CHEMISTRY OF OXALYL DERIVATIVES OF METHYL KETONES.

VII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-AROYLMETHYLENE-3,4,5,6-TETRAHYDRO-3-PYRAZINONES

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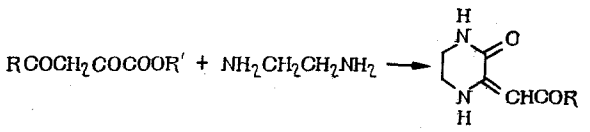
Tetrahydro-3-pyrazinones with 2-alkyl substituents are known [1] to possess analgesic activity. It was of interest to determine the biological activity of tetrahydro-3-pyrazinones in which the ethylene link was present, not in the heterocycle, but in an exo position. With this end in view, the reaction of aroylypyruvic esters with ethylenediamine was investigated. When the starting materials were mixed in a boiling solvent, and subsequently heated, 2-aroylmethylene-3,4,5,6-tetrahydro-3-pyrazinones (I-VIII) were obtained in high yields (see Table 1).



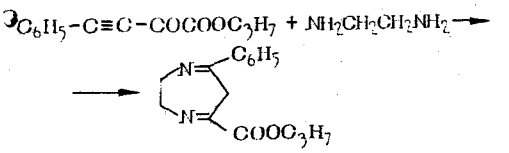
I-VIII

R = C_6H_5, C_6H_4Br, C_6H_4Cl, $C_6H_4CH_3$, $C_6H_4OCH_3$, $C_6H_4C_6H_5$, Mes, $C(CH_3)_3$

The compounds were obtained as yellow crystalline solids which were soluble in acetone, benzene and alcohol, but insoluble in water. The IR spectra displayed bands at 1690 cm^{-1} (amide carbonyl), 1610 cm^{-1} (ketonic carbonyl), and 1580 cm^{-1} (C=C conjugated with C=O).

In the UV spectrum λ_{max} occurred at 350-370 nm. In these compounds, more favorable conditions are present for interaction between the benzoylethylene chromophore and the alkylamide group (rotation is prevented when the ring is formed) than in the α-alkylaminobenzoylacrylic alkylamides, and therefore the change from one compound to the other is accompanied by a hypsochromic shift of λ_{max} by 20-30 nm.

Reaction of arylethynylglyoxalate esters with bifunctional nucleophiles frequently affords the same heterocycles as are formed from aroylpyruvic acids and their derivatives [2, 3]. We therefore carried out the reaction between isopropyl phenylethynylglyoxalate and the ethylenediamine, but instead of the 3-pyrazinone derivative, the product of the reaction was found to be 7-phenyl-5-isopropoxycarbonyl-2,3-dihydro-1,4-diazepine (IX). The IR spectrum of IX was



similar to the spectra of 2-aryl-4-alkoxycarbonylbenzo[b]-1,5-diazepines, prepared previously [4] (1700 cm^{-1}, ester carbonyl; 1600 cm^{-1}, aromatic absorption; 3280 and 3262 cm^{-1}, NH stretching vibrations). In the UV spectrum of IX, the position of λ_{max} was likewise close to that in the corresponding 2-phenyl-4-isopropoxycarbonylbenzo[b]-1,5-diazepine. Like the latter, IX on treatment with concentrated sulfuric acid afforded the deeply colored sulfate salt of 7-phenyl-5-isopropoxycarbonyl-2,3-dihydro-1,4-diazepine.

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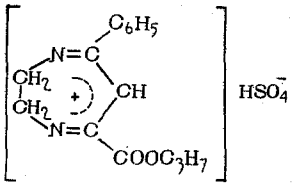
TABLE 1. 2-Aroylmethylene-3,4,5,6-tetrahydro-3-pyrazinones

Compound	R	Yield, %	Melting point, deg	Found, %				Molecular formula	Calculated, %			
				C	H	Hal	N		C	H	Hal	N
I	C_6H_5	81	223	66,54	5,67		12,84	$C_{12}H_{12}N_2O_2$	66,75	5,55		12,95
II	C_6H_4Br	79	257	48,05	4,02	26,84	9,94	$C_{12}H_{11}BrN_2O_2$	48,81	3,73	27,10	9,50
III	C_6H_4Cl	85	244	57,16	4,64	14,52	11,43	$C_{12}H_{11}ClN_2O_2$	57,58	4,40	14,2	11,2
IV	$C_6H_4CH_3$	96	224	67,12	6,34		12,59	$C_{13}H_{14}N_2O_2$	67,82	6,09		12,2
V	$C_6H_4OCH_3$	88	224	62,96	5,73		11,56	$C_{13}H_{14}N_2O_3$	63,42	5,69		11,4
VI	$C_6H_4C_6H_5$	95	272	73,37	5,16		9,22	$C_{18}H_{16}N_2O_2$	73,97	5,48		9,57
VII	*Mes*	90	219	69,31	6,54		10,91	$C_{15}H_{18}N_2O_2$	69,70	6,97		10,85
VIII*	$C(CH_3)_3$	69	179	61,43	8,01		13,9	$C_{10}H_{16}N_2O_2$	61,22	8,16		14,3

*Compound VIII is 2-pivaloylmethylenetetrahydro-3-pyrazinone.



EXPERIMENTAL

Pharmacology

The tetrahydro-3-pyrazinones (I-V) were tested for biological activity (antiinflammatory, antispasmodic, antitremor, and analgesic). Compounds II, IV, and V were found to possess very high antiinflammatory activity, together with slight analgesic and antispasmodic activity. The optimum antiinflammatory effect, which was not inferior to that of phenylbutazone, was displayed by 2-p-methylbenzoylmethylene- and 2-p-methoxybenzoylmethylene-3,4,5,6-tetrahydro-3-pyrazinones (IV and V), which contained the methyl and methoxy groups. Replacement of these groups by halogen (Br or Cl) reduced or completely eliminated the antiinflammatory effects. The compounds were of low toxicity, the LD_{50} of the most active compounds being greater than 1000 mg/kg. The occurrence of high antiinflammatory activity, in conjunction with antispasmodic and analgesic effects, suggest the desirability of further synthesis and study of this class of compounds.

Chemistry

The IR spectra were recorded in vaseline oil on a UR-20 spectrophotometer. UV spectra were recorded on a Specord UV Vis spectrophotometer in solution in ethanol, sample concentration 10^{-4} mole/liter.

2-Benzoylmethylene-3,4,5,6-tetrahydro-3-pyrazinone (I). To a boiling solution of 4.12 g (0.02 mole) of methyl benzoylpyruvate in 150 ml of toluene was added dropwise with stirring a solution of 1.2 g (0.02 mole) of ethylenediamine in 30 ml of ethanol. The reaction mixture was heated for a further 30 min. On cooling, 3.5 g (81%) of I was obtained, mp 223° (ethanol). Found, %: C 66.54; H 5.67; N 12.84. $C_{12}H_{12}N_2O_2$. Calculated, %: C 66.75; H 5.55; N 12.95.

Compounds II-VIII were obtained similarly. Yields, constants, and analytical data for I-VIII are given in Table 1.

7-Phenyl-5-isopropoxycarbonyl-2,3-dihydro-1,4-diazepine (IX). A solution of 0.8 g (0.0037 mole) of phenylethynylglyoxalate in 30 ml of toluene was added dropwise with stirring to a solution of 0.22 g (0.0037 mole) of ethylenediamine in 10 ml of toluene. Evaporation of the solvent afforded 0.4 g (42%) of IX mp 188-189° (from toluene). Found, %: C 69.18; H 6.56; N 10.82. $C_{15}H_{18}N_2O_2$. Calculated, %: C 69.76; H 6.98; N 10.85.

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