259. *New Methods in Stereochemistry. Part III. Some New Optically Active Reagents for Ketones and Aldehydes.*

By Alfred S. Galloway and John Read.

Optically active reagents capable of reacting with ketones and aldehydes are limited in number, and consequently the optical resolution of ketones and aldehydes by such means has been effected only in a few instances. At present, for example, the purest specimens of optically active menthones and *iso*menthones have been obtained solely by oxidising the corresponding optically active secondary alcohols; moreover, it is doubtful whether many of the natural optically active ketones, such as piperitone, have yet been prepared in a state of stereochemical purity. The reagents concerned are mainly substituted hydrazines, semicarbazides, and acid hydrazides. Neuberg (*Ber.*, 1903, **36**, 1192) resolved *dl*-arabinose with *l*-menthylhydrazine (Kijner, *J. Russ. Phys. Chem. Soc.*, 1895, **27**, 524), and Neuberg and Federer (*Ber.*, 1905, **38**, 866) applied α-(*d*-amyl)phenylhydrazine successfully to *dl*-arabinose and *dl*-galactose. Other optically active hydrazines known are α-ethyl-*l*-menthylhydrazine (Kijner, *loc. cit.*), α-methyl-*d*-bornylhydrazine (Forster, J., 1899, **75**, 942), and *d*-bornylhydrazine (Taipale, *Ber.*, 1930, **63**, 246). Wilson and Crawford (J., 1925, **127**, 103) prepared *l*-δ-menthylsemicarbazide, and Hopper and Wilson (J., 1928, 2483) used *d*- and *l*-δ-(α-phenylethyl)semicarbazide to effect a complete resolution of *dl*-benzoin. Crawford and Wilson (J., 1934, 1122) have also obtained *l*- from *dl*-benzoin by means of *l*-δ-menthylsemicarbazide. Few optically active hydrazides have been described. Among them are *d*-tartaric dihydrazide (Rothenburg, *Ber.*, 1893, **26**, 2058), *d*-β-methyladipic hydrazide (Etaix and Freundler, *Bull. Soc. chim.*, 1897, **17**, 806), and *d*-citronellic hydrazide (Sabetay, *Compt. rend.*, 1930, **190**, 1016). These do not appear to have been applied in optical resolutions.

In an investigation of certain new reagents of the type indicated, in particular of possible resolving agents for ketones, some substances have been prepared which owe their optical activity severally to the *d*-camphor-10-sulphonyl, *l*-menthyl, and *d-neo*menthyl radicals. The first of these radicals was attached to a benzene nucleus by means of either an oxygen atom or an imino-group. Experiments on the conversion of mono-*d*-camphor-10-sulphonyl-*p*-phenylenediamine and *p*-aminophenyl *d*-camphor-10-sulphonate (preceding paper) into substituted hydrazines, by way of the diazo-reaction, led to inconclusive results; but a crystalline p-d-*camphor*-10-*sulphonoxyphenyl*-α-*methylhydrazine*,

$$C_{10}H_{15}O\cdot SO_2\cdot O\cdot C_6H_4\cdot NMe\cdot NH_2,$$

was readily prepared from *p*-hydroxymethylaniline sulphate ("metol"). This hydrazine gave crystalline *hydrazones* with benz- and *p*-nitrobenz-aldehyde, but the derivatives of *l*-menthone and *l*-piperitone were syrups. In attempts to obtain α-substituted *l*-menthylhydrazines, both benzyl- and *p*-nitrobenzyl-*l*-menthylamine were easily obtained, but their nitrosoamines resisted reduction to hydrazines: p-*nitrobenzyl*-l-*menthylnitrosoamine*, indeed, furnished p-*aminobenzyl*-l-*menthylnitrosoamine*, the nitro-group being reduced while the nitroso-group remained unaffected.

Esters of *l*-menthyl- and *d-neo*menthyl-glycine, easily accessible by the method of Clark and Read (J., 1934, 1776), were converted into the corresponding hydrazides when boiled with a 50% solution of hydrazine hydrate. d-neo*Menthylglycinehydrazide* readily yielded crystalline *hydrazones* with acetone, benzaldehyde, *l*-menthone, and *dl*-menthone. Although the last of these derivatives appears to be partially racemic, *d-neo*menthylglycine-

hydrazide is a potential resolving agent of great promise for ketones and aldehydes. The derived hydrazones are readily hydrolysed when shaken in ethereal solution with dilute mineral acids.

When heated with benzaldehyde in alcoholic solution, l-*menthylglycinehydrazide* yielded a *benzylidene* derivative of the hydrazone, $C_{10}H_{19}\cdot NH\cdot C(:CHPh)\cdot CO\cdot NH\cdot N:CHPh$, but *d-neo*menthylglycinehydrazide under similar conditions yielded the simple *hydrazone*, $C_{10}H_{19}\cdot NH\cdot CH_2\cdot CO\cdot NH\cdot N:CHPh$. This difference in reaction provides striking evidence in favour of the relative molecular configurations proposed for the *l*- and *d-neo*-menthyl radicals by Read and Grubb (J., 1934, 1781) :

(I.) $H_2N\cdot NH\cdot CO\cdot CH_2\cdot NH-{}^{3}H$, $H-{}^{4}Pr^{\beta}$ (II.) $H-{}^{3}NH\cdot CH_2\cdot CO\cdot NH\cdot NH_2$, $H-{}^{4}Pr^{\beta}$

In *l*-menthylglycinehydrazide (I) the methylene group exerts its reactivity, being in the *cis*-position to hydrogen; but in *d-neo*menthylglycinehydrazide (II) reaction is inhibited through the spatial proximity of Pr^{β} in the *cis*-position.

Experimental.

Optically Active Hydrazines.

p-d-*Camphor*-10-*sulphonoxyphenyl*-α-*methylhydrazine*.—*p*-Hydroxynitrosomethylaniline, m. p. 136°, was prepared by treating an ice-cooled solution of *p*-hydroxymethylaniline sulphate (" metol ") with nitrous acid. A powdered mixture of this substance (10 g.) and *d*-camphor-10-sulphonyl chloride (20 g.) was dissolved in dry pyridine (50 c.c.) and kept over-night. Crude p-d-*camphor*-10-*sulphonoxynitrosomethylaniline* (25 g.) was isolated as usual and recrystallised twice from alcohol; it formed flat, pale yellow needles, m. p. 115°, $[\alpha]_D$ + 40·0° (*c* 2·0, chloroform) (Found : C, 55·7; H, 6·0. $C_{17}H_{22}O_5N_2S$ requires C, 55·7; H, 6·0%). When boiled with concentrated hydrochloric acid (20 c.c.) for an hour, the nitrosoamine (5 g.) yielded p-d-*camphor*-10-*sulphonoxymethylaniline* (3·8 g.), which crystallised from ether–light petroleum in pale brown rectangular plates, m. p. 67—68°, $[\alpha]_D$ + 44·5° (*c* 2·0, chloroform) (Found : C, 60·5; H, 6·7. $C_{17}H_{23}O_4NS$ requires C, 60·5; H, 6·8%). The hydrochloride crystallised from water in colourless needles, m. p. 167°.

To a solution of the above nitrosoamine (10 g.) in alcohol (30 c.c.) and water (5 c.c.) were added glacial acetic acid (20 c.c.), chloroform (5 c.c.), and zinc (15 g.) (cf. Fischer, *Ber.*, 1875, **8**, 1642; *Annalen*, 1878, **190**, 175). Slight warming induced a vigorous reaction, which was controlled by keeping the mixture at 20—30°. When the zinc had dissolved, the mixture was heated on the water-bath and filtered while hot. The solution was cooled in a freezing mixture and treated with an excess of strong sodium hydroxide solution, the precipitated p-d-*camphor*-10-*sulphonoxyphenyl*-α-*methylhydrazine* being extracted with ether : this was isolated as a red syrup (7·7 g.), which crystallised (m. p. 45—46°) when kept for several days in a vacuum desiccator. Its solutions were too deeply coloured to permit of accurate polarimetric examination (Found : C, 58·4; H, 6·8. $C_{17}H_{24}O_4N_2S$ requires C, 58·0; H, 6·8%). The same substance was obtained, in smaller yield, by heating the nitrosoamine (20 g.) in 90% alcohol (220 c.c.) with aluminium amalgam (25 g.) on the water-bath for 12 hours. The hydrochloride was precipitated, upon passing dry hydrogen chloride into a solution of the hydrazine in dry ether, as a white solid which rapidly formed a sticky red oil when exposed to the air.

When the hydrazine was boiled in alcoholic solution with benzaldehyde it yielded the *benzylidene* derivative, which crystallised from alcohol in pale yellow needles, m. p. 138° (Found : C, 65·3; H, 6·4. $C_{24}H_{28}O_4N_2S$ requires C, 65·4; H, 6·4%). The p-*nitrobenzylidene* derivative, prepared by warming the hydrazine with the aldehyde in glacial acetic acid, separated from glacial acetic acid in small, bright red needles, m. p. 200° (Found : C, 59·0; H, 5·8. $C_{24}H_{27}O_6N_3S$ requires C, 59·4; H, 5·6%). When heated in alcoholic solution with *l*-menthone or *l*-piperitone, the hydrazine afforded the corresponding hydrazones as red syrups, which could not be induced to crystallise.

Experiments on the Preparation of Some α-*Substituted* l-*Menthylhydrazines*.—(1) A mixture of *l*-menthylamine (90 g.; 2 mols.) and benzyl bromide (50 g.) was heated under reflux in an oil-bath at 130—140° for 4 hours. The cooled product was treated with water and ether, and the ethereal solution was washed three times with water in order to recover *l*-menthylamine hydrobromide (66 g.). The brown liquid (72 g.) from the dried ethereal extract, when distilled under

diminished pressure in the absence of carbon dioxide, yielded a second fraction (60·3 g.) of benzyl-*l*-menthylamine, a colourless, mobile liquid, b. p. 180°/18 mm., $n_D^{18°}$ 1·5131, $[\alpha]_D$ — 96·3° (*c* 2·2, alcohol). The hydrochloride separated from acetone–light petroleum in colourless prisms, m. p. 144—145°, $[\alpha]_D$ — 62·2° (*c* 2·0, alcohol). p-*Toluenesulphonbenzyl-l-menthylamide*, prepared in pyridine with the aid of *p*-toluenesulphonyl chloride, crystallised from methyl alcohol in colourless needles, m. p. 96—97°, $[\alpha]_D$ — 39·9° (*c* 2·0, chloroform) (Found : C, 71·8; H, 8·0. $C_{24}H_{33}O_2NS$ requires C, 71·7; H, 8·0%).

Benzyl-l-menthylnitrosoamine was prepared by adding sodium nitrite solution to a solution of the secondary base in 30% acetic acid; it crystallised from methyl alcohol in a freezing mixture in yellow needles, m. p. 52°, $[\alpha]_D$ — 2·5° (*c* 2·1, chloroform) (Found : C, 74·3; H, 9·5. $C_{17}H_{26}ON_2$ requires C, 74·4; H, 9·5%). The nitrosoamine was very stable, and resisted reduction with sodium and alcohol, and with zinc and glacial acetic acid in presence of alcohol and a little chloroform (see above).

(2) *p*-Nitrobenzyl bromide and *l*-menthylamine did not react appreciably when heated together at 140° for 10 hours. Reaction occurred, however, with separation of crystalline *l*-menthylamine hydrobromide, when a mixture of *l*-menthylamine (67 g.) and *p*-nitrobenzyl bromide (35 g.) in dry benzene (250 c.c.) was heated under reflux on the water-bath for 6 hours. The cold mixture was treated with 2*N*-sodium hydroxide (90 c.c.), and the excess of *l*-menthylamine was distilled in steam and recovered as hydrochloride (32 g.). The mobile red syrup (49 g.) extracted from the residue with chloroform crystallised when kept; three recrystallisations from methyl alcohol furnished pure p-*nitrobenzyl-l-menthylamine* in pale yellow plates, m. p. 53°, $[\alpha]_D$ — 89·4° (*c* 2·0, chloroform) (Found : C, 70·2; H, 9·0. $C_{17}H_{26}O_2N_2$ requires C, 70·1; H, 8·9%). The amine is insoluble in water and non-volatile in steam; it is readily soluble in organic solvents, and is phototropic, the yellow colour deepening temporarily on exposure to light. The hydrochloride had m. p. 234°, $[\alpha]_D$ — 44·0° (*c* 2·0, alcohol). The p-*toluenesulphonyl* derivative crystallised from methyl alcohol in long yellow needles, m. p. 115°, $[\alpha]_D$ — 49·3° (*c* 1·3, chloroform) (Found : C, 64·5; H, 7·3. $C_{24}H_{32}O_4N_2S$ requires C, 64·9; H, 7·2%).

Upon addition of the base (21·6 g.) to a mixture of glacial acetic acid (13 c.c.) and water (20 c.c.), the acetate separated as an oil. Sodium nitrite (6 g.), dissolved in water (20 c.c.), was added, and the mixture heated on the water-bath for 2 hours. The resulting solid, when collected, washed with water, and dried (23·2 g.), was practically pure p-*nitrobenzyl-l-menthylnitrosoamine*; it crystallised from methyl alcohol in pale yellow prisms, m. p. 132°, $[\alpha]_D$ + 17·6° (*c* 2·0, chloroform) (Found : C, 63·5; H, 7·9. $C_{17}H_{25}O_3N_3$ requires C, 63·7; H, 7·8%). To a solution of the nitrosoamine (10 g.) in alcohol (50 c.c.) were added pure zinc dust (15 g.) and a few crystals of copper acetate. Glacial acetic acid (18 c.c.) was introduced dropwise during the course of the reaction, which was started by warming the mixture gently. After remaining for 20 hours at room temperature, the liquid was heated to boiling and filtered from undissolved zinc, which was washed with hot alcohol. The filtrate and washings were poured into water (200 c.c.) and basified with 2*N*-sodium hydroxide (170 c.c.). The ethereal solution of the precipitate was washed with water and shaken with 2*N*-sulphuric acid (50 c.c.). Unchanged nitrosoamine remained in the ether, and the sulphate of the reduction product formed a bulky yellow precipitate. This was collected, washed, and decomposed with dilute sodium hydroxide in presence of ether, which dissolved the liberated base. This consisted of p-*aminobenzyl-l-menthylnitrosoamine*; it formed brownish-yellow crystals from ether–light petroleum, and had m. p. 88°, $[\alpha]_D$ + 21·8° (*c* 1·0, chloroform) (Found : C, 70·6; H, 9·2. $C_{17}H_{27}ON_3$ requires C, 70·6; H, 9·3%). Reduction of the original nitrosoamine with aluminium amalgam in presence of 90% alcohol gave the same product.

Optically Active Hydrazides.

l-*Menthylglycinehydrazide.*—A solution of ethyl *l*-menthylglycine (24 g.; Clark and Read, *loc. cit.*) and hydrazine hydrate (15 c.c. of 50%) in alcohol (50 c.c.) was boiled gently under reflux for 3 hours. The product was poured into water and extracted with chloroform, the extract being well washed with water and dried. The crude hydrazide (23·5 g.) was purified by precipitation from acid solution with dilute sodium hydroxide. The resulting l-*menthylglycinehydrazide* was a pale green, viscid syrup (20 g.), $n_D^{17°}$ 1·4931, $[\alpha]_D$ — 57·7° (*c* 2·3, chloroform) (Found : C, 61·9; H, 10·7. $C_{12}H_{25}ON_3$ requires C, 63·4; H, 11·0%).

Acetone-*l*-menthylglycinehydrazone, prepared by boiling an acetone solution of the hydrazide for 2 hours, was obtained as a pale yellow syrup which crystallised slowly; m. p. 55°, $[\alpha]_D$ — 52·5°

(*c* 3·4, chloroform). l-*Menthone*-l-*menthylglycinehydrazone*, obtained by boiling an alcoholic solution of the hydrazide (9 g.) and *l*-menthone (10 g.) for 5 hours and then distilling away unchanged menthone in steam, was a viscid amber syrup, having $n_D^{18°}$ 1·4999, $[\alpha]_D$ − 69·1° (*c* 3·0, chloroform) (Found : C, 73·1; H, 11·4. $C_{22}H_{41}ON_3$ requires C, 72·6; H, 11·4%). Upon boiling a solution of the hydrazide (3 g.) and benzaldehyde (10 g.) in alcohol (20 c.c.) under reflux for 5 hours, and removing unchanged benzaldehyde in steam, a product was obtained which crystallised from aqueous alcohol in colourless needles (4·7 g.), m. p. 158°, $[\alpha]_D$ − 266·9° (*c* 2·0, chloroform) : this was a *benzylidene* derivative of benzaldehyde-*l*-menthylglycinehydrazone (Found : C, 77·1; H, 8·3. $C_{26}H_{33}ON_3$ requires C, 77·0; H, 8·2%).

d-neo*Menthylglycinehydrazide*.—The interaction of 183 g. of *d-neo*menthylamine and 71 g. of ethyl chloroacetate, according to the method used by Clark and Read (*loc. cit.*) for preparing ethyl *l*-menthylglycine, gave 106 g. of *ethyl* d-neo*menthylglycine*, a colourless mobile liquid, b. p. 139—141°/11 mm., $n_D^{14°}$ 1·4612, $[\alpha]_D$ + 32·7° (*c* 3·0, chloroform) (Found : C, 68·5; H, 11·4. $C_{14}H_{27}O_2N$ requires C, 69·7; H, 11·2%). When this ester (105 g.) was dissolved in alcohol (200 c.c.) and boiled for 3 hours with hydrazine hydrate (50 c.c. of 50% solution), according to the method outlined above, it yielded d-neo*menthylglycinehydrazide* (92 g.) as a syrup which slowly crystallised. The crystals were separated on porous plate and recrystallised from a little ether : the long colourless needles had m. p. 51°, $[\alpha]_D$ + 40·0° (*c* 2·5, chloroform) (Found : C, 63·4; H, 10·7. $C_{12}H_{25}ON_3$ requires C, 63·4; H, 11·0%). The hydrazide dissolved in dilute acids, and was reprecipitated upon basifying the solution; it reduced Fehling's solution on warming.

Acetone-d-neo*menthylglycinehydrazone* crystallised from aqueous methyl alcohol in colourless needles, m. p. 79·5°, $[\alpha]_D$ + 24·5° (*c* 2·0, chloroform) (Found : C, 67·8; H, 10·7. $C_{15}H_{29}ON_3$ requires C, 67·4; H, 10·9%). The corresponding *derivatives* of benzaldehyde and of *l*-menthone were first obtained as brown syrups; when dissolved in a little alcohol they gave crystalline material which separated from aqueous alcohol in colourless needles, respectively, m. p. 110°, $[\alpha]_D$ + 20·8° (*c* 2·4, chloroform) (Found : C, 72·3; H, 9·4. $C_{19}H_{29}ON_3$ requires C, 72·3; H, 9·3%), and m. p. 102—103°, $[\alpha]_D$ − 9·0° (*c* 2·8, chloroform) (Found : C, 72·5; H, 11·1. $C_{22}H_{41}ON_3$ requires C, 72·6; H, 11·4%). dl-*Menthone*-d-neo*menthylglycinehydrazone* after four recrystallisations from aqueous alcohol gave physical constants which were unaffected by further recrystallisation : m. p. 98—99°, $[\alpha]_D$ + 9·3° (*c* 2·8, chloroform) (Found : C, 72·6; H, 10·9%). Some of this hydrazone was hydrolysed by shaking it in ethereal solution for 30 minutes with an excess of *N*-hydrochloric acid. The resulting oil isolated from the ether had an odour of menthone; it was optically inactive in methyl-alcoholic solution (*c* 2·5, *l* 2). The semicarbazone melted at 157° and appeared to consist mainly of *dl*-menthone-β-semicarbazone (Read and Cook, J., 1925, **127**, 2787).

dl-Piperitone-*d-neo*menthylglycinehydrazone was a viscous yellow syrup, having $n_D^{20°}$ 1·4980, $[\alpha]_D$ + 30·2° (*c* 3·0, chloroform). *dl*-Piperitone oxide-*d-neo*menthylglycinehydrazone was also a viscous yellow syrup, $n_D^{15°}$ 1·5010, $[\alpha]_D$ + 27·3° (*c* 3·5, chloroform).

We are indebted to the Carnegie Trust for the Universities of Scotland for the award of a Fellowship to one of us (A. S. G.), and to Imperial Chemical Industries for a grant.

THE UNIVERSITY, ST. ANDREWS. [*Received, June 19th*, 1936.]