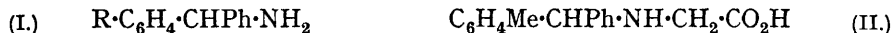


### 401. The Optical Rotatory Powers of Some 4-Substituted Benzhydrylamines.

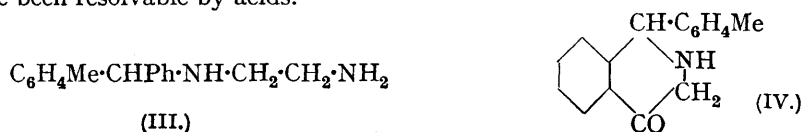
By G. R. CLEMO, C. GARDNER, and R. RAPER.

Attempts to resolve 4-methylbenzhydrylamine in order to compare its rotation with that of  $\alpha$ -pentadeuterophenylbenzylamine recorded by Clemo and McQuillen (J., 1936, 808) have been unsuccessful. The resolution of 4-chloro-, 4-bromo-, and 4-iodo-benzhydrylamines into their optically active components has been accomplished.

GOLDSCHMIDT and STÖCKER (*Ber.*, 1891, **24**, 2800) prepared 4-methylbenzhydrylamine (I, R = Me), but were unable to resolve it. Cohen, Marshall, and Woodman (J., 1915, **107**,



887) claimed to have resolved the base by recrystallisation of its bromocamphorsulphonate but do not record its rotation or that of its derivatives; they state, however, that the alcohol obtained by the action of nitrous acid on its hydrochloride had  $[\alpha]_D = -1.4^\circ$  ( $\alpha_D = -0.24^\circ$ ). We attempted to repeat this resolution with the object of measuring the specific rotation of the base to compare with that obtained for  $\alpha$ -pentadeuterophenylbenzylamine by Clemo and McQuillen (J., 1936, 808) and have also prepared derivatives such as (I), where R = Cl, Br, and I, and (II) in order to discover whether any of such substituted products might have a reasonably high rotation and thus be applicable to the problem presented by  $\alpha$ -pentadeuterophenylbenzylamine. We prepared (I, R = Me) by reducing 4-methylbenzophenoneoxime with sodium amalgam and found its hydrochloride had m. p.  $273^\circ$ , whereas Cohen, Marshall, and Woodman give the m. p. as  $260^\circ$ . The bromocamphorsulphonate has an appreciably higher melting point than that recorded by those authors. It did not exhibit the behaviour recorded by them and we are unable to effect any definite resolution of the salt, the specific rotation remaining unchanged at  $56^\circ$  for five recrystallisations, and in five out of six experiments the base recovered from it was definitely inactive; in the sixth it was either inactive or had a  $\lambda$ -rotation so small as to be within the limits of experimental error. The hydrochloride also showed no measurable rotation. In further attempts to effect a resolution we condensed the base with ethyl bromoacetate, and subsequent hydrolysis gave (II), but this failed to give crystalline salts with the commoner alkaloids. We then attempted to prepare the amide of (II), which we hoped to reduce to *N*-4-methylbenzhydrylethylenediamine (III), which might have been resolvable by acids.



On treating (II) with thionyl chloride and ammonia, however, ring closure apparently takes place with the formation of a substance which is probably the tetrahydroisoquinolone (IV).

We then prepared 4-chloro-, 4-bromo-, and 4-iodo-benzhydrylamines (I, R = Cl, Br, and I) and have resolved them with *d*- and *l*-tartaric acids. The active forms have specific rotations of the order of  $10^\circ$ . Although some bases of this type, therefore, have appreciable and easily measurable activities, the apparent failure to resolve (I, R = Me) indicates that caution must be exercised in drawing conclusions from the failure to resolve  $\alpha$ -pentadeuterophenylbenzylamine (this vol., p. 1960). A further observation in this connection is that in the resolution of (I; R = Cl, Br, or I) the presence of a small amount of impurity in the *dl*-base has a marked effect on the success or otherwise of the resolution.

#### EXPERIMENTAL.

**4-Methylbenzhydrylamine d-Bromocamphorsulphonate.**—The hydrochloride of the base (9.1 g.) and ammonium *d*-bromocamphorsulphonate (13.1 g.) were mixed in 50% alcohol. An oil was precipitated which soon solidified and after repeated crystallisation from 50% alcohol the m. p.'s of successive crops were  $212\text{--}223^\circ$ ,  $227^\circ$ ,  $225^\circ$ ,  $234^\circ$ ,  $228^\circ$ ,  $228^\circ$  (Cohen, Marshall, and Woodman, *loc. cit.*, give  $168^\circ$ , raised to  $208^\circ$  by ten crystallisations) and the  $[\alpha]_D = +57.5^\circ$ ,  $55.5^\circ$ ,  $55.1^\circ$ ,  $55.6^\circ$ ,  $56.0^\circ$  (Found: C, 56.4; H, 6.05. Calc. for  $C_{14}H_{15}N, C_{10}H_{15}O_4BrS$ : C, 56.8; H, 6.0%). The base recovered, in one experiment out of six, gave  $\alpha_D = -0.0125^\circ$  in alcohol ( $c = 7.785$ ,  $l = 1$ ),  $[\alpha]_D = -0.16^\circ$ , mean deviation from mean =  $0.007^\circ$ .

**N-4-Methylbenzhydrylaminoacetic Acid.**—4-Methylbenzhydrylamine (8 g.) and ethyl bromoacetate (7 g.) were shaken with excess of anhydrous potassium carbonate in absolute alcohol (30 c.c.) for 6 hours. The solution was filtered, the alcohol removed, and the residue extracted with ether. On evaporation and distillation a pale yellow oil (5 g.), b. p.  $185\text{--}195^\circ/1\text{ mm.}$ , was obtained. This was hydrolysed to the acid by heating 1 g. for  $\frac{1}{2}$  hour with alcoholic potassium hydroxide (20 c.c., 20%). The alcohol was removed, water (10 c.c.) added, and the solution just neutralised with dilute hydrochloric acid. The precipitate (0.8 g.), m. p.  $185^\circ$ , was unaltered by recrystallisation from alcohol-ether (Found: C, 75.4; H, 5.9; N, 5.5.  $C_{16}H_{17}O_2N$  requires C, 75.3; H, 6.6; N, 5.5%). When this acid was treated with thionyl chloride for 10 minutes, the latter removed, and excess of ammonia added, a white solid separated, m. p.  $207^\circ$  after crystallisation from alcohol (Found: C, 80.6; H, 6.2.  $C_{16}H_{15}ON$  requires C, 81.1; H, 6.3%).

**Formo-4-bromobenzhydrylamide.**—4-Bromobenzophenone (Cone and Long, *J. Amer. Chem. Soc.*, 1906, 28, 521) (9 g.) was heated with formamide (36 c.c.) at  $170\text{--}180^\circ$  for 18 hours, and the product poured into water; after a few minutes the gum solidified. It was washed with water and recrystallised from dilute alcohol, forming white plates (8 g.), m. p.  $127\text{--}128^\circ$  (Found: C, 58.4; H, 4.3.  $C_{14}H_{12}ONBr$  requires C, 57.9; H, 4.1%).

**dl-4-Bromobenzhydrylamine.**—The above formyl derivative (12 g.) was heated with saturated alcoholic hydrogen chloride (30 c.c.) for 1 hour. The white precipitate was filtered off and washed (water), and a further quantity obtained by removal of the alcohol. The product (10 g.) in water was treated with excess of sodium hydroxide solution (40%), and the brown oil extracted with ether, dried, and distilled (6 g., b. p.  $155\text{--}160^\circ/1\text{ mm.}$ ). The base was very unstable and rapidly absorbed carbon dioxide from the air, and was therefore analysed as its *acetyl* derivative. This was prepared by heating the base (0.1 g.) with acetic anhydride (1 c.c.) for 5 minutes. White needles (0.1 g.) separated and were recrystallised from dilute alcohol; m. p.  $153^\circ$  (Found: C, 59.1; H, 4.3.  $C_{15}H_{14}ONBr$  requires C, 59.2; H, 4.6%).

**l-4-Bromobenzhydrylamine.** The *dl*-base (5.5 g.) and *d*-tartaric acid (3.1 g.) were mixed in water (20 c.c.), and the salt (8 g.) recrystallised ten times from water; the specific rotation had then attained a constant value and the m. p. was  $205^\circ$  (Found: C, 49.6; H, 4.3.  $C_{13}H_{12}NBr, C_4H_6O_6$  requires C, 49.5; H, 4.4%).  $\alpha_D = +0.148^\circ$  in alcohol ( $c = 0.9032$ ,  $l = 2$ ),  $[\alpha]_D = +7.2^\circ$ . The base recovered from the tartrate was a liquid, b. p.  $155\text{--}160^\circ/1\text{ mm.}$ ,  $\alpha_D = -0.41^\circ$  in alcohol ( $c = 2.902$ ,  $l = 2$ ),  $[\alpha]_D = -7.1^\circ$ ,  $[\alpha]_{5461} = -12.8$ ,  $[\alpha]_{4358} = -24.6^\circ$ . The *acetyl* derivative, prepared as above, had m. p.  $183^\circ$  (Found: C, 59.1; H, 4.7%).

**d-4-Bromobenzhydrylamine.** The united mother-liquors from the fractions of the above tartrate were concentrated to 20 c.c., and the base (1.03 g.) recovered and combined with *l*-tartaric acid (0.76 g.) in water (20 c.c.). The salt was recrystallised six times; m. p.  $205^\circ$ .  $\alpha_D = -0.13^\circ$  in water ( $c = 1.024$ ,  $l = 2$ ),  $[\alpha]_D = -6.8^\circ$ . The free base had  $\alpha_D = +0.275^\circ$

in alcohol ( $c = 1.347$ ,  $l = 2$ ),  $[\alpha]_D = +10.2^\circ$ . The *acetyl* derivative of the *d*-base had m. p.  $183^\circ$  (Found: C, 59.3; H, 4.9%).

Equal weights of the *d*- and the *l*-acetyl derivative were mixed in alcohol; the *dl*-derivative then crystallised, m. p.  $153^\circ$  alone or mixed with a specimen prepared from the *dl*-base.

*dl*-4-Chlorobenzhydriylamine.—This was prepared from 4-chlorobenzophenone (Gomberg and Cone, *Ber.*, 1906, 39, 3278) in the same way as the bromo-base. The *formyl* derivative had m. p.  $124^\circ$  (Found: C, 68.5; H, 5.1.  $C_{14}H_{12}ONCl$  requires C, 68.4; H, 4.9%). The unstable base had b. p.  $146^\circ/1$  mm., and readily absorbed carbon dioxide from the air. The *acetyl* derivative formed needles from dilute alcohol, m. p.  $130$ — $131^\circ$  (Found: C, 69.4; H, 5.7.  $C_{16}H_{14}ONCl$  requires C, 69.4; H, 5.4%).

*l*-4-Chlorobenzhydriylamine was obtained by resolution with *d*-tartaric acid. The *tartrate*, after recrystallisation to constant rotation, had m. p.  $199^\circ$  (Found: C, 56.0; H, 5.05.  $C_{13}H_{12}NCl, C_4H_6O_6$  requires C, 55.5; H, 4.9%).  $\alpha_D = +0.361^\circ$  in water ( $c = 1.735$ ,  $l = 2$ ),  $[\alpha]_D = +9.8^\circ$ . The unstable *l*-base, b. p.  $145$ — $150^\circ/1$  mm., had  $\alpha_D = -1.1^\circ$  in alcohol ( $c = 5.054$ ,  $l = 2$ ),  $[\alpha]_D = -10.9^\circ$ ,  $[\alpha]_{5790} = -12.9^\circ$ ,  $[\alpha]_{5461} = -14.6^\circ$ ,  $[\alpha]_{4358} = -25.2^\circ$ . The *acetyl* derivative had m. p.  $169^\circ$  (Found: C, 69.7; H, 5.6%).

*d*-4-Chlorobenzhydriylamine was isolated as above with *l*-tartaric acid. The *tartrate* had m. p.  $199^\circ$  (Found: C, 55.5; H, 5.3%),  $\alpha_D = -0.407^\circ$  in water ( $c = 2.065$ ,  $l = 2$ ),  $[\alpha]_D = -9.86^\circ$ . The free base, b. p.  $146^\circ/1$  mm., had  $\alpha_D = +0.473^\circ$  in alcohol ( $c = 2.184$ ,  $l = 2$ ),  $[\alpha]_D = +10.8^\circ$ . The *acetyl* derivative had m. p.  $169^\circ$  (Found: C, 69.1; H, 5.1%).

The *dl*-acetyl derivative prepared from the active forms had m. p.  $130$ — $131^\circ$ , alone or mixed with that prepared from the *dl*-base.

*dl*-4-Iodobenzhydriylamine.—This was prepared from 4-iodobenzophenone (Hoffmann, *Annalen*, 1891, 264, 167) by the action of formamide. The *formyl* derivative had m. p.  $143^\circ$  (Found: C, 49.5; H, 3.7.  $C_{14}H_{12}ONI$  requires C, 49.8; H, 3.6%), the base b. p.  $173$ — $176^\circ/1$  mm., and the *acetyl* derivative m. p.  $170^\circ$  (Found: C, 50.9; H, 4.0.  $C_{16}H_{14}ONI$  requires C, 51.3; H, 3.9%).

The resolution was carried out as before with *d*- and *l*-tartaric acids. The *l*-base *d*-tartrate had m. p.  $206^\circ$ ,  $\alpha_D = +0.095^\circ$  in water ( $c = 1.234$ ,  $l = 2$ ),  $[\alpha]_D = +3.85^\circ$  (Found: C, 44.5; H, 9.0.  $C_{13}H_{12}NI, C_4H_6O_6$  requires C, 44.4; H, 3.8%). The *l*-base had  $\alpha_D = -0.30^\circ$  in alcohol ( $c = 1.418$ ,  $l = 2$ ),  $[\alpha]_D = -10.6^\circ$ ,  $[\alpha]_{5790} = -12.2^\circ$ ,  $[\alpha]_{5461} = -13.7^\circ$ ,  $[\alpha]_{4358} = -23.9^\circ$ . The *acetyl* derivative had m. p.  $195$ — $196^\circ$  (Found: C, 51.4; H, 3.7%). The *d*-base *l*-tartrate had m. p.  $205^\circ$ ,  $\alpha_D = -0.08^\circ$  in water ( $c = 1.044$ ,  $l = 2$ ),  $[\alpha]_D = -3.8^\circ$  (Found: C, 44.2; H, 3.7%). The free base had  $\alpha_D = +0.254^\circ$  in alcohol ( $c = 1.192$ ,  $l = 2$ ),  $[\alpha]_D = +10.6^\circ$ . The *acetyl* derivative had m. p.  $195^\circ$  (Found: C, 51.0; H, 4.0%). The *dl*-acetyl derivative from the active forms had m. p.  $170^\circ$  alone or mixed with that from the *dl*-base.

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