Application of 1,2,4-Triazoline-3,5-diones in the Synthesis of the Piperazic Acids (Hexahydropyridazine-3-carboxylic Acids)

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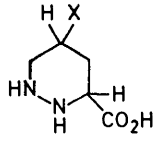
Diels–Alder reactions between penta-2,4-dienoic acid (and substituted analogues) and 4-phenyl-1,2,4-triazoline-3,5-dione (or 1,2,4-triazoline-3,5-dione) give adducts which, after hydrogenation and hydrolysis, yield the piperazic acid residues identified in the hydrolysates of the monamycin series of cyclohexadepsipeptide antibiotics.

THE monamycin family of cyclohexadepsipeptides[1] from *Streptomyces jamaicensis* has been shown to contain the hexahydropyridazine-3-carboxylic acids[2] (piperazic acids) (I)—(III). Confirmation of the structure of the

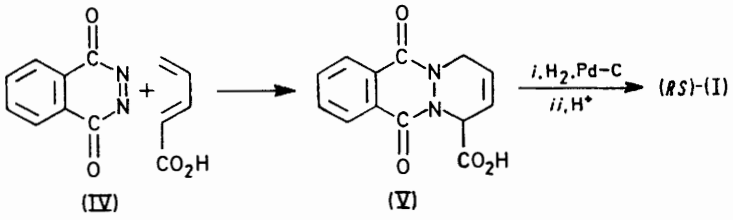


(I) (3*R*) X = H
(II) (3*R*,5*S*) X = Cl
(III) (3*S*,3*S*) X = OH

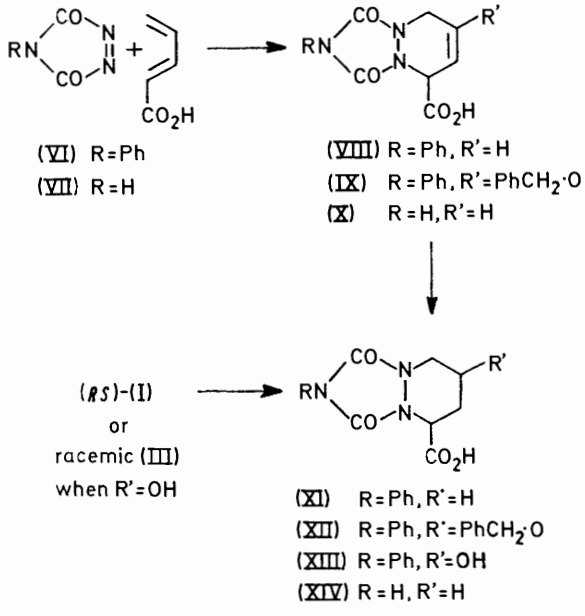
piperazic acid residue by synthesis (Scheme 1) has already been reported.[2] More recently it has been shown[3] that the adduct (V) can be resolved into its optical enantiomers *via* its brucine salt, and Scheme 1 thus provides a route to the natural form of the piperazic acid (I). The formation of the adduct (V), by use of lead(IV) acetate for the *in situ* formation of the dienophile (IV), is a low yielding step. An improvement in the yield of (IV) is achieved when t-butyl hypochlorite is used instead of lead(IV) acetate, but the hydrogen chloride released in this reaction appears to be detrimental to the formation of substituted piperazic acids. The present paper summarises the results of using a more stable dienophile,[4] 4-phenyl-1,2,4-triazoline-3,5-dione (VI), for the Diels–Alder reaction with penta-2,4-dienoic acids. The dienophile (VI) can be synthesised prior to carrying out the cycloaddition reaction, and since it is one of the most reactive dienophiles known it reacts readily with these relatively unreactive dienecarboxylic acids.

[1] C. H. Hassall, R. B. Morton, Y. Ogihara, and D. A. S. Phillips, *J. Chem. Soc.* (*C*), 1971, 526.
[2] K. Bevan, J. S. Davies, C. H. Hassall, R. B. Morton, and D. A. S. Phillips, *J. Chem. Soc.* (*C*), 1971, 514; C. H. Hassall, Y. Ogihara, and W. A. Thomas, *ibid.*, p. 522.
[3] C. H. Hassall and D. H. Rich, unpublished results.
[4] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters*, 1962, 615.

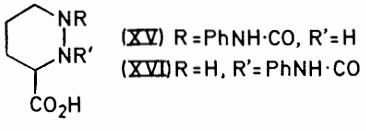
The dienophile (VI) was prepared by oxidation of 4-phenyl-1,2,4-triazolidine-3,5-dione with t-butyl hypochlorite [5] or nitrogen tetraoxide.[6] On treatment with penta-2,4-dienoic acid, a solution of the red dienophile (VI) in dichloromethane slowly deposited the adduct (VIII) in 90% yield. Hydrogenation of the adduct (VIII) over palladium gave a quantitative yield of the piperazic acid derivative (XI). In contrast to the phthalazinedione derivative in Scheme 1 the derivative (XI) was very resistant to acidic hydrolysis, but could be readily hydrolysed to piperazic acid (I) by treatment with aqueous alkali followed by acidification. A small amount of by-product which precipitated out at the final acidification stage appears to be the partially hydrolysed form (XV) or (XVI). Acidic hydrolysis of this product also yields piperazic acid (I). Thus a high yield (75%) of the piperazic acid (I) can be obtained by this reaction sequence.



SCHEME 1



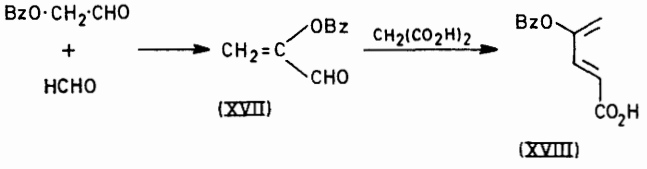
SCHEME 2



The ^1H n.m.r. spectrum favours assignment of the structure (XVI) to the by-product, since there is little change in the chemical shift of the proton at position 3 (τ 5.22) in going from compound (XI) to compound (XVI), and no change in the multiplicity of the signal occurs on exchange with D_2O. This strongly suggests that the nitrogen atom at position 2 is acylated.

The low reactivity of 4-chloropenta-2,4-dienoic acid in the Diels–Alder reaction and the loss of the chlorine atom at the hydrogenation stage led us to conclude that we could not improve on the formation of 5-chloropiperazic acid *via* the conversion of 5-hydroxypiperazic acid with phosphorus(v) chloride.[2] Thus to complete the synthesis of the piperazic acid analogues we concentrated on a synthesis of 5-hydroxypiperazic acid by the Diels–Alder reaction described above. The diene chosen for this synthetic sequence was 4-benzyloxypenta-2,4-dienoic acid (XVIII), prepared according to Scheme 3. The 2-benzyloxyethanal required as starting material was synthesised by a method analogous to the preparation of 2-ethoxyethanal.[7] High yields of (XVII) were obtained, but it was necessary to store the aldehyde at −15 °C to prevent polymerisation.

When the dienophile (VI) reacted with the acid (XVIII) in dichloromethane, the adduct (IX) was obtained in up to 55% yield. Hydrogenation of this adduct was carried out in two stages, to prevent premature removal of the benzyl group, since loss of the latter prior to reduction of the double bond gave rise to some of the keto-analogue. Although reduction of the ketone was expected to give the desired hydroxy-compound some difficulty in obtaining pure material was experienced when this route was used. However, catalytic hydrogenation over rhodium for 2 h gave compound (XII), and further hydrogenation over palladium–charcoal led to removal of the benzyl group, yielding the hydroxy-acid (XIII). Care was taken to control the first hydrogenation stage, since over-exposure brought about hydrogenation of the aromatic rings.



SCHEME 3

[5] R. C. Cookson, S. S. Gupte, I. D. R. Stevens, and G. T. Watts, *Org. Synth.*, 1971, **51**, 121.

[6] J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, 1966, **31**, 3444.

[7] M. F. Shostakovskii and N. A. Keiko, *Doklady Akad. Nauk S.S.S.R.*, 1965, **162**, 362 (*Chem. Abs.*, 1965, **63**, 5520).

The triazolinedione ring was removed from compound (XIII) by mild alkaline hydrolysis followed by acidification. The dinitrophenyl derivative of the hydrolysis product showed physical data similar to those for the hydroxypiperazic acid (III) isolated from monomycin. Small differences could be explained by the fact that the synthesised product exists as a diastereoisomeric mixture (two asymmetric centres). Thus on amino-acid analysis the synthesised product gave two peaks, explained as due to the *cis*-product (retention time 80 min) corresponding to (III) and the *trans*-product (90 min). *cis*- and *trans*-Hydroxyproline show similar chromatographic behaviour.[8]

The stability towards acidic hydrolysis of the *N*-phenyltriazolinedione derivative (XI) led us to investigate the properties of the unsubstituted triazolinedione (XIV). The adduct (X) was readily obtained by generating the dienophile (VII) from 1,2,4-triazolidine-3,5-dione in dioxan by treatment with t-butyl hypochlorite, followed by addition of penta-2,4-dienoic acid.[9] Hydrogenation over palladium yielded the saturated adduct (XIV) in high yield. By using an amino-acid analyser, the yield of piperazic acid (I) released from the adduct (XIV) under several hydrolysis conditions has been monitored. Hydrolysis in 4M-sodium hydroxide for 24 h gave only a 2% breakdown to piperazic acid (I), whereas boiling under reflux in 6M-hydrochloric acid gave a 75% yield of the acid.

There have been previous attempts to hydrolyse *N*-phenyltriazolinedione adducts, and our successful hydrolysis under alkaline conditions correlates with the results of Paquette[10] for the synthesis of semibullvalene by use of potassium hydroxide in aqueous ethylene glycol under nitrogen at 100 °C. The resistance of the unsubstituted adduct (XIV) towards alkali can be explained by the tendency of imides to lose the amino-proton,[11] giving a negatively charged nitrogen atom (stabilised by delocalisation of charge over the two carbonyl groups) which could reduce the probability of nucleophilic attack on the imide carbonyl groups.

Thus by judicious use of the *N*-substituted and unsubstituted triazolinediones, conditions can be devised for producing high yields of piperazic acids; alkaline or acidic conditions may be used for the final hydrolysis step.

EXPERIMENTAL

I.r. spectra were determined for KBr discs or liquid films with Perkin-Elmer 247 spectrophotometers. ^{1}H N.m.r. spectra were obtained at 100 MHz with a Varian HA100 spectrometer (Me_4Si as internal standard). Accurate mass measurements were performed by peak matching relative to fragment ions of heptacosafluorotributylamine with an A.E.I. MS9 spectrometer. Amino-acid analyses were carried out with a Beckman 120C analyser by use of Beckman custom spherical resins (49 cm column), with initial elution at pH 3.25 followed after 85 min with pH 4.30 buffer. Reactions were monitored by using t.l.c. plates of Kieselgel G (Merck) developed in the system (*A*) benzene–acetic acid–ethyl acetate (9 : 2 : 2), (*B*) butan-1-ol–acetic acid–water (3 : 1 : 1), and (*C*) benzene–methanol–acetic acid (10 : 2 : 1).

Penta-2,4-dienoic Acid.—A modification of the procedure of Glushkov and Magidson [9] was used. Malonic acid (75 g, 0.58 mol) in pyridine (105 ml), was treated with acrylaldehyde (51 g, 0.9 mol) added at a rate controlled so as to maintain a temperature of 50—60 °C. Towards the end of the addition heating was necessary to maintain the temperature. After cooling the solution was poured onto ice (400 g). The mixture was acidified to pH 1 (conc. hydrochloric acid) with cooling in an ice-bath; the product then crystallised out. Crystals were filtered off, rapidly washed, dissolved in pentane, and then dried (Na_2SO_4). This method prevented polymerisation of the product. The penta-2,4-dienoic acid was obtained from pentane as crystals, m.p. 72° (lit.,[9] 72°).

2,3,5,8-*Tetrahydro*-1,3-*dioxo*-2-*phenyl*-s-*triazolo*[1,2-a]*pyridazine*-5-*carboxylic Acid* (VIII).—4-Phenyl-1,2,4-triazoline-3,5-dione [5] (VI) (3.5 g) in dichloromethane (180 ml) at room temperature was treated with a solution of penta-2,4-dienoic acid (2 g) in dichloromethane (10 ml) in 2 ml portions over 10 min. The red colour of the dienophile was discharged and the *adduct* (VIII) was deposited. After cooling, the precipitate was collected and dried (93% yield, 5.1 g), m.p. 216—220° (from aqueous ethanol) (Found: C, 57.3; H, 4.15; N, 15.4. $C_{13}H_{11}N_3O_4$ requires C, 57.2; H, 4.05; N, 15.4%), $\nu_{max.}$ 1 770, 1 670 (imide), and 1 730 cm^{-1} (carboxy), τ [$(CD_3)_2SO$] 2.60 (5 H, s, C_6H_5), 3.96 (2 H, m, CH=CH), 4.88 (1 H, s, C*H*·CO_2H), and 5.78 and 6.04 (each 1 H, d, *J* 16 Hz, CH_2·N).

Hexahydro-1,3-*dioxo*-2-*phenyl*-s-*triazolo*[1,2-a]*pyridazine*-5-*carboxylic Acid* (XI).—Compound (VIII) (1.5 g) in methanol (100 ml) was hydrogenated for 3 h over 10% Pd–C to give a quantitative yield of the *piperazic acid adduct* (XI), m.p. 235—238° (from aqueous ethanol) (Found: C, 56.65; H, 4.7; N, 14.9. $C_{13}H_{13}N_3O_4$ requires C, 56.8; H, 4.7; N, 15.3%), $\nu_{max.}$ 1 760, 1 670 (imide), and 1 730 cm^{-1} (carboxy), τ [$(CD_3)_2SO$] 2.65 (5 H, s, C_6H_5), 5.22 (1 H, dd, N·C*H*·CO_2H), 6.1 and 6.84 (each 1 H, t, *J* 12 Hz, CH_2N), and 7.6—8.6 (4 H, m, CH_2·CH_2).

Hydrolysis of the Derivative (XI) *in Alkali*.—The piperazic acid derivative (XI) (1 g) in 4M-sodium hydroxide (5 ml) was heated under reflux for 4 h. After cooling, the solution was acidified to pH 1 (conc. hydrochloric acid); a white precipitate (300 mg) separated which was filtered off, and the filtrate was evaporated to dryness *in vacuo* leaving piperazic acid hydrochloride and sodium chloride. Trituration with methanol followed by removal of insoluble sodium chloride yielded piperazic acid hydrochloride [2] (390 mg, 65%) as a slightly discoloured oil. T.l.c. behaviour, amino-acid analysis, and other physical data were identical with those of authentic samples.

The white precipitate obtained at the acidification stage was 2-(*phenylcarbamoyl*)*piperazic acid* (XVI), m.p. 173—178° (from ethanol–water) (Found: C, 57.4; H, 5.9; N, 17.15. $C_{12}H_{15}N_3O_3$ requires C, 57.8; H, 6.05; N, 16.85%, M^+, 249), $\nu_{max.}$ 1 730 (carboxy) and 1 640 cm^{-1} (ureido CO), τ [$(CD_3)_2SO$] 1.12 (1 H, s, exchangeable with D_2O, CO_2H),

[8] J. C. Sheehan and J. G. Whitney, *J. Amer. Chem. Soc.*, 1963, **85**, 3863.

[9] R. G. Gluskov and O. Y. Magidson, *Med. Prom. S.S.S.R.*, 1962, **16**, 27 (*Chem. Abs.*, 1963, **58**, 442).

[10] L. A. Paquette, *J. Amer. Chem. Soc.*, 1970, **92**, 5765.

[11] O. H. Wheeler and O. Rosado, in ' The Chemistry of Amides,' ed. J. Zabicky, Interscience, 1970, ch. 7, p. 374.

2.46—3.2 (5 H, m, C_6H_5), 5.20 (1 H, dd, N·C*H*·CO_2H), 5.20—5.6br (1 H, removed by D_2O exchange, NH), 7.1br (2 H, t, CH_2·NH), and 7.8—8.7 (4 H, m, CH_2·CH_2).

2-(Phenylcarbamoyl)piperazic acid (XVI) (40 mg) in 6M-hydrochloric acid (3 ml) was boiled under reflux for 3 h. Amino-acid analysis of hydrolysate showed that piperazic acid had been formed as the only detectable product in 40% yield.

The overall yield of piperazic acid from the derivative (XI) (1 g) is therefore 75%. Hydrolysis of the derivative (XI) in 6M-HCl (sealed tube at 110 °C for 24 h) showed no evidence of breakdown to piperazic acid.

2-Benzyloxypropenal (XVII).—Diethylamine hydrochloride (34 g) and aqueous 38% methanal (33 ml) were dissolved in water (850 ml) and the pH of the solution was adjusted to 7—8 by dropwise addition of aqueous 5% sodium carbonate. After flushing with nitrogen, 2-benzyloxyethanal [12] (20 g) was added and the mixture was stirred overnight at 50 °C under nitrogen. The cooled mixture was extracted with ether, and the extract was dried and evaporated *in vacuo* to yield 2-benzyloxypropenal (XVII) (17 g, 79%) as an oil, b.p. 114° at 11 mmHg, n_D^{25} 1.529 9, $\nu_{max.}$ 1 700 (CO) and 1 610 cm^{-1} (C=C), τ ($CDCl_3$) 0.75 (1 H, s, CHO), 2.7 (5 H, s, C_6H_5), 5.0 (2 H, s, CH_2=), and 5.15 (2 H, s, C_6H_5·CH_2), used directly for the next stage.

4-Benzyloxypenta-2,4-dienoic Acid (XVIII).—2-Benzyloxypropenal (0.5 g) and malonic acid (0.7 g) in pyridine (25 ml) were heated at 55—60 °C for 6 h. The solution was poured into ice-cold water (50 ml) and acidified with hydrochloric acid to pH 1, with the temperature maintained below 10 °C. The acidified solution, kept at 0 °C, deposited *4-benzyloxypenta-2,4-dienoic acid* (XVIII) as needles, m.p. 90—92° (0.2 g, 34%) (Found: C, 70.9; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%), $\nu_{max.}$ 1 690 (carboxy) and 1 630 and 1 590 cm^{-1} (C=C), τ ($CDCl_3$) 0.0 (1 H, s, exchangeable with D_2O, CO_2H), 2.72 (5 H, s, C_6H_5), 2.93 (1 H, d, =C*H*·CO_2H, J_{trans} 19 Hz), 3.87 (1 H, d, C*H*=CH, J_{trans} 19 Hz), 5.21 (2 H, s, CH_2=), and 5.47 (2 H, s, C_6H_5·CH_2O).

7-Benzyloxy-2,3,5,8-tetrahydro-1,3-dioxo-2-phenyl-s-triazolo[1,2-a]*pyridazine-5-carboxylic Acid* (IX).—4-Benzyloxypenta-2,4-dienoic acid (XVIII) (0.5 g) in dichloromethane (3 ml) was added in one portion to a solution of the triazolinedione (VI) (0.4 g) in dichloromethane (15 ml). The red colour of the dienophile gradually disappeared and after stirring overnight the solution was concentrated *in vacuo* to crystallisation. Recrystallisation from ethanol–water gave the *adduct* (IX) (0.5 g, 55%) as platelets, m.p. 176—178° (Found: C, 62.9; H, 4.65; N, 11.3. $C_{20}H_{17}N_3O_5$ requires C, 63.0; H, 4.5; N, 11.1%), $\nu_{max.}$ 1 795 and 1 690 (imide) and 1 730 cm^{-1} (carboxy), τ [$(CD_3)_2SO$] 2.60 (5 H, s, N·C_6H_5), 2.69 (5 H, s, C_6H_5·CH_2), 4.76 (1 H, d, =C*H*·CH·CO_2H, J 6.5 Hz), 4.92 (1 H, d, =CH·C*H*·CO_2H, J 6.5 Hz), 5.12 (2 H, s, C_6H_5·CH_2O), and 5.88 (2 H, d, =C·CH_2·N).

7-Benzyloxyhexahydro-1,3-dioxo-2-phenyl-s-triazolo[1,2-a]*pyridazine-5-carboxylic Acid* (XII).—The adduct (IX) (0.5 g) in methanol (20 ml) was hydrogenated for 2 h over 5% rhodium–charcoal. Work-up in the usual way gave the *benzyloxypiperazic acid derivative* (XII) (0.4 g, 80%) as crystals, m.p. 114—115° (from water) (Found: C, 62.15; H, 6.55; N, 11.5. $C_{20}H_{19}N_3O_5$ requires C, 62.9; H, 5.0; N, 11.0%; accurate figures were difficult to obtain owing to the tendency for partial hydrogenation of benzene rings); $\nu_{max.}$ 1 775, 1 690 (imide), and 1 730 cm^{-1} (carboxy), τ [$(CD_3)_2SO$] 2.50 (5 H, s, N·C_6H_5), 2.64 (5 H, s, C_6H_5·CH_2), 5.20 (1 H, d, C*H*·CO_2H), and 5.45 (1 H, d, C_6H_5·CH_2) (higher field resonances were complicated by the presence of a partially hydrogenated mixture).

Hexahydro-7-hydroxy-1,3-dioxo-2-phenyl-s-triazolo[1,2-a]*pyridazine-5-carboxylic Acid* (XIII).—The benzyloxy-adduct (XII) (0.4 g) in methanol (20 ml) was hydrogenated overnight over 10% palladium–charcoal. Work-up gave crystals of the *hydroxypiperazic acid derivative* (XIII) (380 mg), m.p. 190—200° (from ethanol–water) (Found: M^+, 291.085 5 ± 14. $C_{13}H_{13}N_3O_5$ requires M, 291.085 513); $\nu_{max.}$ 3 500 (OH), 3 400—3 300 (CO_2H), 1 760, 1 695 (imide CO), and 1 730 cm^{-1} (CO_2H), τ [$(CD_3)_2SO$] 2.54 (5 H, s, C_6H_5·N), 5.34 (1 H, dd, C*H*·CO_2H), 5.92br (1 H, s, HO·C*H*), 6.10 and 6.70 (each 1 H, d, J 13 Hz, CH_2·N), and 7.7—8.0 (2 H, m, CH_2·CH).

Alkaline Hydrolysis of the Hydroxypiperazic Acid Derivative (XIII).—The 5-hydroxypiperazic acid derivative (XIII) (0.18 g) in 5M-sodium hydroxide (10 ml) was boiled under reflux for 3 h. On cooling, and after extraction with ether to remove phenylamine, the aqueous solution was acidified (hydrochloric acid); a slight precipitate (probably the partially hydrolysed product) separated. Amino-acid analysis of the filtrate showed two peaks at retention times 80 and 90 min, which have been interpreted as due to isomeric forms of 5-hydroxypiperazic acid (III). The products were purified by chromatography on a strong cation-exchange resin (Amberlite CG 120; column 20 × 1.5 cm), with 1M-hydrochloric acid as eluant. Both 5-hydroxypiperazic acid isomers were eluted within the elution volume (70 ml) required for natural 5-hydroxypiperazic acid.[13]

A dinitrophenyl derivative of the 5-hydroxypiperazic acids was prepared as follows. Appropriate fractions from the ion-exchange column were adjusted to pH 9 with alkali before addition of 1-fluoro-2,4-dinitrobenzene (2% solution in ethanol; 2 ml). After removal of the excess of dinitrofluorobenzene (extraction with ether) the aqueous solution was acidified and extracted with ether to give the 2,4-dinitrophenyl derivative of 5-hydroxypiperazic acid (0.136 g), m.p. 188—192° (from acetone–light petroleum) (lit.,[14] 201—202° for pure enantiomer), M^+ 312, with prominent peaks at *m/e* 294 (M − 18), 266, and 249, $\nu_{max.}$ 3 400 (OH), 3 300—2 500 (CO_2H), and 1 735 cm^{-1} (CO_2H), almost identical with spectra for natural 5-hydroxypiperazic acid.[13]

2,3,5,8-Tetrahydro-1,3-dioxo-s-triazolo[1,2-a]*pyridazine-5-carboxylic Acid* (X).—1,2,4-Triazolidine-3,5-dione (0.5 g) and penta-2,4-dienoic acid (0.5 g) in dioxan (50 ml) were treated with small portions of t-butyl hypochlorite at room temperature. The pink colour of the dienophile (VII) was allowed to fade before each addition until no further colour developed on addition of hypochlorite. Any precipitated solid was filtered off, and the remaining solution was evaporated *in vacuo* to give the *adduct* (X) (900 mg), m.p. 233—237° (from water) (Found: C, 42.7; H, 3.2; N, 21.0%; M^+, 197.043 7 ± 6. $C_7H_7N_3O_4$ requires C, 42.65; H, 3.6; N, 21.3%; M, 197.043 65), $\nu_{max.}$ 3 140br, 3 000br (CO_2H, NH), 1 760—1 720s (CO_2H and imide), and 1 690 cm^{-1} (imide), τ [$(CD_3)_2SO$] −1.13 (1 H, s, NH, exchangeable), 4.02 (2 H, d, CH=CH), 5.06 (1 H, m,

[12] L. Palfray and S. Sabetay, *Bull. Soc. chim. France*, 1937, **4**, 950.

[13] D. A. S. Phillips, Ph.D. Thesis, University of Wales, 1970.

[14] C. H. Hassall, R. B. Morton, Y. Ogihara, and W. A. Thomas, *Chem. Comm.*, 1969, 1079.

C*H*·CO_2H), and 5.89 and 6.19 (each 1 H, d, *J* 16 Hz, CH_2·N).

Hexahydro-1,3-*dioxo*-s-*triazolo*[1,2-a]*pyridazine*-5-*carboxylic Acid* (XIV).—Hydrogenation of the adduct (X) (150 mg) in methanol (10 ml) for 3 h over 10% Pd–C gave a quantitative yield of the *piperazic acid derivative* (XIV), m.p. 242—247° (from water) (Found: C, 42.85; H, 4.8; N, 21.5. $C_7H_9N_3O_4$ requires C, 42.2; H, 4.55; N, 21.1%), $\nu_{max.}$ 3 500—3 000 (CO_2H, NH), 1 760, 1 690 (imide CO), and 1 730 cm^{-1} (CO_2H), τ [$(CD_3)_2CO$], 5.36 (1 H, m, C*H*·CO_2H), 6.18 and 7.04 (each 1 H, t, *J* 12 Hz, CH_2·N), and 7.78—8.70 (4 H, complex, CH_2·CH_2).

Hydrolysis of the Derivative (XIV) *to Piperazic Acid* (I).—Compound (XIV) (50 mg) was hydrolysed under the following conditions and the piperazic acid released was analysed on an amino-acid analyser (peak at retention time 144 min): (i) 6M-HCl, reflux, 24 h, yield 76%; (ii) 6M-HCl, sealed tube, 110 °C, 24 h, yield 58%; (iii) 4M-NaOH, reflux, 24 h, yield 2%.

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