Oxygen Heterocycles. Part XV.[1] A Novel Heterocyclic System: 2*H*-Pyrano[6,5-*b*]phenothiazine

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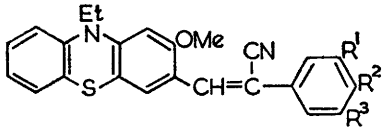
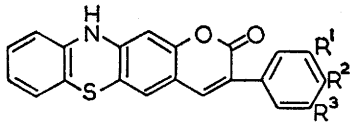
N-Ethyl-2-methoxyphenothiazine underwent formylation at the 3-position in the Vilsmeier–Haack reaction; the resulting aldehyde was condensed with aryl- and heteryl-acetonitriles to give acrylonitriles which were readily converted by pyridine hydrochloride into the 2-oxo-derivatives of the new heterocyclic system 2*H*-pyrano[6,5-*b*]-phenothiazine.

SINCE *N*-alkylphenothiazines are known to undergo formylation at the 3-position in the Vilsmeier–Haack reaction,[2] it was of interest to investigate the reaction of 2-substituted *N*-alkylphenothiazines under similar conditions; here we report the results for *N*-ethyl-2-methoxyphenothiazine (I).

In view of the *ortho*-directing influence of the methoxy-group, acylation was expected to occur at the 3-position to give 10-ethyl-3-formyl-2-methoxyphenothiazine (II), a compound of use in the preparation of derivatives of the hitherto unknown heterocyclic system 2*H*-pyrano-[6,5-*b*]phenothiazine (III). The route to be employed was as follows: (*a*) condensation of *o*-alkyloxybenz-aldehyde with an arylacetonitrile, (*b*) treatment of the α-aryl-β-*o*-alkyloxyarylacrylonitrile thus obtained with boiling pyridine hydrochloride, and (*c*) hydrolysis of the reaction product.[3] The Vilsmeier–Haack reaction afforded the expected aldehyde (II), in excellent yield

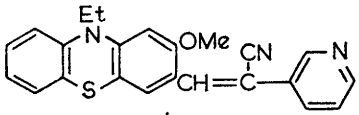


(IV); $R^1 = R^2 = R^3 = H$
(V); $R^1 = R^3 = H$; $R^2 = Me$
(VI); $R^1 = R^3 = H$; $R^2 = OMe$
(VII); $R^1 = R^3 = H$; $R^2 = NO_2$
(VIII); $R^1 = R^2 = OMe$; $R^3 = H$
(IX); $R^1 = R^2 = R^3 = OMe$

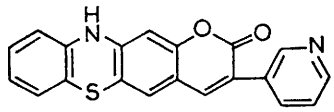


(X); $R^1 = R^2 = R^3 = H$
(XI); $R^1 = R^3 = H$; $R^2 = Me$
(XII); $R^1 = R^3 = H$; $R^2 = OH$
(XIII); $R^1 = R^3 = H$; $R^2 = NO_2$
(XIV); $R^1 = R^2 = OH$; $R^3 = H$
(XV); $R^1 = R^2 = R^3 = OH$

and the structure of the compound was demonstrated by treatment of β-(10-ethyl-2-methoxy-3-phenothiazinyl)-α-phenylacrylonitrile (IV) with pyridine hydrochloride in great excess to give 2-oxo-3-phenyl-2*H*-pyrano-[6,5-*b*]phenothiazine (X); the demethylating agent had the additional effect of eliminating the ethyl group at the 10-position.[4] Application of the same reaction sequence to diversely substituted phenylacetonitriles led to similar coumarins (XI)—(XV) *via* the acrylo-nitriles (V)—(IX). This procedure could also be applied to heterylacetonitriles, as for instance 3-pyridylaceto-nitrile, which afforded 2-oxo-3-(3-pyridyl)-2*H*-pyrano-[6,5-*b*]phenothiazine (XVII) *via* the acrylonitrile (XVI).



(XVI)



(XVII)

The derivatives of the new heterocyclic system (III) thus prepared are of potential biological interest as they include in their structure both the phenothiazine and the coumarin heterocycle, each of which is known to be present in many drugs which induce photo-allergy in animals and in man.[5] The thiosemicarbazone of the aldehyde (II), like that of 3-formyl-10-methylpheno-thiazine,[6] exhibits pronounced *in vitro* tuberculostatic activity (at a concentration of 10^{-6}, strain H37Rv, in Dubos medium). Preliminary pharmacological evalua-tion (Dr. G. Lambelin) showed some of the above com-pounds to possess anti-inflammatory activity; full results will be reported elsewhere.

EXPERIMENTAL

M.p.s uncorrected and taken on a Maquenne block.

N-Ethyl-2-methoxyphenothiazine (I).—This compound was prepared, in 90% yield, by Lespagnol's method for the alkylation of diarylamines;[7] a mixture of 2-methoxy-phenothiazine (100 g.) and ethyl oxalate (150 c.c.) was

[1] Part XIV, N. P. Buu-Hoï, G. Saint-Ruf, and B. Lobert, *J. Chem. Soc.* (*C*), 1969, 2069.

[2] N. P. Buu-Hoï and N. Hoán, *J. Chem. Soc.*, 1951, 1834; G. Cauquil, E. Casedevall, and R. Grèze, *Bull. Soc. chim. France*, 1964, 510.

[3] N. P. Buu-Hoï, N. Hoán, and M. Khenissi, *J. Chem. Soc.*, 1951, 2307; N. P. Buu-Hoï, B. Ekert, and R. Royer, *J. Org. Chem.*, 1954, **19**, 1548.

[4] It was already known that simple *N*-alkylphenothiazines readily undergo dealkylation under similar conditions: N. P. Buu-Hoï, G. Saint-Ruf, and B. Lobert, *Bull. Soc. chim. France*, 1969, 1768.

[5] For a list of known photo-allergens, see E. G. Jung, *Médecine et Hygiène*, 1969, **27**, 217.

[6] N. P. Buu-Hoï, N. D. Xuong, and F. Binon, *J. Chem. Soc.*, 1956, 713.

[7] C. Lespagnol, *Bull. Soc. chim. France*, 1960, 112.

heated at 200° for 60 hr. and the product then fractionated under reduced pressure to give the *product* (I), b.p. 250°/12 mm.; this crystallised as needles, m.p. 105—106° (from ethanol) (Found: C, 70·2; H, 5·8; N, 5·4. $C_{15}H_{15}NOS$ requires C, 70·0; H, 5·9; N, 5·4%).

10-*Ethyl*-3-*formyl*-2-*methoxyphenothiazine* (II).—Phosphorus oxychloride (17 g.) was added dropwise, at 0°, to dimethylformamide (30 c.c.); compound (I) (25 g.) was then added to the complex thus formed and the mixture heated for 2 hr. on a boiling water bath. The mixture was cooled and poured into an ice-cold saturated aqueous solution of sodium acetate; after 3 hr., the precipitate was washed with water and recrystallised from ethanol, to give the *aldehyde* (II) (87%), as bright yellow needles, m.p. 119—120° (Found: C, 67·5; H, 5·3; N, 4·9. $C_{16}H_{15}NO_2S$ requires C, 67·3; H, 5·3; N, 4·9%). The corresponding *thiosemicarbazone* crystallised as yellow prisms, m.p. 240° (from acetic acid) (Found: C, 57·0; H, 5·1; N, 15·6. $C_{17}H_{18}N_4OS_2$ requires C, 57·0; H, 5·1; N, 15·6%). The 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, prepared by briefly heating under reflux equimolar amounts of the above thiosemicarbazone, chloroacetic acid, and sodium acetate,[8] formed yellow microneedles, m.p. 291° (from dioxan) (Found: C, 57·1; H, 4·7; N, 13·9. $C_{19}H_{18}N_4O_2S_2$ requires C, 57·3; H, 4·6; N, 14·1%).

β-(10-*Ethyl*-2-*methoxy*-3-*phenothiazinyl*)-α-*phenylacrylonitrile* (IV).—A solution of the aldehyde (II) (3 g., 0·08 mole) and phenylacetonitrile (1 g., 0·085 mole) in ethanol (50 c.c.) was treated with 4 drops of 20% aqueous sodium hydroxide and the mixture then heated for 15 min. on a water-bath. The mixture was cooled and the precipitate which formed crystallised from acetic acid as silky, orange-yellow needles (3·5 g.), m.p. 164° (Found: C, 75·0; H, 5·0; N, 7·2. $C_{24}H_{20}N_2OS$ requires C, 75·0; H, 5·2; N, 7·3%).

2-*Oxo*-3-*phenyl*-2H-*pyrano*[6,5-b]*phenothiazine* (X).—A mixture of the acrylonitrile (IV) (2 g.) and freshly redistilled pyridine hydrochloride (6 g.) was heated under reflux for 15 min.; the mixture was cooled and the product was treated with boiling water. The precipitate which was obtained was washed with water, dried, and recrystallised from chlorobenzene, to give the *coumarin* (X) (85%) as reddish orange microprisms, m.p. 328° (Found: C, 73·3; H, 4·0; N, 4·1. $C_{21}H_{13}NO_2S$ requires C, 73·4; H, 3·8; N, 4·1%). The other α-arylacrylonitriles (V)—(IX) and the acrylonitrile (XVI), similarly prepared, are listed in Table 1.

TABLE 1

α-Substituted β-(10-ethyl-2-methoxy-3-phenothiazinyl)-acrylonitriles

α-Substituent	M.p.	Formula	Found (%) C	H	N	Required (%) C	H	N
p-Tolyl [a]	156°	$C_{25}H_{22}N_2OS$	75·5	5·6	6·9	75·4	5·6	7·0
p-Chlorophenyl	155	$C_{24}H_{19}ClN_2OS$	68·8	4·5	6·4	68·8	4·7	6·7
p-Methoxyphenyl [a]	165	$C_{25}H_{22}N_2O_2S$	72·7	5·3	6·5	72·5	5·4	6·8
p-Nitrophenyl [b]	205	$C_{24}H_{19}N_3O_3S$	67·1	4·5	10·0	67·1	4·5	9·8
3,4-Dimethoxyphenyl [a]	140	$C_{26}H_{24}N_2O_3S$	70·1	5·4	6·2	70·3	5·5	6·3
3,4,5-Trimethoxyphenyl [a]	191	$C_{27}H_{26}N_2O_4S$	68·6	5·6	5·7	68·3	5·5	5·9
3-Pyridyl [a]	152	$C_{23}H_{19}N_3OS$	71·7	5·1	10·7	71·7	5·0	10·9

Recrystallised from: [a] ethanol; [b] benzene

TABLE 2

3-Substituted 2-oxo-2*H*-pyrano[6,5-*b*]phenothiazines

3-Substituent [a]	M.p.	Formula	Found (%) C	H	N	Required (%) C	H	N
p-Tolyl	311°	$C_{22}H_{15}NO_2S$	73·8	4·3	4·1	73·9	4·2	3·9
p-Chlorophenyl [b]	>360	$C_{21}H_{12}ClNO_2S$	66·3	3·2	4·0	66·7	3·2	3·7
p-Hydroxyphenyl	311	$C_{21}H_{13}NO_3S$	69·9	4·1	3·8	70·2	3·7	3·9
p-Nitrophenyl [c]	>360	$C_{21}H_{12}N_2O_4S$	64·7	3·0	7·0	65·0	3·1	7·2
3,4-Dihydroxyphenyl [d]	327	$C_{21}H_{13}NO_4S$	67·0	3·6	3·5	67·2	3·5	3·7
3,4,5-Trihydroxyphenyl [d]	316	$C_{21}H_{13}NO_5S$	64·0	3·3	3·5	64·4	3·4	3·3
3-Pyridyl [d]	329	$C_{20}H_{12}N_2O_2S$	69·5	3·4	7·9	69·8	3·5	8·1

[a] Ranging in colour from brownish orange to orange-red. [b] Sublimable >343°. [c] From *o*-dichlorobenzene. [d] From methanol–benzene; large excess of pyridine hydrochloride used in preparing these two polyhydroxy-derivatives.

The other coumarins (XI)—(XV) and (XVII) are listed in Table 2.

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[8] *Cf.* P. Chabrier, *Bull. Soc. chim. France*, 1947, **14**, 797; 1950, **17**, 48; see also ref. 2.