SYNTHESIS AND BIOLOGICAL ACTIVITY

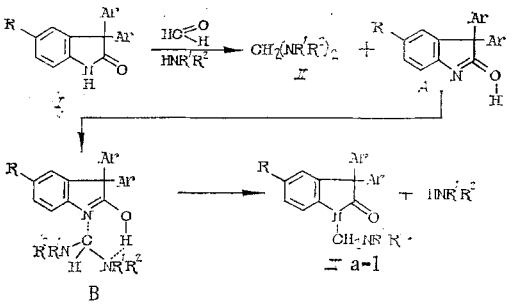
OF 1-AMINOMETHYL-3,3-DIARYL-2-OXOINDOLINES

V. V. Bolotov, V. V. Drugovina,
S. M. Drogovoz, L. V. Yakovleva,
and A. I. Bereznyakova

UDC 615.276:547.754/.012.1

In a continuation of our search for compounds with anti-inflammatory activity among derivatives of 3,3-diaryl-2-oxoindolines [1, 2] it seemed of interest to subject previously obtained (IIIa-f) [3] and newly produced 1-aminomethyl derivatives of the latter (IIIg-l) to a series of studies, since 1-(2¹-diethylaminoethyl)-3,3-diaryl-3-oxoindolines that have such activity are known [4].

1-Aminomethyl-3,3-diaryl-2-oxoindolines IIIg-l (Table 1) were obtained by the reaction of 3,3-diaryl-2-oxoindolines (I) with equimolar amounts of formaldehyde and secondary amines in ethanol [3] or dimethylformamide (DMF) (in the case of slightly soluble I).



IIIa: Ar = $C_6H_4CH_3$-p, R = H, $R^1 = R^2 = C_2H_5$;
IIIb: Ar = $C_6H_4CH_3$-p, R = H, $NR^1R^2 = N(CH_2)_5$;
IIIc: Ar = C_6H_5, R = H, $R^1 = R^2 = C_2H_5$;
IIId: Ar = C_6H_5, R = H, $NR^1R^2 = N(CH_2)_5$;
IIIe: Ar = C_6H_5, R = CH_3, $R^1 = R^2 = C_2H_5$;
IIIf: Ar = $C_6H_4CH_3$-p, R = 5 = Br, $NR^1R^2 = N(CH_2)_5$;
IIIg: Ar = $C_6H_4CH_3$-p, R = H, $R^1 = R^2 = CH_3$;
IIIh: Ar = C_6H_5, R = CH_3CO, $NR^1R^2 = N(CH_2)_4O$;
IIIi: Ar = C_6H_5, R = OCH_3, $NR^1R^2 = N(CH_2)_5$;
IIIj: Ar = $C_6H_4CH_3$-p, R = Br, $R^1 = R^2 = C_2H_5$;
IIIk: Ar = $C_6H_4CH_3$-p, R = Br, $NR^1R^2 = N(CH_2)_4O$;
IIIl: Ar = C_6H_5, R = OCH_3, $R^1 = R^2 = C_2H_5$.

In [3] we showed that I does not undergo aminomethylation when a methyl group is present in the position of the annelated benzene ring.

TABLE 1. 1-Aminomethyl-3,3-diaryl-2-oxoindolines

Compound	Yield, %	mp, °C	N found, %	Empirical formula	Calculated, %
IIIg	69	129—30	7,53	$C_{25}H_{26}N_2O$	7,56
IIIh	72	151—3	6,78	$C_{27}H_{26}N_2O_3$	6,52
IIIi	82	137—8	6,73	$C_{27}H_{28}N_2O_2$	6,79
IIIj	75	143—5	5,74	$C_{27}H_{29}BrN_2O$	5,86
IIIk	71	148—50	5,78	$C_{27}H_{27}BrN_2O_2$	5,70
IIIl	55	100—2	6,66	$C_{26}H_{28}N_2O_2$	6,60

Note: IIIg,i,l were recrystallized from acetone with water, while IIIh,j,k were recrystallized from ethanol with water.

Kharkov Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal Vol. 16, No. 1, pp. 58-61, January, 1982. Original article submitted April 8, 1981.

0091-150X/82/1601-0048$07.50

In this previous study we also established that replacement of the methyl group in this position by halogen atoms (Cl, Br) does not not lead to the desired results. In addition, we were unable to carry out aminomethylation when substituents were present in the ortho positions of the aryl groups of I (R = 5-OCH_3, Ar = o-$C_6H_4CH_3$).

These facts can be explained if it is assumed that aminomethylation proceeds through a step involving the formation of methylenebisamines and a quasi-six-membered cyclic transition state. Nobles and Potti [5] have used this mechanism to explain the aminomethylation of phenols, ketones, and nitroalkanes [5].

In our case the formation of cyclic transition state B evidently may occur as a consequence of the reaction of the methylenebisamines (II) and I in lactim form A, which may be formed under the influence of bases [6]. A similar mechanism was previously adopted [7, 8] for the alkylation of I with alkyl halides; it was demonstrated that substituents in the 7 position of the annelated benzene ring of I and in the ortho positions of the aryl groups create steric hindrance to the formation of a cyclic transition state and that for this reason reactions with them are retarded or do not occur.

Compounds IIIg-l (see Table 1) are colorless crystalline substances that are insoluble in water but soluble in ethanol, dioxane, chloroform, and hexane. Their structure was confirmed by the IR spectra, which contain bands at 1720-1730 cm^{-1} (lactam ring $\nu_{C=O}$) but do not contain a band that is characteristic for the NH group; the spectra of IIIh,k, which contain a morpholine residue, contain a band at 1120 cm^{-1} (ν_{C-O-C}).

EXPERIMENTAL PHARMALOGICAL PART

Pharmacological screening of IIIa-l for anti-inflammatory activity was carried out by determination of the antiexudative activity with respect to mice with masses of 18-20 g by the method in [9] as compared with phenylbutazone. The anti-inflammatory activity was judged from the percent of inhibition of edema induced by injection into the thick part of the thigh of one of the legs of 0.1 ml of a 2.5% solution of formalin. The compounds were injected into the mice in doses of 0.15 and 0.3 g/kg 2 h prior to the injection of the formalin and 5 and 18 h afterwards. Control animals were injected with 0.1 ml of an isotonic solution of sodium chloride. The activity of the substances was determined 24 h after injection of the formalin.

Compounds IIIa-g displayed antiexudative activity comparable to that of phenylbutazone, whereas the activity of IIIi was greater by a factor of 1.5, and the activity of IIIh,j,k was higher by a factor of two.

Thus substances that contain bromine atoms in the 5 position of the annelated benzene ring displayed the greatest antiexudative activity.

TABLE 2. Effect of 1-Aminomethyl-3,3-diaryl-2-oxoindolines on Vascular Permeability (M ± M)

Compound	Inflammatory agent				
	formalin	serotonin	polyglucine	albumin	histamine
	papule-coloring time, min				
IIIg	9,5±0,4 (<0,05)	6,5±0,0 (0,05)	5,5 (<0,01)	4,5±0,0 (0,05)	4,6±0,1 (0,4)
IIIh	15,0±1,0 (<0,01)	4,7±1,0 (>0,2)	4,3±1,2 (0,4)	4,5±0,3 (<0.01)	4,6±0,3 (>0,02)
IIIi	16,5±1,8 (<0,02)	7,3±0,6 (<0,01)	5,2±0,3 (<0,05)	3,5 (<0,05)	4,2±0,3 (>0,05)
IIIk	90,0 (<0,001)	90,0 (<0,001)	8,1±0,3 (<0,001)	7,4±0,4 (<0,001)	6,2±0,7 (<0,1)
Phenylbutazone	18,7±0,4 (<0,01)	12,8±2,5 (<0,05)	10,2±2,5 (<0,05)	9,2±2,3 (<0,05)	12,5±1,8 (<0.01)
Control	7,5±0,5	3,5±0,0	3,0±0,3	2,5±0,0	4,0±0,5

Note: The reliability of the differences as compared with the control is indicated in parentheses.

In the second stage of the investigations we studied the effect of some of the most active compounds (Table 2) on vascular permeability by the method in [10].

Rats were injected intravenously with a 1% solution of trypan blue in doses of 2 mg/kg and 10 min later were injected subcutaneously in the abdominal region with the inflammatory agents, viz., a 3% solution of formalin (0.1 ml), a 0.1% solution of histamine (0.1 ml), a 0.01% solution of serotonin (0.1 ml), and undiluted egg albumin (0.1 ml). The investigated substances were injected intraperitoneally 1 h prior to trypan blue in 1/10 LD_{50} doses; the control animals were injected with 0.1 ml of an isotonic solution of sodium chloride. The increase in the time required for coloration of the section of the skin at the site of injection of the inflammatory agent under the influence of IIIg-i,k served as an index of the activity of the compounds.

The results of the studies (see Table 2) showed that IIIg-i,k, to different degrees and reliably with respect to the control, increased the time required for coloration of the skin at the sites of injection of the individual inflammatory agents.

The most active substance was IIIk. Its activity surpassed the effect of phenylbutazone by a factor of five to six in the case of injection of formalin, whereas it was close to that of phenylbutazone in the case of the other inflammatory agents, except for histamine.

Compounds IIIh,i displayed the greatest activity, which was close to that of phenylbutazone, in the case of injection of formalin, whereas their effect was smaller in the remaining cases.

Thus the study of the effect of IIIg-i,k on vascular permeability impaired by various inflammatory agents also confirms the existence of anti-inflammatory activity among them.

For the most active compounds we determined the acute toxicity with respect to mice in the case of intraperitoneal injection. The observations were made in the course of 24 h. The LD_{50} values calculated by the method in [11] for IIIh-k and phenylbutazone are, respectively, 849, 280, 3950, 1310, and 310 mg/kg.

The results of all of the experiments were processed statistically [12].

EXPERIMENTAL CHEMICAL PART

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

1-Diethylaminomethyl-5-methoxy-3,3-diphenyl-2-oxoindoline (IIIi). A 4-ml sample of dimethylformamide and 0.9 ml (0.011 mole) of a 37% solution of formalin were added to 3.16 g (0.01 mole) of I (R = 5-OCH_3, Ar = C_6H_5), and 0.8 g (0.011 mole) of diethylamine was added to the mixture with cooling. The mixture was stirred for 15 min, after which it was heated on a boiling-water bath for 15 min and allowed to stand for 12 h. Water (100 ml) was then added, and the resulting precipitate was removed by filtration and crystallized from acetone with water.

Compounds IIIg-i were similarly obtained. In the synthesis of IIIj,k 70% ethanol was used instead of dimethylformamide.

LITERATURE CITED

1. V. V. Bolotov, V. V. Drugovina, P. A. Petyunin, et al., Khim.-farm. Zh., No. 11, 45-49 (1979).
2. V. V. Bolotov, P. A. Petyunin, V. V. Drugovina, et al., Khim.-farm. Zh., No. 12, 39-42 (1980).
3. V. V. Bolotov and V. V. Drugovina, Farm. Zh., No. 1, 47-48 (1978).
4. US Patent No. 3,558,653 (1971); Ref. Zh. Khim., No. 20, 20NCH18P (1971).
5. W. L. Nobles and N. D. Potti, J. Pharm. Sci., 57, 1097-1103 (1968).
6. P. A. Petyunin, A. K. Sukhomlinov, and N. G. Panferova, Khim. Geterotsikl. Soedin., No. 6, 1033-1037 (1968).
7. P. A. Petyunin and P. A. Bezuglyi, Khim. Geterotsikl. Soedin, No. 7, 954-958 (1970).
8. P. A. Petyunin, V. V. Bolotov, and A. F. Soldatova, Zh. Org. Khim., 7, No. 5, 1069-1075 (1971).
9. E. Yu. Strel'nikov, Farmakol. Toksikol., No. 6, 526-530 (1960).
10. P. P. Golikov, Farmakol. Toksikol., No. 6, 742-743 (1964).

11. V. B. Prozorovskii, Farmakol. Toksikol., No. 1, 115-118 (1962).
12. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959).

SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ACYL DERIVATIVES OF 4-AMINO- AND 4-(ISOPROPYLAMINO)ANTIPYRINE

E. V. Shmidt, T. P. Prishchep, A. M. Sedov,
N. A. Chernova, L. I. Alekseeva,
and V. M. Biryukova

UCC 615.276:547.77].0.12.1

In continuation of our investigations [1-4] on the synthesis of potential antiinflammatory preparations among the pyrazole group of compounds and establishment of a relationship between their structure and pharmacological properties, we synthesized N-protected aminoacylated (I-XI) and iodo-substituted benzoyl- and phenylacetyl derivatives (XII-XIX) of 4-aminoantipyrine and 4-(isopropylamino)antipyrine.

The reason for the synthesis of antipyrinyl amides of N-substituted amino acids of the fatty acid series was the presence of pronounced antiinflammatory properties in the 4-aminobenzoyl derivatives of 4-aminoantipyrine previously synthesized by us [1, 2], analgesic properties in certain derivatives of 4-aminoantipyrine acylated with N,N-dimethylamino acids of the fatty acid series [5, 6], and antipyretic properties of antipyrinylamide of aminoacetic acid [7]. The antiinflammatory activity of o- and p-iodo-substituted benzoic acid derivatives and their ammonium salts has been described in the literature [8]. We have already observed [2] a considerable increase in the antiinflammatory effect of N-antipyrinyl o-iodobenzamide, compared with that of a compound not substituted by iodine. Moreover, the isopropyl derivative of 4-aminoantipyrine has a higher antiphlogistic activity than 4-aminoantipyrine [9].

EXPERIMENTAL CHEMICAL PART

4-(Isopropylamino)antipyrine was prepared by reductive alkylation of 4-aminoantipyrine with acetone and zinc amalgam in an acid medium [10].

α-Amino acids were subjected to benzoyl and phthalyl protection by generally accepted methods [11, 12].

Iodine-substituted aromatic acids were synthesized by direct iodination or indirect introduction of iodine into the molecule of the corresponding carboxylic acid [11, 13-16].

The acylation of 4-amino- and 4-(isopropylamino)antipyrines was carried out in boiling dry benzene by free acids in the presence of phosphorus trichloride [4].

The IR spectra of the compounds were run on the UR-20 spectrophotometer (GDR) in the 400-4000 cm^{-1} region in mineral oil.

EXPERIMENTAL BIOLOGICAL PART

The antiinflammatory activity of the compounds was studied on rats of both sexes weighing 150-180 g each by determining their effect on the reactivity of capillaries [17], dextran edema [18], and on aseptic peritonitis induced by the introduction of silver nitrate [19], in comparison with butadione. To determine the permeability of the capillaries, the preparations were introduced 1 h before the injection of a dye. The intensity of the dextran edema was determined after the action of antipyrinylamides 3 h and 30 min after the administration of a proinflammatory agent.

The acute toxicity of antipyrinylamides was studied on noninbred male mice, weighing 18-20 g each, with single administration, and the rate of death of the animals was counted

Tomsk Polytechnic Institute. Tomsk Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 1, pp. 61-65, January, 1982. Original article submitted May 22, 1981.

0091-150X/82/1601-0051$07.50