2-Alkyl-3-phenylcinchoninic Acids and Related Products

ELDON H. SUND[1] and HENRY R. HENZE
Department of Chemistry, University of Texas, Austin, Tex. 78712

Eight 2-alkyl-3-phenylcinchoninic acids were prepared by the interaction of isatin and alkyl benzyl ketones. These acids were cyclized to the 6-alkyl-11-indeno[1,2-c]quinolin-11-ones and the oxime derivatives prepared. The acids were also decarboxylated to the 2-alkyl-3-phenylquinolines and their picrates prepared

Eight 2-alkyl-3-phenylcinchoninic (2-alkyl-3-phenyl-4-quinolinecarboxylic acid) acids were prepared by the interaction of the requisite alkyl benzyl ketone with isatin under Pfitzinger conditions (*5*) as modified by Henze and Carroll (*4*). The literature had shown that for the first two members of the series, the methyl and ethyl benzyl ketones, condensation takes place with the methylene adjacent to the phenyl rather than the methylene of the alkyl group (*2*). Each cinchoninic acid was decarboxylated to the quinoline and converted without isolation to its picrate derivative. Each 2-alkyl-3-phenylcinchoninic acid was converted into the corresponding 6-alkyl-11-indeno[1,2-*c*]quinolin-11-one (*1*), from which its oxime derivative was prepared.

Table I lists the data on the 2-alkyl-3-phenylcinchoninic acids and the picrates. Table II lists the data on the 6-alkyl-11-indeno[1,2,-*c*]quinolin-11-ones and oximes.

EXPERIMENTAL

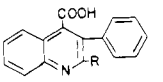
The alkyl benzyl ketones were synthesized (*7*), while the remainder of the reactants were obtained commercially and used without further purification. Elemental analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colo. Melting points were determined in a silicone oil bath and are corrected. The following examples illustrate the synthesis of the 2-alkyl-3-phenylcinchoninic acids and their picrates as well as the synthesis of the 6-alkyl-11-indeno[1,2-*c*]quinolin-11-ones and their oximes.

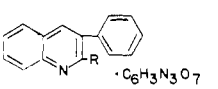
2-Pentyl-3-phenylcinchoninic Acid. A mixture of 7.3 grams (0.05 mole) of isatin, 10.0 grams (0.05 mole + 5% excess) of 1-phenyl-2-heptanone, and 25 ml of a 34% potassium hydroxide in a 50% ethanol-water solution and 40 ml of water was stirred on a steam bath for 72 hours. The solvent was removed by a water aspirator until a moist paste remained, which was dissolved in water, and the solution extracted with ether to remove any unreacted ketone. Addition of concentrated hydrochloric acid to pH 8.0 produced a small amount of brownish gray, noncombustible matter, which was discarded. Further addition of concentrated hydrochloric acid, to pH 5.5, resulted in the formation of a thick, yellow-tan precipitate which was removed by filtration. The 7.0 grams (44%) of the crude 2-pentyl-3-phenylcinchoninic acid, thus obtained, was treated with activated charcoal and recrystallized from 95% ethanol [m.p. 204–05° (dec.)].

2-Pentyl-3-phenylquinoline and Picrate. Approximately 1.0 gram of the 2-pentyl-3-phenylcinchoninic acid was converted to 2-pentyl-3-phenylquinoline by decarboxylation using one third its weight of copper powder as a catalyst (*3*). The cinchoninic acid and the copper powder were intimately mixed, placed in a distilling flask, and heated in a sand bath. Using a vacuum pump, the quinoline was distilled as rapidly as it formed. The quinoline formed was not isolated, but converted immediately into its picrate by the method of Shriner *et al.* (*6*) (m.p. 150–51°).

6-Pentyl-11-indeno[1,2-c]quinolin-11-one. A mixture of 1.0 gram of 2-pentyl-3-phenylcinchoninic acid and 13 ml of concentrated sulfuric acid was heated at 80° for 6 hours. The reaction mixture was poured over ice and neutralized with sodium carbonate. The ketone was removed by filtration and recrystallized from 95% ethanol. There was

Table I. 2-Alkyl-3-Phenylcinchoninic Acids[a] and Picrates of 2-Alkyl-3-Phenylquinolines[b]



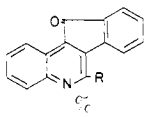


R	% Yield	M.P., °C.	M.P., °C
n-C_3H_7	94	266–67 (dec.)	191–92
Iso-C_3H_7	35	289–90 (dec.)[c]	194–95
n-C_4H_9	77	239–40 (dec.)	186–87
Iso-C_4H_9	46	274–75 (dec.)	185–86
sec-C_4H_9	10	262–63 (dec.)	180–81
n-C_5H_{11}	44	204–05 (dec.)	150–51
Iso-C_5H_{11}	45	239–40 (dec.)	200–01
n-C_6H_{13}	17	192–93	170–71

[a] Elemental analyses for C, H, and N have been reviewed and agree within required limits for the assigned structures. [b] Elemental analyses for N have been reviewed and agree within required limits for the assigned structures. [c] Reported m.p. 284° (dec.) (*1*).

[1] Present address, Department of Chemistry, Midwestern University, Wichita Falls, Tex. 76308.

Table II. 6-Alkyl-11-indeno[1,2-c]quinolin-11-ones[a]



R	Yield	M.P., °C.	Oxime, M.P., °C.
n-C_3H_7	40	150–51	255–56
Iso-C_3H_7	30	185–86[c]	265–66
n-C_4H_9	60	142–43	242–43
Iso-C_4H_9	50	131–32	264–65
sec-C_4H_9	30	122–23	197–99
n-C_5H_{11}	60	146–47	226–28
Iso-C_5H_{11}	60	146–47	236–38
n-C_6H_{13}	30	135–36	235–36

[a] Elemental analyses for N have been reviewed and agree within required limits for the assigned structures. [b] Elemental analyses for C and H have been reviewed and agree within required limits. [c] Reported m.p. 184° (*1*).

obtained 0.6 gram of 6-pentyl-11-indeno[1,2-*c*]quinolin-11-one (m.p. 146–47°). An oxime derivative of this ketone was prepared by the method of Shriner *et al.* (*6*) (m.p. 226–28°).

LITERATURE CITED

(1) Borsche, W., Sinn, F., *Ann.* **532**, 146 (1937).
(2) Borsche, W., Vorbach, O., *Ibid.*, **537**, 22 (1938).
(3) Hauser, C.R., Murray, J.G., *J. Amer. Chem. Soc.* **77**, 3858 (1955).
(4) Henze, H.R., Carroll, D.W., *Ibid.*, **76**, 4580 (1954).
(5) Pfitzinger, W., *J. Prakt. Chem.* [2] **33**, 100 (1886).
(6) Shriner, R.L., Fuson, R.C., Curtin, D.Y., "Systematic Identification of Organic Compounds," 4th ed., pp. 229, 254, Wiley, New York, 1956.
(7) Sund, E.H., Henze, H.R., J. CHEM. ENG. DATA **15**, 200 (1970).

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Synthesis and NMR Data for Dialkyl and Diaryl Trichloromethylphosphonates

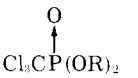
K. DARRELL BERLIN and N. K. ROY
Department of Chemistry, Oklahoma State University, Stillwater, Okla. 74074

The NMR spectra of dialkyl and diaryl trichloromethylphosphonates were recorded. Diaryl trichloromethylphosphonates, a new family of trichloromethylphosphonates, were synthesized by reacting trichloromethylphosphonic dichloride with phenols.

Many organic phosphorus insecticides have been demonstrated to be exceptionally active inhibitors of cholinesterase enzymes and other enzymes with esterase action in mammals and in insects in both *in vivo* and *in vitro* studies (*9, 10*). Trichloromethyl substituted phosphorus compounds are not common but Dipterex, $(CH_3O)_2P(O)CH(OH)CCl_3$, has been reported as a toxicant for baits (*9*). For the most part, structure proof for a very few dialkyl trichloromethylphosphonates rests only on elemental analyses, and diaryl derivatives are unknown. For these reasons, we decided to develop a general synthesis for diaryl trichloromethylphosphonates and to examine the NMR spectra of these compounds and several dialkyl esters.

Although the reaction between carbon tetrachloride and trialkylphosphites has been observed (*5, 6, 8*), compounds containing trichloromethyl groups are not well characterized. Few properties of the dialkyl trichloromethylphosphonates, except melting points or boiling points, are recorded. We have investigated the dialkyl trichloromethylphosphonates by NMR spectroscopy and recorded the coupling constants J_{POCH} in Table I. Values for J_{POCH} for the alkyl derivatives were 6.9 to 11.5 cps, in the normal range for many phosphonates (*3, 4*). The broadness of several group resonances suggests magnetic nonequivalence, a phenomenon not uncommon in phosphorus esters (*1*). We have found a most convenient route to diaryl trichloromethylphosphonates (in high yields) by reacting trichloromethylphosphonic dichloride (*7*) with phenols at room temperature (Table II). The melting points and boiling points and ^{31}P shifts (Table III) for the diaryl trichloromethylphosphonates are positive relative to 85% H_3PO_4. This is surprising in view of the negative shifts for several related phosphonates such as $Cl_3CP(O)(OC_2H_5)_2$ (−6.5 ppm);

Table I. ^1H Data for Dialkyl Trichloromethylphosphonates (CCl_4, TMS)



R	δ Values, J_{POCH}-Hz
—CH_3	4.03(12)-d
—CH_2	4.38(7)-q(b)
CH_3	1.43(7)-t
—CH_2	4.26(~7)-q(bs)[a]
CH_2	1.72(~7)-h(bs)
CH_3	1.00(7.1)-t(bs)
—CH	4.80-m
H_3C CH_3	1.41(~7.1)-d(bs)
—CH_2	4.06-t(bs)[a]
CH	2.02-m
H_3C CH_3	0.98-d(bs)

d = doublet; h = hextet; m = multiplet; q = quintet; t = triplet; b = broad; bs = broad with additional splitting suggesting nonequivalence of the two groups.

[a] The broadness in these two cases is most likely due to small differences in J_{POCH} and J_{HH}.