3. The reaction of the above acetal aminal with cyclohexanone gives 8-(3'-dimethylamino-2'-phenylpropenylidene)-2-dimethylamino-3-phenyl-5,6,7,8-tetrahydrobenzo[b]-2H-pyran, which is a valence isomer of 1,9-bisdimethylamino-2,8-diphenyl-4,6-trimethylenenona-1,3,6,8-tetraen-5-one. When treated with either $Et_3O^{\oplus}BF_4^{\ominus}$ or acids, it is converted to the bicyclic trimethineimmonium salt due to the deamination of the $(CH_3)_2N$ group from the 2H-pyran ring.

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# SYNTHESIS OF 2-HYDROXY-3-CARBETHOXY-5,6-DIALKYLPYRAZINES


S. I. Zav'yalov and A. G. Zavozin



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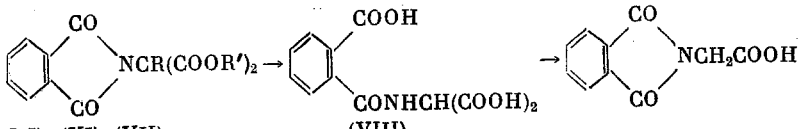
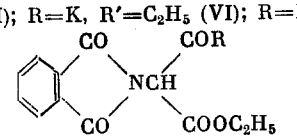
Previously we had described [1] the synthesis of 2-hydroxy-3,5,6-trialkylpyrazines by starting with the hydrochlorides of α-amino ketones (I) and the acid chlorides of N-phthaloyl-α-amino acids. In the present paper, on the basis of the hydrochlorides of α-amino ketones (I), we studied paths for the synthesis of 2-hydroxy-3-carbethoxy-5,6-dialkylpyrazines (II), which can have interest for the preparation of pteridines and their analogs.

Our initial attempts to convert phthalimidomalonic ester (III) to monoester (IV), and the latter via acid chloride (V) to 3-carbethoxypyrazines (II) by the scheme described in [1], gave negative results. The reaction of diester (III) with an equimolar amount of KOH in either alcohol or methanol gave the K derivatives of diester (VI) and the dimethyl ester of phthalimidomalonic acid (VII). The treatment of diester (III) with excess KOH in either alcohol or methanol led to hydrolysis of both ester groups and opening of the phthalimido ring to give N-(o-carboxybenzoyl)aminomalonic acid (VIII), whose structure was confirmed by decarboxylation and cyclization to the known phthalimidoacetic acid [2].




(III), (VI), (VII) (VIII)

R=H, R'=$C_2H_5$ (III); R=K, R'=$C_2H_5$ (VI); R=K, R'=$CH_3$ (VII).




R=OH (IV), Cl (V)

Then we investigated a path for the synthesis of 3-carbethoxypyrazines (II) by starting with acetamidomalonic ester (IX) and α-aminoacetone ethylene ketal (X). N-(Acetamidocarbethoxyacetyl)aminoacetone ethylene ketal (XI) is formed when they are heated due to aminolysis of one ester group, the acid hydrolysis of which gave ketone (XII).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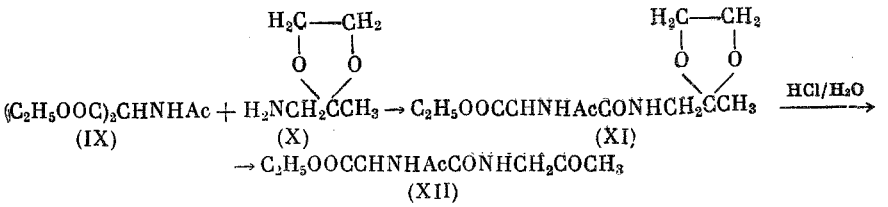
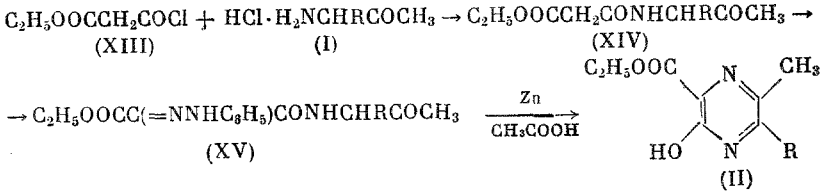
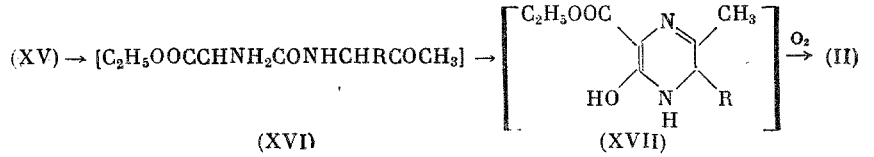


However, the low yield of ketone (XII) and its inability to cyclize under conventional conditions [1] to 2-hydroxy-3-carbethoxy-5-methylpyrazine forced us to reject further study of this path for the synthesis of 3-carbethoxypyrazines (II). We were able to obtain positive results by using carbethoxyacetyl chloride (XIII) as the starting compound, which in acetonitrile, in the presence of N,N-diethylaniline, reacts smoothly with the hydrochlorides of α-amino ketones (I) to form N-(carbethoxyacetyl)-α-amino ketones (XIV). The subsequent azo-coupling of ketones (XIV) with a phenyldiazonium salt made it possible to selectively insert in high yield the nitrous function into the malonic ester moiety and obtain phenylhydrazones (XV). Treatment of the latter with Zn powder in AcOH at ∿20° gave 3-carbethoxypyrazines (II) in 20-30% yields when based on the starting (I) hydrochlorides.



R = $CH_3$ (a), $C_2H_5$ (b), $i$-$C_4H_9$ (c), $CH_2CH_2SCH_3$ (d).

The conversion of phenylhydrazones (XV) to 3-carbethoxypyrazines (II) can be regarded as being a multistep process, which includes the intermediate steps of reducing phenylhydrazones (XV) to amino esters (XVI), cyclization of amino esters (XVI) to dihydropyrazines (XVII), and dehydrogenation of (XVII) by atmospheric oxygen.



The structure of the obtained 3-carbethoxypyrazines (II) was confirmed by the elemental analysis data, and also by the UV and PMR spectra.

## EXPERIMENTAL

The IR spectra were taken as KBr pellets on a UR-20 instrument, the PMR spectra were taken on a Varian DA-60-IL instrument (internal standard = HMDS), and the UV spectra were taken in alcohol solution on a Specord UV-VIS instrument. The TLC was run on Silufol UV-254, with development of the spots in UV light and by iodine vapors.

K Derivative of Phthalimidomalonic Ester (VI). With stirring, to a solution of 0.3 g (1 mmole) of phthalimidomalonic ester (III) [3] in 8 ml of alcohol was gradually added 0.06 g (1.1 mmoles) of KOH in 2 ml of alcohol. The mixture was kept for 23 h at ∿20°, and the precipitate was filtered, washed in succession with alcohol and ether, and dried in the air. We obtained 0.23 g (68%) of (VI), which decomposes above 300°. Found: C 49.91; H 4.32; N 4.31; K 10.87%. $C_{15}H_{14}KNO_6 \cdot H_2O$. Calculated: C 49.86; H 4.43; N 3.88; K 10.80%. The treatment of (VI) with dilute HCl solution (1:1) gave the starting (III) in ∿100% yield.

K Derivative of Dimethyl Phthalimidomalonate (VII). With stirring, to a solution of 0.6 g (2 mmoles) of (III) in 10 ml of MeOH was gradually added 0.12 g (2.2 mmoles) of KOH in 3 ml of MeOH. After standing for 23 h at ∿20° the solution was partially evaporated in vacuo, and the precipitate was filtered, washed with MeOH, and dried in the air. We obtained 0.52 g of (VII), which decomposes above 320°. The treatment of 0.52 g of (VII) with 1:1 HCl solution gave 0.43 g of dimethyl phthalimidomalonate, mp 122-124° [from ethyl acetate (EA)], $R_f$ 0.74 (EA). Infrared spectrum (ν, $cm^{-1}$): 1725, 1785 (phthalimide), 1752 (COOMe). PMR spectrum ($CDCl_3$, δ, ppm): 4.16 s (2 $CH_3O$), 5.86 s (CH), 8.16 d (aromatic ring). Found: C 56.15; H 3.95; N 5.15%. $C_{13}H_{11}NO_6$. Calculated: C 56.32; H 3.97; N 5.05%.

N-(o-Carboxybenzoyl)aminomalonic Acid (VIII). With stirring, to a solution of 0.91 g (3 mmoles) of (III) in 15 ml of MeOH was gradually added 0.37 g (6.6 mmoles) of KOH in 5 ml of MeOH. After keeping the reaction mixture for 26 h at ~20° the precipitate was filtered, treated with 1:1 HCl solution, and extracted with EA. The extract was dried over $MgSO_4$, evaporated, and the residue was washed with ether to give 0.42 g (51%) of tricarboxylic acid (VIII), mp 129-131° (decompn.). Infrared spectrum (ν, $cm^{-1}$): 1625 (amide), 1720 (COOH). Found: C 48.02; H 3.66; N 5.30%. $C_{11}H_9NO_7 \cdot {}^1/_2H_2O$. Calculated: C 47.83; H 3.62; N 5.07%. The hydrolysis of diester (III) with a 3-fold excess of KOH in alcohol gave acid (VIII) in 69% yield. The hydrolysis of diester (III) with a double excess of KOH in either alcohol or MeOH gave a complex mixture of products, which contained a small amount of acid (VIII). The heating of (VIII) up to 200° gave phthalimidoacetic acid with mp 193-194°, $R_f$ 0.60 (EA).

N-(Acetamidocarbethoxyacetyl)aminoacetone Ethylene Ketal (XI). A mixture of 1.8 g (8.3 mmoles) of acetamidomalonic ester (IX) and 1 g (8.6 mmoles) of aminoacetone ethylene ketal (X) [4] was heated for 4 h at 160-170° (bath temperature), and then it was chromatographed on a column packed with $SiO_2$ (L100/160 m, Chemapol). After elution with EA we isolated 0.8 g of an oil, which when treated with ether gave ethylene ketal (XI), mp 127-128°, $R_f$ 0.50 (2:1 EA—alcohol). Infrared spectrum (ν, $cm^{-1}$): 1665 (CONH), 1740 (COOEt). PMR spectrum ($CDCl_3$, δ, ppm): 1.20 m ($OCH_2\underline{CH_3}$, $CH_3$), 1.98 s ($CH_3CONH$), 3.72 m ($CH_2NH$), 3.86 s ($OCH_2CH_2O$), 4.16 q ($O\underline{CH_2}CH_3$), 5.12 d (CH). Found: C 49.93; H 6.97; N 9.62%. $C_{12}H_{20}N_2O_6$. Calculated: C 50.00; H 6.94; N 9.72%.

N-(Acetamidocarbethoxyacetyl)aminoacetone (XII). A mixture of 0.23 g of ethylene ketal (XI) and 5 ml of 1:5 HCl solution was kept for 65 h at ~20°. Then it was evaporated in vacuo and the residue was treated with ether to give 0.1 g (51%) of ketone (XII), mp 117-118° (ether—heptane), $R_f$ 0.50 (2:1 EA—alcohol). Infrared spectrum (ν, $cm^{-1}$): 1645 (CONH), 1730 (CO), 1750 (COOEt). PMR spectrum ($CDCl_3$, δ, ppm): 1.18 t ($OCH_2\underline{CH_3}$), 1.90 s ($CH_3CONH$), 2.03 s ($CH_3CO$), 4.07 m ($OCH_2$, $CH_2CO$), 5.08 d ($CO\underline{CH}NH$). Found: C 49.34; H 6.84; N 11.34%. $C_{10}H_{16}N_2O_5$. Calculated: C 49.18; H 6.56; N 11.48%.

N-(Carbethoxyacetyl)-3-amino-2-butanone (XIVa). With stirring, to a mixture of 2.84 g (20 mmoles) of 3-amino-2-butanone hydrochloride (Ia) [5] and 4.15 g (28 mmoles) of carbethoxyacetyl chloride (XIII) [6] in 12 ml of MeCN was gradually added 7.55 g (51 mmoles) of N,N-diethylaniline. The mixture was stirred for another 20 h at ~20° and then evaporated in vacuo. The residue was treated with EA, the precipitate of N,N-diethylaniline hydrochloride was filtered, and the filtrate was evaporated in vacuo. The residue was chromatographed on a $SiO_2$ column. The N,N-diethylaniline was eluted first with a 1:1 benzene—EA mixture, and then a 1:1 benzene—EA mixture and EA were used to elute 2.8 g (61%) of ketone (XIVa) as an oil with $R_f$ 0.35 (EA). Infrared spectrum (ν, $cm^{-1}$): 1660 (CONH), 1720-1735 (CO, COOEt). PMR spectrum ($CDCl_3$, δ, ppm): 1.20 m ($OCH_2\underline{CH_3}$, $\underline{CH_3}CH$), 2.16 s ($CH_3CO$), 3.30 s ($CH_2COOC_2H_5$), 4.16 q ($O\underline{CH_2}CH_3$), 4.48 m ($\underline{CH}NH$).

In a similar manner, from the hydrochlorides of 3-amino-2-pentanone (Ib) [1], 3-amino-5-methyl-2-hexanone (Ic) [5], and 3-amino-5-methylmercapto-2-pentanone (Id) were obtained as oils: N-(carbethoxyacetyl)-3-amino-2-pentanone (XIVb) in 59% yield, $R_f$ 0.41 (EA), IR spectrum (ν, $cm^{-1}$): 1660, 1725, 1735; and N-(carbethoxyacetyl)-3-amino-5-methyl-2-hexanone (XIVc) in 73% yield, $R_f$ 0.58 (EA). IR spectrum (ν, $cm^{-1}$): 1660, 1725, 1740; and N-(carbethoxyacetyl)-3-amino-5-methylmercapto-2-pentanone (XIVd) in 56% yield, $R_f$ 0.54 (EA), IR spectrum (ν, $cm^{-1}$): 1660, 1725, 1735.

N-(Phenylhydrazonocarbethoxyacetyl)-3-amino-2-butanone (XVa). With stirring, to a solution of 1 g (5 mmoles) of ketone (XIVa) and 2.72 g (20 mmoles) of $AcONa \cdot 3H_2O$ in 20 ml of water, cooled to 0°, was gradually added a cold solution (0-5°) of $PhN_2OAc$, which was prepared by reacting 0.4 g (5.8 mmoles) of $NaNO_2$ with 0.47 g (5 mmoles) of aniline in 3 ml of 1:1 HCl solution at 0-5° and subsequently adding excess $AcONa \cdot 3H_2O$ to pH 6.5-7.0. The reaction mixture was kept for 24 h at 0°, and the precipitate was filtered, washed with water, and dried in the air. We obtained 1.34 g (88%) of (XVa), mp 98-100° (after washing with n-heptane), $R_f$ 0.61 (5:1 benzene—EA). Infrared spectrum (ν, $cm^{-1}$): 1620, 1685, 1720. PMR spectrum ($CCl_4$, δ, ppm): 1.33 m ($\underline{CH_3}CH$, $\underline{CH_3}CH_2O$), 2.12 s ($CH_3CO$), 4.23 q ($CH_3\underline{CH_2}O$), 7.23 s and 7.30 s (aromatic ring). Found: C 58.88; H 6.31; N 13.78%. $C_{15}H_{19}N_3O_4$. Calculated: C 59.02; H 6.23; N 13.77%.

In a similar manner, from ketones (XIVb), (XIVc), and (XIVd) we obtained N-(phenylhydrazonocarbethoxyacetyl)-3-amino-2-pentanone (XVb) as an oil (here and subsequently isolated by extracting the reaction mixture with EA) in 98% yield, $R_f$ 0.71 (EA); N-(phenylhydrazonocarbethoxyacetyl)-3-amino-5-methyl-2-hexanone (XVc) as an oil in 95% yield, $R_f$ 0.76 (EA); N-(phenylhydrazonocarbethoxyacetyl)-3-amino-5-methylmercapto-2-pentanone (XVd) as an oil in 98% yield, $R_f$ 0.79 (EA).

2-Hydroxy-3-carbethoxy-5,6-dimethylpyrazine (IIa). To 0.6 g (2 mmoles) of phenylhydrazone (XVa) in 5.5 ml of AcOH was added 0.51 g (0.008 g-atom) of Zn powder and the mixture was stirred for 5 h at ∿20°, diluted with 25 ml of water, and extracted with EA. The extract was evaporated in vacuo and the residue was chromatographed on a $SiO_2$ column. Elution with EA gave 0.24 g (62%) of carbethoxypyrazine (IIa), mp 98-99° (from EA at −50°), $R_f$ 0.28 (EA). Infrared spectrum (ν, $cm^{-1}$): 1650, 1680, 1735. Ultraviolet spectrum ($\lambda_{max}$, nm): 235 (ε 7400), 323 (ε 5923), 380 (ε 4440). PMR spectrum ($CDCl_3$, δ, ppm): 1.37 t ($\underline{CH_3}CH_2O$), 2.45 s ($2CH_3$), 4.45 q ($CH_3\underline{CH_2}O$). Found: C 55.05; H 6.26; N 14.25%. $C_9H_{12}N_2O_3$. Calculated: C 55.09; H 6.17; N 14.28%.

In a similar manner, from phenylhydrazones (XVb-d) we obtained (IIb-d).

2-Hydroxy-3-carbethoxy-5-methyl-6-ethylpyrazine (IIb). Obtained in 42% yield, mp 69-71° (after chromatographing on a $SiO_2$ column, elution with a 5:1 benzene—EA mixture, and low-temperature recrystallization from ether), $R_f$ 0.47 (EA). Infrared spectrum (ν, $cm^{-1}$): 1650, 1720-1730. Ultraviolet spectrum ($\lambda_{max}$, nm): 235 (ε 6800), 320 (ε 6250), 368 (ε 3680). PMR spectrum ($CDCl_3$, δ, ppm): 1.30 m ($\underline{CH_3}CH_2O$, $\underline{CH_3}CH_2C$), 2.48 s ($CH_3$), 2.73 q ($CH_3\underline{CH_2}C$), 4.43 q ($CH_3\underline{CH_2}O$). Found: C 57.05; H 6.87; N 13.63%. $C_{10}H_{14}N_2O_3$. Calculated: C 57.13; H 6.71; N 13.33%.

2-Hydroxy-3-carbethoxy-5-methyl-6-isobutylpyrazine (IIc). Obtained in 40% yield, mp 86-87° (after chromatographing on a $SiO_2$ column, elution with a 5:1 benzene—EA mixture, and low-temperature recrystallization from ether), $R_f$ 0.60 (EA). Infrared spectrum (ν, $cm^{-1}$): 1645, 1730. Ultraviolet spectrum ($\lambda_{max}$, nm): 234 (ε 6400), 322 (ε 5500), 365 (ε 4600). PMR spectrum ($CDCl_3$, δ, ppm): 0.91 d (2 $CH_3$), 1.38 t ($\underline{CH_3}CH_2O$), 2.15 m (CH), 2.45 s ($CH_3$), 2.59 d ($CH_2$), 4.44 q ($CH_3\underline{CH_2}O$). Found: C 60.55; H 7.75; N 11.67%. $C_{12}H_{18}N_2O_3$. Calculated: C 60.48; H 7.61; N 11.76%.

2-Hydroxy-3-carbethoxy-5-methyl-6-(methylmercaptoethyl)pyrazine (IId). Obtained in 41% yield, mp 82-83° (after elution from a $SiO_2$ column with a 2:1 benzene—EA mixture and low-temperature recrystallization from ether), $R_f$ 0.46 (1:1 benzene—EA). Infrared spectrum (ν, $cm^{-1}$): 1560, 1680. Ultraviolet spectrum ($\lambda_{max}$, nm): 233 (ε 6900), 318 (ε 7900), 363 (ε 3180). PMR spectrum ($CDCl_3$, δ, ppm): 1.41 t ($\underline{CH_3}CH_2O$), 2.09 s ($CH_3S$), 2.50 s ($CH_3$), 2.95 m (2 $CH_2$), 4.46 q ($CH_3\underline{CH_2}O$). Found: C 51.70; H 6.33; N 10.97; S 12.38%. $C_{11}H_{16}N_2O_3S$. Calculated: C 51.56; H 6.29; N 10.93; S 12.49%.

## CONCLUSIONS

Some 2-hydroxy-3-carbethoxy-5,6-dialkylpyrazines were synthesized by reacting the hydrochlorides of α-amino ketones with carbethoxyacetyl chloride in the presence of N,N-diethylaniline, azo-coupling the obtained N-(carbethoxyacetyl)-α-amino ketones with phenyldiazonium salt, and reduction of the intermediate N-(phenylhydrazonocarbethoxyacetyl)-α-amino ketones with zinc.

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