10 m, 8.15–8.20 m, 10.20 s (1H, NH)
Vl[d]	4.95 (7.0)	1.96	1.16–1.25	0.85	–	6.50 d (9.7), 6.70 d (9.0), 6.85 d (9.6), 6.95 d (9.3), 7.10–7.25 m, 7.60–7.70 m, 7.90 d (8.9), 8.00 d (9.0), 10.10 s (1H, NH), 11.60 s (1H, OH)

[a] δ, ppm: 4.35 q (OCH_2CH_3), 1.40 t (OCH_2CH_3). [b] δ, ppm: 4.20 q (OCH_2CH_3), 1.40 t (OCH_2CH_3). [c] δ, ppm: 4.18 q (OCH_2CH_3), 1.45 t (OCH_2CH_3). [d] δ, ppm: 4.35 q (OCH_2CH_3), 1.47 t (OCH_2CH_3).

77, corresponds to the $[C_6H_5]^+$ ions; the other major peaks are *m/z* 308 (22–36%), phenylbutazone ion, and *m/z* 183 (43–72%), $[C_6H_5CHNHC_6H_5]^+$ ion.

The ^{1}H NMR spectra of **Va**–**Vl** (Table 2) contain signals of the butyl substituent, namely, triplet of the terminal CH_3 group (0.80–1.05 ppm), multiplet of two CH_2 groups at 1.15–1.50 ppm, and multiplet at 1.80–2.10 ppm of the α-CH_2 group. 4-Butyl-4-[(*p*-methoxyanilino-*p*-alkylphenyl)methyl]-1,2-diphenylpyrazolidine-3,5-diones **Ve**–**Vh** exhibit a singlet at 3.62–3.72 ppm belonging to three protons of the OCH_3 group; the ethoxy group in **Vi**–**Vl** gives a quartet at 4.18–4.35 ppm (OCH_2) and a triplet at 1.40–1.49 ppm (CH_3).

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protégé-460 spectrometer. The ^{1}H NMR spectra were measured on Bruker DRX-500 (500 MHz) and Tesla BS-576A (100 MHz) spectrometers. Samples were prepared as 2–5% solutions in DMSO-d_6; the chemical shifts were determined relative to internal TMS. The mass spectra were taken on a Finnigan MAT-Incos-50 spectrometer (70 eV).

4-Butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone) **IV** was prepared according to [11] from butyl malonate and hydrazobenzene in alcohol under the action of sodium metal; mp 105°C. Arylidenealkylanilines **IIIa**–**IIIn** were prepared by reaction of *p*-aminobenzoic acid **Ia** or its methyl (**Ib**) or ethyl (**Ic**) ester with appropriate benzaldehyde **IIa**–**IIf**, following the standard procedure [12].

4-[(*p*-Alkylanilino-*p*-alkylphenyl)methyl]-4-butyl-1,2-diphenylpyrazolidine-3,5-diones Va–Vl. Arylidenealkylaniline **IIIa**–**IIIn** (0.001 mol) was dissolved in 20 ml of ethanol on heating to 50–60°C. Then 0.3 g of phenylbutazone was added, and the mixture was refluxed on a water bath for 15–40 min until crystals started to form. The precipitate that formed after cooling was filtered off and recrystallized from ethanol or ethanol–benzene, 2 : 1.

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