8,11a-Methanocycloocta[*d,e*]quinazolines: Diisophoranes Incorporating the Pyrimidine Ring System [1]

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The interaction of 1-chloro(or hydroxy)diisophor-2(7)-en-3-one **1** or **3** with guanidines or ureas produces good yields of substituted 8,11a-methanocycloocta[*d,e*]quinazolines **5-11**, involving a nucleophilic SN_1-substitution at the 1-bridgehead and dehydrative cyclisation at the 3-keto-group of the tricyclic reactants **1, 3**. The structure assigned to members of this novel heterocyclic bridged ring-system is based on both chemical and carbon nmr spectral evidence. The synthesis provides further variants of the incorporation of a fused heterocyclic ring into the tricyclo[7.3.1.$0^{2,7}$]tridecane carbon skeleton. A related condensed [1,3]oxazine **16** is similarly accessible.

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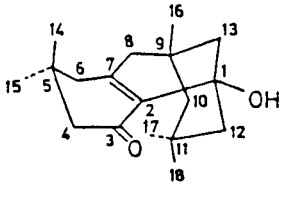
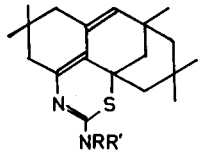
Introduction.

The tricyclo[7.3.1.$0^{2,7}$]tridecane ring-system of diisophorone **A** can be expanded to condensed tetracyclic structures by the incorporation of an additional ring spanning the 1-bridgehead- and 3-positions. Thus, dioxepane- [2], pyridine- [3] and diazepine- [3] rings have been fused with the tricyclic parent framework by the interaction of diisophorones with ethylene glycol, aromatic amines and *o*-diamines. More recently, tetracyclic [1,3]thiazines **B** have become accessible by the condensation of 1-chloro(or hydroxy)diisophor-2(7)-en-3-ones **1** or **3** with thioureas [4]. The scope of this synthetic approach is now extended by the introduction into the tricyclo[7.3.1.$0^{2,7}$]tridecane carbon skeleton of a pyrimidine ring, sharing the C-1, C-2 and C-3 carbon atoms of the original ring system: compounds of this structure were obtained by the interaction of suitable diisophorones with guanidines or ureas.



A

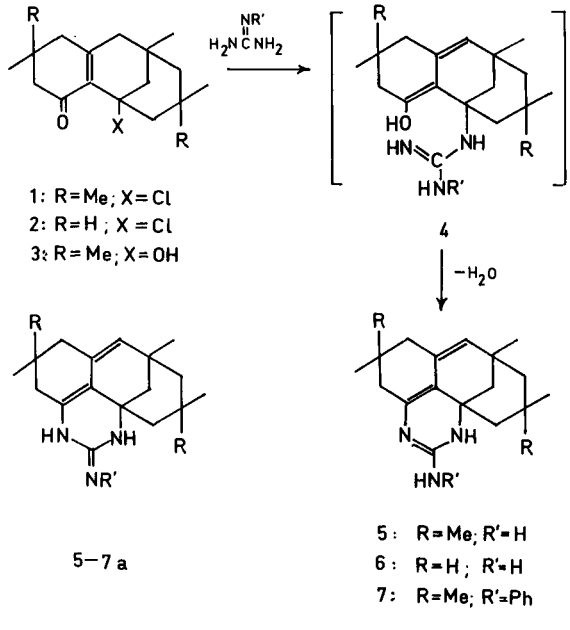


B

Results and Discussion.

Condensation with Guanidines.

The interaction of 1-chloro(or hydroxy)diisophor-2(7)-en-3-one **1** or **3** and guanidine in formic, acetic, or trifluoroacetic acid gave good yields of a product formulated, on the basis of its origin, composition and properties, as the substituted 8,11a-methanocycloocta[*d,e*]quinazoline **5** ("3,21-dehydro-1-guanidinodiisophora-2,7-dien-3-ol", for nomenclature, see footnote [5] and references [6-8]). Trifluoroacetic acid was the preferred medium, because of its superior ionising power [9] and the convenient isolation of the product as the readily crystallisable trifluoroacetate. Acting as a monoacid base, **5** gave other salts (picrate, toluene-*p*-sulphonate), as well as a monotoluene-*p*-sulphonyl derivative **5** (but R' = *p*-$CH_3C_6H_4SO_2$).

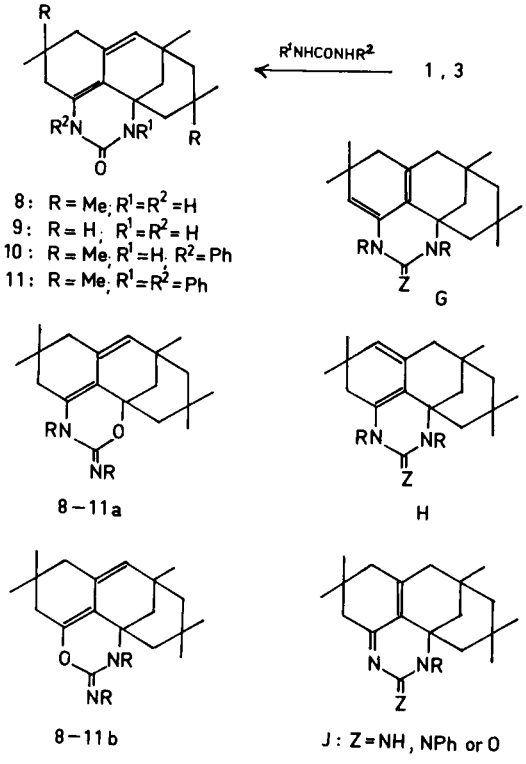


Phenylguanidine similarly gave rise to the 20-anilino-analogue **7**. The proposed location of its phenyl-group (and consequent exclusion of the more crowded 19- or 21-phenyl structures) is based on the more likely involvement in the condensation of the free amino- rather than the anilino-group of the phenylguanidine: it is supported by the failure of 1,2-diphenyl- and 1,2,3-triphenylguanidine to react analogously, and by the carbon nmr spectral data: The newly introduced phenyl-group causes only minimal changes in the chemical shifts of the carbon atoms C-1, C-3 bearing the 19- and 21-NH-moieties: a phenyl-group located in *either* of these positions exerts a distinct deshielding effect on these proximate carbon atoms, as is seen in the comparable urea-condensation products (see

below). By analogy, the monoacyl-derivative of **5** is regarded as the 20-sulphonamido-isomer **5** (R′ = *p*-$CH_3C_6H_4SO_2$).

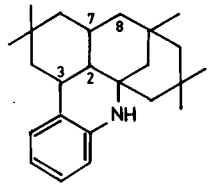
Condensation with Ureas.

The interaction of 1-chlorodiisophor-2(7)-en-3-one (**1**) and urea occurred analogously with elimination of one mole each of hydrogen chloride and water. As in the parallel condensations involving thioureas [4] or guanidines (above), the parent β-ketol **3** was equally suitable as starting material, but the ureas were noticeably less reactive than their counterparts, producing comparable yields only upon prolonged interaction.



Of the three possible isomeric structures of the products, **8**, **8a**, **8b** *etc.*, the first agrees best with both the chemical and spectral evidence. Thus, structures **8a-11a**, corresponding to the molecular pattern **B** of the isothioureido-analogues [4] are discounted, because ureas unlike thioureas are preferentially alkylated and acylated at their nitrogen-function [10]: the formation of condensed 1,3-oxazines **8a-11a** by way of intermediate *O*-substituted isoureas is therefore unlikely. The fact that *N,N*-dimethylurea failed to react also indicates, that it is the two nitrogen functions of the ureas that participate in the condensations, and incidentally disfavours structures **8b-11b** at the same time (but compare compound **16**, below). However, attempts to demonstrate experimentally the presence of a ureido-moiety in **8** by its conversion into the thioureido-grouping by phosphorus pentasulphide-pyridine [11] were frustrated by the rapid resinification of the reactant in this standard procedure.

The adopted structures **8-11** are in accord with the carbon nmr spectral data: the chemical shift of the C-1 singlet of **8** (δ, 54.4 ppm) matches that of 1-(substituted)aminodiisophorone models [3,12] of established structure **12**, **13**; see below. Signals of the 1-bridgehead carbon bearing an oxygen function are known to appear consistently at lower field (*e.g.* 1-hydroxy- [13], 1-acetoxy- [13], 1-alkoxydiisophorones [14]: $\delta_{C\text{-}1}$ 72-80 ppm). Similar results indicate the attachment of the nitrogen- rather than the oxygen-ureido-function at C-3: the chemical shift of C-3 in **8**; (δ, 109.4 ppm) matches that of the guanidine condensation products **5** and **7**, in which the presence of the 3-NH-moiety is beyond doubt, but differs substantially from that of the 3-hydroxy- and 3-acetoxy-2,7-diene models ($\delta_{C\text{-}3}$ 125-130 ppm) [13].



12: 2(7)-Mono-ene
13: 2,7-Diene

Condensation occurred analogously with *N*-phenyl- and *N,N′*-diphenylurea, though not surprisingly in only low yield in the latter example. Within the adopted structural pattern, the location of the two phenyl-substituents in **11** at N-19 and N-21 admits of no choice. They effect a small deshielding of the adjacent C-1 and C-3 carbon atoms (by 4.4 and 6.6 ppm, respectively). In the monophenyl-compound **10**, this displacement is confined to C-3, indicating N-21 to be the point of attachment of its sole phenyl-group.

The condensation products derived from ureas **8**, **10** yield acyl-derivatives, but unlike their guanidino-analogues are not sufficiently basic to form readily crystallisable salts. The stability of their ring-skeleton is reflected in their resistance to acid and alkaline hydrolysis.

The heteroannular distribution of the conjugated 2,7-diene-system in all the tetracyclic products **5-7**, **8-11** is adopted in preference to homoannular alternatives **G**, **H**: It is based on the postulated structural conformity of the tetracyclic condensation products **5-11** and their tricyclic precursors, in which the 2,7-diene disposition is demonstrable by applying the Woodward-Fieser-Scott rules [15] to their uv spectral characteristics. The possible α,β-unsaturated azine structure **J** is excluded by the appearance of a doublet in the carbon nmr spectra of the products *e.g.* **5**, **9**.

As regards the location of the C=N double bond of ring D, a distinction needs to be made between the guanidine-**5-7** and urea-condensation products **8-11**. The

Table I

Carbon-13 NMR Spectra of Tetracyclic 8,11a[Methanocycloocta[*d,e*]quinazolines [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	Reference Compounds									
12	52.5 s	126.5 [c] s	29.9 d	39.6 [d] t	30.1 [e] s	39.8 [d] t	133.9 s	44.2 t	31.5 [e] s	54.6 t
13 [b]	53.4 s	130.2 s	124.9 [c] s	43.9 t	29.9 s	39.7 t	132.5 s	133.9 d	35.1 s	52.2 t
14 [g]	56.2 s	136.2 s	198.8 s	52.1 [c] t	32.3 s	46.2 [d] t	157.6 s	45.7 [d] t	31.3 [e] s	52.2 [c] t
	Condensation Products from Guanidines									
5	52.6 s	132.2 s	110.1 s	43.5 t	30.5 s	43.8 t	137.2 s	126.5 d	34.8 s	53.1 t
7	53.2 s	131.6 s	108.9 s	41.3 t	30.6 s	43.4 t	132.1 s	126.8 d	35.0 s	52.9 t
	Condensation Products from Ureas									
8	54.4 s	128.5 s	109.4 s	40.1 t	30.6 s	43.1 t	130.7 s	128.7 d	35.1 s	53.1 t
10	53.2 s	130.6 s	114.1 s	41.1 t	30.7 s	42.7 t	130.9 s	130.0 [c] d	34.8 s	53.4 t
11	58.8 s	130.7 s	116.0 s	41.5 t	30.6 s	42.8 t	131.0 s	132.4 d	34.9 s	49.7 t
16	53.7 s	130.6 s	112.4 s	40.3 t	30.9 [e] s	42.8 t	145.2 s	130.9 d	35.4 s	54.0 t

Compound	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-20
	Reference Compounds								
12	31.4 [e] s	50.4 t	44.0 t	26.7 q	34.4 q	28.9 q	32.2 q	36.4 q	-
13 [b]	31.4 s	50.9 t	48.4 t	26.4 q	30.4 [d] q	29.3 q	31.0 [c] q	37.3 q	-
14 [g]	31.0 [e] s	45.5 [d] t	43.6 [d] t	27.2 q	29.7 q	28.7 q	32.7 q	37.3 q	166.7 s
	Condensation Products from Guanidines								
5	31.4 s	51.2 t	47.8 t	27.9 q	29.8 q	29.8 q	30.6 q	37.3 q	154.7 s
7	31.6 s	50.9 t	47.7 t	27.6 q	29.8 q	29.8 q	30.5 q	37.2 q	149.6 s
	Condensation Products from Ureas								
8	31.4 s	50.4 t	47.5 t	27.1 q	29.6 [c] q	29.9 [c] q	30.2 [c] q	37.1 q	156.5 s
10	31.5 s	50.0 t	47.3 t	26.2 q	30.3 q	30.3 q	29.5 q	37.0 q	155.4 s
11	31.4 s	48.0 t	46.5 t	26.2 q	29.2 q	30.3 q	30.5 q	37.2 q	154.7 s
16	31.5 [c] s	49.7 t	47.4 t	26.9 q	29.6 [d] q	29.9 [c] q	30.3 q	37.1 q	152.6 s

Supplement to Table I

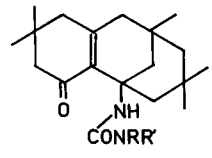
(Aromatic Signals)

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
	Reference Compounds					
12	143.2 s	123.8 [c] s	126.9 d	118.3 d	122.9 d	114.2 d
13	143.9 s	124.3 [c] s	127.6 d	118.0 d	123.3 d	113.5 d
14	134.4 s	128.3 d [f]	126.8 d [f]	130.8 d		
	Condensation Products from Guanidines					
5	See footnote [h]					
7	148.7 s	123.7 d [f]	129.6 d [f]	1220.d		
	Condensation Products from Ureas					
10	137.8 s	128.6 [d] d [f]	129.3 [d] d [f]	127.2 [c] d		
11	138.1 s	128.5 d	129.2 d [f]	127.5 d		130.6 d (21-Ph)
	138.0 s	128.4 d	128.4 d [f]	127.0 d		129.9 d (19-Ph)

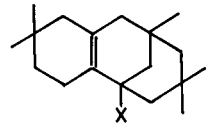
Footnotes to Table I

[a] Spectra were determined in deuteriochloroform, except those of the less soluble compounds **7** and **16**, for which deuteriopyridine was used.
[b] The spectrum of the 5,11[bisnor-homologue of **13** has been recorded previously [13]. It displays the expected close resemblance to that of **13**, except for differences due to the removal of one methyl-group from each of the 5- and 11-positions.
[c,d,e] Signals may need to be interchanged in horizontal lines.
[f] Signal of double intensity.
[g] Compound **14**, not displayed in the reaction schemes, is 1-benzamido-diisophor-2(7)-en-3-one.
[h]
Additional signals originating from ethanol of crystallisation at 57.4 t, and 18.4 q ppm.

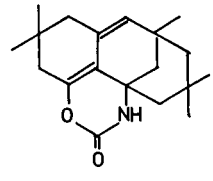
former are regarded as conjugated trienes **5-7** rather than the alternative structures incorporating this unsaturated centre either exocyclically, Scheme I, **5a-7a**, or in the isolated $\Delta^{19\text{-}20}$ position. Support for this choice is available from the uv spectral evidence [4] relating to the comparable condensed [3,1]benzothiazines **B**. In contrast, isourea structures, formally comparable with **5-7**, are generally disfavoured [16], leading to the proposed structures **8-11** for the urea-condensation products. In the *N,N'*-disubstituted example **11**, this amido-configuration is mandatory; since its uv spectrum resembles closely those of its tautomerisable analogues, the ureido-structure is assumed to prevail in *all* the examples **8-11**.



15



17 : X = Cl
18 : X = S.C(:NH)NHR
19 : X = O.C(:NH)NHR
20 : X = NHCONHR



16

Mechanism.

The condensations are visualised, as before [4], to proceed by the attack of the nitrogenous reagent at the 1-substituent of the diisophorone by the S_N1-mechanism obligatory at bridgehead positions [17]. Acid-catalysed cyclodehydration of the intermediate, *e.g.* **4**, between its enolised 3-keto- and ω-amino(or imino)-function completes the process. The individual steps, including the emergence of the 2,7-diene-system, may occur in several possible sequences; the preferred order is at present not settled.

Attempts to intercept intermediates at the C-1 substitution stage by a choice of suitable reactants gave results other than the projected ones. Thus, the expected 1-(ωω-disubstituted)ureido-derivatives **15** were unobtainable from **1** and the appropriately disubstituted ureas: The action of *N,N*-dimethylurea was apparently so slow, that the competing attack of the solvent resulted exclusively in the 1-trifluoroacetyl-compound **3**, (but X = $OCOCF_3$). In an equally slow process, *N,N*-diphenylurea gave very low yields of a product arising by loss of the elements of hydrogen chloride and diphenylamine: its formulation as the condensed [1,3]oxazine **16** is in accord with its origin and composition, and with the close comparability of its car-

bon nmr spectrum and those of the related tetracyclic condensation products.

Nucleophilic replacement of the 1-bridgehead halogen (*e.g.* by hydrolysis or solvolysis) has been found to occur incomparably faster in 1-chlorodiisophor-2(7)-en-3-one (**1**) than in its analogue **17** lacking the activating 3-keto-function [18]. The deoxo-compound **17** does react, however, with thioureas at their thiol-function, giving 1-(*S*-isothioureido)-compounds **18** in good yield [4]. Ureas, expected to produce substituted *N*-ureido- **20** rather than *O*-isoureido-derivatives **19** (see above, [10]), were not sufficiently reactive to effect the 1-bridgehead replacement under the standard conditions.

Carbon NMR Spectra.

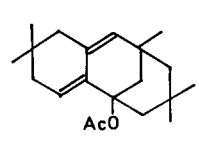
The 13-C nmr spectra of the tetracyclic condensation products **5-11**, and of three authentic reference compounds, **12** [3], **13** [3] and **14** = **1**, X = NHCOPh [12], are displayed in the usual manner [13,19] in accordance with their proposed assignments (Table I). The individual signals were identified by their correlation with those in fully mapped spectra of tricyclo[7.3.1.0^{2,7}]tridecane models [13,19], the assignment of which has previously been established by detailed arguments. Comments relating specifically to the present attributions are briefly set out below. The self-consistency of the spectral characteristics within all three series of condensed heterocyclic products **B**, **5-7**, **8-11** is striking.

Model Compounds.

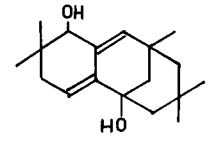
Information concerning the range of the chemical shift of the 1-bridgehead carbon in tricyclotridecane structures **A** bearing a nitrogenous function was obtained by determining the spectra of authentic reference compounds, including 1-benzamidodiisophor-2(7)-en-3-one **14**, *i.e.* **1**, X = NHCOPh [12] and the aniline condensation products **12** and **13** [3]. The appearance of the C-1 signals of the tetracyclic products **5-11** within the narrow limits thus established (53-56 ppm) confirms the attachment of ring D by an NH-grouping at C-1, a point of significance in the formulation of the urea-condensation products. The remaining spectral characteristics of the 1-benzamido-compound **14** deviate barely from those of the parent β-ketol **3**. Not surprisingly, the spectra of the aniline condensation products **12**, **13** [3] resemble those of the tetracyclic compounds rather than their tricyclic precursors. For the assignment of their aromatic signals, the mapped spectrum of *o*-ethylaniline [20a] provided the necessary guidance.

2-Imino-8,11a-methanocycloocta[*d,e*]quinazolines **5-7**.

Amongst all the condensation products now described **5-11**, **5** is subject to the least structural uncertainties and provides the surest guidelines for interpreting their carbon nmr spectra. The resonances of its tricyclo[7.3.1.0^{2,7}]-tridecane-framework match - mostly very closely - those of the parent ketol **3** and more particularly those of comparable 2,7-dienes, *e.g.* **K** and **L** [21]. Any divergences are explicable in terms of the modified structure **5**. Thus, the



K



L

bridgehead C-1 singlet appears at 52.6 ppm under the influence of the adjacent NH-moiety. The chemical shift of C-20 [5] (δ, 154.7 ppm) approximates to that of the comparable C-2 atom in 2-aminopyrimidine [22] (δ, 158.4 ppm) and guanosine [20b] (δ, 153.8 ppm). The remaining three carbon atoms of the pyrimidine ring D, shared with the tricyclic ring-system (A/B/C), are dominated by the latter in their spectral characteristics: their chemical shifts approach those of C-1,2,3 in diisophorones rather than those of C-4,5,6 of the simpler pyrimidine prototypes [20b,22]. The low-field singlets of the carbon atoms flanking the conjugated 2,7-double bonds are allocated in the established [13,21] descending sequence to C-7, C-2 and C-3, and resemble closely those of the tricyclic diene **K** in their chemical shifts. The 2,7-diene system exerts the expected [13,21] deshielding effect on C-4 and C-9 (*ca.* 8 and 3 ppm, respectively) [23], and slight shielding of the spatially proximate C-17. The usual constancy of the resonances of C-10 and C-11 is maintained in **5**, and indeed throughout the series.

2-Oxo-8,11a-methanocycloocta[*d,e*]quinazolines **8-11**.

The interpretation of the spectra of the 2-oxo-compounds **8-11** was facilitated by the remarkable self-consistency of the data for all the members of this type, as well as their thiazine analogues [4]. The exchange of the 20-imino- for a 20-oxo-function had no material effect on the chemical shift of C-20, in accord with the established near-constancy of the signal of the central carbon of guanidino-and ureido-moieties in both linear [24a] and heterocyclic [24b] structures. In conclusion, attention is drawn to the support provided in favour of the proposed condensed 1,3-oxazine structure **16** by the close comparability of its spectrum with those of the group of tetracyclic compounds as a whole.

Conclusion.

The present synthesis of the novel ring systems **F** (X, Z = N; Y = C), and **16** provides further variants of the incorporation of a hetero-ring into the tricyclo[7.3.1.0^{2,7}]tridecane carbon framework **A** at its 1- and 3-position. It may be regarded ultimately as an example of the classical synthesis of pyrimidines [25] from a three-carbon- and an N-C-

N-fragment [25a], being comparable with the condensation of β-diketones and β-keto-esters with guanidines or ureas [25b]. A special feature of the present group of syntheses, apparently without parallel in this general synthetic approach [25c], is the function of β-chloroketones **1** and **2** as an alternative source of the three-carbon segment. The reaction is thought to be promoted by the favourable spacing and orientation of the 1- and 3- substituents in the reactants **1-3**. The newly formed 6-membered hetero-ring is virtually unstrained, and approximately coplanar with rings A/B, which are more than usually flattened by the simultaneous introduction of the conjugated 2,7-diene-system. The C-6, 7 and 8 atoms of the tricyclic precursor **A** form another potential site for the construction of a hetero-ring by the same approach that would lead to yet further heterocyclic ring-systems by the present versatile route.

EXPERIMENTAL

The equipment used in the determination of the spectral data, as well as details concerning general methods, reagents and solvents, and abbreviations have been specified previously [4,6]. Unassigned ir peaks are omitted except for the structural prototypes **5**, **8** and **16**.

Condensation with Guanidines.

3,21-Dehydro-1-guanidinodiisophora-2,7-dien-3-ol (**5**) (2,3,4,5,6,8,-9,10,11,11a-Decahydro-2-imino-5,5,8,10,10-pentamethyl-[1*H*]-8,11a-methanocycloocta[*d,e*]quinazoline, or Alternative Name in Footnote [5]).

(a) Trifluoroacetate.

A solution of 1-chlorodiisophor-2(7)-en-3-one (**1**, 2.95 g, 10 mmoles) or diisophor-2(7)-en-1-ol-3-one (**3**, 2.76 g, 10 mmoles) and guanidine hydrochloride (1.15 g, 12 mmoles) in trifluoroacetic acid (25 ml) was refluxed for 6 hours, distilled to half bulk, and stirred into ice-water (250 ml). The precipitated oil resinified when the suspension was nearly neutralised with (solid) sodium carbonate, and solidified on being stirred with successive portions of water. The drained crude product was quickly dissolved by its addition to hot methanol (10 ml). The seeded liquid deposited massive crystals, mp 162-166°, 1.24-1.42 g, (30-35%) Filtrate F, which gave prisms of **5** trifluoroacetate, mp 164-167° (from methanol, or from 90% ethanol); ir (potassium bromide): 3410 s (NH_3^+), 3130 s vbr, 1565 m (NH), 2950-2880 vs, 1470, 1445 m (CH_3, CH_2), 1695, 1690 d vs vbr (C=N), 1390, 1365 ms (CMe_2), 1210, 1200 vs d, 1180 vs, 1135 vs (CF_3CO_2H), 850 ms, 810 ms 720 s cm^{-1}.

Anal. Calcd. for $C_{19}H_{29}N_3 \cdot CF_3CO_2H$: C, 61.0; H, 7.3; N, 10.2; F, 13.8. Found: C, 60.9; H, 7.15; N, 10.2; F, 13.65.

(b) Base.

The methanolic filtrate F was basified with 3 *M* sodium hydroxide (10 ml). The precipitate, mp 180-186° (28-35%) gave, on crystallisation from ethanol-water (8 and 6 ml per g), pale-yellow needles of **5**, mp 184-188° dec darkening from *ca.* 120°; uv: λ max 218 nm (log ε 4.03), 291 (3.80); ir: 3370 s br, 3200 ms, 1575 vs (NH), 2950-2880 vs, 1465 ms (CH_3, CH_2), 1675 ms sh, 1640 vs br (C=N), 1385, 1365 ms (CMe_2), 1510 ms, 1405 s, 1305 m, 1245 mw, 1045 mw cm^{-1}. The base was partially decomposed on attempted desolvation at 110°/0.5 mm Hg for 3 hours.

Anal. Calcd. for $C_{19}H_{29}N_3 \cdot EtOH$: C, 73.0; H, 10.15; N, 12.2. Found: C, 72.9; H, 9.85; N, 12.6.

(c) The picrate formed deep-yellow needles (64%), mp 238-240° (from ethanol).

Anal. Calcd. for $C_{19}H_{29}N_3 \cdot C_6H_3N_3O_7$: C, 56.8; H, 6.1; N, 15.9. Found: C, 56.8; H, 6.1; N, 15.7.

(d) Toluene-*p*-sulphonate.

A solution of the trifluoroacetate (2.05 g, 5 mmoles) in ethanol (6 ml) was treated with toluene-*p*-sulphonic acid monohydrate (1.15 g, 6 mmoles) dissolved in water (1 ml)-ethanol (3 ml) and the liquid added dropwise to stirred water. The finely divided precipitate was collected at 0°, drained and air-dried, forming a primrose powder of **5** toluene-*p*-sulphonate monohydrate, mp 126-128° (75%); ir: 3225 vs vbr (NH_3^+), 2980-2900 vs, 1465 m br (CH_3, CH_2), 1680 vs br (C=N), 1575 ms (NH), 1395, 1365 m (CMe_2), 1200, 1180 vs d vbr, 1035 s, 1015 s (? $C_7H_7SO_3H$), 820 m (*p*-substituted aryl) cm^{-1}. The salt was not desolvated at 80° and 110° at 3 mms Hg for 5 hours, forming a caked yellow powder, mp 128-130°.

Anal. Calcd. for $C_{19}H_{29}N_3 \cdot C_7H_8O_3S \cdot H_2O$: C, 63.8; H, 8.0; N, 8.6; S, 6.5. Found: C, 63.8; H, 7.7; N, 8.8; S, 6.7.

(e) Toluene-*p*-sulphonyl Derivative.

A solution of solvated **5** (0.69 g, 2 mmoles) in pyridine (12 ml) was treated with toluene-*p*-sulphonyl chloride (0.95 g, 5 mmoles), kept at 100° for 1.5 hours, and stirred into concentrated hydrochloric acid (12 ml)-ice. The precipitate gave the derivative hemihydrate as an opaque buff powder, mp 208-211° from 70% aqueous methanol (55%); ir: 3450 m, 3320 s, 3190 m vbr t (NH), 2980-2890 vs, 1480 ms (CH_3,CH_2), 1680 mw, 1625 vs vbr (C=N), 1390, 1370 s (CMe_2) cm^{-1}.

Anal. Calcd. for $C_{26}H_{35}N_3O_2S \cdot \frac{1}{2} H_2O$: C, 67.5; H, 7.8; N, 9.1; S, 6.9. Found: C, 67.7; H, 7.35; N, 8.6; S, 7.0.

The above hemihydrate was desolvated at 110°/1 mm Hg for 4 hours.

Anal. Calcd. for $C_{26}H_{35}N_3O_2S$: C, 68.9; H, 7.7; N, 9.3. Found: C, 68.4; H, 7.6; N, 9.0.

3,21-Dehydro-1-guanidino-5,11-bisnordiisophora-2,7-dien-3-ol (**6**).

The use of **2** (2.67 g, 10 mmoles) in procedure *a* above gave a yellow gum that failed to crystallise. Its solution in methanol (10 ml), treated with picric acid (2.3 g, 10 mmoles) in hot ethanol (10 ml) deposited **6** picrate as orange platelets, mp 216-218°, 36%, from ethanol.

Anal. Calcd. for $C_{17}H_{25}N_3 \cdot C_6H_3N_3O_7$: C, 55.2; H, 5.6; N, 16.8. Found: C, 55.1; H, 5.7; N, 16.6.

3,21-Dehydro-1(ω-phenylguanidino)diisophora-2,7-dien-3-ol (**7**).

(a) Trifluoroacetate.

A solution of **1** (5.9 g, 20 mmoles) and phenylguanidine toluene-*p*-sulphonate (7.05 g, 23 mmoles) in trifluoroacetic acid (75 ml) was refluxed during 18 hours, then stirred into ice-water. The precipitate gave, on crystallisation from ethanol (3 ml per g, recovery 70%), faintly yellow needles of **7** trifluoroacetate, mp 216-217° (65%); ir: 3430 s (NH_2^+), 3230 s (NH), 2980-2850 vs, 1465 ms, 1435 ms (CH_3, CH_2), 1690, 1680 vs d to 1650 vs br, 1605 vs, 1590 vs sh (? C=N, NH), 1390 s, 1370 s (CMe_2), 1200 vs, 1175 vs, 1130 vs (CF_3CO_2H), 740 ms, 720 ms, 690 m (Ph), 1505 s cm^{-1}.

Anal. Calcd. for $C_{25}H_{33}N_3 \cdot CF_3CO_2H$: C, 66.3; H, 6.95; N, 8.6; F, 11.7. Found: C, 66.5; H, 6.9; N, 8.5; F, 11.95.

(b) Base.

A boiling solution of **7** trifluoroacetate (14.7 g, 3 mmoles) in ethanol (10 ml) was treated with 3*M* sodium hydroxide (3 ml, 9 mmoles). The precipitate, collected at 0°, was boiled with ethanol (10 ml), and the undissolved residue (mp 236-240°, 1.0 g, 90%) crystallised from ethanol-acetone (30 and 10 ml per g, recovery low), giving **7** as a faintly yellow powder, mp 235-238°; uv: λ max 210 nm (log ε 4.05), 250 (4.03, shallow), 297 (4.06); ir: 3420 ms, 3075 ms (NH), 2950-2870 vs mult, 1490 m, 1470 m, 1435 ms br (CH_3, CH_2), 1680 s, 1660-1650 vs d, 1595 vs (? C=N, NH), 1390 ms, 1365 ms (CMe_2), 780 ms, 700 ms (Ph), 1235 s cm^{-1}.

Anal. Calcd. for $C_{25}H_{33}N_3$: C, 80.0; H, 8.8; N, 11.2. Found: C, 79.6; H, 9.0; N, 11.25.

The use of formic acid (40 ml) as solvent in procedure *a*, reflux time, 8 hours, and isolation by procedure *b* also gave **7** in 50% overall yield.

(c) The **7** picrate, obtained from the components in ethanol, formed deep-orange felted needles (75%), mp 212-214° (from ethanol).

Anal. Calcd. for $C_{25}H_{33}N_3 \cdot C_6H_3N_3O_7$: C, 61.6; H, 6.0; N, 13.9. Found: C, 61.8; H, 6.1; N, 13.8.

(d) Diacetyl Derivative.

A solution of **7** (0.38 g, 1 mmole) in acetic anhydride (8 ml) was refluxed for 2 hours, stirred into water, and the precipitated oil, which solidified on storage, crystallised from ethanol, giving prisms of the diacetyl-derivative, mp 180-182°; uv: λ max 210 nm (log ε 4.00), 240 (4.15), 266 (4.10); ir: 3420 ms br (NH amide), 2940-2890 vs, 1435 ms (CH_3, CH_2), 1690 vs, 1665 vs (CO, amide), 1645 ms sh (? C=N), 755 ms, 700 ms (Ph) cm^{-1}.

Anal. Calcd. for $C_{29}H_{37}N_3O_2$: C, 75.8; H, 8.1; N, 9.15. Found: C, 76.2; H, 8.25; N, 9.1.

Use of 1,2,3-Triphenyl- and 1,2-Diphenylguanidine.

A solution of **1** (2.94 g, 10 mmoles) and 1,2,3-triphenylguanidine hydrochloride (3.56 g, 11 mmoles) in trifluoroacetic acid (25 ml) was boiled under reflux for 6 horus, the red liquid distilled to half-volume, and stirred into water. The precipitated resin was rinsed with water and stirred with a little ethanol, when it rapidly set to a white solid and was collected at once; it was 1,2,3-triphenylguanidine trifluoroacetate, mp 218-220°, needles from ethanol, (60%); ir: 3420 mw, 2870 vs vbr (NH, NH^+), 1675 vs d, 1600, 1585 vs d (C=N, NH), 1200 vs br, 1135 vs (CF_3CO_2H), 765 ms, 745 vs, 725, 715 s d, 685 vs (3 Ph) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_3 \cdot CF_3CO_2H$: C, 62.8; H, 4.5. Found: C, 62.4; H, 4.9.

The product separating from the ethanolic filtrate, mp 104-106°, 32%, was 1-trifluoroacetoxydiisophor-2(7)-en-3-one, mp 106-107°, from ethanol, identical, mixed mp, ir, with authentic material [4].

The use of 1,2-diphenylguanidine (2.32 g, 11 mmoles) in the foregoing procedure gave the usual grey-green resin. Dissolved in a little ethanol, and treated with ethanolic picric acid (10 mmoles), it gave 1,2-diphenylguanidine picrate, mp 168-170° (60%), lit [26] mp 169°.

Anal. Calcd. for $C_{13}H_{13}N_3 \cdot C_6H_3N_3O_7$: C, 51.8; H, 3.6; N, 19.1. Found: C, 52.1; H, 3.4; N, 18.8.

Condensation with Ureas.

3,21-Dehydro-1-ureidodiisophora-2,7-dien-3-ol (**8**). (2,3,4,5,6,8,9,-10,11,11a-Decahydro-2-oxo-5,5,8,10,10-pentamethyl-1*H*-8,11a-methanocycloocta[*d,e*]quinazoline [5]).

(a) A solution of **1** (2.95 g, 10 mmoles) and urea (1.8 g, 30 mmoles) in trifluoroacetic acid (30 ml) was refluxed during 48 hours. The liquid was stirred into ice-water, the mixture basified with sodium carbonate, the precipitated powder (*ca.* 3.5 g) washed with water and carefully dried at room temperature. Crystallisation from ethanol (10 ml per g, recovery 80%) gave ivory prisms, 2.2-2.7 g, (64-78%) of solvated **8**, mp 192-194° dec after vigorous sintering at 102-104°, rate-dependent, hence rapidly heated; uv: λ max 217 nm (log ε 3.87), 285 (3.82); ir: 3240 vs, 3110 s (NH), 2960-2860 vs, 1465, 1445, 1430 s br mult (CH_3, CH_2), 1685, 1670-1660 vs (CO amide), 1385, 1365 s (CMe_2), 1335 m, 1225 s, 1165 m, 1145 mw, 1000 mw, 800 m br, 765 cm^{-1}.

Anal. Calcd. for $C_{19}H_{28}N_2O \cdot EtOH$: C, 72.8; H, 9.8; N, 8.1. Found: C, 72.8; H, 9.9; N, 8.1.

It was desolvated without change in appearance on being heated at 110°/3 mm Hg for 5 hours.

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 76.0; H, 9.3; N, 9.3. Found: C, 75.5; H, 9.3; N, 9.7.

(b) The use of formic acid (20 ml) in the foregoing procedure, (time of reflux, 18 hours) also gave **8**, though in much diminished yields (*ca.* 20%).

(c) The use of **3** (6.9 g, 25 mmoles) in procedure *a* (reflux, 18 hours) also gave **8** (72-84%), identical with material obtained in *a*.

3,21-Dehydro-1-ureidodiisophora-2,7-dien-3-ol (**8**): Reactions.

(a) The compound (3 mmoles) was recovered (64%) after being refluxed with phosphorus pentasulfide (1.33 g, 6 mmoles) in anhydrous pyridine (10 ml) for 1.5 hours. It failed to yield a picrate (in ethanol).

(b) Acylation.

A solution of **8** (1.73 g, 5 mmoles) in acetic anhydride (15 ml) was boiled for 2 hours, then stirred into warm water. The precipitated oil which solidified slowly, gave on crystallisation from methanol (8 ml), minute prisms (0.34-0.43 g, 20-25%) of the monoacetyl derivative, mp 209-212°; uv: λ max 208 nm (log ε 3.78), 270 (4.16); ir 3210 s, 3110 s (NH), 2940-2860 vs, 1470, 1455 m (CH_3, CH_2), 1720 vs, 1700-1690 vs (C=N, CO) cm^{-1}.

Anal. Calcd. for $C_{21}H_{30}N_2O_2$: C, 73.7; H, 8.8; N, 8.2. Found: C, 74.1; H, 9.2; N, 8.0.

On evaporation, the filtrate gave discoloured crystals, which afforded prisms (0.61-0.86 g, 32-45%) of the diacetyl derivative, mp 137-139° from very little methanol; uv: λ max 206 nm (log ε 3.88), 267 (4.30); ir: 2960-2880 vs, 1475 m, 1445 m (CH_3, CH_2), 1735 vs (C=N), 1710 vs, 1690 vs (2 CO) cm^{-1}.

Anal. Calcd. for $C_{25}H_{32}N_2O_3$: C, 71.9; H, 8.3; N, 7.3; M, 384. Found: C, 72.2; H, 8.5; N, 7.6; M, mass-spectrometrically, 384.

The base **8** (2 mmoles) was recovered after its solution in pyridine (8 ml), treated with acetyl chloride (4 mmoles) was kept at 100° for 1 hour, or with benzoyl chloride (2.4 mmoles) at 100° for 2 hours (recovery 70 and 52%).

3,21-Dehydro-1-ureido-5,11-bisnordiisophora-2,7-dien-3-ol (**9**).

The use of **2** (2.67 g, 10 mmoles) in the foregoing procedure *a* gave a crude product affording, on crystallisation from ethanol-water (2:1), pale-yellow opaque prisms (56%) of **9**, mp 233-235°

on rapid heating, with shrinking at 100°; uv: λ max 216 nm (log ε 4.00), 284 (4.03); ir: 3220 vs, 3100 s sh (NH), 2950-2820 vs br, 1460-1400 s mult (CH_3, CH_2), 1690, 1685 vs d, 1675, 1665 vs d (C=N, NH) cm^{-1}.

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 75.0; H, 8.8; N, 10.3. Found: C, 74.6; H, 8.7; N, 10.5.

3,21-Dehydro-1-(ω-phenylureido)diisophora-2,7-dien-3-ol (**10**).

A solution of **1** (2.95 g, 10 mmoles) and phenylurea (1.50 g, 11 mmoles) in trifluoroacetic acid (35 ml) was boiled under reflux for 8 hours, reduced to half volume in a vacuum and stirred into ice-water containing 3 *M* sodium hydroxide (20 ml). The soft precipitate solidified slowly and gave minute prisms of **10**, mp 218-220° from ethanol (54-60%); uv: λ max 212 nm (log ε 4.15), 290 (4.24); ir: 3210 vs, 3100 s sh (NH), 2950-2870 vs, 1470 ms, 1460 ms sh, 1410 vs (CH_3, CH_2), 1690 vs, 1680 vs, 1660 s sh (C=N, NH), 1380, 1365 vs (CMe_2), 765 s, 700 vs (Ph) cm^{-1}.

Anal. Calcd. for $C_{25}H_{32}N_2O$: C, 79.8; H, 8.5; N, 7.45. Found: C, 80.2; H, 8.5; N,7.3. The compound failed to give a picrate from the components in ethanol.

Derivatives.

(a) A solution of **10** (0.75 g, 2 mmoles) in acetic anhydride (8 ml) was boiled under reflux for 1 hour, then stirred into water. The crystalline precipitate, mp 225-228° (84%) gave minute prisms of the monoacetyl derivative, mp 230-233° from ethanol-acetone; uv: λ max 211 nm (log ε 4.00), 238 (4.08), 273 (4.05); ir: 2950, 2910 vs d - 2870 s, 1470, 1460 mw d (CH_3, CH_2), 1715 s (CO), 1675 vs, 1660 s sh (C=N), 1370, 1355 vs (CMe_2), 780 mw, 760 m, 730 m, 695 m (Ph) cm^{-1}.

Anal. Calcd. for $C_{27}H_{34}N_2O_2$: C, 77.5; H, 8.1; N, 6.7. Found: C, 77.6; H, 8.1; N, 6.8.

(b) A solution of **10** (0.75 g, 2 mmoles) in pyridine (8 ml), treated with benzoyl chloride (0.34 g, 2.4 mmoles) was kept at 100° for 2 hours, then stirred into concentrated hydrochloric acid (8 ml)-ice. The precipitate gave opaque microprisms (65%) of the monobenzoyl derivative, mp 203-204° from a little methanol; uv: λ max 212 nm (log ε 4.13), 255 (4.22), 272 (4.21); ir: 2950-2880 vs, 1455 m (CH_3, CH_2), 1690, 1680 vs-1660 vbr s (CO, C=N), 1355 s (CMe_2), 755 s, 730 vs, 690 vs (Ph) cm^{-1}.

Anal. Calcd. for $C_{32}H_{36}N_2O_2$: C, 80.0; H, 7.5; N, 5.8. Found: C, 79.8; H, 7.6; N, 5.9.

3,21-Dehydro-1-(*N,N'*-diphenylureido)diisophora-2,7-dien-3-ol (**11**).

The use of *N,N'*-diphenylurea (2.35 g, 11 mmoles) in the standard procedure (see **10** above) gave a resin which hardened slowly and afforded, on crystallisation from methanol or ethanol with addition of a little water, pale-yellow opaque microprisms (15-20%) of **11**, mp 200-202°; uv: λ max 212 nm (log ε 4.10), 289 (4.13); ir: 2940-2860 vs, 1455 m (CH_3, CH_2), 1670-1660 vs br (C=N), 1365 vs br (CMe_2), 755 ms, 720 m, 705, 695 ms d (Ph) cm^{-1}.

Anal. Calcd. for $C_{31}H_{36}N_2O$: C, 82.3; H, 8.0; N, 6.2. Found: C, 82.0; H, 7.9; N, 6.35.

The use of *N,N*-dimethylurea in the standard procedure (5 hours' reflux) gave merely the 1-trifluoroacetic ester of **3** (38%) identified by ir [4].

Attempted Interactions with 3-Deketodiisophorones.

(a) With Guanidine.

Interaction of **17** (5 mmoles) and guanidine hydrochloride (5.5 mmoles) in trifluoroacetic acid (12 ml) for 30 or 6 hours gave, by the usual work-up, a brown oil which failed to solidify and consisted, according to tlc, mainly of 1-chloro- and some 1-hydroxydiisophor-2(7)-ene. From the aqueous phase, guanidine was recovered as the picrate (70%).

(b) With Ureas.

N,N'-Diphenylurea failed to react with **17** under the standard conditions, being recovered (85%) after 8 hours' interaction.

Phenylurea gave noncrystallisable resinous products consisting, according to tlc, of partly hydrolysed reactant. The action of urea on **17** under the standard conditions gave intractable dark-red oils from which no identifiable product was obtainable.

13-Keto-3,3,5,9,9-pentamethyl-12-oxa-14-azatetracyclo[9.3.1.$1^{1,5}$.$0^{7,15}$]hexadeca-6,11(15)-diene (**16**).

Interaction of **1** (1.47 g, 5 mmoles) and *N,N*-diphenylurea (1.17 g, 5.5 mmoles) in boiling trifluoroacetic acid (12 ml, 16 hours), and the usual work-up gave a yellow gum. This was rinsed with water, air-dried, and crystallised from methanol to give microprisms of **16**, mp 253-256° (25%); uv: λ max 208 nm (log ε 3.69), 254 (4.09); ir: 3420 s, 3250-3200 s t, 3130 s (NH), 2950-2870 vs, 1465 m, 1410 m (CH_3, CH_2), 1725 vs br (CO), 1395 m, 1365 s (CMe_2), 1330 m, 1300 ms, 1215 s, 1160 s, 1050 ms, 955 ms, 920 m, 855 mw, 800 m, 750 mw cm^{-1}.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.75; H, 9.0; N, 4.65; M, 301. Found: C, 75.65; H, 9.0; N, 4.6; M, mass-spectrometrically, 301.

Prolonging the time of reaction (24-36 hours) and increasing the proportion of the *N,N*-diphenylurea (1.5-2 moles) led to increased resinification, very little **16** being isolable. After shorter periods of interaction (8 hours), the *N,N*-diphenylurea was substantially recovered. The compound **16** was recovered near-quantitatively after being boiled in acetic anhydride (0.15 g, 0.5 mmole in 5 ml) for 1 hour.

Acknowledgements.

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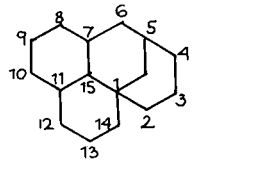
[5] Note on Nomenclature. According to Baeyer's nomenclature of bridged ring structures, which derives the names of compounds from the ultimate saturated homocyclic ring-system (*i.e.* tetracyclo[9.3.1.$1^{1,5}$$0^{7,15}$]-hexadecane for **C**), compound **5** is named 13-imino-3,3,5,9,9-pentamethyl-12,14-diazatetracyclo[9.3.1.$1^{1,5}$.$0^{7,15}$]hexadeca-6,11(15)-diene. The IUPAC system selects the parent heteroaromatic ring as the basis of the name (here: quinazoline **D**). Its fusion with a cyclooctane ring, and numbering of the appropriately oriented carbon framework leads to the fully conjugated parent base **E** and hence to the following name for **5**: 2,3,4,5,6,8,-9,10,11,11a-decahydro-2-imino-5,5,8,10,10-pentamethyl-1*H*-8,11a-methanocycloocta[*d,e*]quinazoline. Because of the complexity of both approved names, our simplified nomenclature [6-8] recently adapted to

comparable hetero-diisophorone patterns [4] is again used. It reflects the formal derivation of the products from hypothetical precursors, *e.g.* **4**, by cyclodehydration, and adheres to the conventional numbering of the carbon framework **F**, thus facilitating the correlation of all the diisophorone



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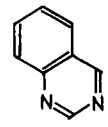

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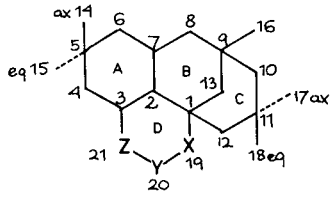

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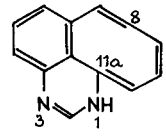

E

variants so far described, especially their carbon nmr spectra.

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