140. Synthesis of [1,6-α,α'-Diaminosuberic acid]oxytocin ('Dicarba-oxytocin')

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(19. IV. 74)

Summary. Starting from a selectively protected derivative of α,α'-diaminosuberic acid (**3**) the linear protected peptide **11** has been obtained. Cyclisation to **12** followed by removal of the protecting groups by hydrogenolysis afforded the 'dicarba' analogue of oxytocin, **1c**, which showed about 5 IU/μmol of uterotonic activity *in vitro*.

The role of the disulfide group in oxytocin (**1a**) was established, in principle, ten years ago by the synthesis of [1,6-(3-carboxypropylcysteine)]oxytocin ('desamino-1-carba-oxytocin', **2b**), an analogue of desamino-oxytocin (**2a**) in which one of the sulfur atoms of the disulfide bridge is replaced by a methylene group [1]. The finding that this analogue had the biological activities of oxytocin [1–5] proved that the *reactivity* of the disulfide grouping as such is not required for binding to the biological receptors or for initiation of the response. On the other hand, comparison with the nearly inactive acyclic [1,6-di-alanine]oxytocin ('desthio-oxytocin', **1d**) and [1,6-di-serine]oxytocin (**1e**) demonstrated the *steric* importance of the bridge for activity [6]. In the event, **2b** and the isomeric '6-carba' analogue **2c** turned out to have higher uterotonic activity than desamino-oxytocin [5] which in turn is more potent than oxytocin [7]; the 'desamino-dicarba' analogue, [1,6-α-aminosuberic acid]oxytocin (**2d**) [3–5] [8–9] was rather less active. Subsequently several other 'carba' analogues were prepared [10–11] but in all cases the terminal amino group was omitted, chiefly for reasons of synthetic convenience.

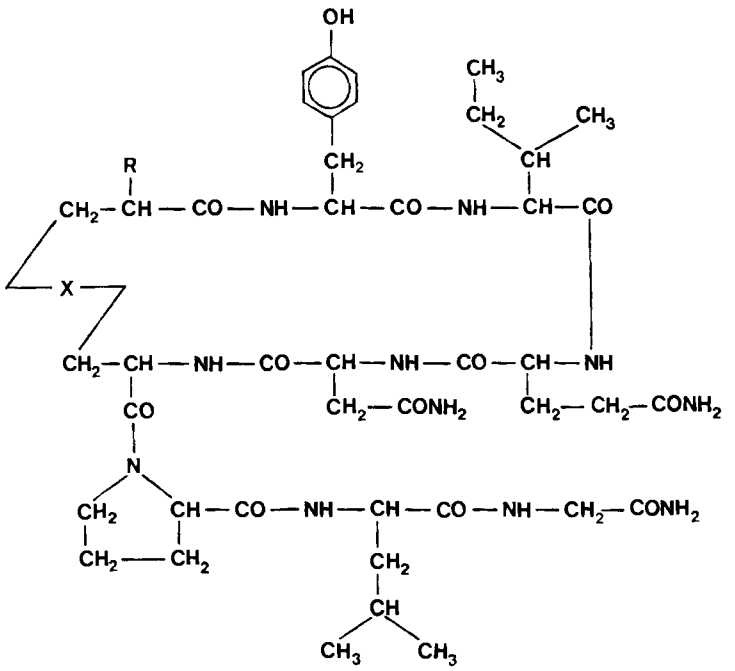
Metabolic studies with the intact rat uterus *in vitro* [12] and *in vivo* [13] have shown the analogues **2b–d** to be more stable than oxytocin; in the isolated uterus, the rate of disposition of these analogues was found to be similar to that of desamino-oxytocin [12].

To determine the relative contributions to activity and to metabolic stability made by the omission of the amino group on the one hand and by methylene replacements in the disulfide bridge on the other, analogues with the terminal amino group present but with a modified bridge structure were obviously required. We have undertaken the synthesis of two such analogues, [6,1-cystathionine]oxytocin ('1-carba-oxytocin', **1b**) and [1,6-α,α'-diaminosuberic acid]oxytocin ('dicarba-oxytocin',

[1]) From the Doctoral Dissertation to be submitted by *O. Keller*.

1c)[2]). While this work was in progress the preparation and properties of **1b** were reported by *Jošt et al.* [17]. Our results with this analogue are similar to theirs and will not be described here (see [18]).

The preparation of the 'dicarba' analogue **1c** is summarised in the Scheme. N(α)-benzyloxycarbonyl-N(α')-*t*-butyloxycarbonyl-α,α'-diaminosuberic acid α-methyl ester (**3**), obtained as the crystalline dicyclohexylamine salt by a procedure described elsewhere [18–19], was coupled with the known [20] tripeptide, prolyl-leucyl-glycine amide (**4**), using dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole [21]. The Boc protecting group was selectively removed with hydrogen chloride and



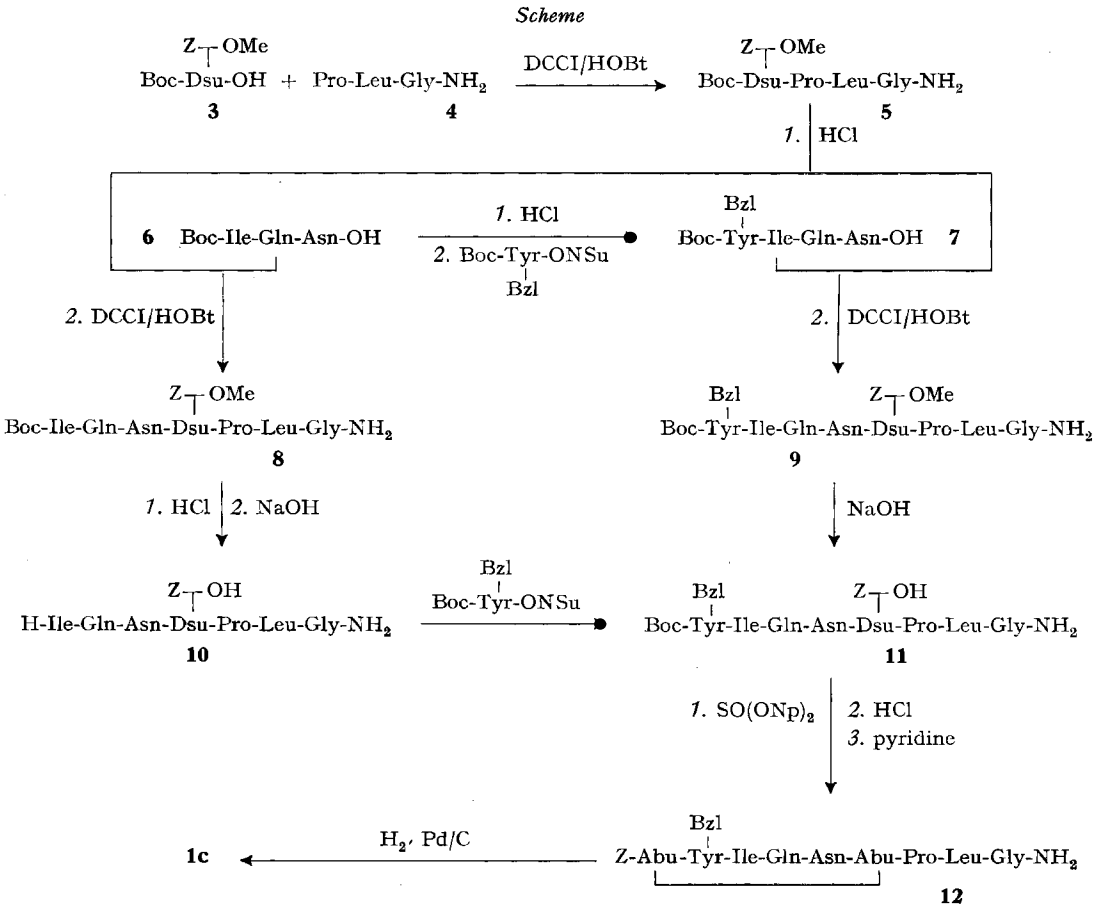
	R	X		R	X
1a	NH_2	S—S	**2a**	H	S—S
1b	NH_2	CH_2—S	**2b**	H	CH_2—S
1c	NH_2	CH_2—CH_2	**2c**	H	S—CH_2
1d	NH_2	CH_3 CH_3	**2d**	H	CH_2—CH_2
1e	NH_2	CH_2OH $HOCH_2$			

[2]) All amino acids (except glycine) are of the L configuration; the α,α'-diaminosuberic acid is the L,L-stereoisomer. Current conventions are used for the designation of hormone analogues [14] and of amino acids and protecting groups [15], except that diaminosuberic acid is represented by Dsu. Substitution in that half of the diaminosuberic acid molecule replacing the hemicystine in position 1 of oxytocin is indicated by the unprimed locant (α), substitution in the other half by the primed locant (α'). The alternate symbolism used for the cyclopeptide **1c** is analogous to that proposed for cystathionine [16] and regards diaminosuberic acid as composed to two α-aminobutyric acid (Abu) residues linked through their γ positions. In the Experimental section and the Scheme, DCCI stands for dicyclohexylcarbodiimide, DMF for N,N-dimethylformamide, NMM for N-methylmorpholine and TFE for 2,2,2-trifluoroethanol.

the resulting peptide amide was coupled, by the same procedure [21], with *t*-butyloxycarbonyl-isoleucyl-glutaminyl-asparagine (**6**) to give **8** and with *t*-butyloxycarbonyl-O-benzyltyrosyl-isoleucyl-glutaminyl-asparagine (**7**) to give **9**. The protected tetrapeptide **7** was prepared from the known [22] Boc-tripeptide **6** by removal of the Boc group and acylation of the product with the N-hydroxysuccinimide ester of *t*-butyloxycarbonyl-O-benzyltyrosine. By cleavage of the Boc group and saponification the methyl ester **8** was converted to **10** which was in turn acylated with the protected tyrosine hydroxysuccinimide ester to give **11**. The same derivative was also obtained directly from **9** by saponification though this route proved less convenient because of the poor solubility of **9**.

Cyclisation was accomplished by *Schwyzer*'s active ester procedure [23] as applied to the synthesis of 'carba' analogues by *Sakakibara et al.* [11] and by *Jošt et al.* [10] [24]: The acid **11** was converted to the *p*-nitrophenyl ester, the Boc group was cleaved, and the peptide bond was formed at high dilution in pyridine. The product **12** was converted to **1c** by hydrogenation. The 'dicarba' analogue **1c** was purified by gel chromatography and solvent precipitation and characterised by amino-acid

Scheme



analysis, elemental analysis, optical rotation, and thin-layer chromatography and electrophoresis.

In preliminary assays the analogue **1c** from two separate syntheses had about 5 IU/μmol uterotonic activity (rat uterus *in vitro* [25] in media [26] with or without magnesium) and less than 0.1 IU/μmol of rat pressor activity [27]. More detailed pharmacological results will be published elsewhere.

Experimental Part. – *General.* For materials and general procedures (determination of melting-points and optical rotations, evaporations, amino-acid analysis) see [22].

Thin-layer chromatography (TLC.) on silica gel was carried out with the solvent systems (composition by volume): A, *n*-BuOH/H_2O/AcOH 4:1:1; B, MeOH/$CHCl_3$ 1:1; C, *i*-PrOH/pyridine/H_2O 7:6:6. Rf values are to be regarded as a general indication of chromatographic behaviour, not as physical constants.

Electrophoresis was carried out on cellulose plates using the electrolytes D: 6% aq. AcOH, pH 2.5, and E: pyridine/AcOH/H_2O 23:6:970, pH 5.6. For details of apparatus and procedures and for methods of detection see [22]. In testing for purity, samples of 50–150 μg were applied.

Analytical. Samples for elemental analysis were dried at 50–60°/0.01 Torr unless otherwise stated. Water was determined with the *Karl Fischer* reagent; inclusion of solvent in the calculated elemental compositions need not imply the existence of defined solvates. In amino-acid analysis, Dsu emerged at the position of Ile and had a colour constant 1.6 times that of Glu on a molar basis.

Bio-assay. Uterotonic activity was assayed [25] on organs taken from virgin rats in natural oestrus or oestrus to metoestrus using *von Dyke-Hastings* medium [26] and isometric recording, against the 'Third International Standard for Oxytocic, Vasopressor and Antidiuretic Substances'. Pressor activity was measured [27] in dibenzyline-treated, urethane-anaesthetised male *Wistar* rats against the same standard.

$Z\text{–}\underset{|}{}OMe$

Boc-Dsu-Pro-Leu-Gly-NH_2 (**5**). The dicyclohexylamine salt of α-methyl N(α)-benzyloxycarbonyl-N(α')-*t*-butyloxycarbonyl-α,α'-diaminosuberate (**3**) (940 mg of the hemihydrate; 1.46 mmol) in ether (80 ml) was washed repeatedly with 0.1 M $KHSO_4$/0.2 M K_2SO_4 [28], with satd. NaCl, dried ($MgSO_4$), and evaporated to dryness. The oily residue with Pro-Leu-Gly-$NH_2 \cdot \frac{1}{2}H_2O$ (**4**) (500 mg; 1.7 mmol) and HOBt (270 mg; 2 mmol) in DMF (3 ml) was treated, at 0°, with DCCI (350 mg; 1.7 mmol) in DMF (1.5 ml) and stirred at 0° 1 h and at 22° 12 h. After addition of AcOH (2 drops) the mixture was stirred at 22° 30 min, kept at 4° 4 h, filtered from dicyclohexylurea, and evaporated to dryness. The residue in EtOAc (75 ml) was washed with 5% $NaHCO_3$ (3 × 3 ml), satd. NaCl, 0.1 M $KHSO_4$/0.2 M K_2SO_4 (3 × 3 ml), and satd. NaCl (4 × 3 ml), dried, and evaporated. The residue was precipitated from 2-propanol with di-2-propyl ether; 990 mg (93%), m.p. 85–90°, $[\alpha]_D = -58.5°$ ($c = 1$, EtOH), Rf 0.65 (A), 0.78 (B). A sample for analysis was dried at 60°/0.1 Torr 15 h.

$C_{35}H_{54}N_6O_{10} \cdot H_2O$	Calc.	C 57.04	H 7.66	N 11.40%
(736.9)	Found	,, 57.25	,, 7.56	,, 11.67%

Boc-Tyr(Bzl)-Ile-Gln-Asn-OH (**7**). The Boc-tripeptide **6** [22] (2.40 g; 5 mmol) was stirred with 90% aq. CF_3COOH (20 ml) at 0° 2 h. After evaporation to 5 ml and dilution with di-2-propyl ether (60 ml) the trifluoroacetate crystallised at 4° overnight. It was washed with di-2-propyl ether (80 ml), dried over NaOH [Rf 0.21 (B), tailing; 0.59 (C)], dissolved in DMF (20 ml) and treated, at 0°, with N,N,N',N'-tetramethylguanidine (1.4 ml; 11 mmol). After addition of Boc-Tyr(Bzl)-ONSu (2.34 g; 5 mmol) and stirring at 0° 20 min and at 22° overnight the solution was evaporated to 10 ml, diluted with 1 M AcOH (70 ml) and kept overnight at 4°. The product was collected, washed with 1 M AcOH (100 ml), ice-water (120 ml), and ether (2 × 20 ml) and dried over NaOH; 3.25 g (90%), m.p. 216° (dec.), $[\alpha]_D = -1.9°$ ($c = 2$, DMF), Rf 0.25 (B) (tailing), 0.75 (C). A sample for analysis was recrystallised from DMF/water and dried at 25°/0.1 Torr 24 h.

$C_{36}H_{50}N_6O_{10} \cdot \frac{1}{2}H_2O$	Calc.	C 58.76	H 6.98	N 11.42	H_2O 1.22%
(735.9)	Found	,, 58.77	,, 7.11	,, 11.21	,, 1.48%

Amino-acid composition: Asp. 1.05, Glu 1.06, Ile 1, Tyr 1.0, NH_3 2.35.

Z–OMe

Boc-Ile-Gln-Asn-Dsu-Pro-Leu-Gly-NH$_2$ (**8**). The Boc-tripeptide **6** (220 mg; 0.46 mmol) was dissolved in DMF (5 ml) with warming and to the cooled solution NMM (51.5 µl; 0.46 mmol), HOBt (62 mg; 0.46 mmol), and the hydrochloride (300 mg; 0.46 mmol) obtained from **5** with HCl as in the preparation of **9** below, were added followed, at 0°, by DCCI (110 mg; 0.53 mmol). The mixture was stirred at 0° 30 min and at 22° overnight, treated with AcOH (3 drops), stirred for 30 min more, diluted with 2-propanol (20 ml), and cooled to 4° (2 h). The product was collected, washed with 2-propanol, dissolved in boiling TFE, the solution was filtered, evaporated to 3 ml, and diluted with 2-propanol (15 ml). After 18 h at 4° the product was collected and washed with a little 2-propanol and copiously with di-2-propyl ether; 350 mg (70%), m.p. 216–218° (dec.), $[\alpha]_D = -59.7°$ ($c = 1$, TFE), Rf 0.46 (A), 0.62 (B). A sample for analysis was recrystallised from TFE/2-propanol.

$C_{50}H_{79}N_{11}O_{15} \cdot \frac{1}{2}H_2O$	Calc.	C 55.44	H 7.35	N 14.22	H_2O 0.83%
(1083.2)	Found	,, 55.48	,, 7.62	,, 13.92	,, 0.95%

Amino-acid composition: Asp 1.02, Glu 0.99, Pro 1.08, Gly 1, Ile + Dsu 2.20, Leu 1.07, NH_3 2.86.

Bzl *Z–OMe*

Boc-Tyr-Ile-Gln-Asn-Dsu-Pro-Leu-Gly-NH$_2$ (**9**). The Boc-peptide **5** (500 mg; 0.68 mmol) was stirred with 2M HCl in dioxan (7 ml) 30 min. The residue after evaporation was twice redissolved in MeOH and again taken to dryness. Precipitation with ether from dioxan, washing with di-2-propyl ether, and drying (NaOH) gave 420 mg of the hydrochloride, Rf 0.27 (A). This material (0.63 mmol) with **7** (465 mg; 0.63 mmol), NMM (71 µl; 0.63 mmol) and HOBt (100 mg; 0.74 mmol) in DMF (8 ml) was treated at 0° with DCCI (144 mg; 0.7 mmol) in DMF (1 ml) and stirred at 0° 1 h and at 22° overnight. The mixture was treated with AcOH (2 drops), stirred 2 h more, diluted with water (40 ml), kept at 4° 4 h, and filtered. The product was washed with ice-water, suspended in boiling 2-propanol (50 ml), cooled (4° overnight), collected, and washed with 2-propanol (10 ml). Yield 710 mg (78%), m.p. 215–216° (dec.), $[\alpha]_D = -31.5°$ ($c = 0.5$, DMF), Rf 0.59 (A), 0.67 (B). A sample for analysis was recrystallised from TFE/2-propanol and dried at 60°/0.1 Torr 15 h.

$C_{86}H_{94}N_{13}O_{17} \cdot H_2O$	Calc.	C 58.91	H 7.19	N 12.49%	
(1345.6)	Found	,, 59.06	,, 7.17	,, 12.18%	

Amino-acid composition: Asp 1.06, Glu 1.05, Pro 1.11, Gly 1, Ile + Dsu 2.20, Leu 1.03, Tyr 0.94, NH_3 2.92.

Z–OH

H-Ile-Gln-Asn-Dsu-Pro-Leu-Gly-NH$_2$ (**10**). The protected peptide **8** (290 mg; 0.27 mmol) was treated with 2M HCl in dioxan (5 ml) at 22° 35 min, the product was precipitated with di-2-propyl ether, collected after 1 h at 4°, washed with di-2-propyl ether, and dried over NaOH; 260 mg, Rf 0.23 (A), m_{Arg} 0.6 (E). Of this material, 250 mg (0.25 mmol) in MeOH (3 ml) were treated with 1M NaOH (1 ml) during 2.5 h. After dilution with water (15 ml) the product was retained on a column of Dowex 50 (H^+ form, 30 ml) and, after washing with water, eluted with 5% aq. pyridine. After evaporation of the eluate the product was precipitated from water with 1,2-dimethoxyethane and collected after 18 h at 4°; 185 mg (73% from **8**), m.p. 193–195° (dec.), $[\alpha]_D = -72.5°$ ($c = 1$, H_2O), Rf 0.14 (A), m_{Arg} 0.3 (D), 0.4 (E).

$C_{44}H_{69}N_{11}O_{13} \cdot H_2O$	Calc.	C 53.98	H 7.11	N 15.74	H_2O 1.84%
(978.1)	Found	,, 54.40	,, 7.43	,, 15.28	,, 1.66%

Bzl *Z–OH*

Boc-Tyr-Ile-Gln-Asn-Dsu-Pro-Leu-Gly-NH$_2$ (**11**). *a*) The methyl ester **9** (610 mg; 0.45 mmol), dissolved in TFE (30 ml) with slight warming, was treated at 22° with 4.25M NaOH (16.6 ml). After 4 h the cooled (0°) solution was diluted with DMF (100 ml) and filtered through a column (100 ml) of Amberlyst 15 (H^+ form, preequilibrated with DMF) and evaporated. The residue after extraction with 2-propanol (570 mg; 93%) was used in the next step; a sample for analysis was precipitated from TFE with water: m.p. 223–224° (dec.), $[\alpha]_D = -28.2°$ ($c = 1$, DMF), Rf 0.46 (A), 0.40 (B). The sample dried at 60°/0.1 Torr 24 h was a trihydrate.

$C_{65}H_{92}N_{12}O_{17} \cdot 3H_2O$	Calc.	C 57.09	H 7.22	N 12.29%
(1367.6)	Found	,, 57.10	,, 6.74	,, 12.06%

Amino-acid composition: Asp 1.07, Glu 1.01, Pro 0.98, Gly 1, Ile + Dsu 2.08, Leu 1.04, Ty 1.02, NH_3 5.31.

b) **10** (365 mg; 0.37 mmol), NMM (42.2 µl; 0.38 mmol), and Boc-Tyr(Bzl)-ONSu (196 mg 0.42 mmol) in Me_2SO (5 ml) were stirred at 22° 17 h, the product was precipitated by dilution wit 1 M AcOH at 0°, collected after 18 h at 4°, washed with 1 M AcOH, dried, and precipitated fror TFE with 2-propanol: 435 mg (88%), m.p. 218–219° (dec.), $[\alpha]_D = -28.8°$ ($c = 1$, DMF), identica in chromatographic behaviour with sample *a*). After drying at 60°/0.01 Torr 52 h it was a mono hydrate.

$C_{65}H_{92}N_{12}O_{17} \cdot H_2O$	Calc.	C 58.63	H 7.12	N 12.62%
(1331.6)	Found	,, 58.79	,, 6.99	,, 12.37%

Amino-acid composition: Asp 1.03, Glu 0.96, Pro 0.96, Gly 1, Ile + Dsu 2.14, Leu 1.04, Ty 0.96, NH_3 2.88.

N-Benzyloxycarbonyl-O-benzyl-[1,6-α,α'-diaminosuberic acid]-oxytocin (**12**). The acid **11** (17(mg; 0.13 mmol) in pyridine (5 ml) was treated, at 50°, with di-4-nitrophenyl sulfite (300 mg); more sulfite (4 × 150 mg) was added at 2 h intervals. After evaporation the residue was suspended in boiling 2-propanol, kept at 4° overnight, collected, washed with ether, and dried. The product (170 mg) was treated with 2 M HCl in dioxan (7 ml) at 22° 30 min. Dilution with di-2-propyl ether, filtration, and drying (NaOH) afforded the hydrochloride (160 mg) which was dissolved in DMF (50 ml, purified by filtration through basic alumina) to which 2 M HCl in dioxan (1.5 ml) had been added. This solution was added continuously during 4 h to pyridine (300 ml) vigorously stirred at 50°. After 1 h more the solution was evaporated to dryness, the residue in EtOH (2 ml) was passed through a column (1.5 × 86 cm) of Sephadex LH-20, the fractions containing the peptide (absorbance at 280 nm) were passed through a mixed bed (8 ml) of Amberlysts 15 and A-21 [22] equilibrated with EtOH and, after evaporation to 2 ml, once more through the same column of Sephadex LH-20. The material recovered from the peak fractions by evaporation was precipitated from methanol with chloroform; 45 mg (29% from **11**), m.p. 168–172° (sintering from 148°), $[\alpha]_D = -11.2°$ ($c = 0.5$, DMF), Rf 0.54 (A), 0.72 (B). A sample dried at 50°/0.01 Torr 80 h was a methanol solvate.

$C_{60}H_{82}N_{12}O_{14} \cdot CH_3OH$	Calc.	C 59.69	H 7.06	N 13.69	O 19.55%
(1227.4)	Found	,, 59.78	,, 6.91	,, 13.41	,, 19.90%

[1,6-α,α'-Diaminosuberic acid]oxytocin ('*dicarba-oxytocin*') (**1c**). The protected peptide **12** (23.3 mg; 0.019 mmol) in 90% aq. MeOH (6 ml) was hydrogenated over 10% Pd/C (6 mg) in a stream of H_2 for 3 h. After filtration (Celite) and evaporation the material was chromatographed on a column (1.5 × 95 cm) of Sephadex G-15 in 0.2 M AcOH [29]. The peptide recovered from the peak fractions (17.0 mg; 82%) by lyophilisation was chromatographically homogeneous. $[\alpha]_D = -64.7°$ ($c = 0.3$, 1 M AcOH), Rf 0.30 (A), 0.08 (B), 0.78 (C), m_{Arg} 0.6 (E).

$C_{45}H_{70}N_{12}O_{12} \cdot 2C_2H_4O_2 \cdot H_2O$	Calc.	C 53.06	H 7.26	N 15.15	O 24.52%
(1109.3)	Found	,, 53.17	,, 7.22	,, 14.93	,, 24.17%

Amino-acid composition: Asp 1.03, Glu 1.00, Pro 0.99, Gly 1, Ile + Dsu 2.16, Leu 1.03, Tyr 1.04, NH_3 3.86.

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141. Bicyclo[4.1.0]hept-3-ene-2,5-dione (Homo-*p*-quinone[1])) and its *Bamford Stevens* Reaction

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Zusammenfassung. Homo-*p*-chinon[1]) (**4** = Bicyclo[4.1.0]hept-3-en-2,5-dion) wurde hergestellt und auf seine Spektraleigenschaften untersucht. Die UV.-, IR.- und NMR.-Spektren sind charakteristisch für die darin enthaltene Endion- und *cis*-disubstituierte Cyclopropan-Substruktur, ohne eine starke Wechselwirkung zwischen den beiden zum Ausdruck zu bringen.

[1]) The prefix 'homo-' before a trivial name signifies that the system (chain or ring) has been enlarged by one carbon member. The special case of double bond to cyclopropane 'enlargement' has received individual attention in connection with *Winstein*'s homoconjugation concept. For this reason and for the sake of brevity we shall, in the following text, refer to compounds **1a** and **2a** as *syn*- and *anti*-bis-homo-*p*-quinone and to compound **4** as homo-*p*-quinone.

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