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The Synthesis of a Series of N,N'-[Bis-disubstituted aminomethyl]-5-arylidenebarbituric Acids, and their Antiinflammatory Activity.

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Summary: 5-Arylidene barbituric acids were obtained by the Perkin condensation between a series of aromatic aldehydes and the active methylene group of barbituric acid. Through Mannich condevation of these barbituric acid derivatives with secodary amines and formaldehyde, twelve Mannich bases were prepared. Six of the final compounds were screened for their antiinflammatory activity and toxicity. Three compounds were found to inhibit inflamation by 20%-32%.

Barbituric acid is a good anesthetic[1] and analgesic[2,3] agent. Further, Stadowska[4] has prepared several barbituric acid derivatives and found them to exhibit antiinflammatory activity equivalent to phenylbutazone. Recently, Tiwari et al.[5] have synthesised some 5-benzylidenylbarbituric acids and found them fairly active against carrageenin induced rat paw edema. Since many tertiary amino compounds have been found active in inflammation[6-8], the authors were prompted to synthesise the title compounds (Scheme-1), having all the aforementioned structural moieties, in order to ascertain their antiinflammatory activity against carragheen induced rat paw edema.

Experimental

5-(3',4'-disubstituted arylidene) barbituric acids

Barbituric acid was condensed with different aldehydes in the presence of fused sodium acetate and glacial acetic acid (Perkin's condensation) by the known method of Tiwari et al.[5]

N,N'-[Bis-diethyl aminomethyl]-5-benzylidene barbituric acid.

5-Benzylidenebarbituric acid (0.01 mole), formaldehyde (0.012 mole) and diethylamine (0.03 mole) were dissolved in methanol (20 ml). The reaction mixture was refluxed on water bath for 4 hrs. The excess of methanol was evaporated. Anhydrous acetone (20 ml) was added to the reaction mixture so as to separate the crystalline solid. The crystals were filtered and recrystallised from acetone: yield 57%, m.p. 210°C

Anal- for $C_{21}H_{30}N_4O_3$.
N(Calcd)=14.5077%: (Found)=14.62%
C(Calcd)=65.2849%: (Found)=64.99%
H(Calcd)= 7.7720%; (Found)= 7.92%

I.R. (KBr phase): –3030 cm^{-1}, 2900 cm^{-1}, 1720 cm^{-1}, 1670 cm^{-1} 1450 cm^{-1}, 820 cm^{-1}, 750 cm^{-1} etc.

The peaks at 2900 cm^{-1} & 1450 cm^{-1} confirm the presence of the 'CH_2' group in the molecule. The peaks at 1670 cm^{-1} and 820 cm^{-1} confirm the benzylidenyl 'c=c' in the moleucle and the peak at 1720 cm^{-1} is indicative of the presence of a 'malonyl urea moiety in the molecule.

Similarly, other N.N' [bis-disubstituted amino methyl]-5-arylidene barbituric acids were also synthesised and their relevant data are noted in Table I.

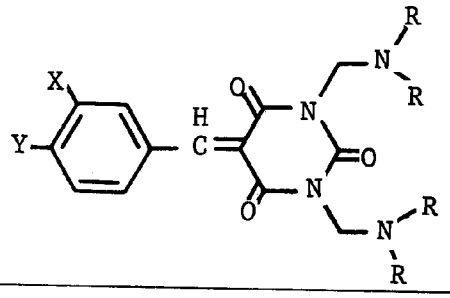
Pharmacological Screenings

Six compounds of the series, namely compound nos. 1,4,5,8,10 and 12, were screened out for their toxicity studies and their antiinflammatory activity.

Toxicity studies

The compounds were administered intraperitoneally to albino mice of either sex in different doses and the death occurred after 24 hrs were noted. Thus the approximate lethal dose in 50% of the aminals tested (ALD_{50}) were determined by the method of Weil[10]. The results of toxicity tests are noted in Table II. All of the compounds are non-toxic except compound No. 4.

Table I, N,N' [bis-dialkylaminomethyl] -5-arylidenebarbituric acids



Compound No.	–NRR	m.p.* °C	%C Calcd/Found		%N Calcd/Found		H% Calcd/Found		Yield %
			X = Y = $-OCH_3$						
1.	Piperidino	217-18	63.8279	63.72	11.9148	12.05	7.2340	7.27	52
2.	Diethylamino	176	61.8834	60.92	12.5560	12.79	7.6233	7.68	49
3.	Morpholino	178	58.2278	58.72	11.8143	11.99	6.3291	6.21	53
4.	Pyrrolidino	234-35	62.4438	63.12	12.6696	12.09	6.7873	6.85	47
			X = H ; Y = $-OCH_3$						
5.	Piperidino	222-24	65.4545	65.98	12.7272	12.27	7.2727	7.38	50
6.	Diethylamino	195	63.4615	62.87	13.4615	13.64	7.6923	7.81	45
7.	Morpholino	197-98	59.4594	60.02	12.6126	12.02	6.3063	6.42	48
8.	Pyrrolidino	244-45	64.0776	63.81	13.5922	13.81	6.7961	6.85	50
			X = Y = H						
9.	Piperdino	220-21	67.3170	67.81	13.6585	13.52	7.3170	7.25	56
10.	Diethylamino	210	65.2849	64.99	14.5077	14.62	7.7720	7.92	57
11.	Morpholino	216-18	60.8695	60.06	13.5265	13.60	6.2801	6.33	50
12.	Pyrrolidino	252	65.9685	64.22	14.6596	15.01	6.8062	6.95	48

*M.P. were determined in open capillaries and are uncorrected.

Table II Results of Pharmacological Screenings of compounds described in Table I

Compound Nos.	Toxicity studies Mortality after 24 hrs. at* 464	1000	215	ALD_{50}	Anti-inflammatory activity at 1/5th of ALD_{50} (%)
1.	0/4	0/4	Not required	> 1000	29%
4.	4/4	Not required	0/4	316	–
5.	0/4	0/4	Not required	> 1000	–
8.	0/4	0/4	Not required	> 1000	–
10.	0/4	2/4	Not required	1000	20%
12.	0/4	0/4	Not required	> 1000	32%

*doses are in mg/kg wt of mice.

Antiinflammatory screenings

The compounds were screened out for their antiinflammatory action on albinomice, following the method of Winder and Co-workers[11]; by measuring the percentage protection of mice against cerrageenin induced inflammation, at the 1/5th of ALD_{50} intraperitoneally. The results are noted in Table II. The inhibition of inflammation ranged between 20-32%.

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