Synthesis of a Bridgehead Nitrogen System. Imidazo[1,5-*b*]pyridazine Derivatives

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3,4-Dibenzoyl-2-oxobutyrate 4-semicarbazone (**6a**), ethyl 2,4-dioxo-3-phenacylvalerate 3-semicarbazone (**6b**) and diethyl phenacyloxalectate 3-semicarbazone (**6c**) *via* acid catalysed intramolecular cyclization afforded 2-phenyl-4-*R*-3*H*-imidazo[1,5-*d*]pyridazine-5,7-(6*H*)diones (**8d,e,f**). Elemental analyses and spectroscopic data (ir, nmr, ms) were in good agreement with the assigned structures.

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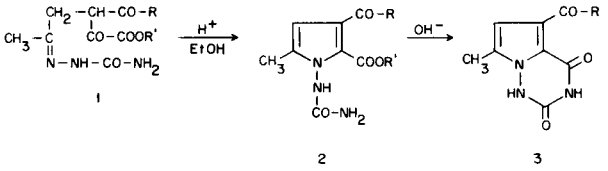
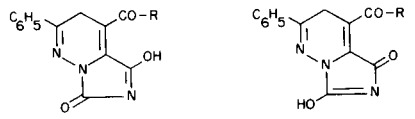
A previous paper (1) has described a convenient synthesis of pyrrolo[2,1-*f*]-1,2,4-triazine derivatives (**3**) involving the acid-catalysed cyclization of semicarbazones of type **1**, giving 1-ureidopyrrole derivatives of type **2**, followed by cyclization in alkaline conditions to give **3**. We wish to report our attempts to extend the above reaction to methyl 3,4-dibenzoyl-2-oxobutyrate 4-semicarbazone (**6a**), ethyl 2,4-dioxo-3-phenacylvalerate 3-semicarbazone (**6b**) and diethyl phenacyloxalacetate 3-semicarbazone (**6c**). By acid-catalysed cyclization, double cyclization products were obtained directly and were assigned the imidazo-[1,5-*b*]pyridazine structure (**8d,e,f**) (Scheme I) (1a)



The starting materials for this synthesis, **6a,b,c** were prepared according to the literature (1) (Experimental).

Elemental analyses and molecular weight determinations (mass spectra) for compounds **8d,e,f** showed that they are formed *via* the loss of one molecule of water and one molecule of alcohol (methanol in the case of **6a** or ethanol in the cases of **6b** and **6c**). The structures of 2-phenyl-4-benzoyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7(6*H*)-dione (**8d**), 2-phenyl-4-acetyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7(6*H*)dione (**8e**) and 2-phenyl-4-carboxyethyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)dione (**8f**), as opposed to the theorically possible pyrrole[3,1-*f*]-1,2,4-triazine derivatives (**7d,e,f**), were proven unequivocally by means of nmr data. The nmr spectra showed a singlet for the cyclic -CH_2- group at δ 3.60 (2H) and a broad signal for -NH- at δ 11.50, which was exchangeable with deuterium oxide.

For the imidazopyridazine derivatives, a lactam (**8d,e,f**)-lactim (**10a,b,c**) tautomerism is possible. In ethanol



10 a,b,c

(50%) solution, these compounds exist predominantly as the lactams. This finding is supported by the fact that in the infrared spectra, very strong carbonyl peaks were observed, rather than absorptions for the OH stretching frequency. Indeed, it should be noted that the uv spectra [λ max nm (log ϵ)] of **8d,e,f** changed dramatically in alkaline medium, showing absorptions with a strong hypochromic effect accompanied by an ipsochromic shift, as is represented in the graph for 2-phenyl-4-acetyl-3*H*-imidazo[1,5-*d*]pyridazine-5,7-(6*H*)dione (**8e**) (Figure I).

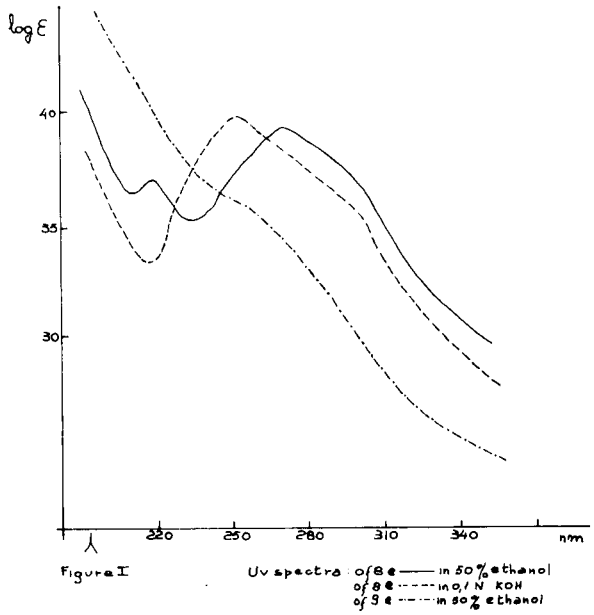


Figure I Uv spectra of 8e —— in 50% ethanol
of 8e - - - - in 0,1 N KOH
of 8e ·-·-· in 50% ethanol

Direct methylation of **8d,e,f** with ethereal diazomethane gave compounds **9d,e,f** (Table I), in which the nitrogen atom of the imidazo ring is methylated. The uv

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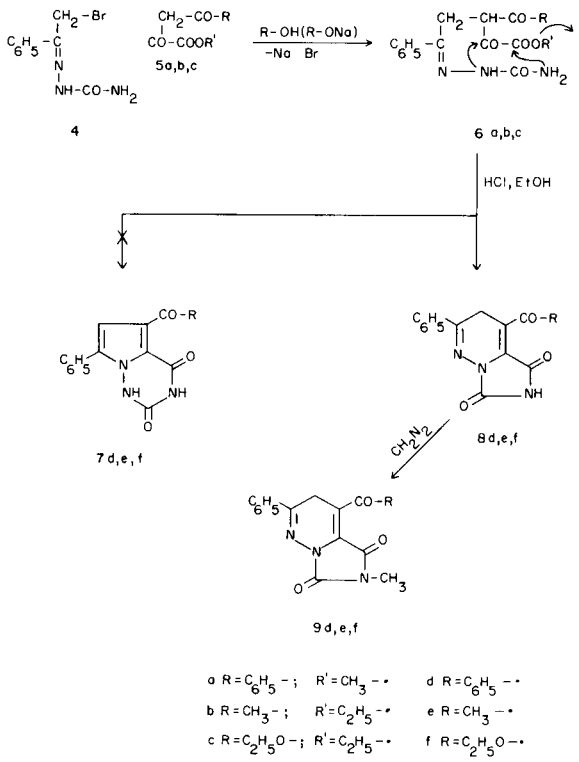
spectra of these compounds were identical with the parent compounds. Further evidence for *N*-methylation as opposed *O*-methylation in the above series of bicyclic compounds was provided by the fact that compound **9e**, by action of aqueous alkali, yielded methylamine, which was identified as hydrochloride salt. The mass spectrum was identical with that of an authentic sample of methylamine hydrochloride.

Table I



EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were determined in ethanol (50%) solution (unless otherwise specified) with a Perkin-Elmer Hitachi 200 Spectrophotometer. Infrared absorption spectra were obtained with a Perkin-Elmer Infracord 137 using nujol mulls. Nmr spectra (DMSO-d_6) were measured using TMS as the internal standard, with a Jeol C-60H spectrometer. The mass spectra were measured with a Jeol JMS-01SG-2 double focusing spectrometer at 75 eV (100 μA).

General Procedure for the Preparation of **6a,b,c**.

To a stirred suspension of sodium salts of methyl oxalyacetophenone (**5a**) (2), ethyl oxalylacetone (**5b**) (3) or diethyl oxalacetate (**5c**) (3) obtained from 0.01 mole of sodium, 100 ml. of absolute ethanol (absolute methanol for **5a**) and 0.01 mole of **5a, 5b** or **5c**, ω-bromo acetophenone semicarbazone (0.01 mole) (**4**) was added in small portions over a period of 15 minutes. After the addition, the mixture was stirred at room temperature for 2-3 additional hours and then stored in the refrigerator overnight. The reaction products precipitated directly from the reaction mixture and were filtered, washed with ice-water and ether and air dried.

Methyl 3,4-Dibenzoyl-2-oxobutyrate 4-Semicarbazone (**6a**).

This compound had m.p. 173° (ethanol) (yield 72%); ir: 3450, 3400, 3200 (NH, NH_2), 1790 and 1680 cm^{-1} (CO).

Anal. Calcd. for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 63.20; H, 5.13; N, 11.03.

Ethyl 2,4-Dioxo-3-phenacylvalerate 3-Semicarbazone (**6b**).

This compound had m.p. 150° (ethanol) (yield 70%); ir: 3490, 3250, 3200 (NH, NH_2) 1790 and 1690 cm^{-1} (CO).

Anal. Calcd. for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.85; H, 5.95; N, 12.73.

Diethyl Phenacyloxalacetate 3-Semicarbazone (**6c**).

This compound had m.p. 179° (ethanol) (yield 60%); ir: 3480, 3350, 3260, 3200 (NH, NH_2) 1750, 1720 and 1690 cm^{-1} (CO).

Anal. Calcd. for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83; N, 11.57. Found: C, 56.36; H, 6.00; N, 11.66.

General Procedure for the Preparation of **8d,e,f**.

Compounds **6a,b,c** (3 mmoles) in 20 ml. of ethanol saturated with hydrochloric acid were stirred at room temperature for 24 hours and then refluxed for 1 hour. After evaporation under reduced pressure a solid was obtained, which was washed with ice-water and air dried. Two crystallizations by appropriate solvents were usually sufficient to give material of analytical purity.

2-Phenyl-4-benzoyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)dione (**8d**).

This compound had m.p. 274-275° (butanol) (yield 80%); ir: 3180 (broad NH) 1770 and 1730 cm^{-1} (CO); uv (50% ethanol): λ max nm (log ϵ) 264 (4.44), 290 sh (4.29); (0.1*N* potassium hydroxide): 255 (3.74); nmr: δ 3.75 (2H, s, $-CH_2-$), 7.20-8.20 (10H, m, 2 × C_6H_5), 11.50 (1H, broad, NH, exchangeable with deuterium oxide); ms: 331 (M^+).

Anal. Calcd. for $C_{19}H_{13}N_3O_3$: C, 68.87; H, 3.96; N, 12.68. Found: C, 68.61; H, 4.07; N, 12.83.

2-Phenyl-4-acetyl-3*H*-imidazo[1,5-*d*]pyridazine-5,7-(6*H*)dione (**8e**).

This compound had m.p. 235° (acetic acid) (yield 70%); ir: 3180 (broad, NH), 1800 and 1750 cm^{-1} (CO); uv (50% ethanol): λ max nm (log ϵ) 220 (3.74), 270 (3.91), 300 sh (3.71); (0.1*N* potassium hydroxide): 260 sh (3.60); nmr: δ 2.60 (3H, s, $-CH_3$), 3.58 (2H, s, $-CH_2-$), 7.35-8.00 (5H, m, $-C_6H_5$), 11.80 (1H, broad, NH, exchangeable with deuterium oxide); ms: 269 (M^+).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.45; H, 4.10; N, 15.47.

2-Phenyl-4-carboxyethyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)dione (**8f**).

This compound had m.p. 217° (ethanol) (yield 60%); ir: 3150 (broad, NH) 1780 and 1740 cm^{-1} (CO); uv (50% ethanol): λ max nm (log ϵ) 220 (3.93), 273 (4.10), 300 sh (3.80); (0.1*N* potassium hydroxide): 260 sh (3.67); nmr: δ 1.28 (3H, t, $-COOCH_2-CH_3$, $J_{CH_3,CH_2} \cong$ 7.0 Hz), 3.68 (2H, s, $-CH_2-$), 4.20 (2H, q, $-COOCH_2-CH_3$, $J_{CH_2,CH_3} \cong$ 7.0 Hz), 7.30-8.10 (5H, m, C_6H_5), 11.70 (1H, broad, NH, exchangeable with deuterium oxide); ms: 299 (M^+).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.38; H, 4.57; N, 14.00.

General Procedure for the Preparation of **9d,e,f**.

A suspension of 0.5 g. of **8d,e,f** in 25 ml. of ether, containing 1.5 g. of diazomethane, was stirred for 24 hours. A solid precipitated which was recrystallized.

6-Methyl-2-phenyl-4-benzoyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)dione (**9d**).

This compound had m.p. 254° dec (butanol) (yield 80%); ir: 1730 and 1770 cm^{-1} (CO); uv: λ max nm (log ϵ) 255 (4.10), 317 sh (3.50); nmr: δ 2.95 (3H, s, $-CH_3$), 3.80 (2H, s, $-CH_2-$), 7.50-8.20 (10H, m, 2x $-C_6H_5$); ms: 345 (M^+).

Anal. Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.55; H, 4.38; N, 12.17. Found: C, 69.76; H, 4.35; N, 12.10.

6-Methyl-2-phenyl-4-acetyl-3*H*-imidazo[1,5-*d*]pyridazine-5,7-(6*H*)dione (**9e**).

This compound had m.p. 228° (acetic acid) (yield 75%); ir: 1730 and 1790 cm^{-1} (CO); uv: λ max nm (log ϵ) 250 (3.96), 315 sh (3.54); nmr: δ 2.65 (3H, s, $-CH_3$), 3.10 (3H, s, $-CH_3$), 3.65 (2H, s, $-CH_2-$), 7.50-8.10 (5H, m,

C_6H_5); ms: 283 (M^+).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.48; H, 4.67; N, 14.87.

6-Methyl-2-phenyl-4-carboxyethyl-3*H*-imidazo[1,5-*b*]pyridazine-5,7-(6*H*)-dione (**9f**).

This compound had m.p. 204° (ethanol) (yield 70%); ir: 1680, 1735 and 1790 cm^{-1} (CO); uv: λ max nm (log ε) 262 (3.97, 318 sh (3.27); nmr: δ 1.35 (3H, t, CH_3-CH_2-, J ≅ 7.0 Hz), 3.05 (3H, s, -CH_3), 3.80 (2H, s, -CH_2-), 4.30 (2H, q, CH_3-CH_2-, J ≅ 7.0), 7.40-8.10 (5H, m, C_6H_5); ms: 318 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.42; H, 4.76; N, 13.36.

Action of Potassium Hydroxide on 6-Methyl-2-phenyl-4-acetyl-3*H*-imidazo-[1,5-*b*]pyridazine-5,7-(6*H*)dione (**9e**).

A solution of 2 g. of **9e** in 30% aqueous potassium hydroxide (50 ml.) was refluxed for 6 hours. The gaseous material, which separated upon refluxing and on vapour distilling the resultant solution, was collected into a 1*N* hydrochloric acid solution, where methylamine hydrochloride readily separated. This compound was identical with an authentic sample (m.p. and mixed m.p., ir, ms).

REFERENCES AND NOTES

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(1a) Previously an example of this ring system **3** was reported by V. A. Chuiguk and G. M. Golubshina, U.S.S.R Patent 407,903; *Chem. Abstr.*, **80**, 9001b (1974); and V. A. Nuiguk, G. M. Golubshina, I. P. Bachkovskii and K. V. Fedotov, *Tezisy Dokl., Simp. Khim. Tekhnol. Geterosikl. Soedin. Goryuch. Iskop., 2nd.*, 17 (1933); *Chem. Abstr.*, **85**, 144683e (1976).

(2) M. Freri, *Gazz. Chim. Ital.*, **68**, 617 (1938).

(3) L. Claisen and N. Stylos, *Ber.*, **20**, 2188 (1887).