indicates that the carboxylic group stretching frequency of the free ligand is lowered from 1700 cm^{-1} to 1675 cm^{-1}, showing the coordination of the ligand through carboxylic group which is further supported by the appearance of another peak at 1460 cm^{-1}. The appearance of a sharp peak at 1100 cm^{-1} indicates the presence of ring system[8]. However, the presence of a new band at 480 cm^{-1} in the spectrum of La (III)-PDA-HQ may be assigned to[9] M-O bond formed through coordination of the oxygen atom of the involved ligands. Another bond at 430 cm^{-1} may probably be assigned to M-N bonding.

Anti-inflammatory studies

The compounds were tested for their anti-inflammatory activity using 100, 200, 400 mg/kg doses in 3 models of inflammation in albino rats. The anti-inflammatory ED_{50} was determined in carrageenin induced oedema[10] (A 6 hr study, after injecting 0.5 ml of 1% carrageenin suspension in normal saline in the planter side of right hand paw of rat); formaldehyde-induced arthritis[11] (A 30-day study, producing arthritis by injecting subcutaneously under planter aponeurosis in each foot on I and III day of 0.1 ml of 2% V/V formaldehyde for 10 days in graded doses); and cotton pellet granuloma[12] (A 7-day study, by implanting 9 mg sterile cotton pellets in both axillae and groins under anaesthesia giving drug for 6 days and sacrificing the animal on the 7th day and weighing the pellet after drying) taking Oxyphenbutazone as standard drug for comparison. However, 1:1:1, La (III)-PDA-HQ mixed chelate has not shown any significant anti-inflammatory activity in acute model of inflammation (Carrageenin-induced oedema) but did show anti-inflammatory activity in sub-acute (cotton pellet granuloma) and chronic models of inflammation (formaldehyde induced arthritis). The ED_{50} was more than 400 mg/kg.

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SYNTHESIS AND ANTIFERTILITY ACTIVITY OF 3,6-DIBENZOYL-1,4-DI-[2-(2'ALKYLBENZIMIDAZOLYL)]-1,4-DIHYDRO-1,2,4,5-TETRAZINES

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THE triazole derivatives have been shown to possess significant anti-implantation activity. The pharmacokinetic properties of a few non-hormonal antifertility agents were studied in rats and hamsters. The ^{14}C labelled compounds were suitably dissolved in aqueous or oily vehicles. In both the species of the compounds, the triazine derivatives had rapidly metabolized and excreted when given intravenously or subcutaneously in aqueous vehicles whereas the kinetics were prolonged when it was administered in oily formulations. Binding studies revealed a high affinity of the compound for rat serum albumen ($ka = 6 \times 10^5 L/mol$). The radioactivity concentrations in different tissues of the pregnant rats appeared to be uniform with the excretory organs and the lungs being the main target tissue. At the site of the activity, the uteroplacental complex and the level of total ^{14}C were comparable to those in plasma, whereas the concentration of unchanged compound was higher and remained so for a long time. A comparison between the kinetic profiles and the activity data after single or multiple dose administration, in different formulations clearly indicates a close relation between the activity and plasma and tissue (utero-embryoplacental complex) levels of the compound[1,2]. The authors therefore, considered it

worthwhile to undertake the synthesis of some new tetrazine derivatives to test their antifertility activity.

2-(Aminoalkyl)-benzimidazoles required in the present synthesis were obtained following the procedure of Cescon and Day[3].

The procedure of Gupta and Ojha[4] was followed for the synthesis of N-acetophenone pyridinium iodide.

3:6-*Dibenzoyl*-1,4-*di*[2-(2'-*alkylbenzimidazolyl*)]-1,4-*dihydro*-1,2,4,5-*tetrazines*

A solution of sodium acetate (1 g, in 25 ml of water) was added to the solution of N-acetophenone pyridinium iodide (0.4 mol in 50 ml of ethanol). The reaction mixture was cooled to 0° and stirred vigorously for 30 min. The amino compound was diazotized by dissolving in dil. HCl and adding an ice-cold sodium nitrite solution. On complete diazotization, the reddish-yellow precipitate appeared and the diazotized material was added to the solution of N-acetophenone pyridinium iodide slowly, with constant stirring. During the addition, the contents were thoroughly cooled. When the addition was complete, the reaction mixture was vigorously stirred for 1 hr at room temperature and kept in an ice-chest overnight. The orange product was filtered off and washed several times with water. The crude product, thus obtained, was further washed with dil. HCl and triturated with petroleum ether (b. p. 60–80°). It was dried overnight in a vacuum desiccator and recrystallized from methanol. The tetrazines, thus synthesised, are recorded in table 1 along with the analytical and spectral data.

Antiimplantation activity[5,6]: The four compounds were subjected for their anti-implantation activity in female albino rats. The compounds under investigation were prepared as suspension in gum acacia with an equal amount of distilled water to obtain a final concentration of 4 mg/ml. The rats in the control group received the vehicle only.

Adult virgin albino female rats (body weight 200 ± 10 g) of proven fertility and regular cyclicity were selected for the assay of antifertility activity. Following cohabitation with the fertile males on the day of proestrus, the vaginal smears were properly checked the next morning and the animals showing sperm positive smears (day 1 of pregnancy) were then put on treatment. The females were used for the tests only after they had one or two litters, proving their fertility. They were maintained at room temperature and fed on a commercial diet and tapwater *ad libitum*. For the anti-implantation activity, 4 to 8 rats were selected for investigation for each compound and the suspension of the compound was fed orally. Subsequently, the

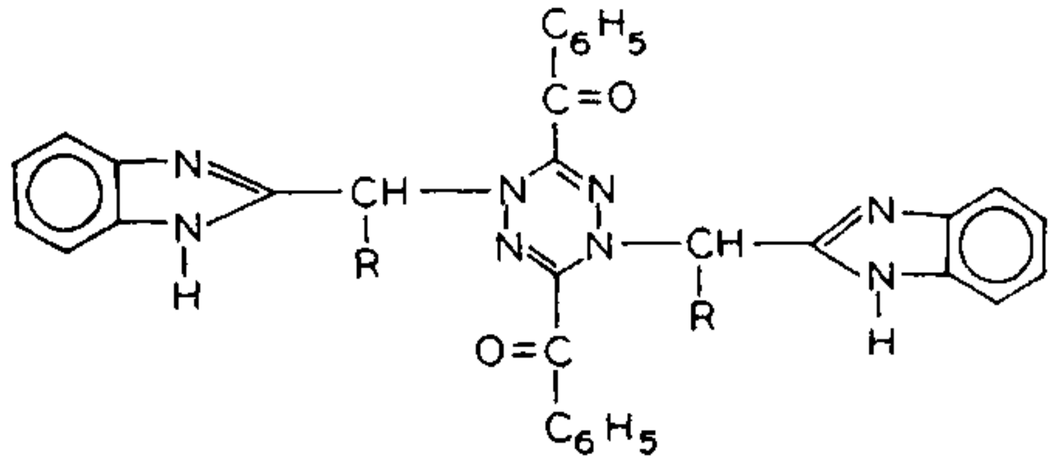

Table 1 3,6-*Dibenzoyl*-1,4-*di* [2-(2'-*alkyl-benzimidazolyl*)] 1,4-*dihydro*-1,2,4,5-*tetrazines*

Compd. No.	R	M. P. °C	Molecular formula	Yield %	Analyses Nitrogen Calcd.	Found
1.	H	118	$C_{32}H_{24}N_8O_2$	45	20.28	20.14
2.	CH_3	86-88	$C_{24}H_{28}O_2$	45	19.37	19.54
3.	3-methylbenzimidazolyl	130	$C_{50}H_{38}H_{10}O_2$	42	17.28	17.46
4.	4-hydroxybenzyl	102	$C_{36}H_{36}N_8O_3$	38	14.97	14.84
5.	5-methylimidazolyl	111	$C_{40}H_{30}N_{12}O_2$	35	23.66	23.44
6*.	$CH_2CH(CH_3)_2$	120	$C_{40}H_{40}N_8O_2$	42	16.87	16.85
7.	CHR = phenyl	100	$C_{48}H_{28}N_8O_2$	41	16.57	16.28
8.	CH_2-CH_2-COOH	104–105	$C_{38}H_{32}N_8O_6$	40	16.9	15.95
9.	$CH_2(CH_2)_3NH_2$	90–92	$C_{40}H_{42}N_{10}O_2$	36	20.17	20.05
10.	$(CH_2)_3NH_2$	107	$C_{38}H_{38}N_{10}O_2$	38	21.62	21.23

*PMR DMSO(D_6): δ 7.5–7.9 (m, 18 protons, aromatic), δ 8.2 (s, 2 protons, NH), δ 2.5 (d, 12 protons, methyl), δ 3.3 (d, 4 protons, methylene) δ 8.2 (t, 2 protons, H-C-N) and δ 6.7 (d, two protons, $(CH_3)_2$.
IR(KBr): All the compounds exhibited a sharp peak in the region 1650–1620 cm^{-1} which was attributable to C = O stretching frequency.

animals were laparotomized on day 9–10 of pregnancy and the number of implantation sites and corpus lutea was recorded. The mean number of implantation sites and corpus lutea in the treated rats was calculated separately and the standard errors ($\pm$ value) from mean value were calculated according to the following equation.

$$\text{Standard Error (S. E.)} = \sqrt{\frac{\sum d^2}{n(n-1)}}$$

where d is the difference from the mean and n is the number of observations i.e. number of rats tested per compound. The per cent effectiveness of the compounds tested for their anti-implantation activity was calculated in two ways.

(i) Incidence: The per cent effectiveness in terms of incidence of pregnancy

$$= \frac{\text{number of animals rendered infertile}}{\text{number of animals treated}} \times 100$$

(ii) Rate: The per cent effectiveness in terms of rate of pregnancy was calculated by comparing the mean number of implantations site found in the treated animals with that of the control.

Early abortifacient activity[7]: The compounds under investigation were prepared as suspension in gum acacia and an equal amount of distilled water to obtain a final concentration of 5 mg/ml and were fed orally on days 8–9 of pregnancy. Day 1 of pregnancy was designated when sperms were found in the vaginal smears of female albino rats (body weight 200 ± 10 g) left overnight with males of proven fertility.

Following administration of the compounds, frank vaginal bleeding was taken as the index of the drug induced abortion of pregnancy. This was further confirmed by laparotomic observations of the uterus, 3–4 days after treatment. Based on the size and shape of the embryos as compared with the controls, the degree of abortifacient activity was graded as mild, midway and complete.

All the four tetrazine derivatives (1, 5, 6 and 9) which were screened for their anti-implantation activity were found inactive in terms of incidence of pregnancy. However, three tetrazine derivatives exhibited mild anti-implantation activity in terms of the rate of pregnancy. Compound no. 5 with a 3-methylimidazolyl substituent was found to possess 14.5% activity in terms of the rate of pregnancy while compounds no. 1 and 4 showed anti-implantation activity to the extent of 5.2% and 9.8% respectively.

All the four tetrazine derivatives (1, 2 and 5) which were screened for their early abortifacient activity showed 33.3% activity. However the degree of resorption in animals aborted was complete in compounds 1 and 5. It was midway for compound no. 2 and mild for compound no. 3. In view of the limited data, the structure activity relationship could not be properly established.

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KINETICS OF OXIDATION OF ACETOPHENONE OXIME BY 1-CHLOROBENZOTRIAZOLE

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A NUMBER of kinetic investigations on oxidation[1–6] and chlorination[7–8] of organic substrates like alcohols, ethers, hydrazo and organic sulphides by 1-Chlorobenzotriazole (CBT) have been reported. The oxidation of oximes typically acetophenone oxime and several substituted acetophenone oximes by CBT has been studied from the kinetic standpoint and the results are reported in this paper.

1-Chlorobenzotriazole was prepared as described by