REACTIONS OF 5,6-DIAMINO-1,3-DIMETHYLURACIL WITH HALOGEN DERIVATIVES OF CHALCONES

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The reaction of 5,6-diamino-1,3-dimethyluracil with 1,3-diaryl-2,3-dibromopropan-1-ones gave β-(5-amino-6-imino-1,3-dimethyluracil)chalcones, and conditions for their cyclocondensation to pyrimidinodiazepines were found. For substantiation of the reaction mechanism, the reaction of the diamine with other halogen derivatives of chalcones was studied. The IR, UV, and mass spectra of the synthesized compounds and their condensation products are discussed.

o-Phenylenediamine and its substituted derivatives react with 1,3-diaryl-2,3-dibromopropan-1-ones (α,β-chalcone dibromides) with formation of photochromic azirinoquinoxalines [1, 2]. In other communications [3, 4], the formation of 1,5-diazepine structures was noted in a study of similar reactions. The purpose of the present paper was an investigation of the reactions of 5,6-diamino-1,3-dimethyluracil (I) with α,β-chalcone dibromides IIa-ℓ and other halogen derivatives of chalcones VIIa, VIIe, VIIIa, VIIIe, and X.

The reaction of diamine I with compounds IIa-k was carried out by boiling (2-2.5 h) methanol solutions of equimolecular amounts of I and IIa-k in the presence of triethylamine. Compounds IIIa-k precipitated (their purity was confirmed by thin-layer chromatography); their yield was 20-40% (Table 1). Under the same experimental conditions, diamine I and 4′-nitrochalcone dibromide (IIl) formed 4′-nitrochalcone (XIℓ) in 67% yield as the only product. The reaction of 4-nitrochalcone dibromide (IIe) with diamine I occurred similarly if the process was carried out in ethanol (the yield of 4-nitrochalcone was 60%).

Subsequent heating of the reaction mixtures and also boiling of ethanolic and methanolic solutions of IIIa-k in the presence of catalytic amounts of triethylamine or acetic acid resulted in a mixture of substances in which the main component was compound IV. Theophylline V was a side component (from trace amounts in methanol to 25-30% in ethanol). Theophyllines Va-g were the main products of thermolysis of compounds IIIa-k and boiling of IIIa-k, IVa-e, and IVi-k in dimethylformamide (DMFA). It is of interest that only 8-(4-R-phenyl)theophyllines (and not R^1-substituted derivatives) were formed in these reactions. The structure of theophyllines Va-g was confirmed by back synthesis from diamine I and the corresponding substituted benzaldehyde with subsequent oxidation of intermediate azomethines by *N*-bromosuccinimide. With respect to their characteristics, theophyllines Va-g were identical to the compounds described in [5].

Compounds IIIa and IIIe were also obtained in reactions of diamine I with 1,3-diphenylpropyn-3-one (VI) and 1-phenyl-3-(4-nitrophenyl)-2-bromo-3-chloropropan-1-one (VIIe), respectively. In the reaction of diamine I with α-bromochalcone (VIIIa), compound IIIa was formed together with the main product, compound IX, which was also the only product of the reaction of compounds I and VIIa.

In all cases, product XII, with intense green fluorescence, was formed in trace amounts. Its yield increased when methanol was replaced by ethanol. It should be noted that in a control experiment, i.e., during boiling of methanolic solutions of diamine I with triethylamine in the absence of dibromide, the product was virtually not formed. (See scheme on following pages.)

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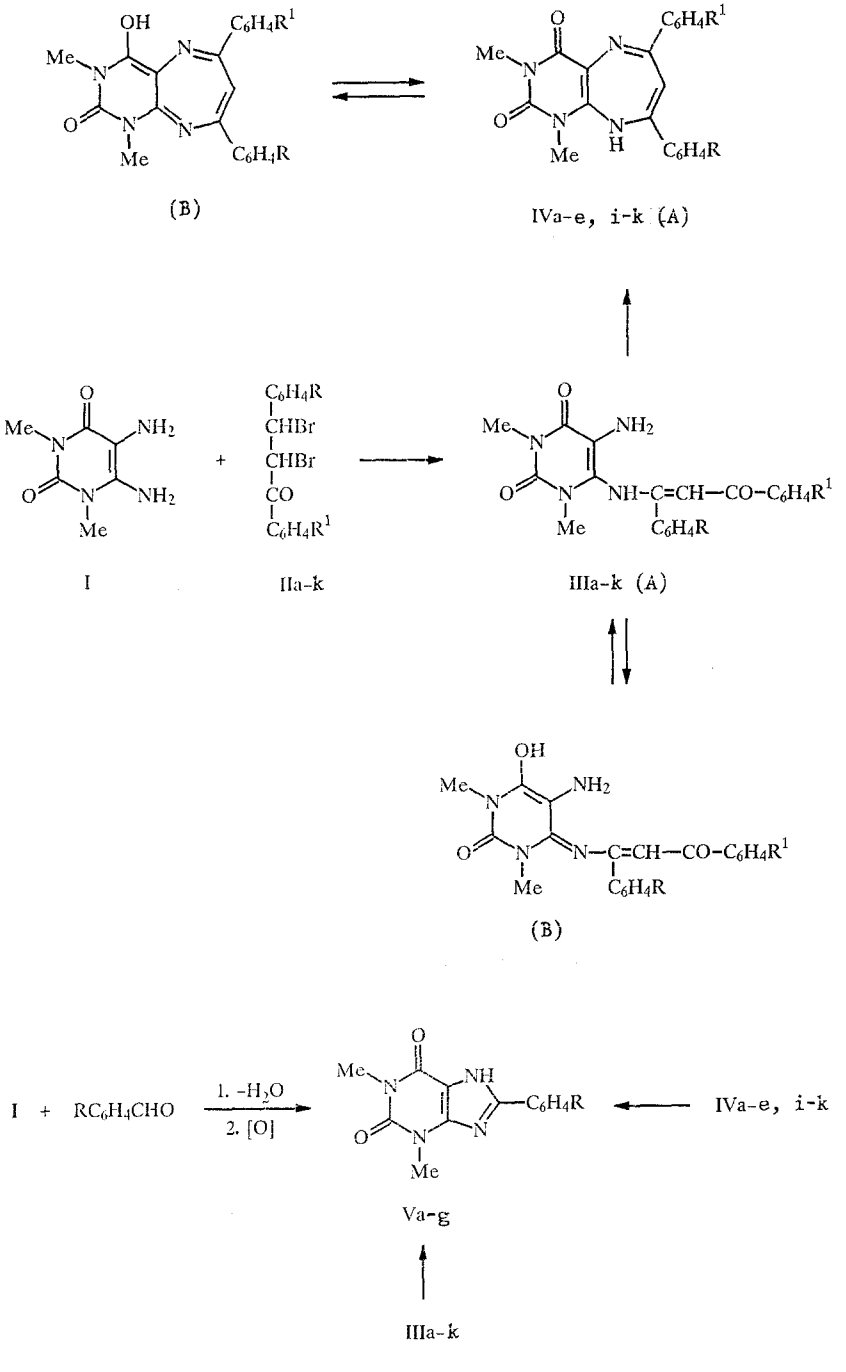
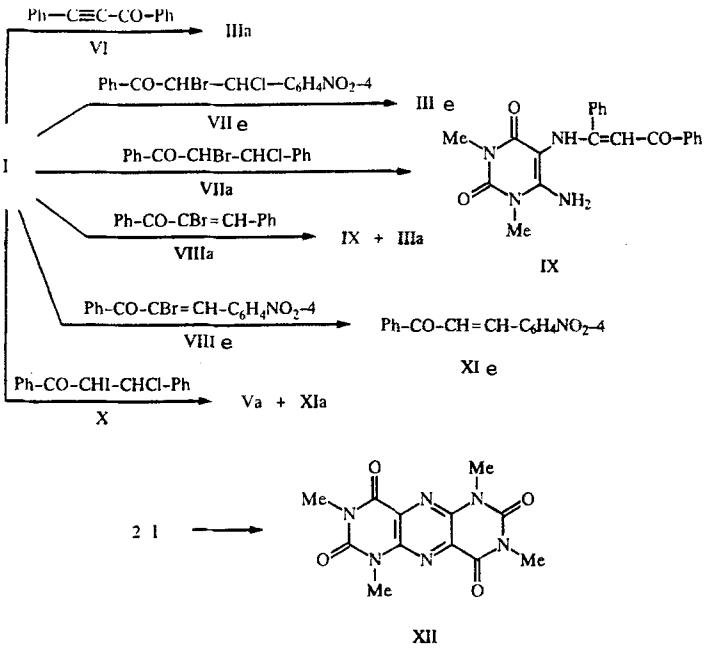
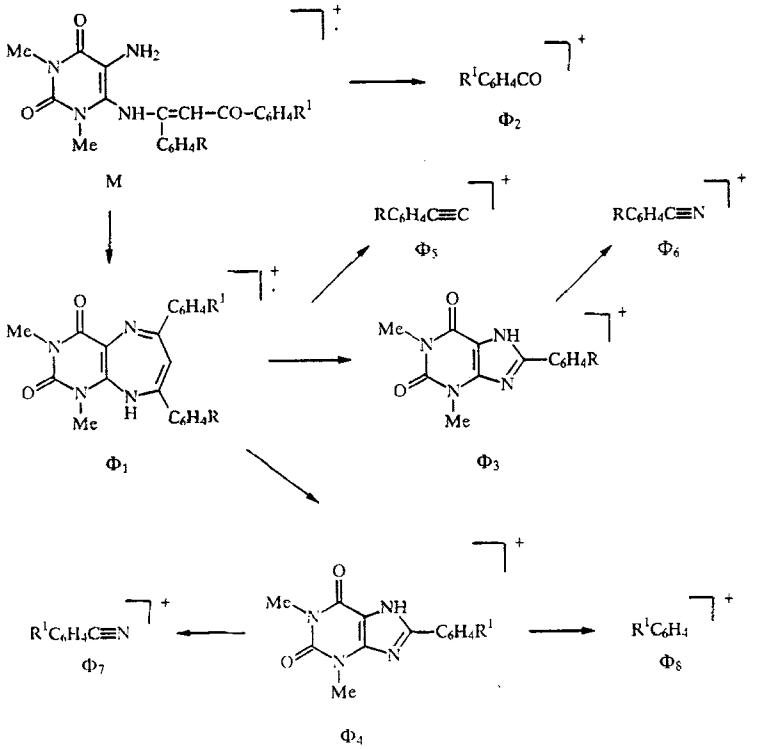

(B)
IVa-e, i-k (A)
I
IIa-k
IIIa-k (A)
(B)
I + RC6H4CHO
1. -H2O
2. [O]
Va-g
IVa-e, i-k
IIIa-k



II—V, VII, VIII, XI a R=H, b R=4-Ph, c R=4-Cl, d R=4-Br, e R=4-NO_2, f R=4-OMe, g R=2-NO_2, a— g R^1=H, h- ℓ R=H, h R^1=4-OMe, i R^1=4-Ph, j R^1=4-Cl, k R^1=4-Br, ℓ R^1=NO_2

According to data of elemental and spectral analyses, compounds IIIa-k were products of β-amination of ketones. That was indicated most convincingly by their mass spectra (Table 2), which contained rather intense peaks of molecular ions and aroyl radicals. The characteristic fragmentation processes were the formation of pyrimidinodiazepine and pyrimidinoimidazole structures and their subsequent decomposition, similar to that described previously [6]:



Interesting information on the structure of compound IIIa was given by its PMR spectra, measured in $CDCl_3$ and deuterated dimethyl sulfoxide (DMSO-D_6) (the low solubility of the remaining compounds of this series hindered measurement of their PMR spectra). The obtained spectra differed significantly from each other. During measurements in $CDCl_3$, we observed singlets of protons of CH_3 (3.13 and 3.31), NH (4.65), NH_2 (5.49), and CH (6.02) groups and multiplets of aromatic protons at 7.3-8.1 ppm (peaks of two pairs of ortho protons were shifted to the region of weak fields). In the spectrum

TABLE 1. Characteristics of Compounds IIIa-k*

Compound	IR spectrum, cm^{-1}				UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	R_f	Yield, %
	$\nu_{C=O}$	$\nu_{C=N}$	ν_{OH}	ν_{NH_2}			
IIIa	1702	1635	3149	3340, 3400	274(17,5), 341(18,4)	0,11	30
IIIb	1702	1638	3209	3339, 3444	271(22,7), 344(22,2)	0,05	30
IIIc	1708	1628	3149	3323, 3406	263(16,7), 342(16,3)	0,07	35
IIId	1702	1622	3156	3323, 3400	262(18,2), 343(19,2)	0,05	35
IIIe	1702	1628	3183	3315, 3400	268(22,5), 340(17,5)	0,11	40
IIIf	1702	1630	3163	3323, 3408	277(22,0), 345(14,0)	0,04	20
IIIg	1702	1628	3183	3321, 3406	268(22,5), 340(17,4)	0,10	38
IIIh	1702	1628	3183	3343, 3440	273(21,4), 344(23,0)	0,03	25
IIIi	1702	1622	3199	3343, 3470	275(23,7), 347(24,6)	0,14	27
IIIj	1708	1628	3196	3349, 3459	266(19,6), 344(16,7)	0,09	30
IIIk	1708	1628	3183	3336, 3430	268(19,9), 344(18,8)	0,12	30

*In the range 270-320°C, compounds IIIa-k were converted to compounds Va-k, respectively.

measured in DMSO-D_6, the peaks of methyl protons were shifted somewhat (2.91 and 3.23); a singlet of the CH proton (6.04), broadened peak of NH_2-group protons (7.18), and a multiplet of aromatic protons in the region of 7.25-8.0 ppm were also observed (peaks of only one pair of ortho protons were observed in weak fields). The observed differences in the PMR spectra of compound IIIa can be explained only by assuming that the solvents, differing in their acid–base properties, stabilized different tautomeric forms, i.e., $CDCl_3$ stabilized 4-oxo form A, and DMSO-D_6 stabilized 4-hydroxy form B.

The chemical unequivalence of the amino groups in diamine I raises the question of the involvement of 5- and 6-amino groups in β-amination. It is known [7] that in uracils the 6-amino group tends toward tautomerism. Therefore, the above-noted fact of the manifestation of tautomerism by compound IIIa indicates that it is previously the 6-amino group that participates in reactions with ketones IIa-k.

In the high-frequency region, against a background of wide absorption, the IR spectra of compounds IIIa-k measured in KBr contained a weakly resolved doublet of bands at 3315-3349 and 3400-3470 cm^{-1}, which should be assigned to amino-group absorption, and a band at 3149-3209 cm^{-1} (ν_{OH}). They also contained a narrow ν_{CO} peak at ~ 1700 cm^{-1} and a broadened ν_{CN} band at ~ 1630 cm^{-1}. These spectra corresponded to the proposed structure of compounds III and corresponded to a greater degree to tautomer B.

As a rule, in the near ultraviolet, the electronic absorption spectra of compounds IIIa-k contained two or three bands. The values of λ_{max} of the long-wave absorption band were virtually not sensitive to the electronic effect of the substituents that were introduced into the aromatic rings.

The above-mentioned fact that α-bromochalcone formed mainly compound IX (compound IIIa was present in trace amounts) in the reaction with I indicates that, in the reaction of dibromides II, direct substitution of the β-bromine atom occurred with subsequent dehydrobromination to compounds III. With respect to its properties, compound IX was identical to the product of the reaction of diamine I with dibenzoylmethane (this product was described in [8], and we repeated the experiment ourselves), which was β-(6-amino-5-imino-1,3-dimethyluracilyl)chalcone. Involvement of precisely the 5-amino group of diamine I in the formation of compound IX was indicated by the fact that, during standing and boiling in ethanol or DMFA, compound IX was converted only to theophylline Va; no traces of compound IVa were observed. Hence, it is also evident that in compound IX the 6-amino group was unable to participate in intramolecular condensation with a keto group. This corresponds to the concepts of [7] about the behavior of amino groups in pyrimidine derivatives. These data also serve as additional confirmation of the correctness of the proposed direction of the formation of compounds IIIa-k.

The following data give additional information for understanding of the mechanism of the studied reaction: In reaction with I, ketones VIIa and VIIIa form compound IX, ketone VIIe forms compound IIIe, and ketone VIIIe forms chalcone XIe. According to the data of [9], the reactions of chalcone dibromides with amines occur via dehydrobromination with subsequent addition of the amine. However, in the processes that we studied, such a sequence occurred only in the first two reactions (with VIIa and VIIIa). Significantly activating the Cβ–Cl bond, the introduction of a nitro group into the β-aromatic ring (compound VIIe) was responsible for direct amination of the compound, analogous to that described above for dibromides II.

TABLE 2. Mass Spectra of Compounds IIIa-e, IIIg, IIIi-k, IVa, IVb, IVd, and IVk

Compound	Intensity of peaks of characteristic ions J_{rel}, %								
	M	Φ_1*	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8
IIIa	25	12	92	100		7	22		77
IIIb	10	54	48	100	9	24	27	17	31
IIIc	12	14	100	39	10	3	10	9	48
IIId	26	11	100	15	30	—	8	15	48
IIIe	17	23	100	55	15	—	—	11	44
IIIg	8	26	100	50	23	—	—	21	44
IIIi	3	9	100	83	3	6	12	7	30
IIIj	30	30	100	93	7	7	21	—	—
IIIk	15	10	49	100	2	11	15	3	24
IVa	—	100	—	47		7	47		20
IVb	—	100	—	24	13	17	17	38	10
IVd	—	94	—	22	100	12	12	65	40
IVk	—	100	—	70	19	81	41	27	16

*For compounds IV, Φ_1 corresponds to the molecular ion.

The behavior of 1,3-diphenyl-2-iodo-3-chloropropan-1-one (X) in the reaction with diamine I was special. In that case, a mixture of theophylline Va and chalcone XIa was formed. In this reaction, purine was possibly formed similarly to the way described above, but, because of the high mobility of iodine, it was not possible to detect any intermediates; therefore, it is difficult to assess the reaction mechanism unambiguously. Chalcone formation can be explained by the presence of a reducing agent such as HI, which evolved during the reaction, in the system. However, it remains unclear whether it acted as a reducing agent in the above-mentioned reactions of the 4- and 4′-chalcone dibromides and ketone VIIIe with diamine I; chalcones were formed in good yields in those reactions, but the salt $N(Et)_3 \cdot HBr$ and resinification products were detected in the reaction systems.

The formation of condensed diazepine, oxazepine, pyrazine, purine, and aziridine-containing systems can be assumed a priori in reactions of cyclocondensation of diamines with chalcone dibromides. The above-noted facts of the conversion of compounds III to IV and also III and V enable us to assign compounds IV to pyrimidinodiazepines. This conclusion was confirmed by the spectral characteristics of compounds IV (Tables 2 and 3).

Thus, the mass spectra of compounds IVa, IVb, IVd, and IVk (see Table 2) contained peaks of pyrimidinodiazepine ions and products of their decomposition analogous to those noted above for compounds III. The IR spectra of compounds IV retained a ν_{OH} band at 3170 cm^{-1} and a ν_{CO} band at 1700 cm^{-1}, although, on the whole, the spectrum changed significantly. The presence of the ν_{OH} band indicates stabilization of the 4-hydroxy form (tautomer B); the reason for such stabilization is probably intramolecular hydrogen bonding. On the whole, the electronic absorption spectra of compounds IV changed insignificantly in comparison with those of the corresponding compounds III: There was a change of the ratios of the intensities of individual bands, and the role of nitro substitution in the aromatic ring increased (see compound IVg).

Returning to luminescing product XII, we must note the following. Its IR spectrum contained no ν_{NH} and ν_{NH_2}* bands, whereas bands of carbonyl groups of the uracil fragment (ν_{CO} = 1666 and 1712 cm^{-1}) were retained. The electronic absorption spectrum of this comound contained several bands in the near ultraviolet and an absorption band in the visible region experiencing splitting. The PMR spectrum measured in CF_3COOH contained only peaks of protons of two methyl groups with chemical shifts 3.18 and 3.23 ppm. Measurement of the mass spectrum of compound XII showed that it was not possible to remove compounds III from it completely, and, probably because of high volatility, even trace amounts of them were effectively manifested in the mass spectrum. Even so, one of the most intense ions (73%), which corresponded to the greatest mass in the spectrum, was an ion with *m/z* 304 ($M^{+\cdot}$, the ion of compound XII) at gas-feed temperature 230°C.

The presented spectral data indicate self-condensation of molecules of I, occurring with formation of 1,3,6,8-tetramethyl-2,4,7,9-tetraoxobispyrimidino[5,6-*b*:5′,6′-*e*]pyrazine (XII). The properties of the obtained compound XII correspond to the properties of the product of oxidation of monoazomethine derivative I, which was described in [10] and [11].

TABLE 3. Characteristics of Compounds IVa-e and IVi-k*

Compound	mp, °C	IR spectrum, cm^{-1}			UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	R_f	Boiling time, h
		$\nu_{C=O}$	$\nu_{C=N}$	ν_{OH}			
IVa	231...232	1702	1648	3173	260(29,71), 343(11,4)	0,35	20
IVb	257...258	1702	1648	3170	278(38,7), 347(20,3)	0,34	24
IVc	240...241	1705	1655	3180	263(33,3), 348(14,6)	0,36	12
IVd	242...243	1715	1668	3184	264(35,1), 348(15,4)	0,34	10
IVe	253...254	1702	1648	3170	267(29,6), 370(16,5)	0,35	5
IVi	280...281	1715	1669	3185	279, 348	0,34	20
IVj	247...248	1702	1662	3206	264(25,3), 348(9,5)	0,34	12
IVk	260...261	1708	1648	3164	266(27,0), 351(12,0)	0,33	10

*The yield of compounds IV fluctuated in the range 50-60%; accurate determination of the yield was difficult because of the complexity of separation of the mixture of products of conversion of compounds III.

EXPERIMENTAL

The IR spectra were recorded with an IR-75 spectrometer in KBr tablets, and the electronic absorption spectra were recorded with a Specord UV-vis instrument in methanol at substance concentrations $1\text{-}5 \times 10^{-5}$ mole/liter. The PMR spectra were recorded with a Bruker WP-360 instrument in DMSO-D_6 (internal standard TMS) and a Gemini-200 instrument in $CDCl_3$. The mass spectra were obtained with a Finnigan MAT 4615P instrument under standard conditions. The purity of the obtained products was monitored by thin-layer chromatography on Silufol UV-254 plates in chloroform.

The data of elemental analysis for N corresponded to the calculated data.

β-(5-Amino-6-imino-1,3-dimethyluracilyl)chalcone (IIIa, $C_{21}H_{20}N_4O_3$). A. A mixture of 0.17 g (1 mmole) of diamine I, 0.368 g (1 mmole) of chalcone dibromide (IIa), and 1 ml of triethylamine (TEA) in 10 ml of methanol was boiled for 2 h, and the light-yellow precipitate that formed from the boiling solution was filtered and crystallized from methanol. We obtained 0.11 g (30%) of compound IIIa.

Compounds IIIb-k were similarly prepared.

Trace amounts of luminescing compound XII ($C_{12}H_{12}N_6O_4$) remained in the filtrates. When the reaction was carried out in ethanol, 0.06-0.07 g (40-47%) of the compound was obtained.

B. A mixture of 0.17 g (1 mmole) of diamine I, 0.2 g (1 mmole) of 1,3-diphenylpropyn-3-one (VI), and 1 ml of acetic acid in 10 ml of methanol was boiled for 30 min, and the light-yellow precipitate that formed from the boiling solution was filtered and crystallized from methanol. We obtained 0.25 g (65.7%) of compound IIIa.

4-Nitro-β-(5-amino-6-imino-1,3-dimethyluracil)chalcone (IIIe, $C_{21}H_{19}N_5O_5$). A mixture of 0.17 g (1 mmole) of diamine I, 0.32 g (1 mmole) of 1-phenyl-3-(4-nitrophenyl)-2-bromo-3-chloropropan-1-one (VIIe), and 1 ml of TEA in 10 ml of methanol was boiled for 40 min, and the bright-yellow precipitate that formed from the boiling solution was filtered and crystallized from methanol. We obtained 0.17 g (40%) of compound IIIe.

Conversion of Compounds IIIa-k. A. A solution containing 0.13 g (0.3 mmole) of compound IIIa and catalytic additions of TEA in 10 ml of methanol was boiled for 20 h. The precipitate that formed during cooling was filtered, and 0.1 g (84%) of compound IVa ($C_{21}H_{18}N_4O_2$) with mp 235°C (from ethanol) was obtained.

B. A solution containing 0.13 g (0.3 mmole) of compound IIIa and catalytic additions of TEA in 10 ml of ethanol was boiled for 20 h. The white precipitate that formed was filtered, and 0.02 g (22%) of compound Va ($C_{13}H_{12}N_4O_2$) with mp > 300°C (from DMFA) was obtained. The filtrate was diluted with water, the resulting yellow precipitate was filtered, and 0.06 g (50%) of compound IVa ($C_{21}H_{18}N_4O_2$) with mp 235°C (from ethanol) was obtained.

Compounds IVb-e, IVi-k, and Vb-g were similarly prepared.

8-Phenyltheophylline (Va, $C_{13}H_{12}N_4O_2$). A. A mixture of 0.17 g (1 mmole) of diamine I and 0.37 g (1 mmole) of 1,3-diphenyl-2-iodo-3-chloropropan-1-one (X) in 10 ml of ethanol was boiled for 2 h, the white precipitate that formed during

cooling was filtered, and 0.1 g (40%) of compound Va with mp > 300°C (from DMFA) was obtained. The filtrate was diluted with water, and 0.05 g (25%) of chalcone XIa ($C_{15}H_{12}O$) with mp 56°C was obtained.

B. A solution of 0.1 g (0.28 mmole) of compound IVa (or IIIa) in 5 ml of DMFA was boiled for 40 min. The white precipitate that formed during cooling was filtered, and 0.07 g (100%) of compound Va with mp >300°C (from DMFA) was obtained.

Compounds Vb-g were similarly prepared.

β-(6-Amino-5-imino-1,3-dimethyluracilyl)chalcone (IX, $C_{21}H_{20}N_4O_3$). A. A mixture of 0.17 g (1 mmole) of diamine I, 0.3 g (1 mmole) of α-bromochalcone VIIIa, and 1 ml of TEA in 10 ml of methanol was boiled for 40 min. The precipitate that formed during cooling was filtered and washed with hot water, and 0.04 g (11%) of compound IX with mp >300°C (from a 1:2 ethanol–isopropanol mixture) was obtained.

B. A mixture of 0.17 g (1 mmole) of diamine I, 0.22 g (1 mmole) of dibenzoylmethane, and 1 ml of acetic acid in 10 ml of isopropyl alcohol was boiled for 11 h. The precipitate that formed during cooling was filtered, and 0.15 g (50%) of compound IX with mp >300°C (from a 1:2 ethanol–isopropanol mixture) was obtained.

C. A mixture of 0.17 g (1 mmole) of diamine I, 0.32 g (1 mmole) of ketone VIIa, and 1 ml of TEA in 10 ml of methanol was boiled for 2 h, the precipitate that formed after cooling was filtered, and 0.19 g (52%) of compound IX with mp >300°C (from a 1:2 ethanol–isopropanol mixture) was obtained.

Reaction of Diamine I with α-Bromo-4-nitrochalcone. A mixture of 0.17 g (1 mmole) of diamine I, 0.33 g (1 mmole) of ketone VIIIe, and 1 ml of TEA in 10 ml of methanol was boiled for 2 h, the precipitate that formed after cooling was filtered, and 0.25 g (100%) of 4-nitrochalcone XIe with mp 165°C (from ethanol) was obtained.

REFERENCES

1. T. Do Minh and A. M. Trozzolo, J. Am. Chem. Soc., **94**, 4046 (1972).
2. A. Padwa, L. Gehlein, and R. B. Kinnel, J. Org. Chem., **40**, 1683 (1972).
3. L. A. Mushkalo and V. A. Chuiguk, Ukr. Khim. Zh., **35**, 740 (1965).
4. V. D. Orlov, N. P. Vorob'eva, N. N. Demenkova, V. S. Chesnovskii, and F. G. Yaremenko, Khim. Geterotsikl. Soedin., No. 3, 328 (1988).
5. K. Senga, J. Sato, K. Shumizu, and S. Nishigaki, Heterocycles, **6**, 1919 (1977).
6. V. D. Orlov, I. Z. Papiashvili, and P. A. Grigorov, Khim. Geterotsikl. Soedin., No. 5, 671 (1983).
7. D. J. Brown, R. F. Evans, and F. I. Batterham, The Pyrimidines, Supplement I, Wiley Interscience, New York (1970), p. 106.
8. St. Wawzonek, J. Org. Chem., **46**, 316 (1976).
9. F. Weber and Ch. Bandlow, Z. Chem., **13**, 467 (1973).
10. S. Mineo, H. Oqura, and K. Nakagawa, Chem. Pharm. Bull., **28**, 2835 (1980).
11. M. Sakaguchi, Y. Miyata, H. Oquara, K. Gonda, S. Koga, and T. Okamoto, Chem. Pharm. Bull., **27**, 1094 (1979).