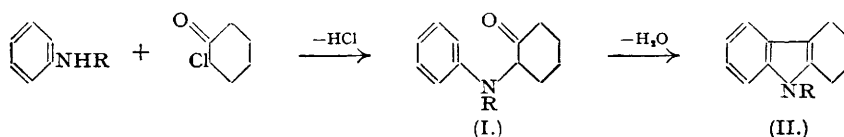


558. The Preparation of Tetrahydrocarbazoles from 2-Chlorocyclohexanone.

By NEIL CAMPBELL and E. B. MCCALL.

Methyl, dimethyl, chloro-, and carbomethoxy-derivatives of 1 : 2 : 3 : 4-tetrahydrocarbazole are readily prepared by condensation of 2-chlorocyclohexanone with excess of the appropriate aniline. The resulting tetrahydrocarbazoles and particularly the dimethyl derivatives readily form peroxides. The reaction of the 2-anilino-cyclohexanones, intermediates in the above synthesis, with 2 : 4-dinitrophenylhydrazine has been studied.

ACCORDING to G.P. 374,098/1923, 2-chlorocyclohexanone condenses with aromatic primary or secondary amines containing at least one unsubstituted *ortho*-position to give by loss of water and hydrogen chloride tetrahydrocarbazoles or their *N*-derivatives as shown by the following scheme (R = H, Me, etc.) :



We have applied the method to eleven primary aromatic amines and with two exceptions have obtained the expected substituted 1 : 2 : 3 : 4-tetrahydrocarbazoles (II), generally in yields of 30—60%. Although these are only moderate, a one-stage process from easily accessible and cheap substances makes the method attractive not only for the preparation of tetrahydrocarbazoles but also for that of the corresponding carbazoles (cf. Barclay and Campbell, *J.*, 1945, 530). It is thus a useful supplement to the Graebe-Ullmann and Borsche methods, both of which have their limitations. We were never able to obtain the excellent or quantitative yields claimed in the patent, and it is somewhat difficult to accept the claims of the German workers since 2-chlorocyclohexanone with aniline yields cyclohex-2-en-1-one (Kötz and Grethe, *J. pr. Chem.*, 1909, 80, 491). The failures were with *o*- and *p*-bromoaniline and these are paralleled

by the failure of Verkade and Janetzky (*Rec. Trav. chim.*, 1946, **65**, 691) to prepare 5-bromo-2 : 3-dimethylindole by ring-closure of 2-*p*-bromoanilinobutanone.

2-Bromocyclohexanone was found to be less effective than 2-chlorocyclohexanone.

The method was successfully applied to the preparation of dimethyltetrahydrocarbazoles with both substituents in the aromatic ring. These substances have not so far been prepared, presumably because of the instability of the (dimethylphenyl)hydrazines (Klauber, *Monatsh.*, 1890, **11**, 285; Willgerodt, *J. pr. Chem.*, 1905, **71**, 399). An interesting property of the resulting dimethyltetrahydrocarbazoles was their readiness to absorb a molecule of oxygen during crystallisation from light petroleum, the main products being the less soluble oxygenated products which are probably peroxides as recently suggested by Beer, McGrath, Robertson, and Woodier (*Nature*, 1949, **164**, 362; cf. Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 1428). To minimise peroxide formation rapid crystallisation from the hot solutions is essential. The peroxides are characterised by their strong bluish-green fluorescence, especially in dilute methanolic solution.

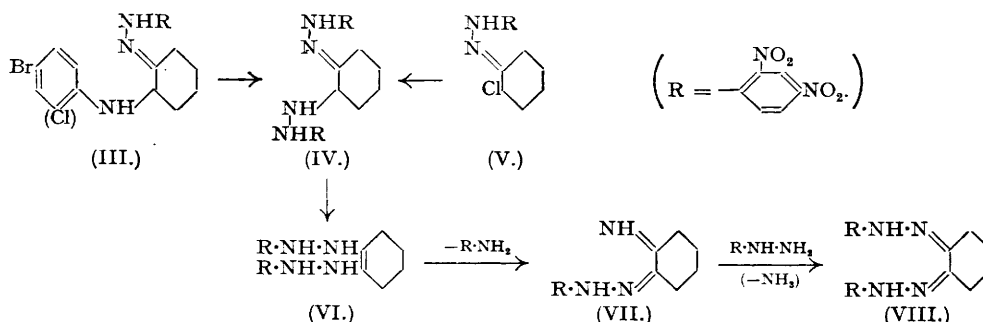
o-4-Xylidine and 2-chlorocyclohexanone gave a 13% yield of 6 : 7-dimethyltetrahydrocarbazole, the constitution of which was proved by dehydrogenation to 2 : 3-dimethylcarbazole identical with a sample prepared from 1-keto-6 : 7-dimethyl-1 : 2 : 3-4-tetrahydrocarbazole by Clemmensen reduction followed by chloranil dehydrogenation (Anderson and Campbell, *J.*, 1950, 2855). No trace of the 5 : 6-dimethyltetrahydrocarbazole was detected, and this is in agreement with Verkade and Janetzky's finding (*loc. cit.*) that *m*-toluidine and methyl α -bromoethyl ketone yield only one trimethylindole and not the two theoretically possible. Ring-closure appears to take place preferentially at a position *para* to a methyl group, and a similar result was found with *m*-chloroaniline, which with 2-chlorocyclohexanone gave only 7-chlorotetrahydrocarbazole. This substance was obtained as crystals, m. p. 171°, b. p. 250–260°/49 mm. No lower-boiling fraction indicative of the 5-isomer, which is a syrup at room temperature, was obtained. It is noteworthy that cyclisation of phenacyl-*m*-chloroaniline hydrochloride gives only one product (Bischler, *Ber.*, 1892, **25**, 2860) although in another type of cyclisation cyclohexanone *m*-chlorophenylhydrazine gives both 5- and 7-chlorotetrahydrocarbazole (Plant and Moggridge, *J.*, 1937, 1125). *m*-Aminobenzoic acid also gave tetrahydrocarbazole-7-carboxylic, but the yield (2.5%) makes comparisons unprofitable.

Aniline and 2-chloro-5-methylcyclohexanone gave a mixture of methyltetrahydrocarbazoles melting over a range of 3° and forming a maroon-coloured picrate with a wide m. p. range. Chloranil dehydrogenation afforded impure 2-methylcarbazole in 27% yield. These facts indicate that the product is 2- and possibly 3-methyltetrahydrocarbazole, the former resulting by the Bischler process or rearrangement (cf. Stevens and Cowper, *J.*, 1947, 1041; Brown and Mann, *J.*, 1947, 847, 858).

There can be little doubt from previous work on analogous syntheses that the above preparation of tetrahydrocarbazoles proceeds *via* intermediate 2-anilinocyclohexanones (I) (Bischler, *loc. cit.*; Strain, *J. Amer. Chem. Soc.*, 1929, **51**, 270; Julian *et al.*, *ibid.*, 1945, **67**, 1203; Cowper and Stevens, *loc. cit.*). These substances are readily prepared by heating the reactants in boiling ethanol with sodium carbonate or acetate. The yields are usually below 50%, again probably owing to dehydrohalogenation of the 2-chlorocyclohexanone. Cyclisation of the amino-ketones was effected by heating them with aromatic amine hydrochlorides; but attempts with glacial acetic acid saturated with hydrogen bromide or acetic anhydride were unsuccessful. This supports Bischler's postulate of an intermediate anilino-anil (*loc. cit.*). It should be noted, however, that 4-aminoveratrole and 2-chlorocyclohexanone in the presence of sodium acetate gave 6 : 7-dimethoxytetrahydrocarbazole in 40% yield (Hughes and Lions, *J. Proc. Roy. Soc. N.S.W.*, 1937–38, **71**, 433). According to Bischler's theory it is the first arylamine molecule to react with the chloro-ketone which is eliminated in the cyclisation, and this is supported by the conversion of 2-*p*-bromoanilinocyclohexanone into tetrahydrocarbazole when heated with aniline hydrochloride.

When an attempt was made to prepare the 2 : 4-dinitrophenylhydrazine (as III) of 2-*p*-bromo- or 2-*o*-chloro-anilinocyclohexanones by Brady's method (*J.*, 1931, 756) the same halogen-free product, m. p. 233–234°, was obtained. This suggested that the hydrazine had not only condensed with the carbonyl group but had also displaced the halogenoanilino-residue to give the hydrazono-hydrazine (IV). The essential correctness of this assumption was confirmed by analysis of the products and by a study of the properties of 2-chlorocyclohexanone 2 : 4-dinitrophenylhydrazine (V) which, when heated with 2 : 4-dinitrophenylhydrazine or boiled in aqueous acetic acid, yielded the product of m. p. 233–234°. Presumably in the second case the dinitrophenylhydrazine undergoes partial hydrolysis, the "freed" dinitrophenylhydrazine then displacing the chlorine atom. Further examination of the product, m. p. 233–234°, showed,

however, that it is not (IV) but *cyclohexane-1:2-dione bis-2:4-dinitrophenylhydrazone* (VIII) identical with a specimen prepared from the dione. This result (see also Bodforss



Ber., 1939, **72**, 468; von Auwers, *Ber.*, 1917, **50**, 1178) may be adequately explained in terms of Weygand's theory of osazone formation (*Ber.*, 1940, **73**, 1259; see also E. G. V. Percival, *Adv. Carbohydrate Chem.*, 1948, **3**, 43) in which intermediate dihydrazino-compounds and imino-derivatives, such as (VI) and (VII), respectively, are postulated.

EXPERIMENTAL.

Analyses were done by Drs. Weiler and Strauss, Oxford. By mixed m. p. is meant the m. p. of a substance when mixed with an authentic sample of proved constitution.

Preparation of Chloro-1:2:3:4-tetrahydrocarbazoles.—2-Chlorocyclohexanone was prepared by the methods of Meyer (*Helv. Chim. Acta*, 1933, **16**, 1291), Kotz and Grethe (*loc. cit.*), or preferably in 55% yield by the method given in *Org. Synth.*, **25**, 22, and can be stored in the refrigerator for long periods without decomposition. 2-Bromocyclohexanone is much less stable. 2-Chlorocyclohexanone (4 g.) was added slowly to *p*-chloroaniline (8 g.) at 150–160°, and the cooled mixture extracted with boiling ether. *p*-Chloroaniline hydrochloride (4.2 g., 85%) separated, and the filtrate was washed twice with dilute hydrochloric acid, and then with water. The dried (Na_2SO_4) ethereal solution gave 6-chloro-1:2:3:4-tetrahydrocarbazole (1.3 g., 20%), prisms (from methanol or light petroleum), m. p. and mixed m. p. 141–143°.

o-Chloroaniline (15 g.) and 2-chlorocyclohexanone (5 g.) similarly gave a brown syrup (2.2 g.), b. p. 180–200°/12 mm., which appeared to be chiefly 8-chloro-1:2:3:4-tetrahydrocarbazole. It formed a *picrate*, brick-red needles (from benzene), m. p. 138–140° (Found: N, 12.3. $\text{C}_{18}\text{H}_{15}\text{O}_7\text{N}_4\text{Cl}$ requires N, 12.9%). Dehydrogenation with chloranil gave 1-chlorocarbazole, prisms (from aqueous methanol), m. p. 113–115° (lit., 110° and 125°) (Found: Cl, 17.4. Calc. for $\text{C}_{12}\text{H}_8\text{NCl}$: Cl, 17.6%). The carbazole formed a *picrate*, dark orange needles (from benzene), m. p. 138–141°, and gave a bluish-green colour with a mixture of sulphuric and nitric acids. Impure 8-chloro-1:2:3:4-tetrahydrocarbazole was dissolved in xylene and after some days the crystalline *peroxide* separated, m. p. 134° (decomp.) (Found: C, 61.3; H, 5.3; N, 6.0; Cl, 14.8. $\text{C}_{14}\text{H}_{12}\text{O}_2\text{N}_2\text{Cl}$ requires C, 60.6; H, 5.1; N, 5.9; Cl, 14.9%).

m-Chloroaniline (10 g.) and 2-chlorocyclohexanone (5 g.) at the b. p. of the former gave 7-chlorotetrahydrocarbazole, m. p. and mixed m. p. 179–180° (lit., 181°) (27%). It forms a *picrate*, maroon needles (from benzene), m. p. 128–130° (Found: N, 12.5%).

Preparation of Dimethylcarbazoles.—2-Chlorocyclohexanone (5 g.), *m*-4-xyldine (10 g.), and ethanol (20 ml.) were boiled for 16 hours, the ethanol evaporated, ether added, and the mixture filtered. The filtrate was washed successively with dilute hydrochloric acid, water, and sodium carbonate, and on evaporation gave 6:8-dimethyltetrahydrocarbazole, purified by distillation *in vacuo* followed by crystallisation from light petroleum; it had b. p. 235–240°/25 mm., and formed colourless prisms, m. p. 101–105° (Found: C, 84.9; H, 8.7; N, 7.0. $\text{C}_{14}\text{H}_{17}\text{N}$ requires C, 84.3; H, 8.6; N, 7.0%). It forms a *picrate*, chocolate-coloured needles (from benzene), m. p. 160–162° (Found: N, 12.6. $\text{C}_{20}\text{H}_{20}\text{O}_7\text{N}_4$ requires N, 13.1%). The tetrahydrocarbazole on recrystallisation from light petroleum gave immediately 50% of the purified tetrahydrocarbazole, and the mother-liquor gradually deposited the *peroxide*, colourless crystals, m. p. 116° (decomp.) (the m. p. depends on the rate of heating), sparingly soluble in benzene or light petroleum, but readily soluble in ethanol to give a strong green fluorescence (Found: C, 73.7; H, 7.7; N, 5.9%; *M*, 242. $\text{C}_{14}\text{H}_{17}\text{O}_2\text{N}$ requires C, 72.7; H, 7.4; N, 6.1%; *M*, 231). The *peroxide* does not form a *picrate*.

p-2-Xyldine similarly gave a 37% yield of 5:8-dimethyltetrahydrocarbazole, b. p. 215–220°/20 mm., m. p. 83–86°, needles (from light petroleum) (Found: C, 84.3; H, 8.4; N, 7.35%). The *picrate* separated as chocolate-coloured needles (from benzene), m. p. 138–141° (Found: N, 13.1%). The *peroxide*, prepared as for its isomer, formed yellow cubic prisms, m. p. 140° (decomp.) (Found: C, 72.7; H, 7.46; N, 6.1%).

o-4-Xyldine similarly yielded 6:7-dimethyltetrahydrocarbazole, elongated prisms, m. p. about 109° (13%), on rapid crystallisation from light petroleum (Found: C, 84.1; H, 8.6; N, 7.0%). It forms a *picrate*, chocolate-coloured needles (from benzene), m. p. 166–168° (Found: N, 13.0%). Crystallisation from light petroleum gave chiefly a product, m. p. 127° (decomp.), probably the *peroxide*, and this accounted for the above poor yield of the tetrahydrocarbazole. Dehydrogenation of the tetrahydro-

carbazole (0.6 g.) with chloranil (1.48 g.) in boiling sulphur-free xylene (15 ml.) for 24 hours, and passage of the product through a column of alumina ($3' \times \frac{1}{4}''$), gave 2 : 3-dimethylcarbazole, colourless plates, m. p. 251—253° (42%) (Found : C, 86.2; H, 6.9. $C_{14}H_{13}N$ requires C, 86.2; H, 6.7%). It forms a picrate, scarlet needles (from benzene), m. p. 167—169° (Found : N, 12.6. $C_{20}H_{16}O_7N_4$ requires N, 13.1%). The carbazole does not give the characteristic bluish-green colour with concentrated sulphuric acid.

1 : 2 : 3 : 4-Tetrahydrocarbazole-carboxylic Acids.—2-Chlorocyclohexanone (5 g.) was added dropwise to methyl anthranilate (12 g.) at 140°, and the temperature was gradually raised to 160° during the addition. The mixture was kept at 160° for 15 minutes, cooled, boiled with dilute hydrochloric acid (50 ml.), and the residue extracted with boiling ether. The extract was washed with acid, and with sodium hydrogen carbonate solution, and the crude product obtained on evaporation was triturated with and recrystallised from methanol. Methyl 1 : 2 : 3 : 4-tetrahydrocarbazole-8-carboxylate was thus obtained in plates, m. p. 123—124° (lit., 124°) (crude yield, 34%) (Found : N, 6.1. Calc. for $C_{14}H_{15}O_2N$: N, 5.9%). It formed a picrate, brick-red needles (from benzene), m. p. 130—132° (Found : N, 11.6. $C_{20}H_{18}O_9N_4$ requires N, 12.2%), and was hydrolysed quantitatively by sodium hydroxide and ethanol to the acid, m. p. and mixed m. p. 200—201° (lit., 203°), also obtained in 35% yield by heating *o*-aminobenzoic acid and 2-chlorocyclohexanone at 150°.

Methyl 1 : 2 : 3 : 4-tetrahydrocarbazole-6-carboxylate was similarly prepared from methyl *p*-aminobenzoate (prepared in 80% yield by catalytic hydrogenation of methyl *p*-nitrobenzoate; *Org. Synth.*, 8, 66), as leaflets (from aqueous acetic acid), m. p. 155—157° (lit., 158°) (30%). Hydrolysis gave 1 : 2 : 3 : 4-tetrahydrocarbazole-6-carboxylic acid, leaflets (from glacial acetic acid), m. p. and mixed m. p. 279—281° (lit., 282°). Attempts to prepare the acid from *p*-aminobenzoic acid and 2-chlorocyclohexanone were unsuccessful.

m-Aminobenzoic acid (11 g.) and 2-chlorocyclohexanone (5 g.) in ethanol (70 ml.) were boiled for 18 hours and worked up as above to give 1 : 2 : 3 : 4-tetrahydrocarbazole-7-carboxylic acid, m. p. 285—286° (lit., 287°) (0.2 g.) (Found : C, 72.2; H, 6.3. Calc. for $C_{13}H_{13}O_3N$: C, 72.5; H, 6.1%).

Miscellaneous Condensations.—2-Bromocyclohexanone (5 g.) and aniline (10 g.) or *o*- or *p*-toluidine (12.5 g.) gave 1 : 2 : 3 : 4-tetrahydrocarbazole or its 8- or 6-methyl derivative, respectively, in 65%, 55%, and 60% yields.

2-Chloro-5-methylcyclohexanone, b. p. 76—86°/12 mm. (5 g.), was added slowly to boiling aniline (10 g.), and the mixture cooled and treated with dilute hydrochloric acid (100 ml.). The product was extracted with ether, and the extract dried and distilled *in vacuo*. The resulting mixture of methyl-tetrahydrocarbazoles, b. p. 180—200°/16 mm. (2.4 g., 38%), was crystallised from light petroleum (b. p. 60—80°) to give prisms, m. p. 78—81° (softening at 73°) (Found : C, 83.9; H, 8.0; N, 7.5. Calc. for $C_{13}H_{15}N$: C, 84.3; H, 8.2; N, 7.6%). Dehydrogenation with chloranil gave a mixture of methylcarbazoles, m. p. 219—229°, in 27% yield which on crystallisation from ethanol and purification on a short alumina column gave plates of 2-methylcarbazole, m. p. 241—243°, undepressed on admixture with the authentic carbazole, m. p. 257—259° (Found : C, 85.4; H, 6.1; N, 8.0. Calc. for $C_{13}H_{11}N$: C, 86.2; H, 6.1; N, 7.7%). It formed a picrate, m. p. 161—163° (lit., 167°).

Substituted 2-Anilinocyclohexanones.—These substances were prepared by the method exemplified below. Anhydrous sodium carbonate (3 g.), 2-chlorocyclohexanone (5 g.), *p*-chloroaniline (6 g.), and ethanol (20 ml.) were boiled for 5 hours and then filtered, and the volume of the filtrate reduced. 2-*p*-Chloroanilinocyclohexanone separated and crystallised from ethanol in prisms, m. p. 132—134° (44%) (Found : C, 64.8; H, 6.5. $C_{12}H_{14}ONCl$ requires C, 64.4; H, 6.3%). The amino-ketone (0.5 g.) and *p*-chloroaniline hydrochloride (2 g.) were heated in an oil-bath at 250° for 1 hour. The semi-solid product was thoroughly extracted with ether and filtered. The filtrate was washed with dilute hydrochloric acid, water, and sodium carbonate, dried (Na_2SO_4), and evaporated. 6-Chlorotetrahydrocarbazole separated and crystallised from ethanol in colourless plates, m. p. 140—143° (22%). Boiling *o*-chloroaniline (5 g.), 2-chlorocyclohexanone (7.8 g.), and sodium carbonate (3.1 g.) in ethanol (20 ml.) for 24 hours gave 2-*o*-chloroanilinocyclohexanone, purified by distillation, b. p. 190—200°/15 mm., followed by crystallisation from light petroleum (b. p. 40—60°), prisms, m. p. 53—54° (yield, 60%) (Found : Cl, 15.5. $C_{12}H_{14}ONCl$ requires Cl, 15.9%). 2-*p*-Bromoanilinocyclohexanone formed elongated prisms (from ethanol), m. p. 143—144° (54%) (Found : Br, 30.8. $C_{12}H_{14}ONBr$ requires Br, 29.9%). Attempts to effect ring-closure of the compound with *p*-bromoaniline or its hydrochloride were unsuccessful, but with aniline hydrochloride at 150° for 30 minutes tetrahydrocarbazole resulted (identified by m. p. and mixed m. p.). 2-*o*-Bromoanilinocyclohexanone was purified by removal of the excess of *o*-bromoaniline *in vacuo* (the compound itself undergoes decomposition when distilled) and crystallisation of the residue from ethanol; prisms, m. p. 66—69° (40%) (Found : N, 5.05; Br, 28.4. $C_{12}H_{14}ONBr$ requires N, 5.2; Br, 29.9%). 2 : 2' : 4'-Dichloroanilinocyclohexanone, similarly purified except that light petroleum was used as solvent, formed prisms, m. p. 81—82° (Found : N, 5.5; Cl, 27.0. $C_{12}H_{13}ONCl_2$ requires N, 5.4; Cl, 27.5%).

2-*o*-Chloroanilinocyclohexanone (or the corresponding *p*-bromo-compound) (0.6 g.) and 2 : 4-dinitrophenylhydrazine (0.5 g.) in ethanol containing sulphuric acid were condensed by Brady's method, and the suspension boiled for 2 hours to ensure complete reaction. cycloHexane-1 : 2-dione 2 : 4-dinitrophenyllosazone was obtained as a scarlet compound which after trituration with boiling glacial acetic acid had m. p. 233—234° (decomp.) (Found : N, 23.1; Cl, 0.0. $C_{18}H_{16}O_8N_8$ requires N, 23.7%). 2-Chlorocyclohexanone and 2 : 4-dinitrophenylhydrazine in ethanol gave by Allen's method (*J. Amer. Chem. Soc.*, 1930, 52, 2955) the 2 : 4-dinitrophenylhydrazone, orange prisms (from tetralin), m. p. 158° (decomp.) (Found : N, 18.3; Cl, 10.9. $C_{12}H_{13}O_4N_4Cl$ requires N, 17.9; Cl, 11.3%). This substance when heated with acetic acid (2 ml.) and water (3 drops) gave a red oil which yielded scarlet crystals, m. p. 233—234° (Found : C, 45.7; H, 3.5; N, 24.3. Calc. for $C_{18}H_{16}O_8N_8$: C, 45.7; H, 3.4; N, 23.7%). This proved

2874 *Ansell and Hey: Intramolecular Acylation. Part II.*

to be the above osazone, and was also obtained by boiling the above dinitrophenylhydrazone or *cyclohexane-1:2-dione* with 2:4-dinitrophenylhydrazine in glacial acetic acid.

ω -Chloroacetophenone by Allen's method gave the 2:4-dinitrophenylhydrazone, orange needles, m. p. 214—215° (decomp.) (lit., 212°), unaltered when boiled with 2:4-dinitrophenylhydrazine and glacial acetic acid for 26 hours. The dinitrophenylhydrazone (0.15 g.) was dissolved in a mixture of water (5 drops) and enough glacial acetic acid to give complete solution at the b. p. After 20 hours, further portions of the dinitrophenylhydrazone (0.15 g.), water (1 ml.), and glacial acetic acid were added, and the solution was boiled for 48 hours. *Phenylglyoxal bis-2:4-dinitrophenylhydrazone* separated in scarlet needles, m. p. 296—297° (0.11 g.), from the boiling solution (Found: C, 48.3; H, 3.3; N, 21.6. $C_{20}H_{14}O_8N_8$ requires C, 48.5; H, 2.8; N, 22.6%).

Thanks are expressed to the Department of Scientific and Industrial Research for the award of a maintenance grant to one of us (E. B. McC.), and to Dr. E. G. V. Percival for helpful advice.

UNIVERSITY OF EDINBURGH.

[Received, June 5th, 1950.]