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Reaction of Antipyrine with Schiff Bases

N. G. Kozlov and L. I. Basalaeva

Institute of Physical Organic Chemistry, Belarussian National Academy of Sciences, ul. Surganova 13, Minsk, 220072 Belarus
e-mail: loc@ifoch.bas-net.by

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Abstract — New dihydropyrazolone derivatives were prepared by condensation of antipyrine with substituted arylmethyleneanilines or arylmethylene-2-naphthylamines.
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1-Phenyl-2,3-dimethylpyrazol-5-one (antipyrine) is an important pyrazolone derivative and is widely used for a long time in medicine as antipyretic, analgetic, and sedative [1, 2]. At present it is one of the main agents for treatment of diseases characterized by cyclic progress and pronounced temperature reaction [3]. The chemical structure of 1-phenyl-2,3-dimethylpyrazol-5-one suggests that one of possible routes to its new derivatives is the reaction with compounds containing an azomethine fragment. Such reactions were examined in this study.

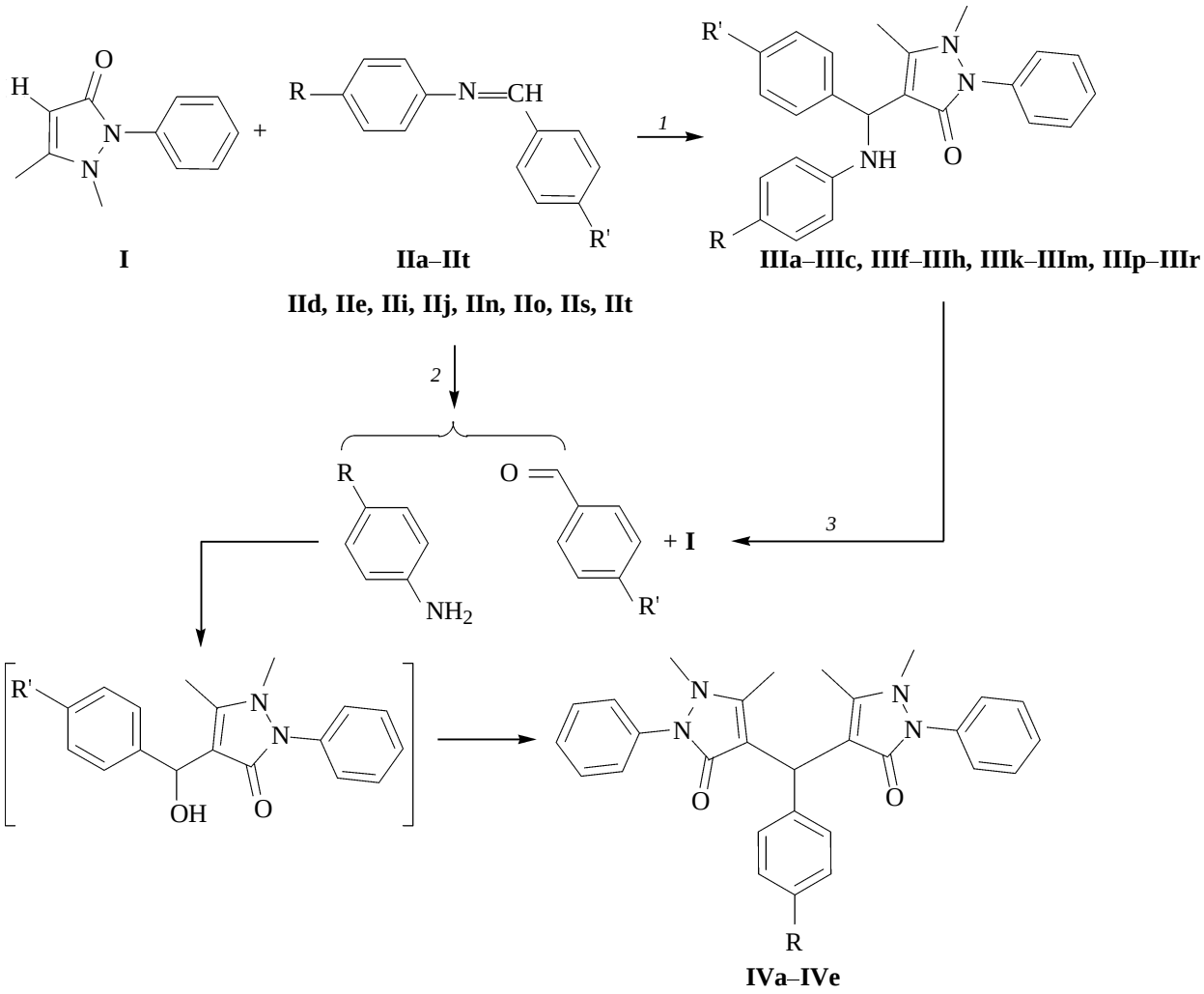
We studied the reactions of antipyrine **I** with Schiff bases **IIa**–**IIt** derived from *p*-aminobenzoic acid, its methyl and ethyl esters, and 2-naphthylamine as amine components and substituted benzaldehydes. The reactions were performed in butanol in the presence of catalytic amounts of HCl on cooling to –5°C, except the reactions with 2-naphthylamine derivatives, which were performed with refluxing for 15 min. The catalyst is required to activate the azomethine in the reaction with relatively low-reactive antipyrine whose amide carbonyl does not enolize and enter the reaction yielding cyclic products. In the presence of an acid catalyst, the antipyrine molecule as a typical nucleophile adds to the azomethine bond to form a new C–C bond (presumed pathway *1* in the scheme below).

We found that the nucleophilic attack of the electron pair of antipyrine at the azomethine carbon atom yields addition products only if the azomethine contains electron-withdrawing substituents (**IIa**–**IIc**, **IIf**–**IIh**, **IIk**–**IIm**). In the reactions of antipyrine with azomethines **IId**, **IIe**, **IIj**, **IIn**, and **IIo** containing electron-donor substituents, alkyl 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)-methyl]amino}benzoates are not formed under these conditions, even on standing for more than 96 h. Heating of the reaction mixture for 25 min caused formation of a crystalline precipitate identified as 4-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one **IVa** or **IVb**, i.e., presumably, at elevated temperatures in an acidic medium azomethines **IId**, **IIe**, **IIi**, **IIj**, **IIn**, **IIo**, **IIs**, and **IIt** undergo "hydramine" cleavage. The aldehyde released in the process reacts with two antipyrine molecules along pathway *2*. The corresponding benzaldehydes were steam-distilled from the remaining solution and identified as phenylhydrazones. After neutralization of the acidic solution with an alkali, *p*-aminobenzoic acid or its esters are separated out, and antipyrine is recovered from the residue according to [4].

All the synthesized antipyrine derivatives **IIIa**–**IIIc**, **IIIf**–**IIIh**, **IIIk**–**IIIm**, and **IIIp**–**IIIr**, when heated in the presence of HCl, decompose to *p*-aminobenzoic acid or its esters (or to 2-naphthylamine), the corresponding benzaldehyde, and arylmethylenediantipyrine **IVc**–**IVe** (pathway *3*).

In this cleavage, only a half of the benzaldehyde fragments are released in the form of free benzaldehyde, and the remaining half of the fragments chemically bind two antipyrine molecules. Apparently, in this case the compounds undergo complete hydrolytic cleavage to the starting substances. In a strongly acidic solution, the conditions for the reaction of *p*-aminobenzoic acid, its esters, or 2-naphthylamine with benzaldehyde are unfavorable; therefore, these compounds are always recovered in the free form. It is known [5] that in a strongly acidic solution one benzaldehyde molecule reacts with two antipyrine molecules to form arylmethylenediantipyrine. Therefore, it becomes understandable why free benzaldehyde is formed among other products in the cleavage of the antipyrine derivatives.

(R-Phenyl)(naphthyl-2-amino)methyl-1,5-dimethyl-



R = COOH, R' = H (**IIa, IIIa**), Br (**IIb, IIIb**), NO_2 (**IIc, IIIc**), OH (**IId**), OCH_3 (**IIe**); R = CH_3OCO, R' = H (**IIf, IIIf**), Br (**IIg, IIIg**), NO_2 (**IIh, IIIh**), OH (**IIi**), OCH_3 (**IIj**); R = C_2H_5OCO, R' = H (**IIk, IIIk**), Br (**IIl, IIIl**), NO_2 (**IIm, IIIm**), OH (**IIn**), OCH_3 (**IIo**); RC_6H_4 = 2-naphthyl-, R' = H (**IIp, IIIp**), Br (**IIq, IIIq**), NO_2 (**IIr, IIIr**), OH (**IIs**), OCH_3 (**IIt**); R = OH (**IVa**), OCH_3 (**IVb**), H (**IVc**), Br (**IVd**), NO_2 (**IVe**).

2-phenyl-1,2-dihydropyrazol-3-ones **IIIp**–**IIIr** appear to be more resistant to the "hydramine" cleavage. Heating of Schiff bases **IIp**–**IIr** with antipyrine in the presence of concentrated HCl on a boiling water bath for 15 min results in formation of naphthyldihydropyrazolones **IIIp**–**IIIr**, and only on refluxing of this reaction mixture for 30 min the products are cleaved into 2-naphthylamine, arylmethylenediantipyrine **IVc**–**IVe**, and the corresponding benzaldehyde. Arylidenenaphthylamines **IIs** and **IIt** containing electron-donor substituents do not form naphthyldihydropyrazolones; heating of the reaction mixture results in direct formation and precipitation of arylmethylenediantipyrines **IVa** and **IVb**.

Arylmethylenediantipyrines **IVa**–**IVe** isolated under these conditions can be prepared by a direct reaction of an aromatic aldehyde and antipyrine in a 1 : 2 ratio, as noted in [6].

The yields, melting points, and elemental analyses of alkyl 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]amino}-benzoates **IIIa**–**IIIc**, **IIIf**–**IIIh**, and **IIIk**–**IIIm**, (R-phenyl)(naphthyl-2-amino)methyl-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-ones **IIIp**–**IIIr**, and 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones **IVa**–**IVe** are listed in Table 1.

The structures of **IIIa**–**IIIc**, **IIIf**–**IIIh**, **IIIk**–**IIIm**, **IIIp**–**IIIr**, and **IVa**–**IVe** were proved by ^{1}H NMR and

Table 1. Yields, melting points, and elemental analyses of the synthesized alkyl 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]amino}benzoates **IIIa**–**IIIc, IIIf**–**IIIh**, and **IIIk**–**IIIm**, (R-phenyl)(naphthyl-2-amino)methyl-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-ones **IIIp**–**IIIr**, and 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones **IVa**–**IVe**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N (Hlg)		C	H	N (Hlg)
IIIa	40	160	72.60	5.58	10.22	$C_{25}H_{23}N_3O_3$	72.62	5.61	10.20
IIIb	43	178–179	61.00	4.48	8.50 (16.25)	$C_{25}H_{22}BrN_3O_3$	60.99	4.50	8.53 (16.23)
IIIc	35	190	65.43	4.87	12.25	$C_{25}H_{22}N_4O_5$	65.49	4.84	12.20
IIIf	50	176 [a]	73.00	5.91	9.85	$C_{26}H_{25}N_3O_3$	73.05	5.89	9.83
IIIg	55	175 [a]	61.70	4.76	8.25 (15.75)	$C_{26}H_{24}BrN_3O_3$	61.67	4.78	8.30 (15.78)
IIIf	51	180	66.03	5.14	11.89	$C_{26}H_{24}N_4O_5$	66.09	5.12	11.90
IIIk	60	200–201 [a]	73.50	6.19	9.50	$C_{27}H_{27}N_3O_3$	73.45	6.12	9.52
IIIl	55	164–165 [a]	62.30	5.00	8.10 (15.37)	$C_{27}H_{26}BrN_3O_3$	62.31	5.04	8.07 (15.35)
IIIm	43	178	66.64	5.42	11.54	$C_{27}H_{26}N_4O_5$	66.66	5.39	11.50
IIIp	54	268 [b]	80.10	6.03	9.97	$C_{28}H_{25}N_3O$	80.16	6.01	10.02
IIIq	65	240–241	67.40	4.90	8.51 (16.00)	$C_{28}H_{24}BrN_3O$	67.47	4.85	8.48 (16.03)
IIIr	57	285–286	72.37	5.18	12.11	$C_{28}H_{24}N_4O_3$	72.40	5.21	12.06
IVa	75	152 [c]	72.45	5.90	11.70	$C_{29}H_{28}N_4O_3$	72.48	5.87	11.66
IVb	47	173	72.94	6.15	11.28	$C_{30}H_{30}N_4O_3$	72.85	6.11	11.33
IVc	60	162	74.86	6.21	12.06	$C_{29}H_{29}N_4O_2$	74.84	6.24	12.04
IVd	51	169 [c]	64.00	5.03	10.33 (14.61)	$C_{29}H_{27}BrN_4O_2$	64.09	5.01	10.31 (14.70)
IVe	43	178	68.27	5.51	13.76	$C_{29}H_{28}N_5O_4$	68.23	5.49	13.73

Note: The melting points agree with the published data: [a] [7], [b] [8], and [c] [9].

IR spectroscopy and by mass spectrometry. The IR spectra of these compounds contain bands at 1755–1600 (amide I) and 1540–1510 cm^{-1} (amide II) corresponding to the carbonyl group of antipyrine, and also a band at 3410–3350 cm^{-1} corresponding to the secondary amino group of alkyl pyrazolylmethylaminobenzoates **IIIa**–**IIIc, IIIf**–**IIIh, IIIk**–**IIIm**, and **IIIp**–**IIIr**. Compounds **IIIb, IIIg, IIIl, IIIp**, and **IVd** exhibit a strong absorption band at 585–565 cm^{-1} assignable to the C–Br stretching vibrations, and compounds **IIIc**, **IIIh, IIIm, IIIr**, and **IVe**, pronounced bands at 1370–1355 and 1545–1530 cm^{-1} originating, respectively, from the symmetric and antisymmetric vibrations of N–O bonds. Compound **IVa** exhibits a band at 3550–3400 cm^{-1} belonging to hydroxyl stretching vibrations, and compound **IVb**, a characteristic band of OCH_3 stretching vibrations at 2845 cm^{-1}. Alkyl benzoates **IIIf**–**IIIh** and **IIIk**–**IIIm** exhibit a strong absorption band at 1600–1540 cm^{-1} assignable to the antisymmetric stretching vibrations of the carboxylate ion $CH_3CO_2^-$ or $C_2H_5CO_2^-$.

The ^{1}H NMR spectra of **IIIa**–**IIIc**, **IIIf**–**IIIh**, **IIIk**–**IIIm**, **IIIp**–**IIIr**, and **IVa**–**IVe** (Table 2) contain a singlet at 1.85–2.40 ppm corresponding to three methyl protons at the double bond in the antipyrine moiety. A singlet at 2.80–3.42 ppm belongs to three protons of the methyl group at the N atom. A doublet at 5.23–5.50 ppm with a coupling constant of 8 Hz corresponds to the proton at the asymmetric C atom in **IIIa**–**IIIc**, **IIIf**–**IIIh**, **IIIk**–**IIIm**, and **IIIp**–**IIIr**, and a doublet at 6.64–6.95 ppm, to the NH proton. Two doublets (2H each) at 6.53–6.76 and 7.04–7.90 ppm are characteristic of the *p*-disubstituted benzene ring in benzoates **IIIb, IIIc, IIIg, IIIh, IIIl**, and **IIIm**, naphthyldihydropyrazolones **IIIq** and **IIIr**, and arylmethylenediantipyrines **IVa**, **IVb**, **IVd**, and **IVe**. A singlet in the spectra of **IIIf**–**IIIh** at 3.58–3.63 ppm belongs to three protons of the $COOCH_3$ group. A quartet at 4.08–4.15 ppm (CH_2) and a triplet at 1.40–1.53 ppm (CH_3), observed in the spectra of **IIIk**–**IIIm**, belong to protons of the ethoxy group. A distinctive feature of the ^{1}H NMR spectra of **IVa**–**IVe** is a singlet at 5.08–5.18 ppm belonging to the proton at the asymmetric carbon atom.

The mass spectra of **IIIa**–**IIIc, IIIf**–**IIIh, IIIk**–**IIIm, IIIp**–**IIIr**, and **IVa**–**IVe** show that the compounds are unstable to electron impact. The molecular peak (M^+) is absent, and only fragment peaks are detected. The strongest (100%) peak, *m/z* 188, belongs to the antipyrine ion.

Table 2. ^{1}H NMR spectra of the synthesized alkyl 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]amino}benzoates **IIIa**–**IIIc, IIIf**–**IIIh**, and **IIIk**–**IIIm**, (R-phenyl)(naphthyl-2-amino)methyl-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-ones **IIIp**–**IIIr**, and 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones **IVa**–**IVe**, δ, ppm (*J*, Hz)

Comp. no.	CH_3, s	N–CH_3, s	CH	NH, d (^3J 8.0)	Aromatic protons and protons of R and R'
IIIa	1.90	2.80	5.30 d	6.70	6.30–6.50 m, 7.28–7.43 m, 7.90–8.00 m, 11.00 br.s (1H, COOH)
IIIb	2.20	3.00	5.50 d	6.85	6.55 d (9.2), 7.22–7.40 m, 7.67 d (9.8), 11.50 br.s (1H, COOH)
IIIc	1.95	3.00	5.45 d	6.80	6.67 d (9.0), 7.30–7.54 m, 7.72 d (8.4), 10.90 br.s (1H, COOH)
IIIf	1.85	2.90	5.40 d	6.95	3.63 s (3H, OCH_3), 6.10–6.38 m, 7.18–7.45 m, 7.87–8.10 m
IIIg	2.00	3.05	5.30 d	6.70	3.60 s (3H, OCH_3), 6.53 d (8.9), 7.10–7.30 m, 7.60 d (8.0)
IIIh	2.07	3.10	5.38 d	6.95	3.58 s (3H, OCH_3), 6.62 d (9.2), 7.00–7.30 m, 7.68 d (8.9)
IIIk	1.97	3.00	5.37 d	6.64	1.48 t (3H, OCH_2CH_3), 4.15 q (2H,OCH_2CH_3), 6.08–6.40 m, 7.20–7.50 m, 7.80–8.00 m
IIIl	2.03	2.87	5.45 d	6.78	1.40 t (3H, OCH_2CH_3), 4.10 q (2H, OCH_2CH_3), 6.72 d (8.6), 7.00–7.20 m, 7.74 d (8.0)
IIIm	2.00	2.95	5.40 d	6.83	1.53 t (3H, OCH_2CH_3), 4.08 q (2H, OCH_2CH_3), 6.76 d (8.1), 6.90–7.10 m, 7.90 d (8.7)
IIIp	2.25	3.17	5.23 d	6.90	7.35–8.03 m, 8.21–8.40 m, 8.80–8.93 m
IIIq	2.18	3.13	5.26	6.87	6.62 d (9.9), 7.27–7.80 m, 7.90 d (10.0), 8.19–8.30 m, 8.90–8.95 m
IIIr	2.21	3.21	5.21 d	6.85	6.70 d (9.6), 7.33–7.72 m, 7.85 d (8.7), 8.17–8.23 m, 8.70–8.87 m
IVa	2.38	3.31	5.13 s	–	6.72 d (9.7), 7.04 d (10.2), 7.38–7.52 m, 10.90 br.s (1H, OH)
IVb	2.36	3.38	5.18 s	–	3.73 s (3H, OCH_3), 6.80 d (9.2), 7.12 d (9.0), 7.29–7.45 m
IVc	2.40	3.37	5.11 s	–	6.30–6.45 m, 6.50–6.72 m, 7.00–7.16 m
IVd	2.39	3.42	5.12 s	–	6.77 d (9.7), 7.08 d (9.9), 7.34–7.52 m
IVe	2.36	3.20	5.08 s	–	6.60 d (9.7), 7.15 d (9.3), 7.30–7.53 m

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protégé-460 IR Fourier spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on Tesla BS-567A (100 MHz) and Bruker AC-500 (500 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 (ionizing electron energy 70 eV) and on a Hewlett–Packard HP-890/5972 gas chromatograph–mass spectrometer (electron impact, 70 eV; HP-5MS 30 000 × 0.25-mm column; stationary phase 5% PLMe Silicone, film thickness 0.25 μm; vaporizer temperature 250°C).

Arylmethyleneanilines IIa–IIo and arylmethylene-2-naphthylamines IIp–IIt were prepared by the reactions of appropriate *p*-aminobenzoic acid derivatives or 2-naphthylamine with alkylbenzaldehydes in an alcoholic solution as described in [10].

Alkyl 4-{[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-amino}benzoates IIIa–IIIc, IIIf–IIIh, and IIIk–IIIm. Arylmethyleneaniline **IIa**–**IIc**, **IIf**–**IIh**, or **IIk**–**IIm** and antipyrine **I** (0.001 mol each) were dissolved separately in 10 ml of alcohol on heating. The solutions were mixed, and three drops of concentrated HCl were added. The mixture was stirred and left in a refrigerator until crystals formed (10 to 48 h). Then excess solvent was filtered off, and the residue was treated with aqueous ammonia. The substances were recrystallized from alcohol–benzene, 2 : 1.

(R-Phenyl)(naphthyl-2-amino)methyl-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-ones IIIp–IIIr. To a solution of 0.001 mol of arylmethylenenaphthylamine **IIp**–**IIr** in 15 ml of alcohol, we added 0.001 mol of antipyrine **I** and three drops of concentrated HCl. The mixture was heated on a boiling water bath for 15 min. After cooling, the precipitated crystals were filtered off, treated with aqueous ammonia, and recrystallized from alcohol–toluene, 2 : 1.

4-{[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(4-alkylphenyl)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones IVa–IVe. Arylmethyleneaniline **IId**, **IIe, IIi, IIj, IIn**, or **IIo**, or aryl- methylenenaphthylamine **IIs** or **IIt** and antipyrine **I** (0.001 mol each) were dissolved separately in 10 ml of butanol on heating. The solutions were

mixed, and three drops of concentrated HCl were added. The mixture was refluxed until crystals started to precipitate (20–30 min); the precipitate that formed after cooling was filtered off, treated with aqueous ammonia, and recrystallized from ethanol.

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