Synthesis and Stereochemistry of Substituted Bi- and Tri-cyclic 4,5-Dihydropyrazoles

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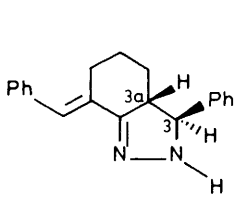
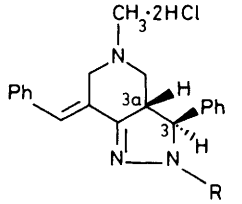
A series of bi- and tricyclic 4,5-dihydropyrazoles have been studied by ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy and *X*-ray crystallography. They were synthesised by treating the corresponding mono- and dibenzylidenecycloalkanones and 2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one with semicarbazide, which gave two diastereoisomers, and thiosemicarbazide, which gave only one. The ^{1}H n.m.r. parameters allowed an unambiguous identification of the diastereoisomers and the configuration of one of the isomeric pairs was confirmed by ^{13}C n.m.r. spectroscopy and *X*-ray crystallography. The crystallographic analysis shows that the six-membered rings assume an intermediate shape between the chair, half-chair and envelope forms, while the five-membered rings have a perfect envelope conformation with C(5) on the flap.

While studying the reactions of α,β-unsaturated ketones with nucleophilic agents, Oszbach and Szabó prepared bicyclic dihydropyrazoles of type (**1**) from hydrazine hydrate and 2,6-diarylidenecycloalkanones.[1] Khalaf *et al.* repeated the synthesis and obtained the same compounds as well as their 2-substituted derivatives. The *trans* configuration of 3- and 3a-H of the dihydropyrazole ring in these derivatives was established by the ^{1}H n.m.r. results,[2] on the basis of earlier results on condensed dihydropyrazoles of type (**2**) prepared by Krapcho; he suggested the *trans* configuration of these protons on the basis of the magnitude (13 Hz) of the J_{vic} coupling constant, determined by shift-reagent and decoupling experiments.[3] Jacquier and Maury synthesized dihydropyrazole derivatives in a two-step reaction of 2-alkylidene- and 2-benzylidene-cycloalkanones with hydrazine.[4] In contrast with the above results, they obtained both the *cis* and *trans* diastereoisomers. Puar *et al.* have synthesized thiopyrano[4,3-*c*]pyrazole derivatives whose structure—namely the *trans* configuration of the 3- and 3a-protons—was corroborated by their ^{13}C n.m.r. spectra and an *X*-ray structure determination.[5]

As dihydropyrazoles of type (**1**) and (**2**) have a wide range of biological activities (*i.e.* they are central nervous system depressants, anti-inflammatory agents, fungicides, and bactericides [6]) we have investigated the reactions of some α,β-unsaturated ketones with semicarbazide and thiosemicarbazide as possible routes to these compounds. We report here the synthesis of compounds of this type and their stereochemistry, which was determined from their ^{1}H n.m.r. and ^{13}C n.m.r. spectra and an *X*-ray analysis.



(**1**)



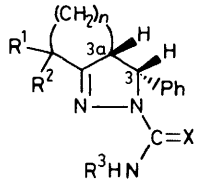
(**2**)

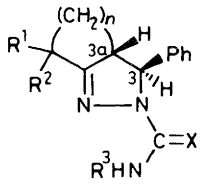
Table 1. Essential ^{1}H n.m.r. parameters and *cis*/*trans* product ratios for compounds (**3**)—(**18**)

Compound	δ (p.p.m.) 3-H	3a-H	$J_{3,3a}$ (Hz)	Ratio (%)
(**3**)	5.41	3.23	11.2	76
(**4**)	4.79	2.77	6.5	24
(**5**)	5.76	3.41	11.5	100
(**6**)	5.30	3.43	10.9	46
(**7**)	4.79	2.87	6.0	54
(**8**)	5.83	3.55	10.3	100
(**9**)	4.89	2.83	7.6	100
(**10**)	5.35	2.92	4.1	100
(**11**)	5.54	3.40	10.8	68
(**12**)	4.83	3.00	10.5	32
(**13**)	6.03	3.45	11.3	100
(**14**)	5.60	3.44	10.7	45
(**15**)	4.89	3.11	10.9	55
(**16**)	5.50	3.68	11.2	94
(**17**)	4.79	3.82	11.3	6
(**18**)	6.09	3.61	10.8	100

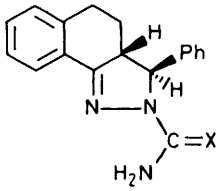
Results and Discussion

Our bicyclic dihydropyrazoles were synthesized by the reactions of some benzylidenecycloalkanones with semicarbazide or thiosemicarbazide in ethanol, catalysed by hydrochloric acid. The essential ^{1}H n.m.r. parameters of the products are summarized in Table 1. With semicarbazide two diastereoisomers were obtained in each case except in the reaction of 2-benzylidenecyclo-octanone. The differences in the chemical shift of 3-H in the diastereoisomeric pairs (**3**)—(**4**), and (**6**)—(**7**), can be attributed to the diamagnetic anisotropy of the neighbouring C(3a)–C(4) bond and to the preferential orientation of the phenyl group.[7] For these compounds, the values of $J_{3,3a}$(*cis*) are greater than those of $J_{3,3a}$(*trans*) and are in the ranges reported by Hassner and Michelson (10—14 Hz for the *cis*, and 3—10 Hz for the *trans* isomer). The difference in the chemical shift of 3a-H indicates that the phenyl group has a quasi-equatorial orientation in the *trans* isomer; thus, the 3a-proton lies in the diamagnetic zone of the hindered phenyl ring, in contrast with the *cis* isomer in which 3a-H and the phenyl group are well separated. The reaction of 2-benzylidenecyclo-octanone with semicarbazide yielded only one diastereoisomer,

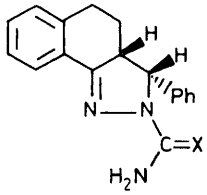




	X	R^1	R^2	R^3	n	
(3)	O	H	H	H	3	(4)
(5)	S	H	H	H	3	
(6)	O	H	H	H	4	(7)
(8)	S	H	H	H	4	
	O	H	H	H	5	(9)
	S	H	H	H	5	(10)
(11)	O	PhCH=		H	3	(12)
(13)	S	PhCH=		H	3	
(14)	O	PhCH=		Ph	3	(15)



(17) X = O



(16) X = O
(18) X = S

(9). As the magnitude of $J_{3,3a}$ and the chemical shift values of these protons 3- and 3a-H are in a good agreement with those of compounds (4) and (7) we assigned the *trans* configuration to this diastereoisomer. This deduction is supported by the dramatic decrease in the *cis*/*trans* ratio on increasing *n* (*i.e.* the size of the cycloalkane ring).

In the reaction of the 2-benzylidenecycloalkanones with thiosemicarbazide, only one diastereoisomer was obtained in each case. Although the coupling constants and chemical shifts for compounds (5) and (8) were similar to those of the urea derivatives (3) and (6), their stereochemistry was confirmed by oxidation of the 2-thiocarbamoyl group of compound (5) with hydrogen peroxide to give the *cis* analogue (3). Compound (10) was similarly converted into compound (9), confirming the *trans* configuration of its 3- and 3a-protons. Similar results were obtained with the 2,6-dibenzylidenecyclohexanone analogues. The $J_{3,3a}$ vicinal coupling constants are nearly equal for both diastereoisomers (11) and (12) as expected from the Karplus equation for dihedral angles of *ca.* 25 and 138.2° (*X*-ray measurements); the difference in configuration is reflected in the different chemical shifts of 3-H and 3a-H, respectively (see Experimental section and ref. 7). The thiocarbamoyl group of compound (13), obtained from the reaction of 2,6-dibenzylidenecyclohexanone with thiosemicarbazide, was oxidized to give the urea derivative (11), thus confirming the *cis* configuration.

For compounds (16)—(18), obtained from 2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one, the variation in chemical shift of 3-H corresponds to the previous observations [$\delta_{cis} > \delta_{trans}$, and that for (18) is greater than that for (16)]. The chemical shift of 3a-H does not differ significantly in the diastereoisomeric pair (16) and (17), but the multiplet due to the axial 4-H is shifted downfield by 1.4 p.p.m. owing to the stereochemically preferred orientation of the phenyl group.

^{13}C *N.M.R. Spectroscopy of Compounds* (11) *and* (12).—The ^{13}C chemical shifts are shown in Table 2. The orientation of the 3-phenyl substituent to the *cis*/*trans* diastereoisomers strongly

Table 2. ^{13}C N.m.r. chemical shifts [δ(p.p.m.)] of compounds (11) and (12)*

	cis (11)	*trans* (12)
C-3	154.6	156.8
C-4	49.4	56.6
C-5	63.6	68.5
C-6	154.7	155.3
C-9	130.6	130.8
C-10	27.7	28.9
C-11	23.3	23.6
C-12	25.0	28.3
C-13	138.4	143.2
C-14, -18	126.9	126.4
C-15, -17	126.0	126.6[a]
		126.7[a]
C-16	129.4	129.3
C-19	127.4	127.4
C-20	136.0	136.0
C-21, -25	128.2[b]	128.3
	128.3[b]	
C-22, -24	126.0	125.7
C-23	129.4	129.3

* For convenience the carbon atoms of (11) and (12) are numbered here by the crystallographic scheme shown in the Figure; this should not be confused with the systematic numbering shown in structures (1) and (2).

[a,b] The assignments of the pairs may be interchanged.

influences the chemical shifts of the carbon atoms in the indazole skeleton. A significant shift difference (4.8 p.p.m.) is seen for the quaternary carbon C(13), where the observed high-field shift of the *cis* isomer may be explained by an interaction with the lone-pair of N(1). Large differences in shift were observed for C(4) and C(5) (7.2 and 4.9 p.p.m. respectively), and the smaller differences for C(3) and C(12) (2.2 and 3.3 p.p.m.) are also important. All these positive shift differences are characteristic of the *trans* isomer (12), thus suggesting that the effects of steric interactions and the average shape of the pyrazole ring differ in the two diastereoisomers. Similar assignments for the *trans* isomer were reported by Puar *et al.*[5]

Discussion of the Crystal Structures of Compounds (11) *and* (12).—*X*-Ray analysis showed compounds (11) and (12) to be *cis* and *trans* diastereoisomers. The perspective views of the molecular structures are given in the Figure and were computed from the final fractional co-ordinates which are given, with their e.s.d.s, in Table 3. The majority of the corresponding bond lengths and angles, listed in Tables 4 and 5, agree with each other within experimental error. However, the C(5)–C(13) C_{sp^3}–C_{ar} bond, assuming axial orientation in (11) (see the corresponding torsion angles in Table 6) is longer by 0.014 Å while the pertaining endocyclic bond angle at C(5) is somewhat smaller (by 1.7°) than that in the diastereoisomer (12) where it is equatorial. In accord with this, the five-membered ring in compound (11) shows a greater puckering amplitude[8] [Q = 0.259(1)°] than that in (12) [Q = 0.166(2) Å] although both possess an almost perfect enevelope conformation [φ^8 = 141.1(2)° for (11) and 144.6(2)° for (12)] with C(5) on the flap. In both structures the six-membered carbocyclic ring, owing to the presence of two sp^2C atoms, has a shape intermediate between a chair, half chair, and envelope [puckering parameters:[8] Q = 0.497(2), 0.503(2) Å; φ = 147.9(4), 141.0(6)°; θ = 31.3(2), 26.1(2)°, respectively].

As shown by the torsion angles (Table 6), C(6) of the quasi-planar carboxamide moiety shows a greater deviation from the perfect equatorial position in the stereoisomer (12) than in (11) in accord with the significant differences between the

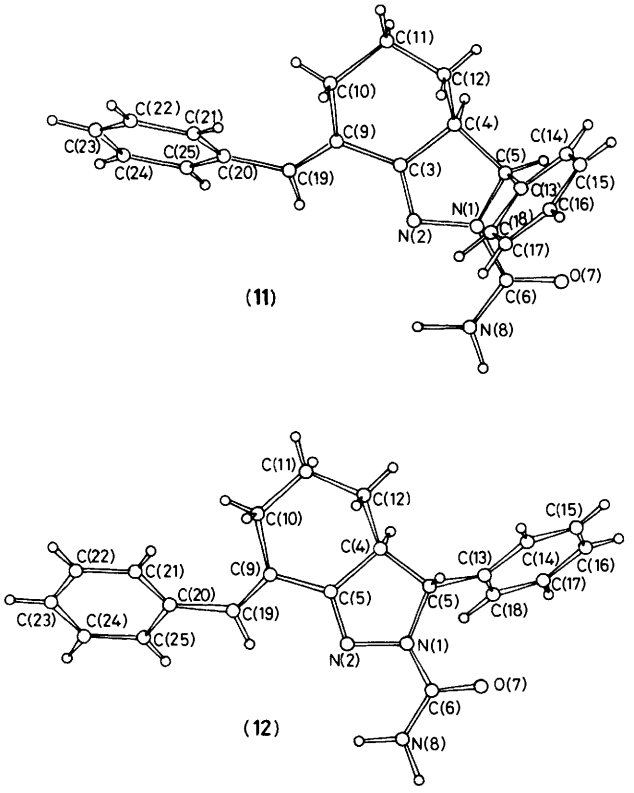


Figure. Perspective view of the molecules (**11**) and (**12**) showing the crystallographic numbering. The H atoms are shown but not labelled

corresponding exocyclic bond angles at N(1). Apart from this slight difference, the steric arrangement of the carboxamide groups is similar, both being fixed in the same way by weak intramolecular N(8)–H(8a) · · · N(2) hydrogen bonds.

	N(8) · · · N(2) (Å)	H(8a) · · · N(2) (Å)	N–H · · · N (°)
(**11**)	2.684(1)	2.32(3)	100.4(1.5)
(**12**)	2.668(1)	2.30(3)	101.8(1.7)

It is worth noting that these hydrogen bonds are presumably weakened by the neighbouring C(19)–H(19) · · · N(2) close contacts characterized by the following parameters.

	C(19) · · · N(2) (Å)	H(19) · · · N(2) (Å)	C–H · · · N (°)
(**11**)	2.898(1)	2.59(3)	99.1(1.9)
(**12**)	2.910(1)	2.61(3)	98.4(1.9)

The C(9)–C(19) distances indicate localized C_{sp^2}–C_{sp^2} double bonds to which the phenyl rings are bound in an *E* arrangement with different degrees of rotation about the C(19)–C(20) bond (Table 6). Nevertheless, each H(19) atom seems to gain enough positive charge to interact weakly with the N(2) atom.

In both crystal lattices the symmetry independent molecules are bound together by intermolecular hydrogen bond pairs of the type N(8)–H · · · O(7), thus forming dimer associates around the centres of symmetry at $(\frac{1}{2},0,-\frac{1}{2})$ and $(\frac{1}{2},-\frac{1}{2},0)$.

	N · · · O (Å)	H · · · O (Å)	N–H · · · O (°)
(**11**) N(8)–H(8b) · · · O(7) [1 − *x*,$\bar{y}$,$\bar{z}$ − 1]	2.894(1)	2.00(2)	160.9(1.1)
(**12**) N(8)–H(8b) · · · O(7) [1 − *x*,$\bar{y}$,$\bar{z}$]	2.896(1)	1.93(3)	171.6(2.3)

Table 3 Atomic fractional co-ordinates of the non-hydrogen atoms of compounds (**11**) and (**12**) with e.s.d.s in parentheses

	x/*a*	*y*/*b*	*z*/*c*
N(1) (**11**)	0.652 3(1)	0.070 8(1)	−0.144 4(1)
(**12**)	0.449 3(1)	−0.185 9(3)	0.178 6(1)
N(2) (**11**)	0.646 3(1)	−0.042 4(1)	0.016 7(1)
(**12**)	0.342 5(1)	−0.048 2(3)	0.156 4(1)
C(3) (**11**)	0.699 8(1)	0.018 6(1)	0.127 4(1)
(**12**)	0.326 7(1)	0.002 5(3)	0.236 0(1)
C(4) (**11**)	0.745 3(1)	0.183 5(1)	0.048 2(1)
(**12**)	0.423 6(1)	−0.099 8(3)	0.323 3(1)
C(5) (**11**)	0.746 2(1)	0.212 7(1)	−0.141 7(1)
(**12**)	0.493 3(1)	−0.271 0(3)	0.279 6(1)
C(6) (**11**)	0.605 0(1)	0.042 5(1)	−0.291 8(1)
(**12**)	0.467 6(2)	−0.323 1(4)	0.108 0(1)
O(7) (**11**)	0.616 3(1)	0.145 7(1)	−0.431 0(1)
(**12**)	0.543 8(1)	−0.486 3(3)	0.131 2(1)
N(8) (**11**)	0.546 3(1)	−0.099 5(1)	−0.269 4(1)
(**12**)	0.400 8(2)	−0.262 3(4)	0.018 2(1)
C(9) (**11**)	0.715 2(1)	−0.062 6(1)	0.312 9(1)
(**12**)	0.221 2(1)	0.138 8(3)	0.242 2(1)
C(10) (**11**)	0.822 7(1)	0.024 1(1)	0.409 8(2)
(**12**)	0.181 1(2)	0.062 6(4)	0.327 9(1)
C(11) (**11**)	0.846 0(1)	0.187 8(1)	0.332 8(2)
(**12**)	0.287 2(2)	−0.015 5(4)	0.417 3(1)
C(12) (**11**)	0.868 6(1)	0.254 7(1)	0.143 7(2)
(**12**)	0.365 8(2)	−0.209 5(4)	0.395 5(1)
C(13) (**11**)	0.879 1(1)	0.248 9(1)	−0.194 6(1)
(**12**)	0.631 7(1)	−0.251 7(3)	0.324 9(1)
C(14) (**11**)	0.961 6(1)	0.393 6(1)	−0.258 0(2)
(**12**)	0.692 6(2)	−0.430 6(3)	0.390 0(1)
C(15) (**11**)	1.085 5(2)	0.429 1(2)	−0.301 1(2)
(**12**)	0.819 4(2)	−0.406 4(4)	0.437 0(2)
C(16) (**11**)	1.127 2(1)	0.320 9(2)	−0.282 6(2)
(**12**)	0.884 4(2)	−0.206 1(4)	0.418 8(2)
C(17) (**11**)	1.046 6(1)	0.177 2(2)	−0.220 3(2)
(**12**)	0.824 4(2)	−0.026 0(4)	0.354 7(1)
C(18) (**11**)	0.922 4(1)	0.140 1(1)	−0.176 6(2)
(**12**)	0.698 4(2)	−0.048 4(4)	0.307 4(1)
C(19) (**11**)	0.635 8(1)	−0.201 6(1)	0.384 1(1)
(**12**)	0.169 0(1)	0.308 0(3)	0.174 4(1)
C(20) (**11**)	0.639 5(1)	−0.303 2(1)	0.564 1(2)
(**12**)	0.056 8(1)	0.448 3(3)	0.159 7(1)
C(21) (**11**)	0.754 7(1)	−0.304 2(2)	0.670 2(2)
(**12**)	−0.040 9(2)	0.368 7(4)	0.192 4(1)
C(22) (**11**)	0.752 8(2)	−0.401 2(2)	0.838 8(2)
(**12**)	−0.145 5(2)	0.505 2(4)	0.174 1(1)
C(23) (**11**)	0.636 1(2)	−0.500 4(2)	0.905 0(2)
(**12**)	−0.156 4(2)	0.722 2(4)	0.121 6(2)
C(24) (**11**)	0.521 2(2)	−0.505 5(2)	0.801 0(2)
(**12**)	−0.063 2(2)	0.801 3(4)	0.086 7(2)
C(25) (**11**)	0.522 5(1)	−0.408 4(1)	0.633 2(2)
(**12**)	0.042 4(2)	0.666 4(3)	0.105 2(1)

Experimental

M.p.s were determined on a Boetius hot plate apparatus and are uncorrected. I.r. spectra were recorded with a Specord F5 type spectrophotometer in KBr pellets. 60 MHz ^{1}H N.m.r. spectra of compounds were recorded at a constant 35.0 °C probe temperature on a Perkin-Elmer R12A spectrometer equipped with a Double Resonance Accessory; tetramethylsilane was used as the internal reference. Double resonance experiments were performed to determine the chemical shift of the 3a protons where necessary. ^{13}C N.m.r. spectra were obtained on a Varian XL-100-FT-15 instrument at 70 °C in [$^2H_6$]dimethyl sulphoxide solution with tetramethylsilane as the internal reference. The α,β-unsaturated ketones were prepared by aldol condensation.[9]

Table 4. Bond lengths (Å) for compounds (**11**) and (**12**) with e.s.d.s in parentheses

	(11)	(12)
N(1)–N(2)	1.395(1)	1.397(2)
N(1)–C(5)	1.465(1)	1.471(2)
N(1)–C(6)	1.374(1)	1.383(2)
N(2)–C(3)	1.289(1)	1.288(2)
C(3)–C(4)	1.504(1)	1.502(2)
C(3)–C(9)	1.467(1)	1.470(2)
C(4)–C(5)	1.543(1)	1.539(2)
C(4)–C(12)	1.517(2)	1.517(2)
C(5)–C(13)	1.517(1)	1.503(2)
C(6)–O(7)	1.227(1)	1.229(3)
C(6)–N(8)	1.339(1)	1.332(2)
C(9)–C(10)	1.514(2)	1.516(2)
C(9)–C(19)	1.338(1)	1.337(2)
C(10)–C(11)	1.522(1)	1.531(3)
C(11)–C(12)	1.521(3)	1.525(3)
C(13)–C(14)	1.383(1)	1.379(2)
C(13)–C(18)	1.385(1)	1.385(2)
C(14)–C(15)	1.387(2)	1.390(3)
C(15)–C(16)	1.365(2)	1.365(3)
C(16)–C(17)	1.368(2)	1.373(3)
C(17)–C(18)	1.388(2)	1.383(3)
C(19)–C(20)	1.470(2)	1.469(2)
C(20)–C(21)	1.390(2)	1.400(2)
C(20)–C(25)	1.395(2)	1.394(2)
C(21)–C(22)	1.380(3)	1.378(3)
C(22)–C(23)	1.371(3)	1.376(3)
C(23)–C(24)	1.374(3)	1.373(3)
C(24)–C(25)	1.375(2)	1.382(3)

Table 5. Bond angles (°) for compounds (**11**) and (**12**) with e.s.d.s in parentheses

	(11)	(12)
N(2)–N(1)–C(5)	112.5(1)	112.6(2)
N(2)–N(1)–C(6)	121.5(1)	118.9(2)
C(5)–N(1)–C(6)	123.5(1)	120.7(2)
N(1)–N(2)–C(3)	106.8(1)	107.5(2)
N(2)–C(3)–C(4)	113.4(1)	113.9(2)
N(2)–C(3)–C(9)	124.2(2)	123.8(2)
C(4)–C(3)–C(9)	122.5(1)	122.3(2)
C(3)–C(4)–C(5)	101.5(1)	102.3(2)
C(3)–C(4)–C(12)	112.5(1)	111.2(2)
C(5)–C(4)–C(12)	119.9(1)	118.0(2)
N(1)–C(5)–C(4)	99.0(1)	100.7(2)
N(1)–C(5)–C(13)	112.6(1)	113.6(2)
C(4)–C(5)–C(13)	114.7(1)	113.2(2)
N(1)–C(6)–O(7)	119.2(2)	119.1(3)
N(1)–C(6)–N(8)	115.7(1)	116.0(3)
O(7)–C(6)–N(8)	125.1(2)	124.9(3)
C(3)–C(9)–C(10)	114.8(1)	113.7(2)
C(3)–C(9)–C(19)	120.1(1)	119.7(2)
C(10)–C(9)–C(19)	125.1(2)	126.5(2)
C(9)–C(10)–C(11)	114.3(2)	114.3(2)
C(10)–C(11)–C(12)	111.5(2)	111.8(3)
C(4)–C(12)–C(11)	108.3(2)	108.2(2)
C(5)–C(13)–C(14)	119.7(2)	119.7(2)
C(5)–C(13)–C(18)	121.7(2)	121.0(2)
C(14)–C(13)–C(18)	118.5(2)	119.1(2)
C(13)–C(14)–C(15)	120.8(2)	120.1(3)
C(14)–C(15)–C(16)	120.1(3)	120.3(3)
C(15)–C(16)–C(17)	119.8(3)	120.0(3)
C(16)–C(17)–C(18)	120.7(3)	120.2(3)
C(13)–C(18)–C(17)	120.0(2)	120.2(3)
C(9)–C(19)–C(20)	128.4(2)	129.7(2)
C(19)–C(20)–C(21)	123.6(2)	123.8(2)
C(19)–C(20)–C(25)	119.2(2)	118.6(2)
C(21)–C(20)–C(25)	117.2(2)	117.5(2)
C(20)–C(21)–C(22)	121.3(3)	121.2(3)
C(21)–C(22)–C(23)	120.3(3)	120.2(3)
C(22)–C(23)–C(24)	119.6(3)	119.8(3)
C(23)–C(24)–C(25)	120.4(3)	120.4(3)
C(20)–C(25)–C(24)	121.2(2)	120.9(3)

General Procedure for the Synthesis of Compounds (**3**)—(**18**).—A mixture of the appropriate α,β-unsaturated ketone (10 mmol) and semicarbazide hydrochloride, 4-phenylsemicarbazide, or thiosemicarbazide (20 mmol) in ethanol (100 ml) and conc. hydrochloric acid (10 ml) was refluxed for 2 h. After cooling, the crystals were filtered off, and washed with ethanol and water. Some precipitate was also obtained from the mother-liquor after it had been neutralized and poured into water. The white crystals obtained were recrystallized from methanol. The following substances were prepared. cis-2-*Carbamoyl*-3-*phenyl*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**3**) (56%), m.p. 219 °C (decomp.; from methanol) (Found: C, 69.3; H, 7.3; N, 17.0. $C_{14}H_{17}N_3O$ requires C, 69.11; H, 7.04; N, 17.27%); $\nu_{max.}$(KBr) 1 665 cm^{-1} (amide I); $\delta_H(CDCl_3)$ 0.4—2.9 (8 H, m, CH_2), 3.2 (1 H, dt, 3a-H), 5.4 (1 H, d, *J* 11.2 Hz, 3-H), 5.1—5.5 (2 H, br s, NH_2), and 6.9—7.5 (5 H, m, Ph).

trans-2-Carbamoyl-3-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indazole (**4**) was not isolated in a pure state; the yield (18%) was estimated on the basis of the ^1H n.m.r. spectrum by measuring the integral of the 3-H protons; $\delta_H(CDCl_3)$ 2.8 (1 H, m, 3a-H) and 4.8 (1 H, d, *J* 6.5 Hz, 3-H).

cis-3-*Phenyl*-2-*thiocarbamoyl*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**5**) (92%), m.p. 139 °C (decomp.; from methanol) (Found: C, 64.6; H, 6.9; N, 16.2; S, 12.5. $C_{14}H_{17}N_3S$ requires C, 64.83; H, 6.61; N, 16.21; S, 12.36%); $\nu_{max.}$(KBr) 1 370 cm^{-1} (thioamide II); $\delta_H[(CD_3)_2SO]$ 0.6—2.9 (8 H, m, CH_2), 3.4 (1 H, m, 3a-H), 5.8 (1 H, d, *J* 11.5 Hz, 3-H), 6.7—7.5 (5 H, m, Ph), and 7.3—7.7 (2 H, br s, NH_2).

The oxidation of compounds (**5**), (**10**), and (**13**) was carried out according to the method described previously.[10]

cis-2-*Carbamoyl*-3-*phenyl*-2,3,3a,4,5,6,7,8-*octahydrocyclohepta*[c]*pyrazole* (**6**) (27%), m.p. 146 °C (decomp.; from methanol) (Found: C, 70.2; H, 7.6; N, 16.1. $C_{15}H_{19}N_3O$ requires C, 70.01; H, 7.44; N, 16.33%); $\nu_{max.}$(KBr) 1 660 cm^{-1} (amide I); $\delta_H(CDCl_3)$ 0.4—3.0 (10 H, m, CH_2), 3.4 (1 H, m, 3a-H), 5.3 (1 H, d, *J* 10.9 Hz, 3-H), 5.3—5.7 (2 H, br s, NH_2), and 6.9—7.4 (5 H, m, Ph).

trans-2-Carbamoyl-3-phenyl-2,3,3a,4,5,6,7,8-octahydrocyclohepta[*c*]pyrazole (**7**) was not isolated in a pure state; the yield (32%) was estimated on the basis of the ^1H n.m.r. spectrum; $\delta_H(CDCl_3)$ 2.9 (1 H, m, 3a-H) and 4.8 (1 H, d, *J* 6.0 Hz, 3-H).

cis-3-*Phenyl*-2-*thiocarbamoyl*-2,3,3a,4,5,6,7,8-*octahydrocyclohepta*[c]*pyrazole* (**8**) (51%), m.p. 190 °C (decomp.; from methanol) (Found: C, 65.7; H, 7.3; N, 15.5; S, 11.5. $C_{15}H_{19}N_3S$ requires C, 65.90; H, 7.01; N, 15.37; S, 11.73%); $\nu_{max.}$(KBr) 1 375 cm^{-1} (thioamide II); $\delta_H(CDCl_3)$ 0.6—3.2 (10 H, m, CH_2), 3.6 (1 H, m, 3a-H), 5.8 (1 H, d, *J* 10.3 Hz, 3-H), 6.1—6.8 (2 H, br s, NH_2), and 6.9—7.6 (5 H, m, Ph).

trans-2-*Carbamoyl*-3-*phenyl*-3,3a,4,5,6,7,8,9-*octahydro*-2H-*cyclo-octa*[c]*pyrazole* (**9**) (85%), m.p. 129—131 °C (from methanol) (Found: C, 70.7; H, 8.0; N, 15.4. $C_{16}H_{21}N_3O$ requires C, 70.82; H, 7.80; N, 15.49%); $\nu_{max.}$(KBr) 1 675 cm^{-1} (amide I); $\delta_H(CDCl_3)$ 1.0—2.7 (12 H, m, CH_2), 2.9 (1 H, m, 3a-H), 4.9 (1 H, d, *J* 7.6 Hz, 3-H), 5.3—5.7 (2 H, br s, NH_2), and 7.0—7.4 (5 H, m, Ph).

trans-3-*Phenyl*-2-*thiocarbamoyl*-3,3a,4,5,6,7,8,9-*octahydro*-2H-*cyclo-octa*[c]*pyrazole* (**10**) (88%), m.p. 150 °C (decomp.; from methanol) (Found: C, 67.0; H, 7.4; N, 14.4; S, 11.3. $C_{16}H_{21}N_3S$ requires C, 66.86; H, 7.36; N, 14.62; S, 11.16%); $\nu_{max.}$(KBr) 1 360 cm^{-1} (thioamide II); $\delta_H(CDCl_3)$ 0.9—2.7 (12 H,

Table 6. Relevant torsion angles (°) for compounds (**11**) and (**12**)

	(11)	(12)
C(3)–C(4)–C(5)–N(1)	23.2(1)	15.1(2)
C(4)–C(5)–N(1)–N(2)	−25.5(1)	−17.2(2)
C(5)–N(1)–N(2)–C(3)	16.5(1)	11.8(2)
N(1)–N(2)–C(3)–C(4)	1.3(1)	−0.4(2)
N(2)–C(3)–C(4)–C(5)	−16.7(1)	−10.1(2)
C(4)–C(3)–C(9)–C(10)	−22.9(1)	−29.3(2)
C(3)–C(9)–C(10)–C(11)	31.4(2)	33.6(2)
C(9)–C(10)–C(11)–C(12)	−53.0(2)	−52.0(2)
C(10)–C(11)–C(12)–C(4)	62.8(2)	62.0(2)
C(11)–C(12)–C(4)–C(3)	−51.8(2)	−54.2(2)
C(12)–C(4)–C(3)–C(9)	34.1(1)	40.6(2)
C(6)–N(1)–N(2)–C(3)	178.9(2)	161.3(3)
C(6)–N(1)–C(5)–C(4)	172.5(2)	−166.1(3)
N(8)–C(6)–N(1)–N(2)	3.9(1)	18.0(3)
O(7)–C(6)–N(1)–C(5)	−17.2(2)	−16.2(2)
C(13)–C(5)–C(4)–C(3)	−96.9(1)	136.8(2)
C(13)–C(5)–N(1)–N(2)	96.2(1)	−138.5(2)
C(19)–C(9)–C(3)–C(4)	155.9(2)	152.0(3)
C(19)–C(9)–C(10)–C(11)	−147.4(2)	−147.8(3)
C(20)–C(19)–C(9)–C(10)	−4.7(2)	−5.3(3)
C(21)–C(20)–C(19)–C(9)	−33.8(2)	−24.8(3)

m, CH_2), 2.9 (1 H, m, 3a-H), 5.4 (1 H, d, *J* 4.1 Hz, 3-H), 6.3—6.8 (2 H, br s, NH_2), and 6.9—7.5 (5 H, m, Ph).

cis-2-*Carbamoyl*-3-*phenyl*-7-*phenylmethylene*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**11**). The mixture of (**11**) and its diastereoisomer (**12**) was subjected to fractional crystallization from methanol. Compound (**11**) (51%) had m.p. 212 °C (decomp.) (Found: C, 76.3; H, 6.1; N, 12.8. $C_{21}H_{21}N_3O$ requires C, 76.11; H, 6.39; N, 12.68%); $\nu_{max.}$(KBr) 1 675 cm^{-1} (amide I); δ_H($CDCl_3$) 0.4—3.2 (6 H, m, CH_2), 3.4 (1 H, m, 3a-H), 5.5 (1 H, d, *J* 10.8 Hz, 3-H), 5.2—5.7 (2 H, br s, NH_2), and 6.9—7.6 (11 H, m, Ph, =CH).

trans-2-*Carbamoyl*-3-*phenyl*-7-*phenylmethylene*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**12**) (24%), m.p. 212 °C (decomp.) (Found: C, 76.05; H, 6.5; N, 12.8. $C_{21}H_{21}N_3O$ requires C, 76.11; H, 6.39; N, 12.68%); $\nu_{max.}$(KBr) 1 680 cm^{-1} (amide I); δ_H($CDCl_3$) 1.0—2.8 (6 H, m, CH_2), 3.0 (1 H, m, 3a-H), 4.8 (1 H, d, *J* 10.5 Hz), 3-H), 5.1—5.7 (2 H, br s, NH_2), and 7.0—7.6 (11 H, m, Ph, =CH).

cis-3-*Phenyl*-7-*phenylmethylene*-2-*thiocarbamoyl*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**13**) (39%), m.p. 210 °C (decomp.; from methanol) (Found: C, 72.6; H, 6.2; N, 12.0; S, 9.4. $C_{21}H_{21}N_3S$ requires C, 72.59; H, 6.09; N, 12.09; S, 9.22%); $\nu_{max.}$(KBr) 1 340 cm^{-1} (thioamide II); δ_H($CDCl_3$) 0.4—3.1 (6 H, m, CH_2), 3.5 (1 H, m, 3a-H), 6.0 (1 H, d, *J* 11.3 Hz, 3-H), 6.1—6.9 (2 H, br s, NH_2), and 6.9—7.5 (11 H, m, Ph, =CH).

cis-3-*Phenyl*-2-*phenylcarbamoyl*-7-*phenylmethylene*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**14**). The mixture of (**14**) and its diastereoisomer (**15**) was subjected to fractional crystallization from methanol. *Compound* (**14**) (34%) had m.p. 175—177 °C (Found: C, 79.7; H, 6.4; N, 10.15. $C_{27}H_{25}N_3O$ requires C, 79.58; H, 6.18; N, 10.31%); $\nu_{max.}$(KBr) 1 685 cm^{-1} (amide I); δ_H($CDCl_3$) 0.5—3.2 (6 H, m, CH_2), 3.4 (1 H, m, 3a-H), 5.6 (1 H, d, *J* 10.7 Hz, 3-H), 6.6—7.7 (16 H, m, Ph, =CH), and 8.16 (1 H, s, NH).

trans-3-*Phenyl*-2-*phenylcarbamoyl*-7-*phenylmethylene*-3,3a,4,5,6,7-*hexahydro*-2H-*indazole* (**15**) (42%), m.p. 150—153 °C (Found: C, 79.7; H, 6.0; N, 10.4. $C_{27}H_{25}N_3O$ requires C, 79.58; H, 6.18; N, 10.31%); $\nu_{max.}$(KBr) 1 685 cm^{-1} (amide I); δ_H($CDCl_3$) 0.9—3.2 (6 H, m, CH_2), 3.1 (1 H, m, 3a-H), 4.9 (1 H, d, *J* 10.9 Hz, 3-H), 6.6—7.6 (16 H, m, Ph, =CH), and 8.1 (1 H, s, NH).

cis-2-*Carbamoyl*-3-*phenyl*-3,3a,4,5-*tetrahydro*-2H-*benz*[g]-*indazole* (**16**) (80%), m.p. 275 °C (decomp.; from methanol) (Found: C, 74.35; H, 5.8; N, 14.6. $C_{18}H_{17}N_3O$ requires C, 74.20; H, 5.88; N, 14.42%); $\nu_{max.}$(KBr) 1 680 cm^{-1} (amide I); δ_H[$(CD_3)_2SO$] 0.3—1.1 (1 H, m, 4-H_A), 1.5—2.0 (1 H, m, 4-H_B), 2.6—3.0 (2 H, m, 5-CH_2), 3.7 (1 H, m, 3a-H), 5.5 (1 H, d, *J* 11.2 Hz, 3-H), 6.4 (2 H, s, NH_2), 6.7—7.6 (8 H, m, Ar), and 7.8—8.1 (1 H, m, 9-H).

trans-2-Carbamoyl-3-phenyl-3,3a,4,5-tetrahydro-2*H*-benz-[*g*]indazole (**17**) was not isolated in a pure state; the yield (6%) was estimated on the basis of the ^1H n.m.r. spectrum; δ_H[$(CD_3)_2SO$] 1.5—2.1 (1 H, m, 4-H_B), 1.9—2.5 (1 H, m, 4-H_A), 2.8—3.3 (2 H, m, 5-CH_2), 3.8 (1 H, m, 3a-H), 4.8 (1 H, d, *J* 11.3 Hz, 3-H), 6.8—7.8 (8 H, m, Ar), and 7.8—8.1 (1 H, m, 9-H).

cis-3-*Phenyl*-2-*thiocarbamoyl*-3,3a,4,5-*tetrahydro*-2H-*benz*-[g]*indazole* (**18**) (78%), m.p. 212 °C (decomp.; from benzene) (Found: C, 70.2; H, 5.8; N, 13.5; S, 10.6. $C_{18}H_{17}N_3S$ requires C, 70.33; H, 5.57; N, 13.67; S, 10.43%); $\nu_{max.}$(KBr) 1 380 cm^{-1} (thioamide II); δ_H($CDCl_3$) 0.6—1.4 (1 H, m, 4-H_A), 1.5—2.0 (1 H, m, 4-H_B), 2.7—3.1 (2 H, m, 5-CH_2), 3.6 (1 H, m, 3a-H), 6.1 (1 H, d, *J* 10.8 Hz, 3-H), 6.2—6.8 (2 H, br s, NH_2), 6.8—7.5 (8 H, m, Ar), and 7.9—8.1 (1 H, m, 9-H).

Crystal Structure of the cis-*Structure* (**11**).—*Crystal data.* $C_{21}H_{21}N_3O$, *M* = 331.42, Triclinic, *a* = 11.244(2), *b* = 10.808(1), *c* = 8.702(2) Å, α = 64.05(1), β = 104.57(1), γ = 114.45(1), *V* = 862.4(4) $Å^3$ (by least-squares refinement) on diffractometer angles for 25 automatically centred reflexions (λ = 0.701 73 Å), space group $P\bar{1}$ (from successful structure refinement), *Z* = 2, D_x = 1.276 g cm^{-3}, *F*(000) = 352. Colourless, transparent needles. Crystal dimensions: 0.18 × 0.35 × 0.65 mm^3, μ(Mo-K_α) = 0.75 cm^{-1}.

Data collection, structure determination and refinement were carried out with a CAD-4 diffractometer, ω/2θ scan in the range $1.5 \leqslant \theta \leqslant 30.0°$ with scan width 0.5 + 0.35tanθ using graphite monochromated Mo-K_α radiation. Three standard reflexions (800, 090, and 007) were monitored every hour and showed no significant (*ca.* 1.6%) deviation. 4 135 Unique reflexions were recorded with *h* = 0—15, *k* = −15—13, *l* = 12—11, of which—after correction for Lorentz and polarization effects (Lp), but not for absorption—3 136 with $I > 3.0\sigma(I)$ were used for structure analysis and refinement. The structure was solved by MULTAN[11] using $300E \geqq 1.20$ normalized structure factors. The full-matrix least-squares refinement minimized $\Sigma w(\Delta F)^2$. 311 Parameters were refined. Final *R* = 0.042, R_w = 0.049, *S* = 2.64, $w = [\sigma^2(F_o) + 0.25\,(pF_o)^2]^{-1}$ where *p* = 0.01. After refinement with isotropic temperature factors a difference Fourier synthesis located the H(8a) and H(8b) atoms bound to the terminal NH_2 moiety. The remaining hydrogens were entered in calculated positions since they were all bonded to carbon atoms of well defined geometry. In the subsequent least squares procedure H positions were refined isotropically together with the heavy atom positions treated already in anisotropic mode.

Crystal Structure of the trans-*Structure* (**12**).—*Crystal data.* $C_{21}H_{21}N_3O$, *M* = 331.42, Triclinic, *a* = 11.413(1), *b* = 5.468(1), *c* = 14.757(1) Å, α = 87.54(1), β = 108.96(1), γ = 92.26(1)°, *V* = 869.8(4) $Å^3$ (by least-squares refinement) on diffractometer angles for 25 automatically centred reflexions (λ = 0.710 73 Å), space group $P\bar{1}$ (from successful structure refinement), *Z* = 2, D_x = 1.265 g cm^{-3}, *F*(000) = 352. Colourless needles. Crystal dimensions: 0.22 × 0.3 × 0.53 mm^3, μ(Mo-K_α) = 0.74 cm^{-1}.

Data collection, structure determination and refinement were carried out with a CAD-4 diffractometer, ω/2θ scan in the range $1.5 \leqslant \theta \leqslant 30.0°$ with scan width 0.5 + 0.35tanθ using graphite monochromated Mo-K_α radiation. Three standard reflexions (800, 040, and 0 014) were monitored every hour and showed no significant (*ca.* 1.7%) deviation. 4 124 Unique observations

were recorded with $h = 0$—16, $k = -7$—7, $l = -20$—19 of which—after correction for Lorentz and polarization effects (Lp) but not for absorption—3 081 with $I > 3.0\sigma(I)$ were used for the structure analysis and refinement.

The structure was solved by MULTAN[11] using $330E \geqslant 1.20$ normalized structure factors. The full-matrix least-squares refinement minimalized $\Sigma w(\Delta F)^2$. 311 Parameters were refined. Final $R = 0.044$, $R_w = 0.053$, $S = 2.75$, $w = [\sigma^2(F_o) + 0.25(pF_o)^2]^{-1}$ where $p = 0.01$. After isotropic refinement for heavy atoms, the positions of H(8a) and H(8b) were obtained from a difference electron density map. The remaining hydrogen positions were generated from assumed geometries as in case of compound (**11**). These hydrogen positions were refined separately in the final stage of the least-squares procedure in the isotropic mode. In both structure analyses, atomic scattering factors were taken from ref. 12. Program system applied: Enraf-Nonius Structure Determination Package with local modifications adapted to PDP 11/34 minicomputer (64k).

Full atomic co-ordinates and temperature factors for compounds (**11**) and (**12**) are available as a Supplementary Publication (SUP No. 56143, 5 pp.).* Structure factor tables are available on request from the editorial office.

Acknowledgements

This work was supported by the Hungarian Ministry of Health. We wish to thank Mr. R. Ohmacht and Mrs. M. Ott for the analyses and the i.r. spectra, and Miss É. Tóth, Miss H. Tencz, and Mrs. E. Bleszity for their valuable technical assistance.

* For details of the Supplementary Publication scheme see Instructions for Authors (1985), *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

References

1 Gy. Oszbach and D. Szabó, *Acta Chim. Acad. Sci. Hung.*, 1975, **86**, 449.
2 A. A. Khalaf, A. K. El-Shafei, and A. M. El-Sayed, *J. Heterocycl. Chem.*, 1982, **19**, 609.
3 J. Krapcho and Ch. F. Turk, *J. Med. Chem.*, 1979, **22**, 207.
4 R. Jacquier and G. Maury, *Bull. Soc. Chim. Fr.*, 1967, 306.
5 M. S. Puar, G. C. Rovnyak, A. I. Cohen, B. Toeplitz, and J. Z. Gougoutas, *J. Org. Chem.*, 1979, **44**, 2513.
6 J. Krapcho and Ch. F. Turk, Ger. Offen., 2 521 299/1975 (*Chem. Abstr.*, 1976, **84**, 59455q); J. Krapcho and Ch. F. Turk, U.S. Pat., 3 923 816/1975 (*Chem. Abstr.*, 1976, **84**, 90151m); J. Krapcho and Ch. F. Turk, U.S. Pat., 3 926 968/1975 (*Chem. Abstr.*, 1976, **84**, 105586h); J. Krapcho and Ch. F. Turk, U.S. Pat., 3 931 169/1976 (*Chem. Abstr.*, 1976, **84**, 105588k).
7 A. Hassner and M. J. Michelson, *J. Org. Chem.*, 1962, **27**, 3974.
8 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354.
9 A. T. Nielsen and W. J. Houlihan, 'The Aldol Condensation in Organic Reactions,' Wiley and Sons, New York, London, Sydney, 1968, vol. 16; W. S. Rapson and R. G. Souttleworth, *J. Chem. Soc.*, 1940, 636.
10 T. Lóránd, D. Szabó, and A. Neszmélyi, *Acta Chim. Acad. Sci. Hung.*, 1977, **93**, 51.
11 P. Main, S. E. Hull, G. Germain, P. J. Declerq, and M. M. Woolfson, A System of Computer Programs of Automatic Solution of Crystal Structures from *X*-ray Diffraction Data, (MULTAN), 1978, University of York, England and Louvain, Belgium.
12 'International Tables for *X*-ray Crystallography,' Kynoch Press, Birmingham, 1962, vol. III.

Received 30*th May* 1984; *Paper* 4/883