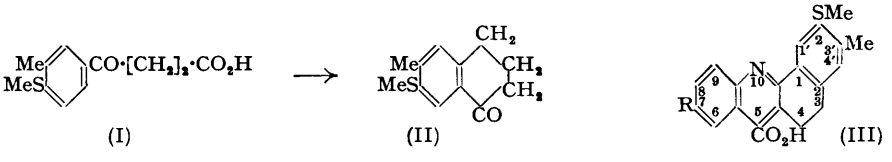
638. *Carcinogenic Nitrogen Compounds. Part VII.* 6-Methyl-7-methylthio-1-tetralone, and its Use in Syntheses of Nitrogenous Heterocyclic Compounds.*

By Ng. Ph. Buu-Hoï and Ng. Hoán.

The preparation is described of 6-methyl-7-methylthio-1-tetralone from methyl *o*-tolyl sulphide by the succinic anhydride method. This ketone was used for the synthesis of acridine and carbazole compounds by known methods.

In continuation of earlier investigations into the use of diversely substituted tetralones in the preparation of 1 : 2-benzacridines (Buu-Hoï, *J.*, 1946, 792) and benzocarbazoles (Buu-Hoï, Hoán, *et al.*, *J. Org. Chem.*, 1949, **14**, 492, 802; 1950, **15**, 511, 957, 962) for cancer research, we became interested in tetralones bearing sulphide groups (cf. Fieser and Wood, *J. Amer. Chem. Soc.*, 1940, **62**, 2674; 1941, **63**, 2323; Boyland, *Biochem. J.*, 1938, **32**, 1207; Berenblum, Kendall, and Orr, *ibid.*, 1936, **30**, 709). The present work deals with 6-methyl-7-methylthio-1-tetralone (III), a new ketone easily accessible from methyl *o*-tolyl sulphide by the standard succinic anhydride synthesis. β-(3-Methyl-4-methylthiobenzoyl)propionic acid (I) was converted by Kishner–Wolff–Huang-Minlon reduction (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) into γ-(3-methyl-4-methylthiophenyl)butyric acid, and by cyclisation with aluminium chloride into the tetralone (II). The yields were excellent, and the cyclisation was much smoother than that of γ-(*p*-



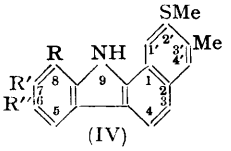
(I) (II) (III)

methylthiophenyl)butyryl chloride owing to the *para*-directing influence of the additional methyl group. The cyclic ketones thus obtained condensed readily with aromatic aldehydes (and with furfuraldehyde), to give a series of crystalline 2-arylidene-6-methyl-7-methylthio-1-tetralones, giving deep halochromic colours with sulphuric acid (see Table, p. 2870).

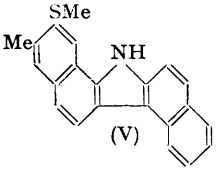
In view of the strychnine-like activity (von Braun, *Annalen*, 1926, **451**, 1) and analeptic properties of 1 : 2-dihydro-3 : 4-benzacridine-9-carboxylic acid (" Tetrophan ") and of similar sulphur-containing compounds (Buu-Hoï and Royer, *Compt. rend.*, 1946, **223**, 806), 6-methyl-7-methylthio-1-tetralone was combined with isatin and 5-bromoisatin to give 3 : 4-dihydro-3′-methyl- (V; R = H) and 7-bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic acid (V; R = Br).

* Part VI, *J.*, 1951, 795.

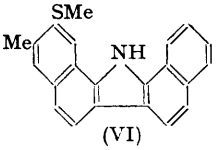
The activity of angular benzocarbazoles and dibenzocarbazoles as tumour-producing agents (cf. Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635) led us to prepare similar compounds from (II). Its arylhydrazones were converted by hydrogen chloride in acetic acid into 3 : 4-dihydrocarbazoles, which were subsequently dehydrogenated by means of chloranil. Thus was obtained a series of 1 : 2-benzocarbazoles (IV). A similar synthesis performed with the 2-diphenylylhydrazone



(IV)



(V)



(VI)

probably gave 3′-methyl-2′-methylthio-8-phenyl-1 : 2-benzocarbazole (VI; R = Ph, R′ = R″ = H), although the alternative cyclisation into the 2′-position of the diphenyl residue is not excluded. The pentacyclic compounds (V) and (VI) were easily prepared by dehydrogenation of their corresponding 3 : 4-dihydro-derivatives.

Experimental.

β-(3-Methyl-4-methylthiobenzoyl)propionic Acid.—Methyl *o*-tolyl sulphide (b. p. 207°) was prepared in >96% yield from *o*-thiocresol with methyl sulphate and potassium hydroxide. To an ice-cooled, well-stirred mixture of this sulphide (69 g.) and succinic anhydride (60 g.) with dry nitrobenzene (300 c.c.), powdered aluminium chloride (150 g.) was added in small portions; the mixture was kept over-night at room temperature and then poured on ice, and the nitrobenzene removed with steam. The solid, obtained after cooling, was treated with boiling aqueous sodium carbonate; after filtration and acidification with dilute hydrochloric acid, a 98% yield of the crude *acid* (I) was obtained; recrystallisation from benzene gave fine shiny colourless needles, m. p. 136° (Found : C, 60·3; H, 5·9; S, 13·1. $C_{12}H_{14}O_3S$ requires C, 60·5; H, 5·9; S, 13·4%).

γ-(3-Methyl-4-methylthiophenyl)butyric Acid.—A solution of the foregoing keto-acid (110 g.) in a mixture of 85% hydrazine hydrate (90 g.), potassium hydroxide (90 g.), and diethylene glycol (350 c.c.) was heated with removal of water until the temperature reached 190—195°, and refluxed for a further 2 hours. After cooling, the reaction mixture was diluted with water, and yielded on acidification with dilute hydrochloric acid an oil which was taken up in chloroform. The chloroform solution was dried (Na_2SO_4) and the solvent removed; the solid residue (103 g.) crystallised from ligroin (b. p. 80—120°) in shiny colourless leaflets, m. p. 52° (Found : C, 64·2; H, 7·2. $C_{12}H_{16}O_2S$ requires C, 64·3; H, 7·1%).

6-Methyl-7-methylthio-1-tetralone.—Redistilled thionyl chloride (60 g.) was cautiously added in small portions to the foregoing *acid* (100 g.), and the mixture kept overnight at room temperature. The oil obtained after removal of thionyl chloride on a water-bath was dissolved in dry carbon disulphide (350 c.c.), and powdered aluminium chloride (68 g.) was added in small portions with ice-cooling. After 5 hours at room temperature, the mixture was poured on ice, the organic layer washed thoroughly with 5% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed, and the residue vacuum-fractionated. This yielded the *tetralone* (76 g.), b. p. 210—218°/15 mm., crystallising from methanol in fine colourless prisms, m. p. 65°, and giving an orange colour with sulphuric acid (Found : C, 69·8; H, 6·9; S, 15·1. $C_{12}H_{14}OS$ requires C, 69·9; H, 6·8; S, 15·5%). The semicarbazone crystallised from ethanol in shiny needles, m. p. 251°; the thiosemicarbazone (prepared in acetic acid) formed from acetic acid a microcrystalline powder, m. p. 201°.

3 : 4-Dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic Acid (III; R = H).—A mixture of the ketone (II) (2 g.), isatin (1·7 g.), and a solution of potassium hydroxide (1·7 g.) in water (2 c.c.)–ethanol (20 c.c.) was refluxed for 12 hours; after dilution with water and removal of impurities by ether-extraction, the aqueous layer was slightly acidified with acetic acid. The yellow precipitate (2 g.) was recrystallised from methanol, yielding long yellow needles which softened at about 235°, but did not liquefy completely until 288° (Found : N, 4·2. $C_{20}H_{17}O_2NS$ requires N, 4·1%).

7-Bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic Acid (III; R = Br).—Similarly prepared from the ketone (II) (2 g.), 5-bromoisatin (2·5 g.), and potassium hydroxide (1·7 g.), this *acid* formed from ethanol fine yellow needles, m. p. >320° (Found : N, 3·0; Br, 19·0. $C_{20}H_{16}O_2NSBr$ requires N, 3·4; Br, 19·3%). Decarboxylation by heat gave 7-bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine, characterised as its *picrate*, which formed from xylene fine orange prisms, m. p. 248° (decomp.), sublimable at >210° (Found : N, 9·0. $C_{25}H_{19}O_7N_4SBr$ requires N, 9·3%).

3 : 4-Dihydro-3′-methyl-2′-methylthio-1 : 2-benzocarbazole.—A solution of the ketone (II) (2·2 g.) and phenylhydrazine (2 g.) in ethanol (40 c.c.) was refluxed for 1 hour. After cooling and addition of water, the crude phenylhydrazone was collected and cyclised by a few minutes' heating with a solution of hydrogen chloride in acetic acid (20 c.c.). The reaction product was poured into water and the *benzocarbazole* was collected, dried, and recrystallised from ligroin (b. p. 80—120°), giving a 92% yield

of fine colourless needles, m. p. 157° (Found : C, 77·3; H, 6·0. $C_{18}H_{17}NS$ requires C, 77·4; H, 6·1%), and giving an orange-yellow colour with sulphuric acid, and a violet picrate.

3'-Methyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R' = R'' = H).—A solution of the foregoing compound (1 g.) and chloranil (1·1 g.) in dry xylene (25 c.c.) was gently refluxed for 6 hours. After cooling and filtration from tetrachloroquinol, the solution was washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the solid residual *carbazole* recrystallised twice from benzene, giving shiny colourless leaflets (90%), m. p. 218° (orange-red colour with sulphuric acid) (Found : C, 78·0; H, 5·6. $C_{18}H_{15}NS$ requires C, 77·9; H, 5·4%). The corresponding picrate formed from ethanol fine shiny violet needles, m. p. 220°.

3 : 4-Dihydro-3' : 6-dimethyl-2'-methylthio-1 : 2-benzocarbazole crystallised from ligroin in fine colourless leaflets, m. p. 167°, giving an orange colour with sulphuric acid (Found : N, 4·6. $C_{19}H_{19}NS$ requires N, 4·7%).

3' : 6-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R' = H, R'' = Me) formed, from ligroin, colourless microscopic needles, m. p. 223°, giving, like its isomers described below, an orange-red colour with sulphuric acid (Found : C, 78·1; H, 5·6. $C_{19}H_{17}NS$ requires C, 78·3; H, 5·8%).

3 : 4-Dihydro-3' : 7-dimethyl-2'-methylthio-1 : 2-benzocarbazole.—Obtained in 85% yield as apparently the sole product from the *m*-tolylhydrazone of the ketone (II), a reaction which could theoretically be expected to give two isomeric products, this *compound* formed, from ligroin, fine colourless needles, m. p. 155° (Found : N, 4·5%).

3' : 7-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R'' = H, R' = Me) crystallised from benzene–ligroin in grey-tinged prisms, m. p. 199° (Found : C, 78·0; H, 6·0%).

3' : 8-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = Me, R' = R'' = H).—The corresponding 3 : 4-dihydro-compound was not isolated in a pure form. The dehydrogenation *product* crystallised from ligroin in microscopic grey-tinged needles, m. p. 189° (Found : C, 78·1; H, 6·0%).

3'-Methyl-2'-methylthio-8-phenyl-1 : 2-benzocarbazole (?) (IV; R = Ph, R' = R'' = H) formed, from ligroin, fine colourless needles, m. p. 177° (Found : C, 81·4; H, 5·1. $C_{24}H_{19}NS$ requires C, 81·5; H, 5·3%).

3 : 4-Dihydro-3'-methyl-2'-methylthio-1 : 2-5 : 6-dibenzocarbazole.—Obtained in 87% yield, this *derivative* formed, from ligroin, fine yellowish needles, m. p. 183°, giving an orange-red colour with sulphuric acid (Found : N, 4·2. $C_{22}H_{19}NS$ requires N, 4·2%).

3'-Methyl-2'-methylthio-1 : 2-5 : 6-dibenzocarbazole (V) formed from benzene almost colourless microscopic needles, m. p. 232° (Found : C, 80·7; H, 5·3. $C_{22}H_{17}NS$ requires C, 81·0; H, 5·2%), giving a brown-red colour with sulphuric acid, and a brownish-violet picrate.

3 : 4-Dihydro-3'-methyl-2'-methylthio-1 : 2-7 : 8-dibenzocarbazole, obtained in 90% yield, formed, from benzene–ligroin, fine colourless leaflets, m. p. 148°, giving an orange-red colour with sulphuric acid (Found : N, 4·0%).

3'-Methyl-2'-methylthio-1 : 2-7 : 8-dibenzocarbazole (VI) formed from benzene fine grey-tinged needles, m. p. 204°, giving a brown-red colour with sulphuric acid (Found : C, 80·8; H, 5·2. $C_{22}H_{17}NS$ requires C, 81·0; H, 5·2%), and a brown-violet picrate.

Condensation of Aldehydes with the Ketone (II).—The procedure was that generally used for the preparation of chalcones : equimolecular amounts of the ketone and the appropriate aldehyde were dissolved in the minimum volume of ethanol, and the solution shaken with some drops of a 40% aqueous solution of sodium or potassium hydroxide. The precipitate formed after cooling was collected, and recrystallised twice from ethanol, except for the derivative from furfuraldehyde which was recrystallised from methanol. The *compounds* prepared are listed in the Table.

2-Arylidene-6-methyl-7-methylthio-1-tetralones.

Arylidene radical	M. p.	Colour with H_2SO_4	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-Furfurylidene *	95°	scarlet	$C_{17}H_{16}O_2S$	71·6	5·5	71·8	5·6
p-$C_6H_4Cl\cdot CH$:	156	orange-red	$C_{19}H_{17}OSCl$	69·1	5·2	69·4	5·1
o-$C_6H_4Cl\cdot CH$:	149	brown-red	,,	69·5	5·3	69·4	5·1
2 : 4 : 1-$C_6H_3Cl_2\cdot CH$:	135	orange-brown	$C_{19}H_{16}OSCl_2$	62·5	4·5	62·8	4·4
3 : 4 : 1-$C_6H_3Cl_2\cdot CH$:	145	dark red	,,	62·8	4·6	62·8	4·4
m-$NO_2\cdot C_6H_4\cdot CH$:	178	brown	$C_{19}H_{17}O_3NS$	67·0	5·2	67·2	5·0
p-$OMe\cdot C_6H_4\cdot CH$:	146	blood red	$C_{20}H_{20}O_2S$	74·1	6·4	74·0	6·1
3 : 4 : 1-$(OMe)_2C_6H_3\cdot CH$:	148	crimson	$C_{21}H_{22}O_3S$	71·1	6·4	71·2	6·2
3 : 4 : 1-$(CH_2O_2)C_6H_3\cdot CH$:	137	violet-red	$C_{20}H_{18}O_3S$	70·8	5·4	71·0	5·3
3-Pyrenylmethylene	214	blue	$C_{29}H_{22}OS$	83·3	5·0	83·2	5·2

* The first five compounds formed long, almost colourless needles, the four following ones formed long yellow needles, and the last one formed fine, bright yellow prisms.

DEPARTMENT OF ORGANIC CHEMISTRY,
THE RADIUM INSTITUTE, UNIVERSITY OF PARIS.

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