THE BECKMANN REARRANGEMENT OF OXIMES OF β-SUBSTITUTED β-(3-INDOLYL) KETONES

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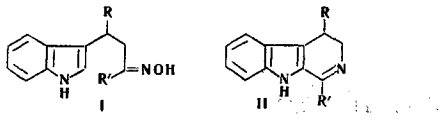
Earlier [1, 2], one of us had found that oximes of α-substituted β-(3-indolyl) ketones cyclize on undergoing the Beckmann rearrangement with the formation of 3-substituted 3, 4-dihydro-β-carbolines.

In an attempt to extend the method to oximes of β-substituted ketones (I), it was found that both the methods given previously [1, 2] and the classical procedures for performing the Beckmann rearrangement could not always be applied to this case. Only compounds in which R' was a phenyl radical reacted smoothly under the action of p-toluenesulfonyl chloride in pyridine and gave the normal rearrangement products, β-(3-indolyl)-β-R-propionanilides. For example, the oxime of 1, 3-diphenyl-3-(3-indolyl)propanone (I, R = R' = C_6H_5) [3], on treatment with p-toluenesulfonyl chloride in pyridine solution at 20° C for 8 hr, was converted almost quantitatively into β-(3-indolyl)-β-phenylpropionanilide, mp 193°—195° C. Found, %: C 81.1; H 6.1; N 8.0. Calculated for $C_{23}H_{20}N_2O$, %: C 81.2; H 5.9; N 8.2. IR spectrum (paraffin oil), ν, cm^{-1}: 3400 (N—H of an indole), 3270, 1643, 1530 (amide).



In numerous experiments, oximes with methyl substituents in the oximino function (I, R' = CH_3) either remained unchanged or underwent far-reaching decomposition. The reaction could be carried out only by using PCl_5 in such polar solvents as nitrobenzene and nitromethane. Under these conditions cyclization to 1, 4-disubstituted 3, 4-dihydro-β-carbolines (II) took place. Thus, the oxime of 4-(3-indolyl)-2-pentanone (I, R = C_3H_7, R' = CH_3) [3] after brief heating with PCl_5 in nitrobenzene at 70° C, was converted into the unstable 1-methyl-4-propyl-3, 4-dihydro-β-carbolene (II, R = CH_3, R' = C_3H_7), which was isolated in the form of the hydrochloride, mp 203°—204° C. Found, %: C 68.7; H 7.0; N 10.6. Calculated for $C_{15}H_{18}N_2 \cdot HCl$, %: C 68.6; H 7.3; N 10.7. UV spectrum (ethanol), λ_{max}, nm (log ε): 214 (4.36), 246 (4.14), 353 (4.47).

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SYNTHESIS OF 8-BENZYLGUANINE

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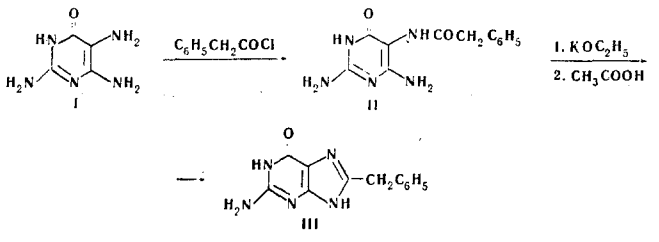
In order to study the physiological activity of purine derivatives we have synthesized 8-benzylguanine (III), the guanine analog of 2-benzylbenzimidazole, for the first time and have studied its antitumoral activity.

The synthesis was carried out by the following route.



2, 4-Diamino-5-phenylacetylamino-6-hydroxypyrimidine (II) was obtained by a published method for acylating the 5-amino group of pyrimidines [1] with a yield of 65% in the form of a colorless substance with mp 299°—300° C (decomp.). Found, %: C 55.00; H 5.11; N 26.87. Calculated for $C_{12}H_{13}N_5O_2$, %: C 55.59; H 5.02; N 27.02.

The cyclization of II into III was performed by a slight modification of the method of Haggerty et al. [2]. Compound III was obtained with a yield of 20% in the form of a light yellow substance with mp 303°—305° C (decomp., from aqueous ethanol). Found, %: C 58.92; H 5.04; N 29.02. Calculated for $C_{12}H_{11}N_5O$, %: C 59.45; H 4.56; N 29.20.

The two substances were characterized by ascending chromatography on FN 12 paper and by their UV spectra.

The antitumoral activity of compound III was studied on Walker's carcinosarcoma and Pleace's lymphosarcoma. The substance exhibited

	R_f in systems*				UV spectrum			
					0.1 *N* HCl		0.5 *N* NaOH	
	1	*2*	*3*	*4*	λ_{max}, nm	ε	λ_{max}, nm	ε
II	0.70	0.54	0.24	0.12	264	16 800	260	13 200
III	0.80	0.70	0.72	0.45	252	18 400	279	14 000

*Systems: 1) isopropanol–water–concentrated hydrochloric acid (65.0:18.4:16.4); 2) ethyl acetate–98% formic acid–water (70:20:10); 3) tert-butanol–methyl ethyl ketone–water–98% formic acid (44:44:11:0.26); 4) n-butanol–2 N aqueous ammonia–ethanol (20:5:2).

no inhibiting activity on the growth of the tumors in either males or females. Compound II inhibited the growth of transplated Walker's carcinosarcoma in the rat to the extent of 37% after ten doses of 60 mg/kg of the substance and to the extent of 57% after a similar administration of 120 mg/kg. The inhibiting effect was shown similarly in males and females. Compound II had no clear inhibiting effect on the growth of Pleace's lymphosarcoma. The LD_{50} in white mice with intraperitoneal administration was 600 mg/kg for compound II and 300 mg/kg for compound III.

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FORMATION OF 5-METHYL-4-PHENYL-1, 2-DITHIOLEN-3-THIONE BY THE REACTION OF 2-PHENYLBUTANE WITH ELEMENTARY SULFUR

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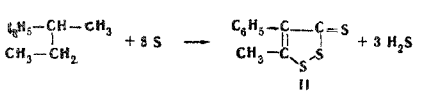
Previously, one of us has shown [1, 2] that the reaction of sulfur with 1- and 2-phenylbutanes leads to the formation of 2- and 3-phenylthiophenes, respectively, with yields of about 5%. The action of sulfur on 2-methyl-4-phenylbutane has given 4-methyl-2-phenylthiophene (yield about 12%) [3]. On the other hand, the catalytic reaction of sulfur with 1- and 2-phenylpropanes leads to the formation of 5- and 4-phenyl-1, 2-dithiolen-3-thiones, respectively [4, 5].

Continuing our investigation of the reaction of sulfur with aryl-substituted butanes and higher arylalkanes, we have shown that when it is carried out catalytically the corresponding aryl-1, 2-dithiolen-3-thiones are formed in many cases in addition to arylthiophenes. Thus, for example, when 185.0 g (1.375 mole) of 2-phenylbutane was heated with 88.0 g (2.75 g-atom) of sulfur in the presence of 0.7 g (0.016 mole-%) of mercuriacetamide at 180°–200° C for 30 hr, 5.5 g (5.6% of theoretical, calculated on the 2-phenyl-butane that had reacted) of 3-phenylthiophene (I) and 1.5 g (1.1%) of 5-methyl-4-phenyl-1, 2-dithiolen-3-thione (II) were isolated, the latter having been formed in the following way.



To isolate the reaction products, the unchanged 2-phenylbutane was distilled off (102 g or 0.76 mole), the free sulfur was eliminated from the residue by means of dimethylformamide, and it was distilled with superheated steam. The resulting reddish crystals were separated chromatographically on a column of silica gel. The eluant was a mixture of petroleum ether and benzene (5:1). From the appropriate fraction of the eluate were obtained red plate-like crystals with mp 91°–92° C (from acetic acid), which corresponds to literature data [6] for II (mp 92° C). Found, %: C 53.40; H 4.00; S 42.64. Calculated for $C_{10}H_8S_3$, %: C 53.53; H 3.59; S 42.88.

Similarly, I was isolated with mp 91°–92° C (literature data [2], mp 91.5°–92° C). This substance was shown to be 3-phenylthiophene by a mixed melting point.

By modifying the reaction conditions (for example, by the dropwise addition of 2-phenylbutane containing 5 mole-% of morpholine into an excess of sulfur heated to 200°–210° C), the yield of I can be raised to 10—15%.

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