11-Methyl-2,3,4,5-tetrahydropyrimido(2,1-b)quinazolin-2,10-dione (IX). The acid chloride of (IId) (0.9 g, 0.01 mole) in DMF (70 ml) is added with stirring to a mixture of 3-methyl-2-aminoquinazol-4-one (1.6 g, 0.01 mole) and triethylamine (1.0 g, 0.01 mole) in DMF (100 ml). The mixture is heated for 7 h at 90°C, then treated with water (100 ml). Yield 0.33 g (14%). mp 260-262°C (from ethanol). IR spectrum: 1635 (C=N), 1695 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 3.0 (2H, t, $COCH_2$); 3.55 (3H, s, CH_3); 4.50 ppm (2H, t, NCH_2). UV spectrum (ethanol), λ_{max} (log ε): 230 (3.03), 255 (3.32), 282 (4.3) nm. Mass spectrum, m/z (%): 229 (M, 100), 201 (50).

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REACTION OF 2,4,6-TRIPHENYLVERDAZYL WITH TRIFLUOROMETHYLSULFONYLCARBETHOXYDIBROMOMETHANE

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An unusual acylation of 2,4,6-triphenylverdazyl by trifluoromethylsulfonylcarbethoxydibromomethane in benzene has been discovered leading to 1-ethoxalyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-sym-tetrazine (1-ethoxalyl-2,4,6-triphenylleukoverdazyl).

Formation of 1-acyl-2,4,6-triaryl-1,2,3,4-tetrahydro-sym-tetrazine has been postulated in the reaction of 2,4,6-triarylverdazyl with benzoyl peroxide [1] but the isolation of materials with this structure has not proved successful up to this time. We have found that 2,4,6-triphenylverdazyl (I) reacts with trifluoromethylsulfonylcarbethoxydibromomethane (II) in benzene at 20°C to give a small yield of the known 1,3-diphenyl-5-carbethoxy-1,2,4-triazole (IV) but a 96% yield of the acylation product from I, i.e., 1-ethoxalyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-sym-tetrazine (V) (1-ethoxalyl-2,4,6-triphenylleukoverdazyl). The structure was confirmed by elemental analysis, spectral data, and chemical reactions.

The PMR spectrum of V showed three multiplets for the three phenyl groups at 7.73, 7.34, and 7.02 ppm (15 H) and the ethyl group was identified by a triplet at 1.22 and a quartet at 4.32 ppm. The signals for the geminal methylene group of the tetrazine heterocycle were at 5.13 and 6.16 ppm with J_{AB} = 13.5 Hz. Such a spectral pattern is typical of leukoverdazyls and is explained by substituent inversion at N_2 [2]. The structure is further confirmed by molecular ion (M^+) fragmentation and by IR spectroscopy. The first stage of dissociation of M^+ (m/z 414) involves elimination of the $COCO_2C_2H_5$ radical to form a fragment with m/z 313. The ethoxalyl fragment further loses acetaldehyde to form $HO^+{=}C{=}C{=}O$ (m/z 57). The presence of two carbonyls in V was seen by IR. Evidently the acylating agent is a product of the reaction of reagent II. To investigate the source of oxygen in the acyl fragment of V the experiment was carried out in a Warburg [3] manometric apparatus and also in an

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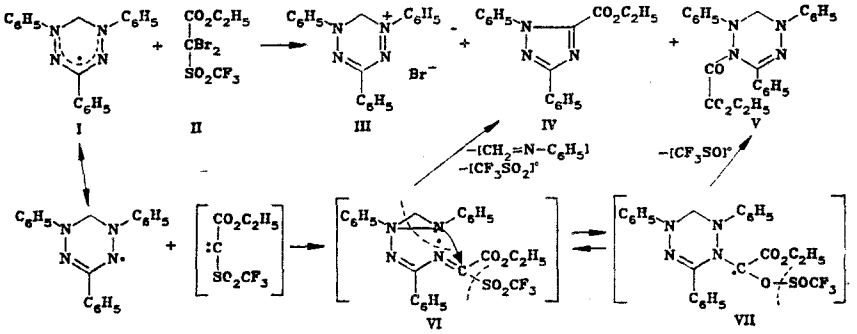
argon atmosphere. In a hermetically sealed system neither evolution nor absorption of gas was recorded. In an argon atmosphere neither the composition nor the quantities of reaction products was changed. The following reaction scheme can be proposed bearing in mind the obtained data, the known tendency of verdazyl radicals towards one electron reaction [1], and the ability of the trifluoromethylsulfonyl group simultaneously to behave as a powerful electron acceptor [4] and as a good leaving group [5] (particularly when adjoining carbonyl or carbethoxy groups).

A carbene [6] is initially formed via a series of consecutive stages of one electron transition and then reacts with a further molecule of verdazyl. It is possible for the intermediate formed sulfone radical VI to be in equilibrium with the sulfinic ester VII [7]. With or without intramolecular cyclization it is then possible for elimination to a mixture of products IV and V to occur. Evidently the equilibrium was significantly to the right because of the predominance of the acylation product V.



EXPERIMENTAL

2,4,6-Triphenylverdazyl was synthesized as described in [1]. Reagent II was obtained by direct bromination of ethyl trifluoromethylsulfonylacetate [8] in water using bromine at 20°C. The obtained oily product was separated, dried, and distilled in vacuo (~15 gPa) with bp 114-115°C, n_D^{20} 1.467. Benzene was distilled from calcium hydride under argon.

The UV spectrum of V was recorded on a Specord M-40, the IR spectrum on a UR-20, and the PMR spectrum on a Bruker WP-200 (200 MHz) instrument in acetone-d_6 referred to HMDS. The mass spectrum was measured on an MS-1302.

Compound V. Mixing radical I (1.42 g, 4.5 mmole) and the dibromomethane II (0.55 g, 1.45 mmole) in benzene (30 ml) caused an immediate reaction. The 2,4,6-triphenylverdazyl bromide III was filtered off, dried, and converted back to I according to [1]. The filtrate was evaporated in vacuo (~15 gPa), heated on a water bath (40-50°C), and the residue treated with ethanol. There were filtered off 0.585 g (1.4 mmole) of air-stable, pale yellow crystalline V with mp 172°C (ethanol). Found: C 69.94; H 5.31; N 13.33%. $C_{24}H_{22}N_4O_3$. Calculated: C 69.55; H 5.35; N 13.52%. UV spectrum (CH_3CN), λ_{max} (log ε): 230 (4.37), 352 nm (4.25). IR spectrum (KBr tablet): 1700, 1720 cm^{-1} (C=O twin peaks). Mass spectrum, m/e (%): 414 (41), 313 (67), 104 (98), 91 (28), 77 (100), 73 (33), 57 (78), 45 (57). TLC was used on an alcohol solution (silica gel, 100/160 μ, eluent 1:1 benzene:n-butanol) to give triazole IV (0.012 g, 0.04 mmole) with mp 117-118°C (from a mixture of n-hexane/benzene) and R_f 0.49 (Silufol UV-254, same solvent) [6].

Hydrolysis of V. Compound V (0.096 g, 0.23 mmole) was stirred at 20°C with aqueous ammonia (25%, 20 ml) for 3 days. The mixture turned green. After filtration the dried product (0.085 g) had mp 134°C (from 1:1 methanol:acetone). The UV spectrum and the melting point of the dark green crystals taken under the microscope (142°C) corresponded to those of the starting verdazyl [1].

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SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND MASS SPECTROMETRIC STUDY OF SOME 8-METHYL-6H-THIAZOLO[3,2-f]XANTHINES

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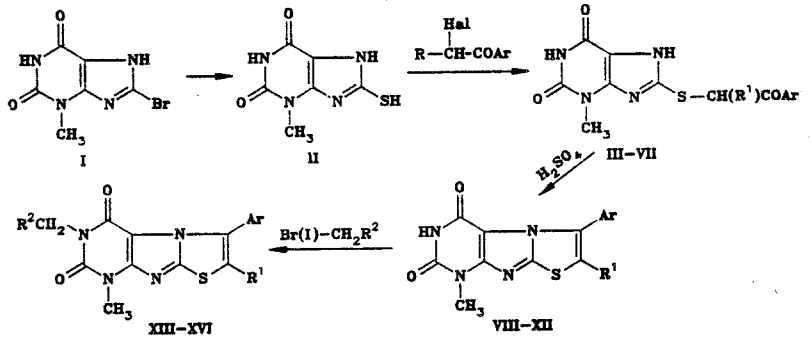
Alkylation of 8-mercapto-3-methylxanthine with α-haloketones has given the corresponding aroylmethylthio-3-methylxanthines, from which have been obtained some novel 3-aryl-8-methyl-6H-thiazolo[3,2-f]xanthines.

Reports have appeared in the literature on the preparation [1-3] and chemical properties [4] of derivatives of 6,8-dimethylthiazolo[3,2-f]xanthine. 8-Methyl-6H-thiazolo[3,2-f]-xanthines have not been described, and are of interest in terms of extending the synthetic possibilities by modifying the uracil fragment, by alkylation and conversion from the tricyclic thiazoloxanthine system into thiazolopurines, which are in the final analysis of special importance in the search for biologically active compounds and potential drugs.

Treatment of 8-bromo-3-methylxanthine (I) [5] with an excess of potassium hydrosulfide at 170-175°C in a sealed ampul results in the formation of 8-mercapto-3-methylxanthine (II), alkylation of which with α-haloketones in DMF affords the 8-aroylmethylthio-3-methylxanthines (III-VII).



III—VI, VIII—X, XIII, XIV R^1=H, VII, XI R^1=C_2H_5; XII, XIV, XVI R^1—Ar=—$(CH_2)_4$—; III, VII, VIII, XI, XIII, XV Ar=C_6H_5, IV Ar=$C_6H_4CH_3$-*p*, V, IX Ar=C_6H_4Cl-*p*, VI, X Ar=$C_6H_4NO_2$-*p*; XIII, XIV R^2=COC_6H_4Cl-*p*, XV, XVI R^2=H

It should be noted that on reaction of 2-bromocyclohexanone with the xanthine (II), the reaction does not stop at the formation of 8-(2-oxocyclohexylthio)-3-methylxanthine, but affords the tetracyclic compound (XII). 8-Methyl-6H-thiazolo[3,2-f]xanthine may be further alkylated at the unsubstituted nitrogen $N_{(6)}$ of the uracil moiety. For example, reaction of α-bromo-p-chloroacetophenone with (VIII) or (XII) in DMF in the presence of anhydrous potassium carbonate gives the 6-p-chlorobenzoylmethylated (XIII) and (XIV). Alkylation of these compounds with methyl iodide under similar conditions affords the known thiazoloxanthines (XV) and (XVI) [1].

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