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SYNTHESIS OF 4-KETO-1*H*,4,5-DIHYDRO-1,2,5-BENZOTRIAZEPINES AND THEIR CHEMICAL BEHAVIOUR*

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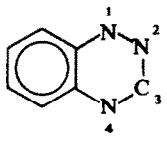
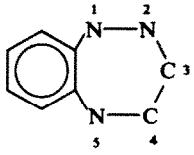
Abstract- Several 4-keto,1*H*,4,5-dihydro-1,2,5-benzotriazepines have been prepared by a new method and the catalytic hydrogenation of 4-keto-5-methyl-1*H*,4,5-dihydro-1,2,5-benzotriazepine (XI) and reaction with warm hydrochloric acid investigated. Hydrogenation produces fission of the 7-membered ring between positions 1 and 2 and heating with acid produces a ring-contraction yielding an isomer of XI. The structure of this isomer is 1-methyl-2-keto-4-imino-1,2-dihydroquinoxaline (XXV).

THE discovery of important psychosedative drugs belonging to the 1,4-benzodiazepine group has given rise to widespread interest in 7-membered heterocycles and particularly their benzo derivatives. In this field, we were interested in aza derivatives of 1,4-benzodiazepines (III) resulting from expansion of the benzo-1,2,4-triazine (I) system,



I



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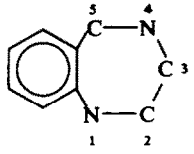


III

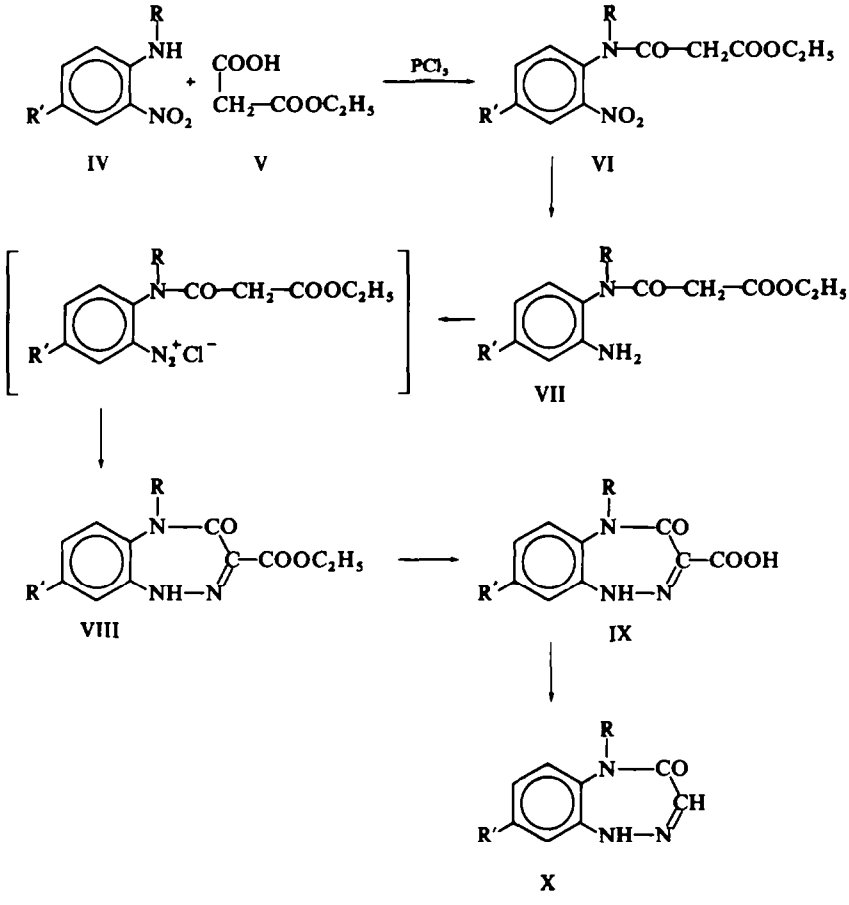
previously investigated.[1,2] The 1,2,5-benzotriazepine system, has not been adequately investigated and the few derivatives reported are insufficiently described.† The structure of 4,5-dihydro-3,4-cyclotetramethylene-1*H*-1,2,5-benzotriazepine was assigned[3] to a reduction product of cyclohexanone-*o*-nitrophenylhydrazone, but this assignment has been seriously questioned by Sparatore.[4] The only examples of 1,2,5-benzotriazepines known at present have been prepared[5] by condensing α-dicarbonyl compounds with *o*-aminophenylhydrazine, but the experimental difficulties involved in the synthesis of this hydrazine derivative[6] make the process impractical. The new procedure followed to synthesise benzo-1,2,5-triazepines, given in Chart 1, employs as starting materials the *o*-nitro-N-substituted-N-carbethoxyacetylanilines corresponding to the general formula VI. These compounds are easily available from the reaction of monoethyl malonate (V), or its potassium salt,

* First paper in the series: studies on 7-membered, benzo condensed heterocycles.

† A comprehensive critical survey of the literature on 1,2,5-benzotriazepines and of the problems involved in their preparation has been published.[2]

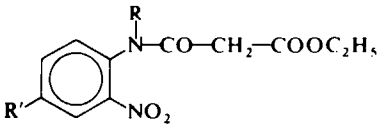
with N-monosubstituted *o*-nitroanilines (IV) and phosphorous pentachloride in anhydrous benzene. By this procedure the chloride of acid V reacts immediately with the *o*-nitroanilines and is not isolated.

CHART I



The *o*-nitroanilines of general formula VI are low-melting yellow colored solids which can be easily purified by crystallization. Data related to these compounds are listed in Table 1 and the preparation of N-carbethoxyacetyl,N-methyl-o-nitroaniline (VI—R = CH_3; R′ = H) is described in detail (Experimental). The nitro group in compounds VI can be reduced to an amino group either by zinc and hydrochloric acid or catalytically. The latter method was generally preferred being simpler and affording better yields. The acyl-*o*-phenylenediamines of general formula VII have a slightly higher m.p. than the corresponding nitro derivatives. Data related to these compounds are listed in Table 2 and the preparation of VII (R = CH_3; R′ = H and R = C_6H_{11}; R′ = H) is described in detail (Experimental).

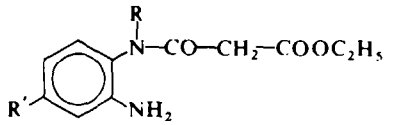
TABLE 1. N-CARBETHOXYACETYL-*o*-NITROANILINES



R	R'	Yields %	m.p. (solvents)*	Formula	C%		H%		N%		Ref. for intermediate o-nitroanilines
					Req.	Found	Req.	Found	Req.	Found	
CH_3	H	80	54°–5(xylene/petr. ether)	$C_{12}H_{14}N_2O_5$	54·13	54·02	5·30	5·23	10·52	10·77	7
CH_3	Cl	92	45°–7(ligroine/IsoPrOH)	$C_{12}H_{13}ClN_2O_5$	47·93	48·11	4·36	4·56	9·32	9·30	7
C_6H_5	H	84	63°–5(benzene/ligroine)	$C_{17}H_{16}N_2O_5$	62·19	61·98	4·91	5·19	8·53	8·40	8
C_6H_{11}	H	85	96°–7(benzene/petr. ether)	$C_{17}H_{22}N_2O_5$	61·06	61·18	6·63	6·56	8·38	8·46	8
CH_2—C_6H_5	H	84	75°–6(IsoPrOH)	$C_{18}H_{18}N_2O_5$	63·15	62·80	5·30	5·60	8·18	8·15	8

* Not corrected.

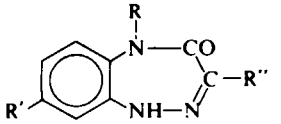
TABLE 2. N-CARBETHOXYACETYL-*o*-PHENYLENEDIAMINES



R	R′	Yields % *a*	Yields % *b*	m.p. (solvents)[d]	Formula	C% Req.	C% Found	H% Req.	H% Found	N% Req.	N% Found
CH_3	H	74	69	63–64°(xylene)	$C_{12}H_{16}N_2O_3$	61·00	61·19	6·83	6·98	11·86	12·00
CH_3	Cl	60	90	112–114°(EtOH)	$C_{12}H_{15}ClN_2O_3$	53·24	53·35	5·59	5·61	10·35	10·45
C_6H_{11}	H	—	91·5	117–118°(ligroine)	$C_{17}H_{24}N_2O_3$	67·08	67·31	7·95	7·96	9·20	8·95
CH_2—C_6H_5	H	—	94	74–75°(IsoPrOH/ligroine)	$C_{18}H_{20}N_2O_3$	69·21	69·03	6·45	6·68	8·97	8·92
C_6H_5	H[c]										

[a] Chemical reduction (Zn/HCl).
[b] Catalytic reduction (Pd/C 10% or Pt).
[c] Physical and Analytical data are not reported since this compound was obtained as an undistillable oil and it was used as such for the following step.
[d] Not corrected.

TABLE 3. 4-KETO-1,*H*,4,5-DIHYDRO-1,2,5-BENZOTRIAZEPINES



R	R'	R''	m.p. (solvents)*	Formula	C%		H%		N%	
					Req.	Found	Req.	Found	Req.	Found
CH_3	H	—$COOC_2H_5$	182–183°(xylene)	$C_{12}H_{13}N_3O_3$	58·29	58·41	5·30	5·23	17·00	17·10
CH_3	H	—$COOCH_3$	195–196°(xylene)	$C_{11}H_{11}N_3O_3$	56·65	56·77	4·75	4·84	18·02	18·10
CH_3	Cl	—$COOC_2H_5$	204–206°(xylene)	$C_{12}H_{12}ClN_3O_3$	51·16	52·57	4·29	4·76	14·92	15·31
C_6H_{11}	H	—$COOC_2H_5$	181–183°(xylene)	$C_{17}H_{21}N_3O_3$	64·74	65·10	6·71	6·55	13·33	13·37
C_6H_5	H	—$COOC_2H_5$	185–187°(EtOH 95%)	$C_{17}H_{15}N_3O_3$	66·01	65·77	4·89	4·82	13·59	13·79
CH_2—C_6H_5	H	—$COOC_2H_5$	160–161°(xylene)	$C_{18}H_{17}N_3O_3$	66·86	66·94	5·30	5·35	13·00	13·02
CH_3	H	—COOH	158–159°dec.(IsoPrOH)	$C_{10}H_9N_3O_3$	54·79	54·92	4·14	4·00	19·17	19·35
CH_3	Cl	—COOH	157–159°dec.(EtOH 70%)	$C_{10}H_8ClN_3O_3$	47·35	47·40	3·18	3·40	16·57	16·60
C_6H_{11}	H	—COOH	160–161°dec.(EtOH 60%)	$C_{15}H_{17}N_3O_3$	62·70	62·43	5·96	6·14	14·63	14·43
CH_2—C_6H_5	H	—COOH	140–142°dec.(IsoPrOH)	$C_{16}H_{13}N_3O_3$	65·07	64·83	4·44	6·27	—	—
C_6H_5	H	—COOH	160–161°dec.(EtOH 95%)	$C_{15}H_{11}N_3O_3$	64·05	64·06	3·94	3·86	14·94	14·80
CH_3	H	H	119–121°(toluene)	$C_9H_9N_3O$	61·70	61·95	5·18	5·17	23·99	23·90
CH_3	Cl	H	128–130°(EtOH 50%)	$C_9H_8ClN_3O$	51·56	51·52	3·85	4·09	20·05	20·25
C_6H_{11}	H	H	135–137°(EtOH 60%)	$C_{14}H_{17}N_3O$	69·11	69·03	7·04	7·21	17·27	17·28
C_6H_5	H	H	158–160°(IsoPrOH + petr. ether)	$C_{14}H_{11}N_3O$	70·87	70·90	4·67	4·75	17·71	17·56
CH_2—C_6H_5	H	H	148–150°(xylene)	$C_{15}H_{13}N_3O$	71·69	71·47	5·22	5·48	16·72	16·63

* Not corrected.

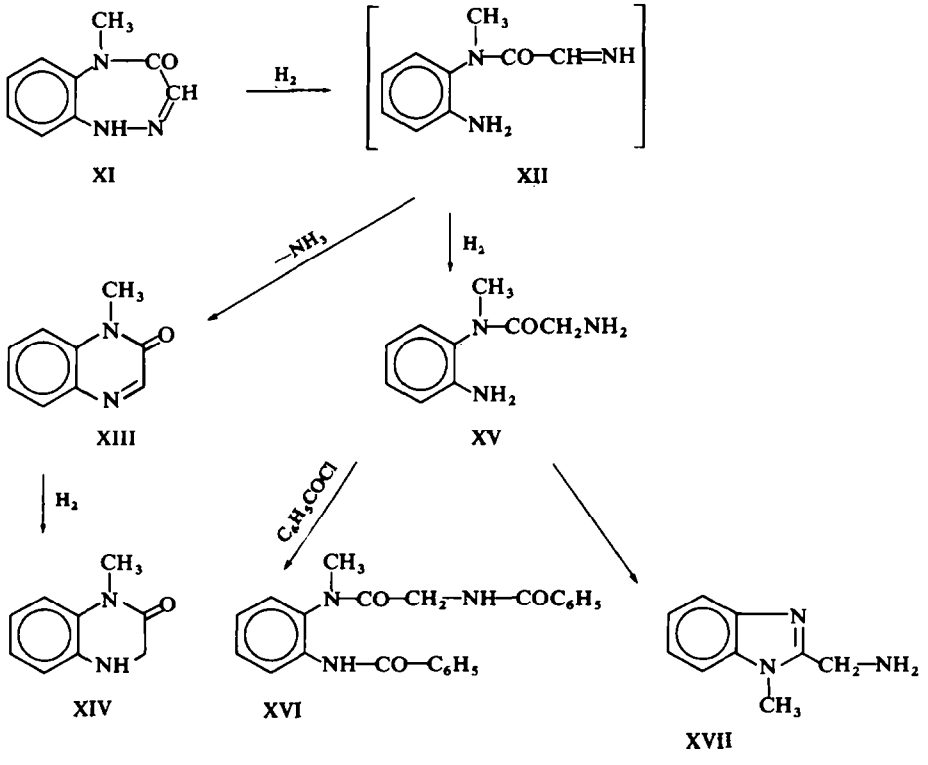
Compounds VII give rise to the 1,2,5-triazepine ring upon diazotization and intramolecular coupling. This reaction may occur spontaneously if the diazotization is carried out at sufficiently low acidity. The coupling reaction can otherwise be favoured by pH correction in the diazonium salt solution using a suitable buffer (e.g. sodium acetate). The ethyl esters obtained by this reaction are crystalline solids varying in colour from yellow to orange. They are listed in Table 3 together with the corresponding carboxylic acids which are easily prepared by alkaline hydrolysis.

Decarboxylation of the acids (IX) occurs by heating without catalysts at temperatures slightly above their m.ps. This reaction affords the corresponding 4-keto-1*H*,4,5-dihydro-1,2,5-benzotriazepines unsubstituted at position 3 (X). They are crystalline, light yellow coloured solids insoluble in water, in petrol ether and in dilute acids but soluble in the common organic solvents. They are very stable to heat and may be purified by distillation or sublimation at sufficiently reduced pressures (1 Torr. and lower). Data related to products X are listed in Table 3 and the preparation of 4-keto-5-methyl-1H,4,5-dihydro-1,2,5-benzotriazepine (X—R = CH_3; R′ = H; XI) is described. (Experimental) The IR and NMR spectra have been recorded and are in accord with the assigned structure.

All the compounds listed in Table 3 were screened for pharmacological activity and the results will be published elsewhere.

One of the simpler benzotriazepines prepared—4-keto,5-methyl-1*H*,4,5-dihydro-1,2,5-benzotriazepine (XI) was selected in order to study the chemical behaviour of the group.

CHART 2

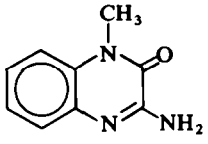


Hydrogenation of XI at room temperature and atmospheric pressure employing palladium as catalyst produced fission of the triazepine ring at the N—N bond (Chart 2) with consumption of two molecular equivalents of hydrogen.

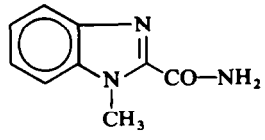
The reaction product consisted of a mixture of 1-methyl-2-keto-1,2,3,4-tetrahydroquinoxaline (XIV) and N-methyl-N-α-aminoacetyl-*o*-phenylenediamine (XV). The former was identified by comparison with a sample obtained by hydrogenation of authentic 1-methyl-2-keto-1,2-dihydroquinoxaline (XIII).[9] N-methyl,N-α-aminoacetyl-*o*-phenylenediamine (XV), owing to its instability, had to be identified through its dibenzoyl derivative (XVI) and by cyclization to the known 1-methyl-2-aminomethylbenzimidazole (XVII),[10] according to a classical scheme for benzimidazole synthesis.[11]

The formation of the two hydrogenation products XIV and XV can be rationalized by assuming compound XII as the common precursor. This was confirmed by the isolation of 1-methyl-2-keto-1,2-dihydroquinoxaline (XIII) in experiments which were stopped after consumption of the first molar equivalent of hydrogen.

Benzotriazepine (XI) is practically insoluble in cold dilute hydrochloric acid, on heating the resulting suspension the solid rapidly dissolved but it was not recovered on cooling. Neutralization of the cold acidic solution yielded a colorless precipitate with properties different from those of the starting material. The new product was a high melting (250–252° with decomp) solid insoluble in most organic solvents. Elemental analysis and mol wt determination were in agreement with empirical formula $C_9H_9N_3O$ corresponding to an isomer of benzotriazepine (XI). The IR spectrum shows bands of a carbonyl (1680 cm^{-1}) and of an NH group (3320 cm^{-1}); determination of the NMR spectrum was prevented by lack of solubility in the media commonly used for this technique. The compound with m.p. 250–252° is not 1-methyl-2-keto-3-amino-1,2-dihydroquinoxaline (XVIII) (comparison with an authentic sample)[12] and structure XIX (1-methyl,2-carbamidobenzimidazole) was also rejected because alkaline hydrolysis (KOH) yielded ammonia and an acid (see later) which differed from the known 1-methyl-2-carboxybenzimidazole.[13]



XVIII



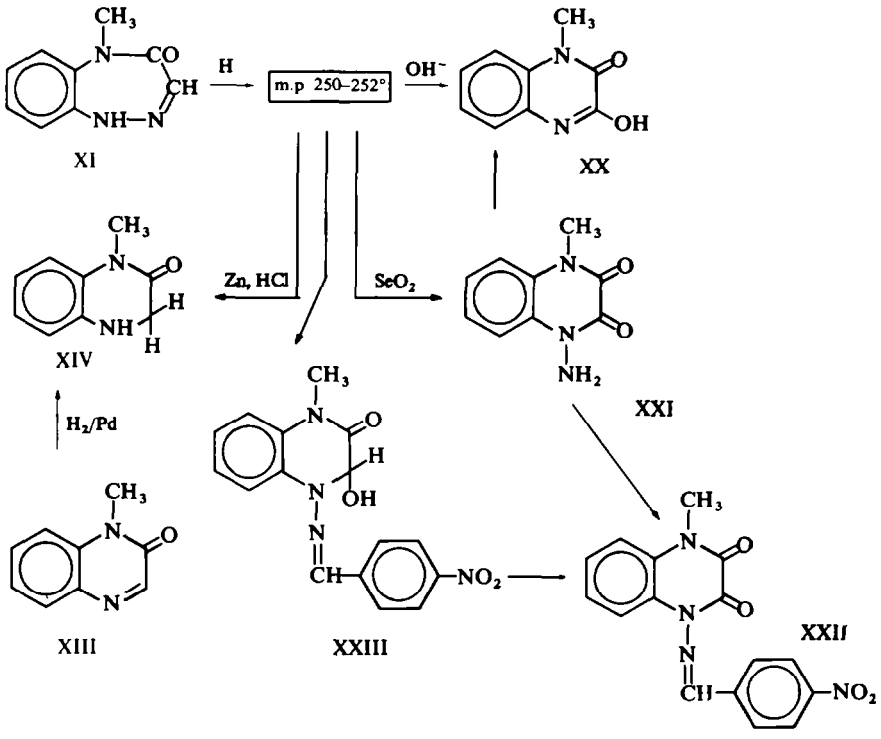
XIX

Evidence for the correct structure was obtained by the transformations outlined in Chart 3.

The acid produced by hydrolysis with aqueous potassium hydroxide was identified as 1-methyl-2-keto-3-hydroxy-1,2-dihydroquinoxaline (XX) by comparison with an authentic sample.[12] Reduction with zinc and hydrochloric acid afforded 1-methyl-2-keto-1,2,3,4-tetrahydroquinoxaline (XIV) which was independently prepared by hydrogenation of the known[9] dihydro derivative (XIII). Selenium dioxide oxidation in cold hydrochloric acid yielded 1-methyl-2,3-diketo-4-amino-1,2,3,4-tetrahydroquinoxaline (XXI) which could be deaminated to XX by treatment with Raney nickel

in boiling alcohol. Reaction with *p*-nitrobenzaldehyde in acetic acid furnished 1-methyl-2-keto-3-hydroxy-4-*p*-nitrobenzalamino-1,2,3,4-tetrahydroquinoxaline (XXIII) and the product (XXII) obtained by potassium dichromate oxidation of the latter

CHART 3



was identical with the *p*-nitrobenzal derivative of XXI. These results are consistent with a 1-methyl-2-quinoxalone structure in which the N atoms 1 and 2 of the original benzotriazepine (XI) are still bound together either in a diaziridine ring (XXIV) or

to form an N-imino derivative (XXV). On the other hand some of the physical properties of this compound (high m.p., low solubility) are in favour of a dipolar structure particularly as the oxidizing character common to all diaziridine derivatives[14] is lacking.

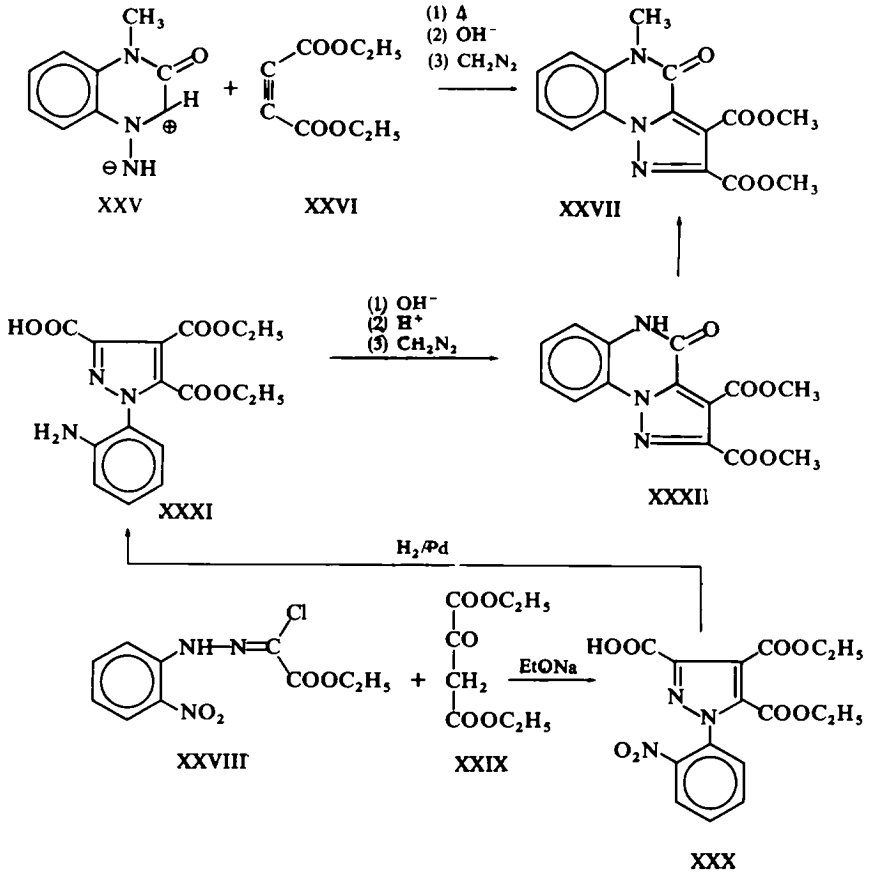
In order to gain conclusive evidence of its structure compound m.p. 250–252° was treated with diethyl acetylene dicarboxylate (XXVI) according to the 1-3-cycloaddition scheme[15] for heterocyclic N-imino derivatives. The reaction easily furnished

a product which led to the dimethylester of 4-keto-5-methyl-4-5-dihydropyrazole [1.5-a]quinoxaline 2,3-dicarboxylic acid (XXVII).* The structure of this compound was based on analytical and NMR data (Experimental) and by independent synthesis.

The above results indicate that the isomerization product formed by treatment of XI with hot hydrochloric acid has the structure XXV. Chart 4 summarizes the independent synthesis of the cycloaddition product XXVII. The procedure was similar in part to the synthesis originally described[16] for the parent heterocycle pyrazole [1.5-a]-quinoxaline.

Condensation of ethyl *o*-nitrophenylazo chloroacetate (XXVIII) with ethyl oxalacetate (XXIX) in presence of sodium ethoxide furnished 1-*o*-nitrophenyl-4,5-dicarbethoxy-3-pyrazole carboxylic acid XXX.†

CHART 4



* Dehydrogenation in the course of cycloaddition reactions of heterocyclic N-imino derivatives with acetylenic dipolarophyles was also observed by other Authors.[15]

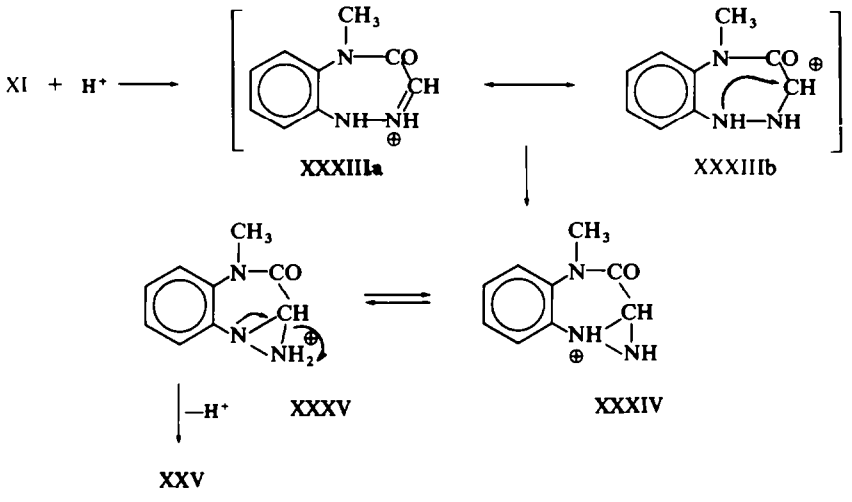
† Hydrolysis of a single carbethoxyl group occurred presumably in the course of the isolation procedure. The structure assigned to the resulting product (XXX) did not rest on experimental evidence but was deemed as the most reasonable considering the greater reactivity of the group placed at less hindered position 3.

The nitro group was catalytically reduced, the two carbethoxyl functions were hydrolysed and the corresponding di-acid was isolated and analysed as the dimethyl ester (diazomethane; XXXII). Methylation of the N atom at position 5 furnished XXVII which was identical in every respect with the diester obtained by hydrolysis of the cycloaddition product followed by treatment with diazomethane.

The isomerization reaction under the influence of acids proved to be general for all the 3-unsubstituted benzotriazepines described and it can be considered as an interesting new example of heterocyclic ring contraction.

Similar rearrangements have been described for 1,2-benzodiazepines[17–19] but the more pertinent to our case is the ring-contraction of 5-methyl-6-phenyl-2,3-dihydro-4*H*,1,2-diazepin-4-one to the corresponding 1-imino pyridine derivative, described by Moore.[20] The reaction pathway leading to XXV may be interpreted as a rearrangement involving (Chart 5) the protonated form of benzotriazepine XI (XXXIII, a–b). One possible intermediate is the diaziridine XXXIV ⇄ XXXV which could give rise to the imino derivative by fission of the 3-membered ring and deprotonation.

CHART 5



EXPERIMENTAL*

N-Carboxyacetyl-N-methyl-o-nitroaniline (VI—R = CH_3; R′ = H). 75 g of IV (R = CH_3; R′ = H)[7] and 70 g of V[21] were dissolved in anhyd benzene (550 ml) and to the stirred soln 106 g of finely powdered PCl_5 was added during 5 min. By external cooling the temp was held at 20–23°. The mixture was stirred 3 hr at room temp, then heated to 70° for 1 hr; a yellow ppt was first formed and later dissolved yielding a clear orange soln. Water and ice were added with stirring to a total volume of about 1500 ml while the temp was held below 30°. The benzene layer was decanted, washed with water, with sat $NaHCO_3$aq, again with water, dried over Na_2SO_4 and evaporated under reduced press. The crude residue afforded, on crystallization from xylene–pet ether (2·5:1 by volume), 107 g (80%) of pure product, m.p. 54–55°. Analysis is given in Table 1.

N-Carbethoxyacetyl-N-methyl-o-phenylenediamine (VII—R = CH_3; R′ = H). 11 g of VI (R = CH_3; R′ = H) was mixed with 16·2 g Zn powder and added with stirring to 100 g crushed ice. Conc HCl (62 ml)

* M.ps are not corrected.

diluted with ice-cold water (250 ml) was added and the mixture cooled to −5–10° for 10–15 min. The temp was allowed to rise to +5° in about 30 min, then the mixture was filtered, the resulting soln was made alkaline with NH_4OH and extracted with $CHCl_3$.

The extracts were washed with water, dried over Na_2SO_4 and evaporated under reduced press. The residue was taken up in xylene (30 ml), filtered and the soln kept overnight at −10°. The ppt was collected, washed with ethyl ether and crystallized from xylene, yield 7·2 g (74%) m.p. 63–64°. Analysis is given in Table 2.

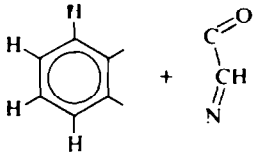
N-*Carbethoxyacetyl*-N-*cyclohexyl*-o-*phenylenediamine* (VII—R = C_6H_{11}; R′ = H). 45·6 g of VI (R = C_6H_{11}; R′ = H) was dissolved in 95% EtOH (250 ml); 0·45 g PtO_2 was added and the mixture was hydrogenated at room temp and atm press. Three molar equivs of H_2 were absorbed in 35 min. The catalyst was removed and the solvent evaporated under reduced press. The residue was crystallized from light pet ether (130 ml) yielding 38 g (91·5%) of pure material m.p. 117–118°. Analysis is given in Table 2.

3-*Carbethoxy*-4-*keto*-5-*methyl*-1H,4,5-*dihydro*-1,2,5-*benzotriazepine* (VIII—R = CH_3; R′ = H). 3% HCl (270 ml) was cooled to −5° and 6·5 g $NaNO_2$ dissolved in 25 ml water, was added while keeping the temp at −5°–0° by external cooling. To the stirred soln 20·5 g of VII (R = CH_3; R′ = H) was added in 10 min. Stirring of the mixture was continued for 1 hr at −5°–0° and for one night at room temp. The suspension was extracted twice with $CHCl_3$, the extracts were dried over Na_2SO_4 and the solvent removed under reduced press. The residue was crystallized from xylene (70 ml), and washed with pet ether, m.p. 182–183°, yield 15·5 g (72%). Analysis is given in Table 3.

3-*Carboxy*-4-*keto*-5-*methyl*-1H,4,5-*dihydro*-1,2,5-*benzotriazepine* (IX—R = CH_3; R′ = H). 2 g of VIII (R = CH_3; R′ = H) was suspended in 50% MeOH (50 ml) and 2 ml of 30% NaOH aq was added with stirring. The mixture was slowly heated to 40° and the resulting clear soln was diluted with water (20 ml), kept for 20 min at room temp and acidified with conc HCl. The ppt was purified by crystallization from isopropanol, orange-red crystals, m.p. 158–159° (dec), yield 1·5 g (85%). Analysis is given in Table 3.

Treatment of the acid with an EtOH soln of diazomethane afforded the corresponding methyl ester, m.p. 195–196° (from xylene). Analysis is given in Table 3.

4-*Keto*-5-*methyl*-1H,4,5-*dihydro*-1,2,5-*benzotriazepine* (XI). 3·1 g of IX (R = CH_3; R′ = H) was charged into a small distilling flask and heated to 150–160° under reduced press (1 mm Hg). The material decomposed with evolution of CO_2 and the residue was directly distilled b.p. 162–163° (1 mm Hg). The distillate was further purified by crystallization from toluene, yellow needles, m.p. 119–121°, yield 2·5 g (97%). Analysis is given in Table 3. IR spectrum: NH at 3350 cm^{-1} (sharp) amidic carbonyl at 1660 cm^{-1}; NMR spectrum (in $CDCl_3$, TMS as internal standard, recorded on a Perkin–Elmer R-10 spectrometer) showed the following features:

Bands	Chemical shift	Areas	Attribution
Single	2·5	1H	—NH—
Multiple enlarged	2·8–3·0	5H	
Single	6·55	3H	—N—CH_3

Hydrogenation of 4-*keto*-5-*methyl*-1H,4,5-*dihydro*-1,2,5-*benzotriazepine* (XI). 0·875 g of XI was dissolved in 95% EtOH (50 ml), 0·1 g of 10% Pd–C was added and the mixture was hydrogenated at room temp and atm press. Two molar equivs of H_2 were absorbed in about 3 hr. The catalyst was filtered off, the solvent removed under reduced press and the waxy residue was examined by TLC.* Two spots, neither of which corresponded to the starting material, were developed: one at the seeding point and the second at R_f 0·31.

* Layer of 250 mμ of Silica Gel GF 254 (purchased from Merck, A. G.) activated for 2 hr at 80°. Solvent: benzene–EtOAc 50:20 (by volume). Developer: UV light (254 mμ).

The residue was treated with cold benzene (40 ml) and the insoluble solid collected on a suction filter and crystallized from toluene (15 ml). The crystalline product (0·4 g) was very unstable (XV) melting at around 140° and containing an aromatic primary amino group (diazo reaction). TLC analysis showed it to correspond to the spot at the seeding point. For elemental analysis it was transformed into its dibenzoyl derivative (XVI), m.p. 178–179° (isopropanol). (Found: C, 71·15; H, 5·31; N, 10·60. $C_{23}H_{21}N_3O_3$ requires: C, 71·30; H, 5·46; N, 10·85%). A brief heating of compound m.p. 140° (XV; 0·2 g) with 4% NaOH aq (5 ml) yielded XVII m.p. 66–68° which was identified by comparison with an authentic sample[10] prepared from N-methyl-*o*-phenylenediamine and ethyl glycinate. The benzene liquors from treatment of the original hydrogenation mixture were evaporated to 10 ml and charged into a chromatographic column containing 30 g of neutral alumina.* Elution was carried out with benzene–EtOAc 80:20 (by volume) and eight 50 ml fractions were collected. TLC analysis of the eluates showed the presence of a single spot at R_f = 0·31. The combined fractions were evaporated under reduced press and the residue crystallized from light pet ether (0·150 g) m.p. 80–82°.

The product was identified as XIV by comparison (IR spectrum) with an authentic sample. Hydrogenation experiments carried out under similar conditions but using only one molar equiv of H_2 afforded XV and XIII (m.p. 116–118°—identified by comparison with authentic sample[9]) together with some starting material.

Isomerization of 4-*keto*-5-*methyl*-1H,4,5-*dihydro*-1,2,5-*benzotriazepine* (XI) *by hydrochloric acid*

1-*Methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV). 1·4 g of XI was suspended in 12% HCl (40 ml) and the mixture was heated to 50° with stirring for 15 min. After cooling, a yellow ppt was removed by filtration, the filtrate was made alkaline with conc NH_4OH, diluted with 300 ml water and kept at room temp for 1 hr.

The ppt was washed thoroughly with cold water and crystallized from pyridine, yield 0·8 g (57%) m.p. 250–252° (dec). The product was insoluble in the common organic solvents; slightly soluble in AcOH and pyridine; soluble in conc HCl. Mol wt (mass spectrometer): 175. (Found: C, 61·81; H, 5·41; N, 24·22. $C_9H_9N_3O$ requires: C, 61·70; H, 5·18; N, 23·99%).

Zinc and hydrochloric acid reduction of 1-*methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV)

1-*Methyl*-2-*keto*-1,2,3,4-*tetrahydroquinoxaline* (XIV). 0·35 g of XXV was dissolved in 20 ml 18% HCl and 2·6 g Zn powder was gradually added with stirring. The mixture was filtered, made alkaline with NH_4OH and extracted with $CHCl_3$. The extracts were dried over K_2CO_3 and the solvent removed under reduced press yielding 0·3 g of a straw-colored oil which crystallized on standing, m.p. 86–87° (from light pet ether). The product was identical in every respect with XIV independently prepared by catalytic reduction of XIII.

1-*Methyl*-2-*keto*-1,2,3,4-*tetrahydroquinoxaline* (XIV). 0·8 g of XIII[9] was dissolved in 95% EtOH (50 ml), 0·2 g Pd C was added and the mixture hydrogenated at room temp and atm press. In a few min one molar equiv of H_2 was absorbed. The catalyst was filtered off, the solvent removed under reduced press and the residue crystallized from light pet ether, yield 0·6 g (74·5%). m.p. 86–87°. (Found: C, 67·20; H, 7·37; N, 17·40. $C_9H_{10}N_2O$ requires: C, 66·65; H, 7·22; N, 17·27%).

Action of alkalies on 1-*methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV)

1-*Methyl*-2-*keto*-3-*hydroxy*-1,2-*dihydroquinoxaline* (XX). 0·5 g of XXV was suspended in a mixture of 2 g KOH, 4 ml 95% EtOH and 2 ml water. The mixture was heated under reflux for 15 hr while the solid slowly dissolved and NH_3 was evolved.

After cooling to room temp the K salt (0·3 g) was collected and dissolved in water (5 ml), the soln filtered and acidified to pH3 with HCl, m.p. 278–280° from EtOH. (Found: C, 61·49; H, 4·96; N, 15·67. $C_9H_8N_2O_2$ requires: C, 61·36; H, 4·58; N, 15·90%).

The product was identical in all respects with a sample of XX independently prepared.[12]

Reaction of 1-*methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV) *with* p-*nitrobenzaldehyde*

1-*Methyl*-2-*keto*-3-*hydroxy*-4-p-*nitrobenzalamino*-1,2,3,4-*tetrahydroquinoxaline* (XXIII). 0·7 g of XXV was dissolved in 50 ml 90% AcOH by brief heating and a soln of 0·75 g *p*-nitrobenzaldehyde in 5 ml AcOH was added. The mixture was heated under reflux until complete soln of the reagents. After cooling to room temp a red crystalline ppt was collected, washed with cold water and crystallized from dioxan, yield

* Neutral chromatography grade alumina type RS; purchased from Carlo Erba S.p.A., Milano.

0·85 g (65%), m.p. 218–219°. (Found: C, 59·09; H, 4·41; N, 16·88. $C_{16}H_{14}N_4O_4$ requires: C, 58·89: H, 4·32; N, 17·17%).

Reaction of 1-*methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV) *with selenium dioxide*

1-*Methyl*-2,3-*diketo*-4-*amino*-1,2,3,4-*tetrahydroquinoxaline* (XXI). 0·1 g of XXV was dissolved in 4 ml 18% HCl by brief heating. After cooling to room temp 0·1 g of SeO_2 was added. Se separated instantaneously and the reaction was completed by heating for a few min on a steam bath. The soln was made alkaline with 30% NaOH aq and extracted with $CHCl_3$. The solvent was removed and the residue crystallized from water, m.p. 219–221°. (Found: C, 56·25; H, 5·07; N, 21·80. $C_9H_9N_3O_2$ requires: C, 56·54; H, 4·75; N, 21·98%). The product reacted with *p*-nitrobenzaldehyde in AcOH furnishing a *p*-nitrobenzal derivative (XXII), m.p. 262–263° from dioxan.

Deamination of 1-*methyl*-2,3-*diketo*-4-*amino*-1,2,3,4-*tetrahydroquinoxaline* (XXI) *to* 1-*methyl*-2,3-*diketo*-3-*hydroxy*-1,2-*dihydroquinoxaline* (XX). 0·1 g of XXI was dissolved in EtOH (7·5 ml) and 1 g freshly prepared Raney Ni added. The mixture was heated under reflux for 2 hr until NH_3 evolution ceased. The Ni was removed by filtration and the soln acidified to pH3 with HCl and evaporated under reduced press to a volume of about 2 ml. On cooling to 10° a crystalline ppt was formed, m.p. 280–282 (EtOH). The product was identical in all respects with a sample of XX independently prepared.[12]

1-*Methyl*-2,3-*diketo*-4-p-*nitrobenzalamino*-1,2,3,4-*tetrahydroquinoxaline* (XXII) *by oxidation of the* 3-*hydroxy derivative* (XXIII). 0·1 g of XXIII was dissolved in AcOH (5 ml) and treated with a soln of potassium dichromate (0·05 g) in water (2 ml). The mixture was stirred at room temp for 20 min; 3 ml water was added and the yellow ppt was collected, m.p. 262–263° from dioxan. (Found: C, 58·96; H, 3·99; N, 17·10. $C_{16}H_{12}N_4O_4$ requires: C, 59·25; H, 3·73; N, 17·28%). The product was identical in all respects with that obtained by the reaction of XXI with *p*-nitrobenzaldehyde.

Addition of diethylacetylene dicarboxylate (XXVI) *to* 1-*methyl*-2-*keto*-4-*imino*-1,2-*dihydroquinoxaline* (XXV)

2,3-*Dicarboxy*-4-*keto*-5-*methyl*-4,5-*dihydropyrazole* [1·5-a]*quinoxaline and its dimethyl ester* (XXVII). A mixture of 0·875 g of XXV and of 4 g of XXVI* was heated with stirring at 140–150° for 3 hr.

Excess acetylene dicarboxylate was removed under reduced press and the residue was treated with alcoholic NaOH aq (10 ml 10% NaOH + 40 ml 95% EtOH) and heated under reflux for 10 min. 250 ml water was added and the resulting soln was acidified with conc HCl. The mixture was cooled to 10 yielding a ppt, (0·9 g 62·8%) of 2,3-dicarboxy-4-keto-5-methyl-4,5-dihydropyrazole [1·5-a]quinoxaline. m.p. 284–285° from dioxan. (Found: C, 53·69; H, 3·57; N, 14·22. $C_{13}H_9N_3O_5$ requires: C, 54·36; H, 3·16; N, 14·63%). The diacid m.p. 284–285° (0·25 g) was suspended in dry dioxan (10 ml) and treated with a dioxan soln (25 ml) containing 0·015 moles of diazomethane. The diacid dissolved; the solvent was removed under reduced press and the residue was crystallized from MeOH; m.p. 165–166°. (Found: C, 56·86; H, 3·85; N, 13·24. $C_{15}H_{13}N_3O_5$ requires: C, 57·14; H, 4·16; N, 13·33%).

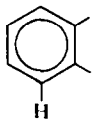
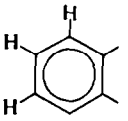
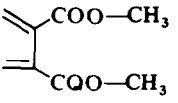
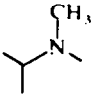
Examined on TLC* the product showed a single spot at R_f 0·7 with blue fluorescence at 254 mμ. The NMR spectrum ($CDCl_3$ soln, TMS as internal standard, recorded on a Perkin–Elmer R-10 spectrometer) showed the following features:

1-o-*Nitrophenyl*-4,5-*dicarbethoxy*-3-*pyrazole carboxylic acid* (XXX). An EtOH soln of NaOEt was prepared by dissolving 1·84 g Na in 100 ml anhyd EtOH and 11·04 g of XXIX, followed by a slurry of 21·7 g of XXVIII[22] and EtOH (200 ml) was added. The mixture was stirred at room temp for 5 hr then filtered and the solvent removed under reduced press. The residue was taken up in water (300 ml) and the mixture thoroughly extracted with $CHCl_3$. The organic layer was discarded, the aqueous layer was acidified and extracted twice with $CHCl_3$. The combined extracts were dried over Na_2SO_4, the solvent was removed under reduced press and the residue was triturated with toluene and crystallized from 95% EtOH, m.p. 191–192°. (Found: C, 50·93; H, 4·04; N, 11·37. $C_{16}H_{15}N_3O_8$ requires: C, 50·93; H, 4·00; N, 11·14%).

1-o-*Aminophenyl*-4,5-*dicarbethoxy*-3-*pyrazolecarboxylic acid* (XXXI). 3 g of XXX was dissolved in 95% EtOH (500 ml) by heating briefly on a steam bath. 0·5 g of 10% Pd–C was added and the mixture was hydrogenated at room temp and atm press. 3 Molar equivs of H_2 were absorbed. The catalyst was removed and the solvent evaporated under reduced press. The residual crude material was crystallized from EtOH, yield 2·3 g (83·4%), m.p. 185–186°. (Found: C, 55·33; H, 4·89; N, 12·40. $C_{16}H_{17}N_3O_6$ requires: C, 55·33; H, 4·93; N, 12·10%).

2,3-*Dicarbomethoxy*-4-*keto*-4,5-*dihydropyrazole*[1·5-a]*quinoxaline* (XXXII). 2 g of XXXI was dissolved in a 2·5% NaOH aq (40 ml) and heated under reflux for 30 min.

* Purchased from Fluka A.G. Buchs, Switzerland.

Bands	Chemical shift	Areas	Attribution
Multiple enlarged	1·4–1·6	1H	
Multiple	2·4–2·6	3H	
Single	5·9	6H	
Single	6·25	3H	

After cooling to room temp, 100 ml water and 30 g sulphonic ion-exchange resin (Amberlite IR 120) was added. The soln was stirred for 15 min at room temp, then the resin was discarded and the mixture was treated again twice as above. A colorless ppt was formed and after 2 hr storage in an ice box it was collected and dried under vacuum at 130°. 1 g of this material was added to a dioxan soln (100 ml) containing 2 g diazomethane. The product dissolved in a few min, the mixture was kept at room temp for 1 hr then the solvent was removed under reduced press and the residue was taken up in 95% EtOH (10 ml). Some insoluble material was removed and the alcohol was completely evaporated under reduced press. The residue was dissolved in dry benzene (20 ml) and chromatographed on a column of alumina† (50 g) employing as the eluent a mixture of benzene–EtOAc: 80–20 by volume. The collected fractions corresponding to the first 80 ml of eluate were combined and the solvent removed under reduced press. The residue (0·45 g) crystallized from xylene as light yellow crystals m.p. 141–142°, soluble in $CHCl_3$ and in EtOAc. Examined by TLC the product showed a single spot at R_f 0·83*. (Found: C, 55·95; H, 3·70; N, 13·81. $C_{14}H_{11}N_3O_5$ requires: C, 55·80; H, 3·68; N, 13·95%).

2,3-Dicarbomethoxy-4-keto-5-methyl-4,5-dihydropyrazole[1·5-a]*quinoxaline* (XXVII). 0·45 g of XXXII was dissolved in dry xylene (25 ml) and treated with 0·6 g of 50% oil-dispersed NaH. The mixture was heated under reflux with stirring for 4 hr, then MeI (3 ml) was added and heating was resumed for 2 hr. The solvent was removed under reduced press and the residue was crystallized from isopropanol, m.p. 164–165°. The product was identical in all respects (mixed m.p., IR and NMR spectra) with XXVII obtained by hydrolysis and diazomethane esterification of the cycloaddition product of XXV with XXVI.

Examined on TLC* it showed a single spot at R_f 0·7 with a typical blue fluorescence at 254 mμ.

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* See footnote on page 6405
† See footnote on page 6406.

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