[Contribution from the Laboratory of Organic Chemistry, Radium Institute,
University of Paris]

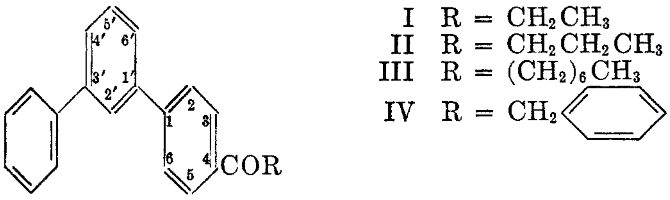
SOME NEW DERIVATIVES OF *m*-TERPHENYL

NG. PH. BUU-HOÏ AND RENÉ ROYER

Received October 31, 1950

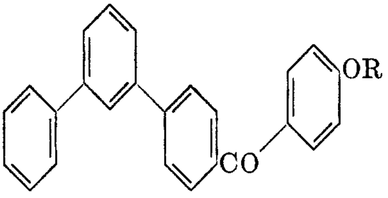
Since the discovery that derivatives of the biphenyl (1) series have carcinogenic activity, the search for carcinogens can no longer be confined to condensed ring systems. It is quite possible that certain derivatives of the polyphenyls will have carcinogenic activity. It has been reported (2) that 1,3,5-triphenylbenzene produces skin tumors.

This work is to report the preparation of some new derivatives of *m*-terphenyl, a hydrocarbon now available in quantity, and which has recently been investigated intensively (3 and 4).

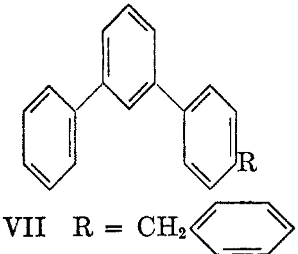


I R = CH_2CH_3
II R = $CH_2CH_2CH_3$
III R = $(CH_2)_6CH_3$
IV R = CH_2

Propionylation of *m*-terphenyl, using the ordinary procedure for Friedel-Crafts reactions, yielded as the main product 4-propionyl-*m*-terphenyl (I) (along with some oily ketonic material, probably an isomer). Constitution of this ketone was proved by Beckmann rearrangment of its oxime and saponofication of the resulting amide to give a product identical with 4-amino-*m*-terphenyl, which was recently synthesized by Bradsher and Swerlick (5) through an unequivocal method.



V R = CH_3
VI R = H



VII R = CH_2
VIII R = $CH_2CH_2CH_3$
IX R = $(CH_2)_7CH_3$

Other new ketones prepared in the same way were 4-*n*-butyryl-(II), 4-*n*-octanoyl- (III), 4-phenacetyl- (IV), and 4-(4-methoxybenzoyl)-*m*-terphenyl (V). The last was easily converted into 4-(4-hydroxybenzoyl)-*m*-terphenyl (VI) by boiling with pyridine hydrochloride, a procedure which has been employed with repeated success for the demethylation of ketones bearing phenolic ether groups (6). The same ketone was obtained as a by-product in the Friedel-Crafts synthesis of its methyl ether (V).

Benzoylation of *m*-terpheyl in carbon disulfide gave in good yield predominantly the 4-benzoyl compound. There is thus practically no difference in the behavior of the chlorides of aliphatic and aromatic acids, whereas in many instances, such as for naphthalene, the position entered by the substituent is not the same in the two cases (7).

4-Benzoyl-*m*-terphenyl was reduced by the Wolff-Kishner method as modified by Huang-Minlon (8) to 4-benzyl-*m*-terphenyl (VII); an isomer, 4′-benzyl-*m*-terphenyl had been prepared by Bradsher and Swerlick (5). 4-*n*-Propyl- (VIII) and 4-*n*-octyl-*m*-terphenyl (IX), two liquid homologs of *m*-terphenyl, were also prepared from the corresponding ketones.

EXPERIMENTAL

4-Propionyl-m-terphenyl. To an ice-cooled solution of 100 g. of *m*-terphenyl and 45 g. of propionyl chloride in carbon disulfide (300 ml.), 65 g. of finely powdered aluminum chloride was slowly added with stirring. The mixture was kept at room temperature for a further 24 hours, and then decomposed with ice and hydrochloric acid. The organic layer was washed with a dilute aqueous sodium hydroxide solution, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. The portion, b.p. 280–300° at 18 mm., was crystallized twice from ethanol, giving large colorless, lustrous leaflets, m.p. 117°, and giving with sulfuric acid a golden yellow coloration; yield, 32 g.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.1; H, 6.3.
Found: C, 88.0; H, 6.2.

The corresponding *semicarbazone* separated from benzene as fine, shiny colorless needles, m.p. 206–207°.

Anal. Calc'd for $C_{22}H_{21}N_3O$: N, 12.2. Found: N, 11.9.

The *oxime*, obtained in quantitative yield by 3-days' refluxing of 10 g. of ketone with 7.5 g. of hydroxylamine hydrochloride and 4.5 g. of sodium carbonate, crystallized from ethanol as fine shiny, colorless needles, m.p. *circa* 173°.

Anal. Calc'd for $C_{21}H_{19}NO$: N, 4.6. Found: N, 4.3.

The mother liquors from the crystallization of 4-propionyl-*m*-terphenyl yielded a ketonic oil which was apparently a mixture of two isomers. Ketone I was further characterized by a Pfitzinger reaction with 5-bromoisatin, resulting in a quantitative yield of *4-(6-bromo-4-carboxy-3-methyl-2-quinolyl)-m-terphenyl,* which crystallized from much acetic acid in fine, pale yellow needles, m.p. 318–320° (decomp. above 300°).

Anal. Calc'd for $C_{29}H_{20}BrNO_2$: C, 70.4; H, 4.0.
Found: C, 70.5; H, 4.2.

4-Propionylamino-m-terphenyl. Into an ice-cooled suspension of 10 g. of the foregoing oxime in anhydrous ether, 7 g. of finely powdered phosphorus pentachloride was cautiously stirred. After 15-minutes' standing at room temperature, the mixture was poured on to ice, the ether allowed to evaporate, and the rearrangement-product washed thoroughly with sodium bicarbonate. It crystallized from ethanol in fine colorless prisms, m.p. 137°.

Anal. Calc'd for $C_{21}H_{19}NO$: N, 4.6. Found: N, 4.6.

This amide was saponified by 4-hours' heating with concentrated hydrochloric acid; the sparingly soluble *4-amino-m-terphenyl hydrochloride* thus formed (long colorless needles), gave on treatment with ammonia an amine which crystallized from ethanol in fine colorless needles, m.p. 100°. Bradsher and Swerlick (5) gave m.p. 101.5–102° for a sample of 4-amino-*m*-terphenyl prepared from 4-*m*-terphenoic acid. This amine was further characterized by refluxing in ethanol with 2,3-dichloro-1,4-naphthoquinone and sodium acetate, to give *4-(2,3-dichloro-1,4-naphthoquinonyl)amino-m-terphenyl,* which separated from ethanol in fine violet-red needles, giving with sulfuric acid a lilac-blue coloration.

4-n-Propyl-m-terphenyl (VIII). A mixture of 15 g. of ketone I, 30 g. of 80% hydrazine hydrate, and 22 g. of potassium hydroxide in diethylene glycol (200 ml.) was heated with removal of water up to 198° and kept at this temperature until no more nitrogen was evolved. The reaction product was diluted with water, neutralized with dilute hydrochloric acid, and the hydrocarbon taken up in benzene and purified by vacuum distillation. Yield, 12 g. of a pale yellow viscous oil, b.p. 260–265° at 18 mm.

Anal. Calc'd for $C_{21}H_{20}$: C, 92.6; H, 7.3.
Found: C, 92.5; H, 6.9.

4-n-Butyryl-m-terphenyl (II). *m*-Terphenyl (40 g.) and 20 g. of *n*-butyryl chloride in carbon disulfide were treated with 34 g. of aluminum chloride as for the lower homolog, to yield 20 g. of a ketone, b.p. 280° at 18 mm., which crystallized from methanol in lustrous colorless leaflets, m.p. 62–63°; no cinchoninic acid could be obtained when this ketone was submitted for five days to a Pfitzinger reaction with isatin and potassium hydroxide.

Anal. Calc'd for $C_{22}H_{20}O$: C, 88.0; H, 6.6.
Found: C, 88.0; H, 6.8.

There was obtained as a by-product in this preparation, a substance of unknown constitution, crystallizing from ethanol in fine shiny colorless needles, m.p. 207°.

4-n-Octanoyl-m-terphenyl (III). This compound, prepared in 65% yield from *m*-terphenyl and *n*-octanoyl chloride, was a pale yellow viscous oil, b.p. 298–300° at 18 mm.

Anal. Calc'd for $C_{26}H_{28}O$: C, 87.6; H, 7.8.
Found: C, 87.6; H, 7.9.

4-n-Octyl-m-terphenyl (IX). Six grams of the above ketone, reduced with 10 g. of 80% hydrazine hydrate and 12 g. of potassium hydroxide in diethylene glycol in the usual way (three hours), gave 4 g. of a pale yellow, rather fluid oil, b.p. 280° at 20 mm.

Anal. Calc'd for $C_{26}H_{30}$: C, 91.2; H, 8.7.
Found: C, 91.0; H, 8.8.

4-Phenacetyl-m-terphenyl (IV). This was prepared in the usual way from 30 g. of *m*-terphenyl, 23 g. of phenacetyl chloride, and 19 g. of aluminum chloride in carbon disulfide; yield, 8 g. of a ketone crystallizing from ethanol in fine colorless needles, m.p. 118°, and giving with sulfuric acid a golden yellow coloration; here too, the presence of a lower-melting isomer in the crude ketone was evident.

Anal. Calc'd for $C_{26}H_{20}O$: C, 89.6; H, 5.7.
Found: C, 89.4; H, 5.7.

4-Benzoyl-m-terphenyl. This was prepared, at variance with both Goodman and Lowy (3) and Bradsher and Swerlick (5), from 50 g. of *m*-terphenyl, 34 g. of benzoyl chloride, and 43 g. of aluminum chloride in carbon disulfide in our usual way. The yield was 49 g. of a crude ketone which gave, after two recrystallizations, long, shiny, colorless needles, m.p. 117°.

4-Benzyl-m-terphenyl (VII). Twenty grams of the above ketone, reduced by 40 g. of 80% hydrazine hydrate and 35 g. of sodium hydroxide in diethylene glycol (250 ml.), gave an 80% yield of a hydrocarbon cystallizing from ligroin in long shiny colorless needles m.p. 78°. The isomeric 4′-benzyl-*m*-terphenyl (5) had m.p. 69–70°.

Anal. Calc'd for $C_{25}H_{20}$: C, 93.4; H, 6.2.
Found: C, 93.2; H, 6.1.

4-(4-Methoxybenzoyl)-m-terphenyl (V). This was obtained from 50 g. of *m*-terphenyl, 40 g. of anisoyl chloride, and 44 g. of aluminum chloride in carbon disulfide. Yield, 18 g. of a ketone, b.p. 340–350° at 18 mm., crystallizing from a mixture of benzene and ethanol in long shiny colorless needles, m.p. 138°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{26}H_{20}O_2$: C, 85.7; H, 5.5.
Found: C, 85.7; H, 5.6.

4-(4-Hydroxybenzoyl)-m-terphenyl (VI). A mixture of 10 g. of the foregoing ketone with 50 g. of redistilled pyridine hydroclhoride was gently refluxed for 20 minutes. The reaction product was treated with water, and the precipitate thus obtained in 90% yield was washed thoroughly with water, and recrystallized from benzene; fine colorless needles. m.p. 172°, giving with sulfuric acid a deep orange coloration, and bright yellow solutions with aqueous sodium hydroxide.

Anal. Calc'd for $C_{25}H_{18}O_2$: C, 85.7; H, 5.1.

Found: C, 85.5; H, 5.2.

The same ketone was obtained once in good yield in a Friedel-Crafts reaction of anisoyl upon *m*-terphenyl with insufficient cooling.

Acknowledgement. Our thanks are due to Miss P. F. Boshell (M. A. Oxon) and to Mr. P. Jacquignon for assistance in this work. The microanalyses were by the Chemical Analyses Department of the Centre National de la Recherche Scientifique, Paris.

SUMMARY

Several new derivatives of *m*-terphenyl have been prepared for biological investigation.

PARIS V^e, FRANCE

REFERENCES

(1) BAKER, Communication to the 5th International Congress of Cancer (Paris, 1950) upon the carcinogenicity of 4,4′-diamino-3,3′-dihydroxydiphenyl.
(2) MORTON, BRANCH, AND CLAPP, *Am. J. Cancer*, **26,** 754 (1936).
(3) GOODMAN AND LOWY, *J. Am. Chem. Soc.*, **60,** 2155 (1938).
(4) FRANCE, HEILBRON, AND HEY, *J. Chem. Soc.*, 1288 (1939); COOK AND COOK, *J. Am. Chem. Soc.*, **64,** 2485 (1942): ALLEN AND BURNESS, *J. Org. Chem.*, **14,** 175 (1949).
(5) BRADSHER AND SWERLICK, *J. Am. Chem. Soc.*, **72,** 4189 (1950).
(6) BUU-HOÏ, *Rec. trav. chim.*, **68,** 759 (1949); BUU-HOÏ, HÓAN, AND XUONG, *J. Am. Chem. Soc.*, **72,** 3992 (1950).
(7) See for instance BUU-HOÏ AND CAGNIANT, *Bull. soc. chim.*, [5] **11,** 307 (1945).
(8) HUANG-MINLON, *J. Am. Chem. Soc.*, **68,** 2487 (1946).