5-, 6- AND 7-SUBSTITUTION DERIVATIVES OF 7-OXO-7*H*-BENZO(*c*)FLUORENE*

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Intramolecular ring closure of anhydrides *IIa—IIc*, under conditions of the Friedel–Crafts reaction, gave 6-carboxy derivatives *III—V*. Esterification of the acid *V* by the chloride method led to esters *VI* and *VII*. Reaction of the ester *VI* with hydrazine hydrate gave rise to compound *XXI*, having a pentacyclic structure. Alkylation or acylation of the 5-hydroxy group in compounds *Ia—Ic* with alkyl halides or acyl chlorides afforded compounds *VIII—XIII* and *XVIII*. Compound *XI* was also formed as a by-product in the Friedel–Crafts reaction of compound *Ic* with acetyl chloride in 1,2-dichloroethane, in addition to the 6-acetyl derivative *XV*. An analogous reaction of *Ic* with dichloroacetyl chloride gave compound *XIV* as a sole product. Substitution reactions on the 7-oxo group in *Ic* afforded semicarbazone *XVI* and thiosemicarbazone *XVII*, and reaction of the compound *XVIII* with hydroxylamine hydrochloride gave the oxime *XIX*. The action of N-methylolchloracetamide on *Ia* in sulphuric acid produced compound *XX*. The compounds prepared proved to have no antineoplastic effects. In tests for activity against the viruses of vaccinia and encephalomyocarditis they proved to be weaker than Tiloron as control. In assessing the efficacy against influenza virus A2 Singapore compound *V* exhibited the same effect as Tiloron.

As part of our attempts to synthetize compounds that might prove to have antineoplastic efficacy, we have described[1] the syntheses of 5-hydroxy-7-oxo-(7*H*)-benzo(*c*)-fluorene (*Ia*), and its 3,9-dimethyl-(*Ib*) and 3,9-diethyl (*Ic*) analogues. Since the compounds *Ia—Ic* showed some antiviral activity, and since the fluorene grouping occurs as a structural unit in biologically active substances (*e.g.* those exhibiting antiaggregation[2], interferonogenic and antiviral[3–7], and antineoplastic[3,8] action), we have focussed our attention on some simpler modifications of the benzo(*c*)fluorene skeleton, with a view to obtaining substances with a more potent biological activity. The present paper describes syntheses of benzo(*c*)fluorene derivatives with substituents in positions 5,6 or 7 (*III—XXI*, Table I) and assessment of these compounds in screening tests for antineoplastic and antiviral activity.

By intramolecular ring closure of the Friedel–Crafts type, anhydrides of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic acids, *IIa—IIc* (ref.[1]), in 1,2-dichloroethane, were converted into the 6-carboxy derivatives *III—V*. The compound *V* was used

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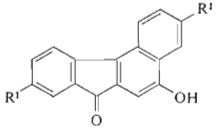
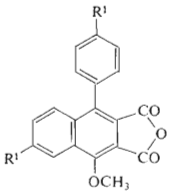
to synthetize the esters *VI* and *VII*. Since the common method of esterification in the presence of sulphuric acid failed to produce esters, as a consequence of decarboxylation of the acid *V*, the syntheses were accomplished by the chloride method; reaction of the acid *V* with thionyl chloride in tetrachloromethane gave chloride of the acid, which was used directly (without any purification) for the reaction with ethanol (ester *VI*) or 1-(2-hydroxyethyl)piperidine (ester *VII*).

Alkylation of the 5-hydroxy group in compounds *Ia–Ic* by 1-chloro-2,3-epoxypropane in a methanolic solution of sodium hydroxide afforded good yields of the epoxy derivatives *VIII–X*. By acylation of the 5-hydroxy group in *Ic* with acyl chlorides (acetyl. pentanoyl, hexadecanoyl) in pyridine we obtained the 5-acyloxy derivatives *XI–XIII*. Acylation of *Ic* by dichloroacetyl chloride under the conditions of a Friedel–Crafts reaction gave the 5-dichloroacetoxy derivative *XIV* as a sole product, whereas the reaction with acetyl chloride, conducted analogously, led to a mixture of compound *XI* and the 6-acetyl derivative *XV* (main product).

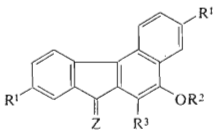
Reaction of the 7-oxo group in *Ic* with semicarbazide and/or thiosemicarbazide yielded compounds *XVI* and *XVII*, respectively. Methylation of *Ia* by dimethyl sulphate, carried out as described in ref.[10], gave the 5-methoxy derivative *XVIII*, whose reaction with hydroxylamine hydrochloride[9] afforded the oxime *XIX*.



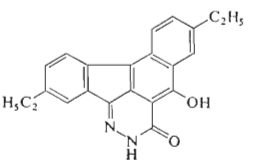
Ia: $R^1 = H$
Ib: $R^1 = CH_3$
Ic: $R^1 = C_2H_5$



IIa: $R^1 = H$
IIb: $R^1 = CH_3$
IIc: $R^1 = C_2H_5$



III–XVII, XIX, XX



XXI

TABLE I

Derivatives of 7-oxo(7*H*)-benzo(*c*)fluorene, *III*—*XX*

Compound	R^2 / R^3	*Z*	Formula (mol.mass)	M.p., °C solvent	Calcul./Found %C	%H	%N
III	H	O	$C_{18}H_{10}O_4$	286—288	74·48	3·47	—
H	COOH		(290·3)	(ethanol)	74·77	3·57	—
IV	H	O	$C_{20}H_{14}O_4$	243—236	75·46	4·43	—
CH_3	COOH		(318·3)	(ethanol)	75·67	4·61	—
V	H	O	$C_{22}H_{18}O_4$	258—260	76·29	5·23	—
C_2H_5	COOH		(346·4)	(chloroform–ethanol)	76·37	5·28	—
VI	H	O	$C_{24}H_{22}O_4$	110—113	76·98	5·92	—
C_2H_5	$COOC_2H_5$		(374·4)	(ethanol)	76·89	6·08	—
VII	H	O	$C_{29}H_{32}NO_4$	186—187	75·95	7·03	3·05
C_2H_5	$COOCH_2CH_2NC_5H_{10}$		(458·6)	(ethanol)	76·12	6·90	2·83
VIII	$CH_2C_2H_3O$-cyclo	O	$C_{20}H_{14}O_3$	157—158	79·45	4·67	—
H	H		(302·3)	(chloroform–methanol)	79·03	4·68	—
IX	$CH_2C_2H_3O$-cyclo	O	$C_{22}H_{18}O_3$	163—165	79·97	5·49	—
CH_3	H		(330·4)	(chloroform–ethanol)	80·10	5·39	—
X	$CH_2C_2H_3O$-cyclo	O	$C_{24}H_{22}O_3$	153—155	80·42	6·18	—
C_2H_5	H		(358·4)	(chloroform–ethanol)	80·64	6·14	—
XI	$COCH_3$	O	$C_{23}H_{20}O_3$	138—140	80·21	5·85	—
C_2H_5	H		(344·4)	(ethanol)	79·99	5·92	—
XII	$CO(CH_2)_3CH_3$	O	$C_{26}H_{26}O_3$	131—133	80·80	6·78	—
C_2H_5	H		(386·5)	(ethanol)	81·04	6·82	—
XIII	$CO(CH_2)_{14}CH_3$	O	$C_{37}H_{48}O_3$	94—95	82·17	8·95	—
C_2H_5	H		(540·8)	(ethanol)	82·48	9·16	—
XIV [a]	$COCHCl_2$	O	$C_{23}H_{18}Cl_2O_3$	185—187	66·84	4·39	—
C_2H_5	H		(413·3	(benzene–hexane)	67·05	4·62	—
XV	H	O	$C_{23}H_{20}O_3$	173—174	80·21	5·85	—
C_2H_5	$COCH_3$		(344·4)	(benzene)	80·06	5·81	—
XVI	H	$NNHCONH_2$	$C_{22}H_{21}N_3O_2$	248—252	73·52	5·89	11·69
C_2H_5	H		(359·4)	(ethanol)	73·35	6·11	11·99

TABLE I
(*Continued*)

Compound	R^2 / R^3	Z	Formula (mol.mass)	M.p., °C solvent	Calcul./Found % C	% H	% N
XVII[b]	H	$NNHCSNH_2$	$C_{22}H_{21}N_3OS$	228–230	70·37	5·64	11·19
C_2H_5	H		(375·5)	(chloroform–ethanol)	70·16	5·64	11·23
XIX	CH_3	NOH	$C_{18}H_{13}NO_2$	198–199	78·52	4·76	5·09
H	H		(275·3)	(chloroform–ethanol)	78·22	4·78	4·71
XX[c]	H	O	$C_{20}H_{14}ClNO_3$	212–214	68·28	4·01	3·98
H	$CH_2NHCOCH_2Cl$		(351·8)	(ethanol)	68·55	4·04	3·78

[a] Calculated: 17·16% Cl, found: 17·05% Cl; [b] calculated: 8·54% S, found: 8·74% S; [c] calculated: 10·08% Cl, found: 10·18% Cl.

To prepare more 6-substitution derivatives of benzo(*c*)fluorene we attempted formylation of *Ia* and *XVIII*, under conditions of the Gatterman reaction[11] and the Vilsmeier–Haack reaction[12], by the action of formic acid[13], and indirectly by the action of 2-methoxy-1,3-dithiolane in the presence of titanium(IV) chloride[14]. However, all these attempts ended in failure. Compound *XX* was finally obtained by reaction of *Ia* with N-methylolchloroacetamide by a modification of the method described by Einhorn[15] and Semonský[16], with sulphuric acid as condensation agent.

Reaction of the ethyl ester *VI* with hydrazine hydrate gave compound *XXI*, whose pentacyclic structure was produced by condensation of hydrazine hydrate with the 1,3-diketone grouping of the starting ester, probably *via* a hydrazone or hydrazide derivative.

The structures of the 7-oxo-(7*H*)-benzo(*c*)fluorene derivatives follow unequivocally from the IR spectra, where the band at 1 700–1 720 cm^{-1} belongs to the carbonyl group of a cyclic five-membered conjugated ketone. The absence of this band demonstrated replacement of oxygen in the 7-oxo group by nitrogen in compounds *XVI*, *XVII*, *XIX* and *XXI*. The IR spectrum of the 6-acetyl derivative *XV* contained, in addition to the band at 1 720 cm^1, characteristic of conjugated five-membered ketones, one more band at 1 630 cm^{-1}, belonging to the acetyl group carbonyl, whose shift to lower wave numbers is due to a hydrogen bond with the hydroxy group in position 5.

The synthetized compounds were tested for antineoplastic and antiviral action *in vivo*. In a preliminary antineoplastic screening, using the common dosing scheme, they exhibited no antitumorous activity in animals grafted with transplantable tumours. The antiviral activity, in comparison with that of Tiloron as standard, was tested on the viruses of vaccinium variolae, encephalomyocarditis and influenza A_2 Singapore (for the method of assessment see ref.[3]). With the first two viruses the efficacy of the compounds tested was lower than that of Tiloron. With the influenza virus A_2 Singapore compound *V*, as the most efficacious one, had the same activity as Tiloron. No interferonogenic activity was observed with any of the compounds tested.

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. Elemental analyses were performed with samples that had been dried over phosphorus pentoxide at a pressure of 70 Pa and temperatures adequate to their melting points. Homogeneity of the samples and composition of the reaction mixtures were followed by TLC on reflex foils Silufol UV_{254} (Kavalier), monitored by the quenching of UV light at 254 nm. The reaction mixtures were resloved by column chromatography on Kieselgel 60 reinst (Merck), using generally a 30-fold weight of the sample. ^{1}H NMR spectra were measured with an apparatus Tesla BS487C (80 MHz) using 10% solutions in deuteriochloroform or hexadeutero acetone, and tetramethylsilane as internal standard. IR spectra were recorded with a spectrometer Perkin–Elmer 577; 5% solutions in chloroform or KBr pellets were used. Mass spectra were measured in an apparatus MS-9.

Cyclization of Anhydrides *IIa*—*IIc*

To a stirred solution of *IIa* (6·09 g, 20 mmol), or *IIb* (6·65 g), or *IIc* (7·2 g) in 200 ml of dichloroethane was added anhydrous aluminium chloride (5·6 g, 42 mmol). The mixture was stirred at 20—25°C for 1 h, then refluxed for 3 h. The dichloroethane was distilled off and the residue was decomposed in a mixture of ice (400 g) and concentrated hydrochloric acid (40 ml). After 1 h of stirring the precipitate was collected on a filter, washed with water and dried, then briefly refluxed with benzene (100 ml), collected on a filter and recrystallized. Yields: 3·94 g (67·9%) of *III*, 4·30 g (67·7%) of *IV*, 4·28 g (61·8)% of *V*. *III*: IR spectrum (KBr): 1 555, 1 590, 1 610 (Ar), 1 640 (C=O), 3 400 cm^{-1} (OH). Mass spectrum: *m/e* 290 (M^+, $C_{18}H_{10}O_4$).

IV: Mass spectrum: *m/e* 318 (M^+, $C_{20}H_{14}O_4$).

V: IR spectrum (KBr): 840, 870 (1,2,4-trisubstituted Ar), 1 605, 1 688 (Ar), 1 640 (C=O), 2 500, 2 650 cm^{-1} (OH).

Esterification of Compound *V*

Thionyl chloride 2·36 g, 20 mmol) and 3 drops of dimethylformamide were added to a suspension of the acid *V* (3·46 g, 10 mmol) in 50 ml of tetrachloromethane and the mixture was refluxed for 4 h. The red precipitate was collected on a filter, washed with tetrachloromethane and taken into 50 ml of ethanol (compound *VI*) or a mixture of 50 ml of benzene and 4 ml of 1-(2-hydroxyethyl)piperidine (compound *VII*), and the mixture was refluxed for 5 h. After standing overnight at —5°C in a refrigerator the precipitate was collected on a filter and recrystallized

(2·78 g, 74·3%, compound *VI*), or 2 ml of triethylamine were added at the end of the reaction and the mixture was taken to dryness and chromatographed with chloroform as eluant (1·61 g, 35·4%, compound *VII*).

VI: ^{1}H NMR spectrum (deuteriochloroform): δ 11·42 (s, 1 H, OH), 8·16 (m, 2 H, $C_{(8)}$—H, $C_{(11)}$—H), 7·00—7·70 (m, 4 H, ArH), 4·50 (q, J = 7·0 Hz, 2 H, OCH_2), 2·70 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·60 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·50 (t, J = 7·0 Hz, 3 H, OCH_2—CH_3), 1·35 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·26 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). IR spectrum (chloroform): 840 (trisubstituted Ar), 1 580, 1 595, 1 620 (Ar), 1 660 (C=O), ester), 1 713 (C=O, conjugated ketone), 3 250 cm^{-1} (OH).

VII: ^{1}H NMR spectrum (deuteriochloroform): δ 10·72 (bs, 1 H, OH), 8·30 (d, J = 8·5 Hz, 1 H, $C_{(11)}$—H), 8·20 (d, J = 2·0 Hz, 1 H, $C_{(8)}$—H), 7·70 (d, J = 8·0 Hz, 1 H, $C_{(1)}$—H), 7·50 (dd, J = 8·5, 2·0 Hz, 1 H, $C_{(10)}$—H), 7·39 (d, J = 2·0 Hz, 1 H, $C_{(4)}$—H), 7·21 (dd, J = 8·0, 2·0 Hz, 1 H, $C_{(2)}$—H), 4·71 (t, J = 6·0 Hz, 2 H, $COOCH_2$), 2·50—3·00 (m, 10 H, NCH_2, $ArCH_2$), 1·70 (m, 6 H, cycl. $(CH_2)_3$), 1·36 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·27 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). IR spectrum (KBr): 1 620, 1 500 (Ar), 1 720 cm^{-1} (C=O).

Reaction of *Ia*—*Ic* with 1-Chloro-2,3-epoxypropane

To a solution of sodium hydroxide (1·84 g, 46 mmol) in 40 ml of methanol was added 20 mmol of *Ia* (4·9 g), or *Ib* (5·48 g) or *Ic* (6·04 g) and the reaction mixture was stirred until the compound had gone into the solution. Then 1-chloro-2,3-epoxypropane (5·7 g, 60 mmol) was added and the mixture was stirred for 5 days at room temperature. Then it was left standing overnight at −5°C, the precipitate was collected on a filter, washed with 10 ml of methanol, dried and recrystallized. Yields: 3·8 g (62·9%) of *VIII*, 4·2 g (63·6%) of *IX*, and 4·6 g (64·1%) of *X*.

VIII: ^{1}H NMR spectrum (deuteriochloroform): δ 6·90—8·30 (m, 8 H, ArH), 6·80 (s, 1 H, $C_{(6)}$—H), 4·40, 3·90 (m, 2 H, OCH_3), 3·45 (m, 1 H, cycl. CH), 2·98 (m, 2 H, cycl. CH_2).

IX: ^{1}H NMR spectrum (deuteriochloroform): δ 7·90 (d, J = 8·5 Hz, 1 H, $C_{(1)}$ or $C_{(11)}$—H), 7·38 (d, J = 8·5 Hz, 1 H, $C_{(1)}$ or $C_{(11)}$—H), 7·82 (bs, 1 H, $C_{(8)}$ or $C_{(4)}$—H), 7·18 (bs, 1 H, $C_{(4)}$ or $C_{(8)}$—H), 6·85—7·20 (m, 2 H, $C_{(2)}$—H, $C_{(10)}$—H), 6·70 (s, 1 H, $C_{(6)}$—H), 4·31, 3·90 (m, 2 H, OCH_2), 3·40 (m, 1 H, cycl. CH), 2·80 (m, 2 H, cycl. CH_2), 2·40 (s, 3 H, $ArCH_3$), 2·20 (s, 3 H, $ArCH_3$).

X: ^{1}H NMR spectrum (deuteriochloroform): δ 8·10 (d, J = 8·5 Hz, 1 H, $C_{(1)}$ or $C_{(11)}$—H), 7·55 (d, J = 8·5 Hz, 1 H, $C_{(11)}$ or $C_{(1)}$—H), 7·98 (bs, 1 H, $C_{(8)}$ or $C_{(4)}$—H), 7·30 (bs, 1 H, $C_{(4)}$ or $C_{(8)}$—H), 7·00—7·40 (m, 2 H, $C_{(2)}$—H), $C_{(10)}$—H), 6·85 (s, 1 H, $C_{(6)}$—H), 4·40, 4·00 (m, 2 H, OCH_2), 3·45 (m, 1 H, cycl. CH), 2·80 (m, 2 H, cycl. CH_2), 2·65 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·55 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·30 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·21 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3).

Acylation of *Ic*

To a solution of *Ic* (0·60 g, 2 mmol) in a mixture of pyridine (2 ml) and chloroform (3 ml), cooled to 0°C, was added 1·2 mol equivalent of acetyl chloride (*XI*), or pentanoyl chloride (*XII*) or hexadecanoylchloride (*XIII*). The mixture was stirred at 0°C for 1 h, then refluxed for 3 h. After evaporation of the volatile components the residue was purified by chromatography on a column of silica gel with chloroform as eluant. The pure fractions were combined and the product was crystallized. Yields: 0·53 g (76·9%) of *XI*, 0·64 g (82·8%) of *XII* and 0·55 g (50·8%) of *XIII*.

XI: ^{1}H NMR spectrum (deuteriochloroform): δ 7·00—8·30 (m, 7 H, ArH), 2·78 (q, J = 7·0 Hz,

2 H, $ArCH_2$), 2·62 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·45 (s, 3 H, $COCH_3$), 1·31 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·25 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). IR spectrum (chloroform): 840 (trisubstituted Ar), 1 192 (C—O), 1 580, 1 619, 1 632 (Ar), 1 711 (C=O), conjugated ketone), 1 767 cm^{-1} (C=O, ester).

XII: ^{1}H NMR spectrum (deuteriochloroform): δ 8·11 (d, J = 8·5 Hz, 1 H, $C_{(1)}$ or $C_{(11)}$—H), 7·60 (d, J = 8·5 Hz, 1 H, $C_{(11)}$ or $C_{(1)}$—H), 7·00—7·50 (m, 5 H, ArH), 2·65 (t, J = 7·0 Hz, 2 H, $COCH_2$), 2·75 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·58 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·30—2·00 (m, 4 H, —$(CH_2)_2$—), 1·28 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·21 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·00 (bt, 3 H, aliph. CH_3).

XIII: ^{1}H NMR spectrum (deuteriochloroform): 8·14 (d, J = 8·5 Hz, 1 H, $C_{(1)}$ or $C_{(11)}$—H), 7·62 (d, J = 8·5 Hz, 1 H, $C_{(11)}$ or $C_{(1)}$—H), 7·00—7·50 (m, 5 H, ArH), 2·66 (t, J = 7·0 Hz, 2 H, $COCH_2$), 2·75 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·58 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·75 (m, 2 H, CH_2—CH_3), 1·22 (bs, 24 H, —$(CH_2)_{12}$—), 1·28 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·21 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 0·82 (bt, 3 H, aliph. CH_3).

Friedel–Crafts Acetylation of *Ic*

To a solution of *Ic* (0·3 g, 1 mmol) in 10 ml of dichloroethane was added 0·27 g (2 mmol) of anhydrous aluminium chloride and 85 mg (1·1 mmol) of acetyl chloride and the mixture was refluxed for 2 h, then decomposed with 20 g of ice and 5 ml of concentrated hydrochloric acid. The product was extracted into three 15 ml portions of chloroform, which were combined, filtered and taken to dryness. Column chromatography on silica gel, with benzene as eluant, gave compound *XI* (90 mg, 23·2%) in the first fractions, and compound *XV* (200 mg, 58·1%) in the following ones. *XV*: ^{1}H-NMR spectrum (deuteriochloroform):

δ 7·00—8·25 (m, 6 H, ArH), 2·75 (s, 3 H, $COCH_3$), 2·80 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·62 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·35 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·26 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). IR spectrum (chloroform): 1 570, 1 581, 1 600 (Ar), 1 630 (H_3C—C=O... ...HO—), 1 720 cm^{-1} (C=O, conjugated ketone).

An analogous procedure with dichloroacetyl chloride (162 mg, 1·1 mmol) afforded compound *XIV*; yield 0·27 g (65·3%). IR spectrum (KBr): 1 718 (C=O, conjugated ketone), 1 790 cm^{-1} ($OCOCHCl_2$).

Semicarbazone *XVI*

Semicarbazide hydrochloride (2 g) and sodium acetate (2 g) were triturated in a grinding mortar, the mixture was taken into 20 ml of ethanol, briefly boiled and filtered. To the filtrate was added 0·3 g (1 mmol) of *Ic* and the mixture was refluxed for 1·5 h, cooled, diluted with 10 ml of water and allowed to crystallize in a refrigerator at −5°C. The crude product was recrystallized; yield 0·32 g (89%). IR spectrum: (KBr): 820 (1,2,4-trisubstituted Ar), 1 555 (NH, amide), 1 665 cm^{-1} (C=O, amide). Mass spectrum: m/e 359 (M^+, $C_{22}H_{21}N_3O_2$).

Thiosemicarbazone *XVII*

To a solution of *Ic* (0·3 g, 1 mmol) in 10 ml of ethanol was added 0·3 ml of acetic acid and 1·0 g of thiosemicarbazide, the mixture was refluxed for 4 h, filtered hot, and the filtrate was put into a refrigerator to crystallize. The crude product was washed with 5 ml of ethanol and 20 ml of water and recrystallized; yield 0·30 g (79·8%). IR spectrum (KBr): 821 (1,2,4-trisubstituted Ar), 1 575 cm^{-1} (thioamide).

Reaction of Compound *XVIII* with Hydroxylamine Hydrochloride

To a solution of 0·5 g of hydroxylamine hydrochloride in 2 ml of water and 2 ml of ethanol was added 2 ml of a 10% aqueous solution of sodium hydroxide and 0·26 g (1 mmol) of *XVIII*. After refluxing for 12 h the mixture was taken to dryness, the residue was stirred up in 20 ml of chloroform and filtered. The filtrate was purified by column chromatography with chloroform as eluant. The first fractions contained the unreacted *XVIII*, the following fractions yielded the product *XIX*, which was purified by crystallization; yield 0·12 g (43·6%). ^{1}H NMR spectrum (hexadeuteroacetone): δ 7·10—8·80 (m, 8 H, ArH), 7·25 (s, 1 H, $C_{(6)}$—H), 4·06 (s, 3 H, OCH_3)

Reaction of *Ia* with N-Methylolchloroacetamide

To a solution of *Ia* (0·49 g, 2 mmol) in 3·4 ml of concentrated sulphuric acid, cooled to 0°C, was added N-methylolchloroacetamide (0·25 g, 2 mmol). The mixture was stirred at 0°C for 24 h, diluted with 25 ml of water and cooled in an ice-water bath with a simultaneous neutralization with solid sodium carbonate. The precipitate was collected on a filter, dissolved in 10 ml of chloroform, and purified by column chromatography on silica gel, with chloroform as eluant. The corresponding fractions were combined and crystallized; yield 0·11 g (31%). ^{1}H NMR spectrum (hexadeuteroacetone): δ 10·70 (s, 1 H, OH), 9·30 (bt, J = 6·0 Hz, 1 H, CONH), 7·00 to 8·50 (m, 8 H, ArH), 4·75 (d, J = 6·0 Hz, 2 H, $ArCH_2$), 4·15 (s, 2 H, $COCH_2Cl$). IR spectrum (KBr): 735 (*ortho*-disubstituted Ar), 1 550 (NH, amide), 1 570, 1 600 (Ar), 1 640 (C=O, amide), 1 700 (C=O), conjugated ketone), 3 350 cm^{-1} (OH, NH).

Reaction of Ester *VI* with Hydrazine Hydrate

Ester *VI* (0·75 g, 2 mmol) was added to 20 ml of a 103% preparation of hydrazine hydrate and the mixture was refluxed for 4 h under stirring with a stream of nitrogen. After cooling the precipitate was collected on a filter, washed with water, taken to dryness and purified by crystallization from a system chloroform–ethanol (2 : 1); yield 280 mg (41%) of *XXI*, m.p. 282—284°C. For $C_{22}H_{18}N_2O_2$ (342·4) calculated: 77·17% C, 5·29% H, 8·18% N; found: 77·35% C, 5·42% H, 8·34% N. IR spectrum (KBr): 1 600, 1 628 (Ar), 1 660 (C=O, amide), 3 200 cm^{-1} (NH, OH).

The elemental analyses were performed by Mrs J. Komancová of the Analytical Department (head Dr J. Körbl), screening tests for antineoplastic action by Mrs S. Pokorná of the Pharmacological Department (head Dr K. Řežábek), assessment of antiviral activity by Dr F. Šmejkal and coworkers of the Virological Department (head Dr F. Šmejkal), and mass spectroscopy by Dr M. Ryska and Dr J. Schlanger of the Physico-Chemical Department (head Dr B. Kakáč).

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