## Synthesis of Hexahydro-bis[benzo-dipyrazolones, benzo-diazepinone] and Dithiopyrimidoquinazolinetetrone

Fathy Abdel Kader Amer, El-Sayed Afsah, Mohamed Tawfik El-Zimaity, and Mohamed Abbas Metwally

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, A. R., Egypt

Z. Naturforsch. 34b, 95-98 (1979); received June 5, 1978

Pyrazolones, Diazonium Salts, Synthesis

A new series of hexahydro-bis-benzodipyrazolones ( $2\,a-e$ ) were obtained by the interaction of 1 with hydrazines. These pyrazolones underwent coupling reaction with different diazonium salts to give  $7\,a-g$ . Compound 1 when treated with acid hydrazides gave  $3\,a$ , b, and when subjected to Japp-Klingemann reaction in alkaline medium gave  $6\,a-e$ . The hexahydro-bis-benzodiazepine (8), and dithiopyrimidoquinazolinetetrone (10) were obtained by the interaction of 1 with o-phenylenediamine and thiourea respectively.

For continuing our previous work [1] on the synthesis of new pyrazolones and their application as disperse dyes and also our investigation on the biological activity, derivatives [2, 6, 7, 8, 10] were required.

The earliest significant work on the reaction of diethyl 1,4-cyclohexanedione-2,5-dicarboxylate (1) with amines was first reported by Baeyer [2]. This was followed by a series of chemical interactions with substituted aromatic [3] and aliphatic amines [4, 5]. This prompted us to investigate the behaviour of 1 towards hydrazines, acid hydrazides, o-phenylenediamine and thiourea.

Thus, 1 reacted with hydrazines to give 2.3a.4.6.7a.8-hexahydro-2.6-bis(substituted)benzo 1.2-c:4.5-c' dipyrazole-3.7-diones (2a-e). Formulation of 2a-e was based on the elemental analyses and the IR spectra, which shows the regular absorption bands at 1690, 1670 and 1610 cm<sup>-1</sup> attributable to the pyrazolone moity.

In view of the reported formation of 4-arylazo-1-isonicotinoyl-3-methyl-5-pyrazolones [6a] an attempt was made to obtain 2 (R=CO  $\cdot$  C<sub>6</sub>H<sub>5</sub>) by the action of the acid hydrazides on 1 lead to the formation of 3a, b [6b]. The structure of these compounds was confirmed by the IR and NMR spectral data. The carbethoxy group protons appear at 1 ppm, t for CH<sub>3</sub> and 4 ppm, q for CH<sub>2</sub>; the ring methylene protons at 2.9 ppm, d.

When 2a was treated with acetic anhydride in presence of sodium acetate, the N-acteyl derivative 4 was isolated.

Requests for reprints should be sent to Dr. F. Abdel Kader Amer, Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, A. R. Egypt.

$$\begin{array}{c} \text{EtO}_2\text{C} \\ \text{RCONHNH}_2 \\ \text{O} \\ \text{CO}_2\text{Et} \\ \text{RNHNN}_2 \\ \text{O} \\ \text{RCOHN.N} \\ \text{CO}_2\text{Et} \\ \text{RNHNN}_2 \\ \text{O} \\ \text{RCOHN.N} \\ \text{O} \\ \text{CO}_2\text{Et} \\ \text{RNHNN}_2 \\ \text{O} \\ \text{ROHN.N} \\ \text{O} \\ \text{ROHN.N} \\ \text{O} \\ \text{O}_2\text{Et} \\ \text{RNHNN}_2 \\ \text{O} \\ \text{ROHN.N} \\ \text{O} \\ \text{O} \\ \text{O} \\ \text{E} \\ \text{ROHN.N} \\ \text{O} \\ \text{O} \\ \text{O} \\ \text{E} \\ \text{ROHN.N} \\ \text{O} \\$$

In contrast to the action of acetic anhydride, treatment of 2a with benzenesulphonyl chloride in pyridin afforded the o-benzenesulphonyl derivative (5). Structure 5 was inferred from the correct analytical data, the disappearance of CO absorption band in its IR spectrum, and the monidentity with the N-benzenesulphonyl derivative (2e). Similar behaviour has been reported for the reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one and 5-methyl-1-phenyl-2-pyrazolin-3-one [7].

Yasuda [8] reported that 1 reacted with diazonium salts, in acetone, to give 1-aryl-4-arylazo-3-carbethoxy-5-pyrazolones, instead of the expected 1,2,4,5-cyclohexatetrone-2,5-bis(arylhydrazones) (6). In this work we found that 6 was obtained on treating 1 with dilute NaOH overnight, before coupling with diazonium salts.

On the other hand compounds 2a-e were treated with aryldiazonium salts to give bis-arylazo derivatives (7a-g). This behaviour is analogous to that reported on the interaction of aryldiazonium salts with cyclohexylpyrazolone [9]. These bis-arylazobenzodipyrazolones (7a-g) were characterized by their intense colours, rangeing from yellow to deep-red and their structures were assigned from their correct analytical data and IR spectra.

a: R = H;  $Ar = C_6H_4CH_3 - p$ , b: R = H;  $Ar = C_6H_4NO_2 - p$ , c:  $R = C_6H_5SO_2$ ;  $Ar = C_6H_4NO_2 - p$ , d:  $R = Ar = C_6H_4NO_2 - p$ , e:  $R = C_6H_4NO_2 - p$ ;  $Ar = C_6H_4CH_3 - p$ , f:  $R = C_6H_3(NO_2)_2 - 2.4$ ;  $Ar = C_6H_4NO_2 - p$ , g:  $R = C_6H_3(NO_2)_2 - 2.4$ ;  $Ar = C_6H_4CH_3 - p$ .

Treatment of 1 with o-phenylenediamine in hot acetic acid, afforded 6,6a,8,14,14a,16-hexahydrobenzo 1,2 b: 4,5-b' bis[1,5]benzodiazepine-7,15-dione (8). Structure 8 was assigned on the basis of analytical data and the CO stretching band at 1639 cm<sup>-1</sup> and N-H stretching band at 3333 cm<sup>-1</sup>. Further evidence was obtained by the isolation of the intermediate dianilide 9. The formation of 8 and 9 is confirmed by the work of Ried and Draishbach [10] on the condensation of 2-carbethoxycyclohexanone with o-phenylenediamine.

In view of the reported formation of cyclohexyl-2-thiouracil [11], by the interaction of ethyl cyclohexanone-2-carboxylate with thiourea treatment of 1 in ethanolic sodium ethoxide with thiourea afforded 4a,5,9a,10-tetrahydro-2,7-dithiopyrimido-[4,5-9]quinazoline-2,4,7,9 ( $3\,\underline{\mathrm{H}},8\,\underline{\mathrm{H}}$ )-tetrone (10). Structuce 10 was confirmed by elemental analysis and IR spectra, which showed bands at 1395 and  $1565~\mathrm{cm}^{-1}$  (C = S [12]), and at  $1690~\mathrm{cm}^{-1}$  (CO).

## **Experimental**

All melting points are uncorrected. Infrared spectra were determined by the KBr waffer technique on a Unicam SP 2000 Infrared Spectrophotometer. NMR spectra were recorded on a Varian Model T-60 NMR spectrometer.

Reaction of diethyl 1,4-cyclohexanedione-2,5dicarboxylate with hydrazines and acid hydrazides

General procedures: A mixture of (0.02 mole) of hydrazines or acid hydrazides, (0.01 mole) of 1 and (50 ml) ethanol was refluxed for 4 h. The solid product which separated on cooling was filtered and crystallized from the appropriate solvent. The results are given in Table I.

2,3a,4,6,7a,8-Hexahydro-2,6-bis(acetyl)benzo 1,2-C:4,5-C' dipyrazole-3,7-dione (4)

A suspension of 2a (0.01 mole) and fused sodium acetate (0.02 mole) in acetic anhydride (30 ml) was refluxed for 6 h. The reaction mixture was cooled, and poured into ice-cold water to give a white solid, which was filtered off and washed with ethanol.

The acetyl derivative (4) is a white solid powder, m.p. 250 °C, yield 85%.

 $\begin{array}{cccc} Analysis: & C_{12}H_{12}N_4O_4 & (276.25) \\ & \text{Caled} & \text{C } 52.17 & \text{H } 4.38 & \text{N } 20.28, \\ & \text{Found} & \text{C } 52.3 & \text{H } 5.1 & \text{N } 20.0. \end{array}$ 

3a,4,7a,8-Tetrahydrobenzo[1,2-C:4,5-C'] dipyrazole-3,7-diol dibenzenesulphonate (ester) (5)

To a suspension of 2a (0.01 mole) in pyridine (15 ml) benzenesulphonyl chloride (0.02 mole) was added, the reaction mixture was refluxed for 6 h, set aside at room temperature for several hours, and then poured into ice-cold water. The brown solid that separated was filtered, and crystallized from ethanol.

Compound 5 is a brown solid powder, m.p. 220 °C,

yield 80%.

Table I. Products obtained from the interaction of 1 with hydrazines and acid hydrazides (2 a-e and 3 a, b).

Compound	m.p. [°C]	Yield [%]	Formula (mol. wt.)		n [%] calcd		ogen [%] L calcd	Nitrog found	gen[%] calcd
2 a	300 (decomp.)	85	$C_8H_8N_4O_2$ (192.17)	49.9	50.0	4.I	4.2	29.2	29.16
2 b	300 (decomp.)	90	$C_{20}H_{16}N_4O_2$ (344.36)	$\boldsymbol{69.4}$	69.75	<b>5.0</b>	4.68	16.3	16.27
2 e	300 (decomp.)	95	$C_{20}H_{14}N_6O_6 \ (434.36)$	55	55.3	<b>3.</b> I	3.25	16.2	19.35
2 d	300 (decomp.)	95	$C_{20}H_{12}N_8O_{10} \ (524.36)$	46	45.8	2.4	2.3	22	21.37
2 e	121	70	$C_{20}H_{16}H_4S_2O_6 \ (472.49)$	50.6	50.84	3.5	3.41	11.9	11.86
3 a	203	60	$C_{22}H_{16}N_4O_4  (400.38)$	63.3	63.4	5.3	5.73	11.6	11.38
3 b	232	60	$C_{22}H_{16}N_4O_6 \ (432.38)$	59.4	59.53	4.8	5.38	10.8	10.68

N. B. Compounds 2a-d washed with ethanol, compound 2e crystallized from benzene, and compounds 3a, b crystallized from ethanol.

Table II. 1,2,4,5-Cyclohexatetrone-2,5-bis(arylhydrazones) (6a-e).

Compound	m.p. [°C]	Yield [%]	Formula (mol. wt.)	Carbon found		Hydro found	gen[%] calcd	Nitrog found	
6 a	110	75	$C_{18}H_{16}N_4O_2$ (320.34)	67.5	67.48	4.7	5.04	17.5	17.49
6 b	105	80	$C_{20}H_{20}N_4O_2$ (348.39)	68.7	68.95	5.8	5.79	16.1	16.08
6 c	106	70	$C_{20}H_{20}N_4O_4$ (380.39)	63.2	63.15	4.9	5.3	14.8	14.73
6 d	122	72	$C_{18}H_{14}N_4O_2Cl_2$ (389.23)	55.3	<b>55.54</b>	3.7	3.63	14.5	14.4
6 e	180	78	$C_{18}H_{14}N_6O_6$ (410.34)	52.6	52.68	3.2	3.44	20.7	20.48

Analysis:  $C_{20}H_{16}N_4S_2O_6$  (472.4 $\oplus$ )

Calcd C 50.84 H 3.41 N 11.86 S 13.57, Found C 51.3 H 4.1 N 11.7 S 13.4.

## 1,2,4,5-Cyclohexatetrone-2,5-bis-(arylhydrazones) (6 a-e)

General procedures: To (0.01 mole) of 1, sodium hydroxide (50 ml) (2.5%) was added, left to stand at 0 °C for 24 h. The reaction mixture was diluted with 50 ml water, and the appropriate diazonium salt (0.02 mole) was added. After the complete addition of the diazonium salt, the pH of the medium was adjusted to 7–8, and left to stand for 12 h at 5 °C. The solid product which separated was filtered and crystallized from ethanol. The results are given in Table II.

Reaction of 2a, c-e with diazonium salts. Formation of 7a-g

General procedures: To a cold solution of 2a, c-e (0.01 mole) in pyridine (40 ml), the appropriate

diazonium salt (0.02 mole) was added. The solid products which separated were filtered off and crystallized from ethanol. The results are given in Table III.

6,6a,8,14,14a,16-Hexahydrobenzo[1,2-b:4,5-b']bis-[1,5]benzodiazepine-7,15-dione (8)

A mixture of 1 (0.01 mole) and o-phenylenediamine (0.02 mole) in acetic acid (40 ml) was heated at 70 °C for 20 min and filtered at the same temperature. The deep-red solid separating on standing was filtered, and crystallized from acetic acid.

Compound 8 is a deep-red solid crystal, m.p. 290 °C, yield 65%.

Analysis:  $C_{20}H_{16}N_4O_2$  (344)

Calcd C 69.77 H 4.65 N 16.28, Found C 69.3 H 4.5 N 16.7.

Fusion of 1 with o-phenylenediamine. Formation of 9

A mixture of 1 (0.01 mole) and o-phenylenediamine (0.02 mole) was fused for 1 h at  $140~^{\circ}\text{C}$  in an

Table III. Bis-arylazobenzodipyrazolones (7a-g).

Compound	m.p. [°C]	Yield [%]	Formula (mol. wt.)	Carbon found		Hydro found	gen[%] calcd	Nitroge found	
7 a	80	45	$C_{22}H_{20}N_8O_2$ (428.44)	61.3	61.17	4.6	4.71	26.3	26.16
7 b	95	35	$^{(428.44)}_{\mathrm{C}_{20}\mathrm{H}_{14}\mathrm{N}_{8}\mathrm{O}_{6}} \ (462.37)$	51.7	51.95	3.2	3.05	24.1	24.24
7 e	135	40	$C_{32}H_{22}N_{10}O_{10}S_2$ (770.71)	49.6	49.87	2.7	2.88	18.3	18.18
7 d	151	70	$C_{32}H_{20}N_{12}O_{10}$ (732.58)	52.46	52.46	2.6	2.75	22.7	22.95
7 e	160	65	$C_{34}H_{26}N_8O_6$ (642.61)	63.4	$\boldsymbol{63.54}$	4.2	4.08	17.3	17.44
7 f	236	70	$C_{32}H_{18}N_{14}O_{14} $ (822.57)	46.9	46.72	2.1	2.21	23.6	23.84
7 g	125	40	$^{ m C_{34}H_{24}N_{12}O_{10}}_{ m (760.63)}$	53.5	53.68	3.3	3.18	22.3	22.1

oil-bath. After cooling the solid material was crystallized from ethanol.

Compound 9 is a redish solid crystals, m.p. 225 °C, yield 70%.

Analysis:  $C_{20}H_{20}N_4O_4$  (328)

Calcd C 63.15 H 5.26N 14.73, Found C 63.6 H 5.8 N 14.1.

## Conversion of 9 into 8

0.5 g of 9 was heated in 30 ml glacial acetic acid. The solid product obtained on cooling proved to be 8 (m.p. and mixed m.p.).

4a.5.9a.10-Tetrahydro-2.7-dithiopyrimido [4.5-9]quinazoline-2,4,7,9(3H,8H)-tetrone (10)

To 0.02 mole of sodium ethoxide a mixture of 1 (0.01 mole) and thiourea (0.02 mole) was added and refluxed for 10 h. The solid product which separated on dilution with dilute acetic acid was filtered off and washed with ethanol.

Compound 10 is a pale-yellow powder, m.p. 300 °C, vield 80%.

Analysis:  $C_{10}H_8N_4S_2O_2$  (280.32)

C 42.84 H 2.87 N 19.98 S 22.87. Calcd Found C 42.7 H 3.1 N 19.7 S 22.9.

A. Baeyer, Ber. 19, 430 (1886).

<sup>[1]</sup> F. A. Amer, A. Harhash, and M. A. Metwally, Z. Naturforsch. 32b, 943 (1977).

<sup>[3]</sup> E. Iwamoto, Toyo Soda Kenkyu Hokoku 19(2),

<sup>71 (1975);</sup> C. A. 85, 125771 (1972).
[4] J. A. Moore and J. E. Kochanowski, Polym. Prepr. Am. Chem. Soc., Div. Polym. Chem. 14(2),

<sup>1175 (1973);</sup> C. A. 82, 171502 (1975). [5] J. E. Kochanowski and J. A. Moore, Macromolecules 8 (2), 121 (1975); C. A. 83, 10958 (1975).

<sup>[6]</sup> a) K. Srivastava and J. K. Mehrotra, Indian J. Appl. Chem. **32**, 116 (1969). b) B. Lai and A. P. Bhaduri, Indian J. Chem. 15B, 359 (1977).

<sup>[7]</sup> G. A. Galoyan, S. G. Agbalyan, and G. T. Esayan, Arm. Khim. 22(5), 430 (1969) (Russ.); C. A. 71, 70535 (1969).

<sup>[8]</sup> H. Yasuda, Sci. Papers Inst. Phys. Chem. Res. (Tokyo) **53**, 348 (1959); C. A. **54**, 15364 (1960). [9] R. B. Linsted and A. B. L. Wang, J. Chem. Soc.

<sup>1937, 807;</sup> C. A. 31, 5355 (1937).

<sup>[10]</sup> W. Ried and A. Draishbach, Chem. Ber. 92, 949 (1959); C. A. **53**, 2249 (1959). [11] E. Taschner, Roczniki Chem. **25**, 329 (1951);

C. A. 48, 5803 (1954).

<sup>[12]</sup> R. M. Silverstein and G. C. Bassler, Spectroscopic Identification of Organic Compounds, 2. Ed. John Wiley and Sons, New York 1968.