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Reactions of 2-Piperidylacetohydrazides with Ethyl Acetoacetate or Acetylenic Acid Esters. Formation of 3,4-Dimethylpyrano-[2,3-*c*]pyrazol(6)ones and Perhydropyrazolo[2,3-*a*]-pyrido[1,2-*c*]pyrimidin-2,5-diones[1)]

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2-Piperidylacetohydrazides (I—III) were reacted with ethyl acetoacetate (EA), methyl tetrolate (MT), and ethyl phenylpropiolate (EP) with the aim of obtaining tricyclic heterocycles (IV). The desired compounds were produced when the following hydrazides and esters were heated under reflux in ethanol: II and EA, III and MT, II and EP. Interestingly, when 2-piperidylacetohydrazide (I) and its N′-phenyl derivative (III) were reacted with EA or MT and with EA, respectively, they afforded 3,4-dimethylpyrano[2,3-*c*]-pyrazol(6)ones (Va and Vb) with the expulsion of ethyl 2-piperidylacetate (VII). The mechanism of formation of Va and Vb is discussed.

Keywords——2-piperidylacetohydrazides; ethyl acetoacetate; methyl tetrolate; ethyl phenylpropiolate; pyranopyrazolones; pyrazolopyrimidopyridine derivatives; expulsion of piperidylacetyl group; perhydro-pyrazolo[2′,3′: 1,2]pyrimido[1,6-*a*]pyridin-2,11-diones

As part of a study on 3-azaquinolizidines, we have attempted to synthesize tricyclic heterocycles by a double cyclization reaction of piperidylacetohydrazides (I—III) with ethyl acetoacetate or methyl tetrolate. In addition to the desired heterocycles (IV), we obtained pyranopyrazolones (V) from the reaction of some hydrazides with β-keto and acetylenic esters. This paper reports the synthesis of these tricyclic compounds and the formation of the pyranopyrazolones.

Prior to the present investigation, many bicyclic 3-azaquinolizidine derivatives (VI) were prepared from piperidylacetohydrazides (I—III) and aldehydes.[3)] The piperidylacetohydrazides readily undergo condensation reactions with aldehydes to yield 2-aminoperhydropyrido[1,2-*c*]pyrimidin-3-one derivatives (VI). In view of their reaction with the carbonyl group, the hydrazides were reacted with ethyl acetoacetate, phenylpropiolate, and methyl tetrolate in the present work. A tricyclic heterocycle possessing a 3-azaquinolizine nucleus was produced when the methyl hydrazide II was reacted with ethyl acetoacetate or methyl tetrolate in boiling benzene or ethanol. Spectral data for the condensation product (IVa) were consistent with the empirical formula, $C_{12}H_{19}N_3O_2$. The nuclear magnetic resonance (NMR) spectrum exhibited two methyl singlets at 1.38 and 3.37 ppm which can be assigned to the C-methyl and N-methyl protons, respectively. The presence of the hydrazido carbonyl groups was indicated by the strong IR absorption bands at 1700 and 1670 cm^{-1}. The high frequency of the two absorption bands is reasonable, since heterocycles possessing the moiety –CON–NCO– in ring systems exhibit carbonyl absorption bands at 1700—1735 cm^{-1}.[4)] The

1) T. Tanaka, A. Terada, T. Miyadera, and R. Tachikawa, Abstracts of papers, The 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1973, p. 153.
2) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo, 140 Japan.*
3) T. Tanaka and T. Miyadera, unpublished data.
4) G. Cignarella, G. Pagliarini, and E. Testa, *Il Farmaco. Ed. Sc.*, **21**, 370 (1966); E. Bellasio, G. Pagani, A. Ripamonti, and E. Testa, *ibid.*, **20**, 428 (1965).

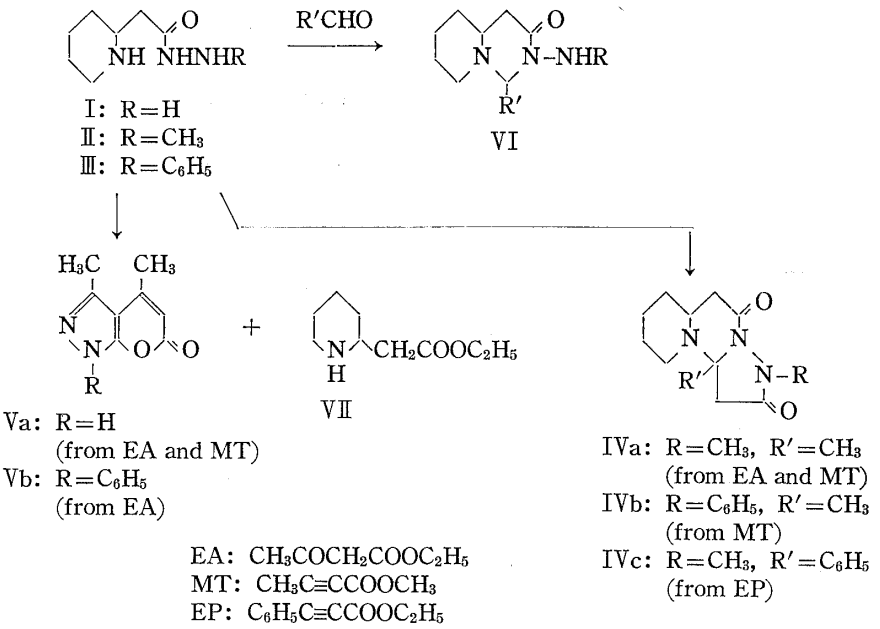

Chart 1

phenyl-substituted derivative IVb was similarly produced on treatment of N'-phenyl-2-piperidylacetohydrazide (III) with methyl tetrolate.

On the other hand, an unexpected compound (Va) of mp 248—250° (dec.). was formed on similar treatment of the unsubstituted hydrazide I with ethyl acetoacetate or methyl tetrolate in ethanol. The NMR spectrum of Va showed no indication of the piperidylacetyl moiety and instead showed two methyl singlets at 2.34 and 2.46 ppm, a singlet at 5.78 ppm, and one proton peak at 12.94 ppm. The analytical data and mass spectrum (*m/e* 164 (M^+)) were consistent with the formula $C_8H_8N_2O_2$, which suggested the formation of an aromatic heterocyclic compound with loss of the piperidylacetyl moiety. The piperidylacetyl residue was isolated by column chromatography as ethyl piperidylacetate (VII), which was identified by spectroscopic comparison with an authentic sample. The incorporation of two methyl groups indicates the participation of two molecules of ethyl acetoacetate or methyl tetrolate in the condensation reaction. A similar reaction also took place when the phenylhydrazide derivative III was treated in the same way with ethyl acetoacetate, giving the corresponding product Vb with the empirical formula $C_{14}H_{12}N_2O_2$. Based on mechanistic assumptions and spectroscopic data, the product was assumed to be a pyranopyrazolone derivative and this was finally confirmed by comparison with an authentic sample prepared by treatment of 3-methylpyrazol-5-one with ethyl acetoacetate at 160°.[5]

The possibility of hydrazine formation from the hydrazide I followed by reaction with ethyl acetoacetate leading to Va can be precluded on the ground that hydrazine did not afford

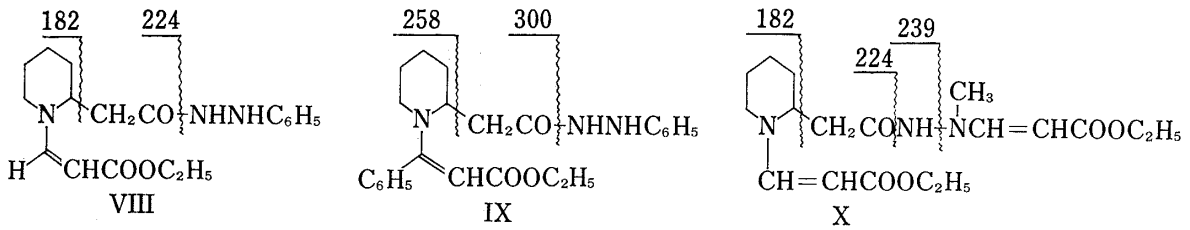

Chart 2

5) L. Wolff, *Chem. Ber.*, **38**, 3036 (1905).

Va on treatment with ethyl acetoacetate in refluxing ethanol. A plausible mechanism for the formation of Va is shown in Chart 3. It appears that the initial step in this reaction involves attack of the secondary amine of the piperidine on the carbonyl group of ethyl acetoacetate or the β-carbon of the acetylenic bond to give an enamine ester (XI). This kind of enamine ester (VIII or IX) could be obtained when the phenylhydrazide (III) was reacted with ethyl propiolate and ethyl phenylpropiolate in refluxing ethanol. The mass spectrum indicated that addition of the acetylenic bond occurred at the piperidine nitrogen atom.[6] The important fragments for the structural assignments arise from the molecular ion by C–C and CO–N bond fission, giving rise to fragment peaks at *m/e* 182 and 224 for VIII and *m/e* 258 and 300 for IX. Ethyl propiolate can undergo further addition with hydrazido NH, as can be seen in the reaction of the methylhydrazide II with ethyl propiolate to form the adduct X. The position of the second molecule of the ester in the adduct was determined from the mass spectrum. The diester showed a fragment peak at *m/e* 239 due to the amido radical ion, possibly arising by N–N bond fission of the molecular ion (*m/e* 369).

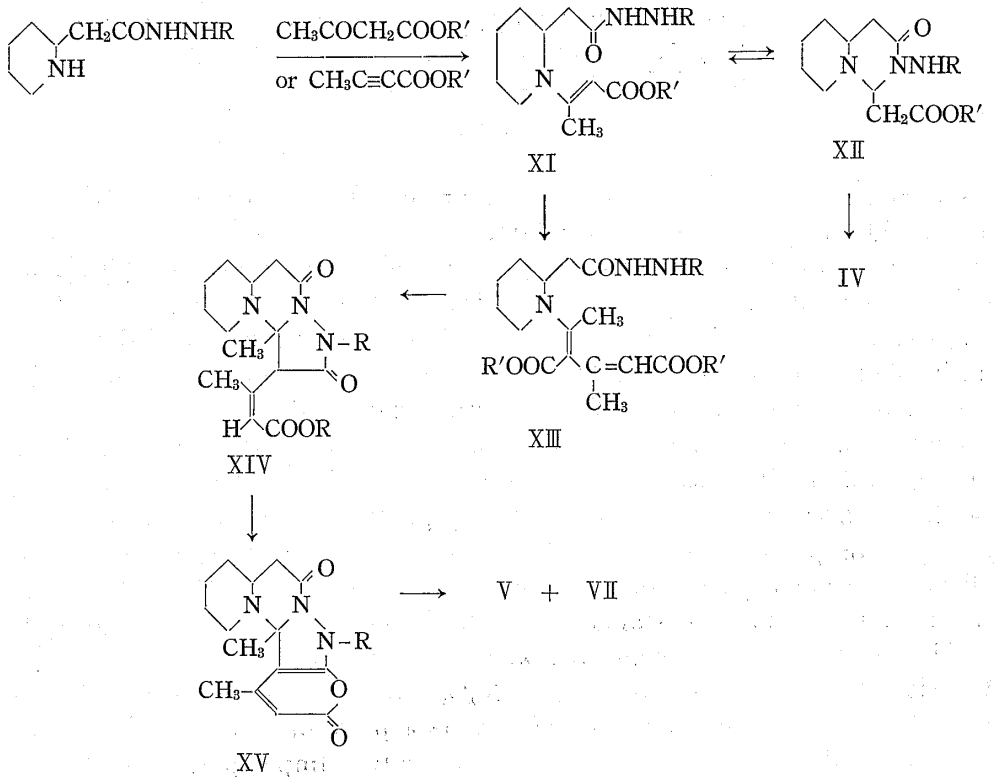

Chart 3

The enamine intermediate XI thus formed may undergo cyclization to XII and then IV or condensation with the second ethyl acetoacetate molecule to give a diester (XIII). It can be assumed that XI and XII are interconvertible, since the *cis* and *trans* isomers of VI (R=R'=C_6H_5) isomerize to give an equilibrium mixture in boiling ethanol.[7] The subsequent cyclization to XIV would be initiated by the formation of an azaquinolizidine nucleus. The consecutive cyclizations should result in the formation of a tetracyclic intermediate (XV) via intramolecular reaction between the amido carbonyl and the ester. The tetracyclic compound XV may undergo decomposition to the heteroaromatic bicyclic compounds Va and Vb and ethyl 2-piperidylacetate VII following attack of ethanol at the hydrazide carbonyl

6) B. Giese and R. Huisgen, *Tetrahedron Lett.*, **1967**, 1889.
7) T. Tanaka and T. Miyadera, unpublished results.

group. The formation of Va and Vb is a result of aromatization, which presumably provides the driving force for the degradation reaction. A possible alternative pathway in this reaction involves the formation of 1-methyl- and 1-phenyl-3-methylpyrazol-5-one from IV. However, this seems unlikely, since the pyrazol-5-ones did not afford V on heating under the same conditions.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 machine; chemical shifts were recorded in parts per million downfield from Me_4Si. IR spectra were taken using a Perkin–Elmer 225 spectrometer. Mass spectra were recorded using a JEOL JMS-01SG machine. The alumina used for column chromatography was obtained from E. Merck, Darmstadt, West Germany.

Preparations of 2-Piperidylacetohydrazides

2-Piperidylacetohydrazide (I)——A solution of ethyl 2-piperidylacetate (25 g) and 85% hydrazine hydrate (13 g) in EtOH (100 ml) was refluxed for 9 hr. After removal of the solvent, the residue was recrystallized from benzene to give I as colorless crystals, mp 73—74°. MS *m/e*: 157 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3330, 3250 (sh), 1670.

N′-Methyl-2-piperidylacetohydrazide (II)——A mixture of ethyl 2-piperidylacetate (8.5 g) and methylhydrazine (2.5 g) was heated under reflux for 27 hr. The solid material formed was recrystallized from benzene to give II as needles, mp 117—118°. Yield, 2.1 g. *Anal.* Calcd for $C_8H_{17}N_3O$: C, 56.11; H, 10.01; N, 24.54. Found: C, 56.20; H, 9.94; N, 24.64. MS *m/e* 171 (M^+).

N′-Phenyl-2-piperidylacetohydrazide (III)——A mixture of ethyl 2-piperidylacetate (1.5 g) and phenylhydrazine (0.95 g) was heated at 150° for 15.5 hr under slightly reduced pressure. The resulting solid material was washed with benzene–*n*-hexane and recrystallized from benzene to give III as fine needles, mp 131—133°. Yield, 1.56 g. *Anal.* Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.80; H, 8.12; N, 18.13. MS *m/e*: 233 (M^+).

3,11a-Dimethylperhydropyrazolo[2,3-*a*]pyrido[1,2-*c*]pyrimidin-2,5-dione (IVa)——A solution of the methylhydrazide (II, 1.57 g) and methyl tetrolate (500 mg) in EtOH (20 ml) was refluxed for 10 hr. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography on alumina, eluting with AcOEt, and then recrystallized from benzene–*n*-hexane to give IVa as colorless crystals (1.4 g), mp 153—154°. *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.71. Found: C, 60.90; H, 7.91; N, 18.01. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1670. MS *m/e*: 237 (M^+). NMR ($CDCl_3$) δ: 3.37 (3H, s, NCH_3), 1.38 (3H, s, C–CH_3), 3.11—1.07 (13H, m).

IVa was also obtained by treatment of II (2.9 g) with ethyl acetoacetate (2.43 g) in benzene (20 ml) (refluxed for 44 hr; yield, 350 mg).

11a-Methyl-3-phenylperhydropyrazolo[2,3-*a*]pyrido[1,2-*c*]pyrimidin-2,5-dione (IVb)——A mixture of the phenylhydrazide (III, 1.17 g) and methyl tetrolate (0.65 g) in EtOH (20 ml) was refluxed for 7 hr. After removal of the solvent, the residue was chromatographed on alumina, eluting with AcOEt, to give an oil which was crystallized as the hydrochloride (0.4 g) by treatment with iso-PrOH–HCl. Recrystallization from EtOH gave the hydrochloride of IVb as colorless prisms, mp 243—244° (dec.). *Anal.* Calcd for $C_{17}H_{21}N_3O_2 \cdot HCl$: C, 60.80; H, 6.60; N, 12.51; Cl, 10.56. Found: C, 60.68; H, 6.66; N, 12.64; Cl, 10.76. MS *m/e*: 299 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1685.

3-Methyl-11a-phenylperhydropyrazolo[2,3-*a*]pyrido[1,2-*c*]pyrimidin-2,5-dione (IVc)——A solution of the methylhydrazide (II, 1.0 g) and ethyl phenylpropiolate (1.1 g) in EtOH (20 ml) was refluxed for 21 hr. The solvent was evaporated off *in vacuo* and the residue was recrystallized from AcOEt to give IVc as colorless prisms (0.47 g), mp 181—182°. *Anal.* Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 67.96; H, 7.05; N, 14.26. NMR ($CDCl_3$) δ: 7.40 (5H, s, phenyl protons), 3.32 (3H, s, NCH_3), 3.23—0.92 (13H, m). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1650.

3,4-Dimethylpyrano[2,3-*c*]pyrazol(6)one (Va)——A solution of 2-piperidylacetohydrazide (I, 1.6 g) and methyl tetrolate (1.3 g) in EtOH (20 ml) was refluxed for 8 hr. The precipitate was collected by filtration and recrystallized from EtOH to give Va as colorless prisms, mp 248—250° (dec.). Yield, 0.35 g. *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.69; H, 5.04; N, 17.02. The mother liquor was concentrated to leave an oil, which was purified by column chromatography, eluting with AcOEt, to give 0.25 g of ethyl 2-piperidylacetate (VII) as an oil. The oil was identified by comparison of the IR spectrum with that of an authentic sample.

A solution of I (1.6 g) and ethyl acetoacetate (1.0 g) in EtOH (20 ml) was refluxed for 8 hr. The reaction mixture was worked up as described above to give 310 mg of IVa as crystals, mp 248—251° (dec.). Work-up of the mother liquor as described above afforded VII, bp 60—70° (bath temp.)/0.1 mmHg.

3,4-Dimethyl-1-phenylpyrano[2,3-*c*]pyrazol(6)one (Vb)——A solution of the phenylhydrazide (III, 4.9 g) and ethyl acetoacetate (3.1 g) in toluene (100 ml) was refluxed for 20 hr. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography, eluting with $CHCl_3$, to give Vb as prisms (0.5 g). Recrystallization from benzene–*n*-hexane gave crystals, mp 147—148°. *Anal.* Calcd for

$C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.03; N, 11.65. Found: C, 69.65; H, 5.15; N, 11.51. IR ν_{max}^{Nujol} cm^{-1}: 1750. NMR ($CDCl_3$) δ: 7.20—7.95 (5H, m, phenyl protons), 5.77 (1H, d, J=1.0 Hz, pyrone proton), 2.48 (3H, s, 3-CH_3), 2.38 (3H, s, 4-CH_3).

2-[1-(2-Ethoxycarbonylvinyl)]piperidyl-N′-phenylacetohydrazide (VIII)——A solution of the phenylhydrazide (III, 1.4 g) and ethyl propiolate (0.7 g) in EtOH (20 ml) was refluxed for 4 hr. The solvent was evaporated off *in vacuo* and the residue was chromatographed on alumina, eluting with AcOEt, to give VIII as crystals (0.10 g), mp 132—136°. *Anal.* Calcd for $C_{18}H_{25}N_3O_3$: C, 65.23; H, 7.60; N, 12.68. Found: C, 65.19; H, 7.52; N, 12.71. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1750, 1650. MS *m/e*: 331 (M^+), 286, 285, 244, 224, 182 (base peak). NMR ($CDCl_3$) ppm: 4.84—4.57 (1H, m, NCH=C<u>H</u>-), 4.15 (2H, q, J=7 Hz, C<u>H</u>$_2$$CH_3$), 1.22 (3H, t, J=7 Hz, CH_2C<u>H</u>$_3$). 7.43—6.72 (5H, m, phenyl protons), 3.77—1.47 (14H, m).

2-[1-(2-Ethoxycarbonyl-1-phenylvinyl)]piperidyl-N′-phenylacetohydrazide (IX)——A solution of the phenylhydrazide (III, 2.3 g) and ethyl phenylpropiolate (1.9 g) in EtOH (20 ml) was refluxed for 10 hr. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography on alumina, eluting with AcOEt, to give IX as colorless prisms (2.8 g), mp 131—132° (from AcOEt–*n*-hexane). *Anal.* Calcd for $C_{24}H_{29}N_3O_3$: C, 70.73; H, 7.17; N, 10.31. Found: C, 70.38; H, 7.31; N, 9.92. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1680, 1610, 1570. MS *m/e*: 407 (M^+), 362, 361, 300, 258 (base peak).

Ethyl 3-[2-[1-(2-Ethoxycarbonylvinyl)]piperidylacetyl-N′-methylhydrazino]acrylate (X)——A solution of the methylhydrazide (II, 1.57 g) and ethyl propiolate (1.1 g) in EtOH (20 ml) was refluxed for 30 hr. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with AcOEt, to give X as crystals (0.30 g), mp 112—114° (from benzene–*n*-hexane). *Anal.* Calcd for $C_{18}H_{29}N_3O_5$: C, 58.83; H, 7.96; N, 11.44. Found: C, 58.40; H, 7.85; N, 10.98. IR ν_{max}^{Nujol} cm^{-1}: 3210, 1680, 1660, 1620. NMR ($CDCl_3$) δ: 9.54 (1H, s, CONH), 7.37, 7.34 (2H, 2×d, J=13 Hz, 2×NC<u>H</u>=CH–), 4.70, 4.67 (2H, d-d, J=13 Hz, 2×NCH=C<u>H</u>–), 4.10 (4H, q, J=7 Hz, 2×C<u>H</u>$_2$$CH_3$), 3.08 (3H, s, NCH_3), 1.23 (6H, t, J=7 Hz, 2×CH_2C<u>H</u>$_3$). MS *m/e*: 367 (M^+), 182 (100), 224 (26), 239 (very weak).