9. G. Ohloff, J. Siebl, and E. Sz. Kováts, Liebigs Ann. Chem., 675, 83 (1964).
10. C. W. L. Bevan, D. E. V. Ekong, and J. I. Okogun, J. Chem. Soc., C, 1963 (1968).
11. P. Albriktsen, A. V. Cunliffe, and R. K. Harris, J. Magn. Reson., 2, 150 (1970).
12. A. M. Becker and R. W. Richards, Helv. Chim. Acta, 59, 2393 (1976).
13. E. V. Polunin, A. M. Moiseenkov, and A. V. Semenovskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1354 (1981).
14. R. C. Krug, J. A. Rigney, and G. R. Tichelaar, J. Org. Chem., 27, 1305 (1962).
15. T. G. Konstantinova, A. M. Moiseenkov, and V. P. Gul'myai, Izv. Akad. Nauk SSSR, Ser. Khim., 2101 (1983).

SYNTHESIS OF 7-ALKYLPTERINS

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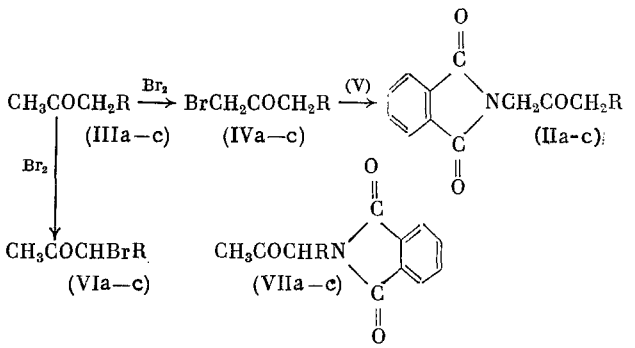
2,5,6-Triamino-4-oxo-3,4-dihydropyrimidine (I) undergoes cyclocondensation with N-acyl-α-aminoketones to give substituted pterins [1]. We here examine the possibility of using phthalimidomethyl alkyl ketones (IIa-c) to synthesize substituted pterins. These ketones are obtained by the regioselective bromination of methyl alkyl ketones (IIIa-c) in DMF in the presence of urea [2], followed by reaction of the intermediate bromomethyl alkyl ketones (IVa-c) with potassium phthalimide (V). Bromination of the ketones (IIIa-c) under these conditions gives, in addition to the main products (IVa-c) (~80%), the isomeric 3-bromo-2-alkanones (VIa-c) (~20%). However, the higher reactivity of the 1-bromo-2-alkanones (IVa-c) [3] enables the unseparated mixture of (IVa-c) and (VIa-c) to be reacted with (V) to give the required phthalimidoketones (IIa-c) uncontaminated by the isomeric 3-phthalimido-2-alkanones (VIIa-c).



R = Me (a), $(CH_2)_3Me$ (b), $(CH_2)_4Me$ (c).

The phthalimidoketones (IIa-c) were reacted with (I) in aqueous solution in the presence of piperidine, i.e., under the conditions in which (I) undergoes cyclocondensation with N-acyl-α-aminoketones [1]. After prolonged standing at ~20°C, the reaction mixture afforded 60-80% yields of the 7-alkylpterins (VIIIa-c), identified by comparison with authentic samples [3-5]. Reaction of (I) with phthalimidoacetone afforded a complex mixture of products from which the required 7-methylpterin could not be isolated.

By analogy with the synthesis of 7-substituted pterins from (I) and N-acyl-α-aminoketones [1], the reaction of (I) with phthalimidoketones can be regarded as a multistage process involving initial formation of the imine (IX), its intramolecular cyclization with the elimination of the phthalimide residue, and dehydrogenation of the intermediate dihydro-compound (X) by atmospheric oxygen (Scheme 1).

We attempted to use the mixture of bromoketones (IVa) and (VIa) for the preparation of pure 7-ethylpterin (VIIIa) without prior conversion of (IVa) into the phthalimidoketone (IIa).

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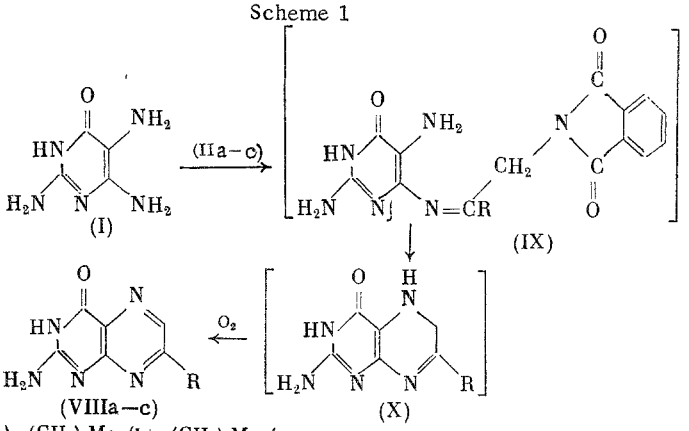
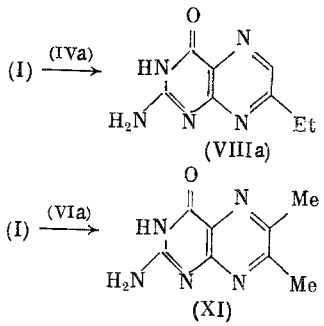
Scheme 1



R = Et (a), $(CH_2)_4Me$ (b), $(CH_2)_5Me$ (c).

It was however found that both of the isomeric bromoketones (IVa) and (VIa) underwent cyclocondensation with (I) to give a mixture of 7-ethyl- and 6,7-dimethylpterins (VIIIa) and (XI).



Similarly unsuccessful was our attempt to selectively alkylate potassium caproate with the mixture of bromoketones (IVa) and (VIa) with the aim of obtaining the pure ester (XII) with a view to using it in the synthesis of 7-ethylpterin (VIIIa). When potassium caproate was reacted with the mixture of ketones in DMF, alkylation proceeded nonselectively and the required ester (XII) was obtained mixed with the isomeric ester (XIII) (11%).

$$Me(CH_2)_5COOK \xrightarrow{(IVa)+(VIa)} \underset{(XII)}{Me(CH_2)_8COOCH_2COEt} + \underset{(XIII)}{Me(CH_2)_8COOCHMeCOMe}$$

An authentic sample of 7-methylpterin, required for the identification of the product of cyclocondensation of (I) with phthalimide, was obtained by a previously described method [6] from (I) and methylglyoxal (XIV)

$$\underset{(XV)}{MeCONHCH_2COMe} \rightarrow \underset{(XVI)}{MeCONHCHBrCOMe} \rightarrow \underset{(XIV)}{MeCOCHO}$$

$$\underset{(XVII)}{HON=CHC(=NOH)Me} \xrightarrow[b)\ H_2SO_4]{a)\ NaHSO_3} MeCOCHO$$

The methylglyoxal (XIV) was itself obtained by brominating acetamidoacetone (XV) and hydrolysis of the intermediate 1-bromo-1-acetamidoacetone, and also by cleavage of methylglyoxime (XVII) with $NaHSO_3$ by the Pechmann reaction [7].

EXPERIMENTAL

UV spectra were obtained in 0.1 N KOH on a Specord UV-VIS instrument, IR spectra in KBr disks on a UR-20 instrument, and PMR spectra on a Varian DA-60-IL instrument (for pterins (VIIIa-c) and (XI), the external standard was HMDS, and for the remaining compounds, the internal standard was TMS). TLC was carried out on Silufol UV-254 (inspected in UV light). GLC was carried out on a LKhM-8M chromatograph with a flame ionization detector, a 1 m × 3 m stainless steel column with 5% silicone SE-30 on Chromaton N-AW, 0.160-0.200 mm (123-124°C), carrier gas nitrogen.

1-Phthalimidobutan-2-one (IIa). To a solution of 3 ml of methyl ethyl ketone in 10 ml of DMF were added successively with stirring 3.6 g of urea and 2 ml of bromine. When the bromine had disappeared (~1 h), the mixture was diluted with water and extracted with methylene

chloride. The extract was washed with sodium bicarbonate solution, dried over $MgSO_4$, and the solvent removed to give 5.5 g of an oily mixture of 1- and 3-bromobutan-2-ones (IVa) and (VIa), PMR spectrum (CCl_4, δ, ppm): 1.05 t ($\underline{CH_3}CH_2$, J = 7.5 Hz), 1.98 s (CH_3CO), 2.65 q ($CH_3\underline{CH_2}$, J = 7.5 Hz), 3.88 s ($BrCH_2$), 4.35 m ($COCHBrCH_3$). According to GLC, the ratio of (IVa) to (VIa) was 78:22. Bromination of methyl ethyl ketone in absolute methanol [8] or acetonitrile gave mixtures of (IVa) and (VIa) in ratios of 70:30 and 83:17.

To a solution of 5.5 g of this mixture of bromoketones (IVa) and (VIa) in 8 ml of DMF was added slowly with stirring 5.5 g of potassium phthalimide (V), and when evolution of heat ceased the mixture was kept for 0.5 h at 20°C, diluted with water, and the solid washed with water and air-dried to give 2.5 g (60%) of (IIa), mp 106-108°C (from ether at −70°C) [9], R_f 0.48 (ethyl acetate–heptane, 1:1). PMR spectrum (CF_3COOH, δ, ppm): 1.23 t (CH_3, J = 7 Hz), 2.80 q ($CH_3\underline{CH_2}$, J = 7 Hz), 4.80 s (NCH_2CO), 7.90 br. s (arom. ring).

1-Phthalimidoheptan-2-one (IIb). To a solution of 3 ml of methyl pentyl ketone (IIIb) in 12 ml of DMF were added successively with stirring 4.8 g of urea and 1.3 ml of bromine. The mixture was kept for 12 h at 0°C then 4 h at 20°C, diluted with water, and extracted with methylene chloride. The extract was washed with sodium bicarbonate solution, dried over magnesium sulfate, and the solvent removed to give 3.5 g of an oily mixture of 1- and 3-bromoheptan-2-ones (IVb) and (VIb). PMR spectrum (CCl_4, δ, ppm): 3.84 s ($BrCH_2CO$), 4.18 t ($COCHBr$). According to GLC, the ratio of (IVb) to (VIb) was 85:15. When (IIIb) was brominated in methanol in the presence of urea, there was previously obtained a mixture of bromoketones (IVb) and (VIb) in a ratio of 82:18 [2].

The mixture of bromoketones (IVb) and (VIb) (3 g) was stirred with 2.5 g of (V) for 3 h at 20°C, diluted with water, and the solid washed with water and air-dried to give 2.5 g (60%) of (IIb), mp 47-51°C, after recrystallization from light petroleum, mp 61-63°C [10], R_f 0.61 (ethyl acetate–heptane, 1:1). PMR spectrum (CF_3COOH, δ, ppm): 0.92 t (CH_3, J = 7 Hz), 1.17-2.07 m ($CH_2CH_2CH_2$), 2.77 t ($COCH_2$, J = 7 Hz), 4.80 s (NCH_2CO), 7.88 d (arom. ring).

1-Phthalimidooctan-2-one (IIc). Reaction of 3 ml of methyl hexyl ketone (IIIc) with 1.2 ml of bromine in 12 ml of DMF in the presence of 4.8 g of urea as described above gave 3.8 g of an oily mixture of 1- and 3-bromooctan-2-ones (IVc) and (VIc) [2] in a ratio of 84:16 (GLC). PMR spectrum (CCl_4, δ, ppm): 3.76 s ($BrCH_2CO$), 4.15 t ($COCHBr$).

Alkylation of 2.3 g of (V) with 3 g of the mixture of ketones (IVc) and (VIc) (3 h, 20°C) gave 2.6 g (65%) of (IIc), mp 54-57°C (from ether at −70°C), R_f 0.65 (ethyl acetate–heptane, 1:1). PMR spectrum (CF_3COOH, δ, ppm): 0.93 m (CH_3), 1.43 m ($-(CH_2)_4-$), 2.80 t ($COCH_2$, J = 7.5 Hz), 4.83 s (NCH_2CO), 7.88 s (arom. ring).

7-Ethylpterin (VIIIa). A mixture of 0.3 g of (I) sulfate, 0.42 g of ketone (IIa), and 2 ml of piperidine in 10 ml of water was stirred for 145 h at 20°C, then heated to the boil, acidified to pH 5-6 with acetic acid, and kept for 12 h at 20°C. The solid was washed with water, alcohol, acetone, and ether, and dried in vacuo at 100°C to give 0.17 g (71%) of (VIIIa), decomp. >360°C, R_f 0.53 (i-PrOH–H_2O–NH_4OH, 7:2:1, blue fluorescence under UV). IR spectrum (ν, cm^{-1}): 1128, 1180, 1230 1290, 1310, 1420, 1460, 1520, 1545, 1630, 1690, 1730. PMR spectrum (1 N KOH, δ, ppm): 1.40 t (CH_3, J = 7 Hz), 2.88 q (CH_2, J = 7 Hz), 8.25 s (H at C^6). Authentic (VIIIa) [4] had the same values.

7-Pentylpterin (VIIIb). Similarly, from 0.6 g of (I) sulfate and 1 g of ketone (IIb) there was obtained 0.48 g (83%) of (VIIIb), decomp. >360°C (from 85% formic acid), R_f 0.67 (i-PrOH–H_2O–NH_4OH, 7:2:1). UV spectrum: λ_{max} 210, 252, and 360 nm. PMR spectrum (1 N KOH, δ, ppm): 1.02 t (CH_3, J = 7 Hz), 1.50 m ($-CH_2CH_2CH_2-$), 2.92 t ($=CCH_2$, J = 7 Hz), 8.47 s (H at C^6). Found: C 56.39; H 6.96; N 29.87%. $C_{11}H_{15}N_5O$. Calculated: C 56.63; H 6.48; N 30.03%.

7-Hexylpterin (VIIIc). Similarly, from 0.6 g of (I) sulfate and 1.06 g of ketone (IIc) there was obtained 0.36 g (58%) of (VIIIc), decomp. >360°C, R_f 0.67 (i-PrOH–H_2O–NH_4OH, 7:2:1). UV spectrum: λ_{max} 210, 252, and 360 nm [5]. PMR spectrum (1 N KOH, δ, ppm): 1.12 t (CH_3, J = 7 Hz), 1.48 m ($-(CH_2)_4-$), 2.90 t ($=CH_2$, J = 7 Hz), 8.38 s (H at C^6).

Mixture of 7-Ethyl and 6,7-Dimethylpterins (VIIIa) and (XI). To a solution of 2 ml of piperidine in 10 ml of water was added 0.6 g of a mixture of bromoketones (IVa) and (VIa), the mixture was kept for 2 h at 20°C, 0.4 g of (I) sulfate added, stirred for 166 h at 120°C, and worked up as described above to give 0.17 g (53%) of a mixture of (VIIIa) and (XI), decomp. >360°C, R_f 0.53 and 0.48 (i-PrOH–H_2O–NH_4OH, 7:2:1). PMR spectrum (1 N KOH, δ, ppm): 1.42 t ($\underline{CH_3}CH_2$, J = 7 Hz), 2.53 s ($=CCH_3$), 2.90 q ($\underline{CH_2}CH_3$, J = 7 Hz), 8.23 s (H at C^6). According to the integral intensities of the C_2H_5 and CH_3 group signals, the ratio of (VIIIa)

to (XI) was 2:1. Authentic samples of (VIIIa) [4] and (XI) [4] had R_f values of 0.53 and 0.48 respectively.

2-Oxobutyl Caproate (XII). To a solution of 1.4 g of KOH in 3 ml of water were added successively with stirring 4 g of caproic acid, 13 ml of DMF, and 5.7 g of the mixture of ketones (IVa) and (VIa) obtained above. The mixture was stirred for a further 2 h at 20°C, diluted with water, and extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent removed, and the residue distilled in vacuo to give 3 g of (XII) contaminated by 1-methyl-2-oxopropyl caproate (XIII), bp 198-200°C (45 mm). PMR spectrum (CCl_4, δ, ppm): 1.03 m (CH_3), 1.28 br. s ($-(CH_2)_7-$), 2.07 s (CH_3CO), 2.33 m (CH_2), 4.53 s (OCH_2CO), 4.90 m ($OCH(CH_3CO)$). Found: C 69.52; H 10.57%. $C_{14}H_{26}O_3$. Calculated: C 69.38; H 10.81%. From the integral intensities of the signals for the OCH_2CO and CH_3CO groups, the ratio of (XII) to (XIII) was 89:11.

Methylglyoxal (XIV). To a solution of 0.7 g of acetamidoacetone (XV) in 6 ml of conc. hydrochloric acid was added with stirring 1.3 g of N-bromosuccinimide. The mixture was kept for 5 h at 20°C, diluted with 40 ml of water, treated with sodium carbonate to pH ~4, and the solution partially evaporated at atmospheric pressure with the periodic addition of water to the residue. The distillate (100 ml) consisted of an aqueous solution of (XIV), R_f 0.45 (acetone, visualized with 2,4-dinitrophenylhydrazine solution). Treatment of the distillate after neutralization with sodium bicarbonate with an excess of phenylhydrazine in acetic acid (1 h, 20°C) gave 0.65 g of (XIV) phenylhydrazone, mp 146-147°C (from dil. alcohol) [7], R_f 0.65 (benzene).

To a solution of 3.72 g of $Na_2S_2O_5$ on 10 ml of water was added with stirring 1 g of methylglyoxime (XVII). The mixture was kept for 24 h at 20°C, acidified with 20% sulfuric acid to pH ~2, and the (XIV) steam-distilled as described above. The distillate was neutralized with sodium bicarbonate and treated with an excess of phenylhydrazine in acetic acid to give 0.85 g (34%) of (XIV) diphenylhydrazone, mp 145-146°C.

CONCLUSIONS

Cyclocondensation of 2,5,6-triamino-4-oxo-3,4-dihydropyrimidine with 1-phthalimido-2-alkanones in aqueous piperidine has given 7-alkylpterins.

LITERATURE CITED

1. S. I. Zab'yalov, A. G. Zavozin, and G. I. Ezhova, Izv. Akad. Nauk SSSR, Ser. Khim., 2626 (1981).
2. S. I. Zav'yalov and N. E. Kravchenko, Izv. Akad. Nauk SSSR, Ser. Khim., 454 (1984).
3. S. I. Zav'yalov and N. E. Knyaz'kova, Izv. Akad. Nauk SSSR, Ser. Khim., 215 (1983).
4. S. I. Zav'yalov and T. K. Budkova, Izv. Akad. Nauk SSSR, Ser. Khim., 1323 (1979).
5. A. Rosowsky and K. K. Chen, J. Org. Chem., 38, 2073 (1973).
6. W. Pfleiderer, H. Zondler, and R. Mengel, Liebigs Ann. Chem., 64, 741 (1970).
7. H. Pechmann, Chem. Ber., 20, 2539 (1887).
8. M. Gaudry and A. Marquet, Tetrahedron, 26, 5611 (1970).
9. S. I. Zav'yalov, G. I. Ezhova, T. K. Budkova, O. V. Dorofeeva, and O. K. Taganova, Izv. Akad. Nauk SSSR, Ser. Khim., 468 (1982).
10. J. F. Bunnett and D. S. Tarbell, J. Am. Chem. Soc., 67, 1944 (1945).