[CONTRIBUTION FROM THE LABORATORY OF APPLIED ORGANIC CHEMISTRY, RESEARCH COUNCIL OF ISRAEL]

Synthesis of Thieno[b]quinolizinium Salts

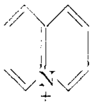
BY M. NEEMAN,[1] E. KRAKAUER AND Y. SHORR

RECEIVED JANUARY 28, 1957

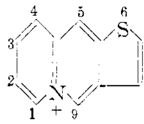
3-Thenyl bromide and pyridine-2-aldehyde reacted to form a quaternary salt, which was cyclodehydrated in boiling hydrobromic acid. The structure of the product, thieno[2,3-b]quinolizinium bromide, was established by desulfurization–reduction with Raney nickel to 3-ethylquinolizidine hydrobromide, which was converted into its known picrate. An analogous synthesis starting from 2-thenyl chloride and pyridine-2-aldehyde yielded a small amount of product to which the structure of thieno[3,2-b]quinolizinium bromide is assigned. The linear thieno- and benzoquinolizinium ions show ultraviolet spectra of considerable similarity.

The synthesis of the quinolizinium ion I is of recent date.[2,3] A number of benzologs of the quinolizinium ion have been reported.[4–6]

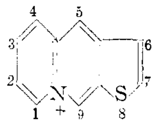
The present study was undertaken to prepare heterocyclic ions of a new type, in which the quinolizinium ion is condensed with a thieno ring (thienologs of quinolizinium). The synthesis of the two linear thieno[b]quinolizinium ions (II) and (III) was attempted first, as it was expected that the two linear isomers would be accessible by cyclodehydration of more readily available intermediates than would be required for the synthesis of any of the six possible angular isomers, or of the third linear isomer, thieno[3,4-b]quinolizinium ion.



I

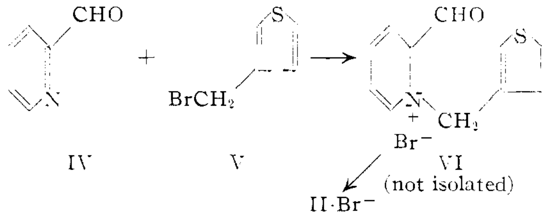


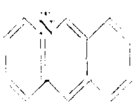
II



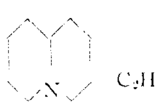
III

The synthesis of the thieno[2,3-b]quinolizinium ion was effected in good over-all yield (72%) by a reaction sequence analogous to the reported synthesis of the acridizinium ion (VII) by Bradsher and Beavers.[5] The pyridine-2-aldehyde (IV) reacted with 3-thenyl bromide (V) to form a quaternary salt VI. The crude salt VI, which was not isolated, was cyclized in boiling aqueous hydrobromic acid to thieno[2,3-b]quinolizinium bromide (II·Br⁻). The product had an ultraviolet absorption spectrum (Table I) which was closely related to that of the acridizinium ion (VII).[5] The new heterocyclic ion II showed a spectrum which indicated a high degree of conjugation.





VII



VIII

TABLE I

ULTRAVIOLET ABSORPTION CHARACTERISTICS OF LINEAR BENZO- AND THIENO-QUINOLIZINIUM IONS (IN ETHANOL)

Acridizinium perchlorate[5] (VII·ClO$_4^-$)		Thieno[2,3-b]quinolizinium bromide (II·Br$^-$)		Thieno[3,2-b]quinolizinium bromide (III·Br$^-$)	
λ_{max}, mμ	log ϵ_{mol}	λ_{max}, mμ	log ϵ_{mol}	λ_{max}, mμ	log ϵ_{mol}
242	4.68	247	4.61	247	4.57
		350 (sh)	4.08	353	3.87
361	3.99	362	4.36		
379.5	4.01				
				387	4.11
399	3.93				

The structure of II was established by desulfurization–reduction of its bromide with Raney nickel to a sulfur-free hydrobromide (VIII·HBr), which was converted into a picrate. The latter was proved to be 3-ethylquinolizidine picrate (VIII·picrate)[7] by comparison of infrared spectra and melting points with an authentic sample kindly supplied by Dr. Boekelheide. Apparently the same racemate was obtained by both routes. The ultraviolet and infrared spectra of VIII·HBr support this structure. Hence, the formally possible isomeric structure of thieno[3,4-b]quinolizinium ion is excluded for the product of the cyclodehydration. This result is in accord with the known higher electron density at the α-position relative to that at the β-position of thiophene.[8] Accordingly, the electrophilic cyclizing attack at the α-position of thiophene in VI was favored.

The reaction of 2-thenyl chloride with pyridine-2-aldehyde was considerably slower than the corresponding quaternization with 3-thenyl bromide. The glassy reaction product gave an intractable black residue after attempted cyclization with boiling 48% hydrobromic acid. A crystalline reaction product could be isolated in 4% yield by alumina chromatography. It afforded analytical values in accord with the formulation of a thienoquinolizinium bromide. The product showed spectral characteristics of pronounced similarity to those of the acridizinium ion and of the isomeric II·Br⁻ (Table I). Salts of the two ions also showed comparable, though distinct, properties. The structure of thieno[3,2-b]quinolizinium bromide (III·Br⁻) is assigned tentatively to the second cyclodehydration product pending its conversion into a compound of established structure.

Biological Activity. Thieno[2,3-b]quinolizinium bromide was tested for curariform activity. It showed no effect by itself, but it was observed to

---

(1) Department of Chemistry, University of Wisconsin, Madison, Wisconsin (on leave of absence from the Technion Israel Institute of Technology, Haifa).

(2) V. Boekelheide and W. G. Gall, THIS JOURNAL, **76**, 1832 (1954).

(3) V. Boekelheide and J. M. Ross, *ibid.*, **77**, 5691 (1955).

(4) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 453 (1955).

(5) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).

(6) C. K. Bradsher and L. E. Beavers, *ibid.*, **78**, 2459 (1956).

(7) V. Boekelheide and S. Rothchild, *ibid.*, **71**, 879 (1949).

(8) *Cf.* J. de Heer, *ibid.*, **76**, 4802 (1954).

potentiate the effect of succinylcholine when tested on the sciatic nerve in male cats.

Acknowledgment.—Thanks are due to Dr. F. Bergmann for biological tests.

Experimental

3-Thenyl bromide (V) was prepared by the method of Campaigne and LeSuer.[9]

Thieno[2,3-b]quinolizinium Bromide (II·Br⁻).—The method of Bradsher and Beavers[5] was used. Pyridine-2-aldehyde (7.35 g.) and 3-thenyl bromide (12.1 g.) were mixed and kept at 25–30° for 12 days. The reaction mixture formed a dark reddish-brown glass-like mass. On the ninth day about 1 ml. of a light yellow liquid was decanted. The mass was washed with ether and taken up in 48% aqueous hydrobromic acid (110 ml.) with gentle heating. The resulting solution was left overnight. A small amount of a dark impurity was filtered off. The dark red-brown solution was refluxed for 20 hr. The hydrobromic acid was distilled off at 20 mm. pressure. The black solid residue was taken up in hot water (130 ml.), boiled with charcoal (0.15 g.) and filtered. Dark-colored crystals were deposited from the solution on standing overnight in the refrigerator, which were filtered off and washed with ice-water. The yield was 12.1 g., m.p. 226–228°. The mother liquor was concentrated to a small volume at 20 mm. giving 1 g. of the product with the same m.p. The total yield was 72%. Recrystallization from ethanol (charcoal) yielded light brown needles, 10.5 g., m.p. 227–228°. The product was subjected to alumina chromatography (ethanol as solvent and eluent), yielding long glistening lemon-yellow needles, m.p. 227–228° (hot-stage).

Anal. Calcd. for $C_{11}H_8NSBr$: C, 49.64; H, 3.03; N, 5.26. Found: C, 49.39; H, 3.07; N, 4.96, 5.18.

The infrared spectrum of II·Br⁻ (solid, potassium bromide pellet) showed the following bands (cm.⁻¹): 3400-(strong); 3050(s); 2924; 2850; 2359(weak); 1616(s); 1500(w); 1475; 1460(s); 1430(w); 1385(s); 1312(s); 1293; 1247(w); 1174(w); 1167(w); 1152; 1130; 1033; 952(w); 910(w); 870(s); 830(w); 799(w); 765–760(s); 674–670; 664(w).

The picrate was precipitated from an ethanolic solution of the bromide and was crystallized twice from nitromethane. It was obtained as felted yellow needles, m.p. 213–214° (hot-stage).

Anal. Calcd. for $C_{17}H_{10}O_7N_4S$: C, 49.28; H, 2.43; N, 13.52; S, 7.74. Found: C, 49.64; H, 2.49; N, 13.63; S, 7.48.

3-Ethylquinolizidine Hydrobromide (VIII·HBr).—Thieno-(2,3-b)quinolizinium bromide (II·Br⁻) (1.06 g., 0.004 mole) and Raney nickel W-2[10] (12 g.) in ethanol (50 ml.) were refluxed for 2 hr. Fresh Raney nickel (4 g.) and ethanol (100 ml.) were added, and hydrogen was introduced (in a Parr apparatus) for 3 hr. at 2 atm. and 25°. The catalyst was filtered off, washed with ethanol and finally extracted with ethanol in a Soxhlet extractor. The combined ethanol extracts gave on evaporation a sticky brown product, which yielded 0.13 g. (13%) of a crystalline product, m.p. 184°, from butyl acetate. Recrystallization from this solvent gave a product of m.p. 190–191.5° (0.07 g.).

Anal. Calcd. for $C_{11}H_{22}NBr$: C, 53.22; H, 8.94; N, 5.64. Found: C, 52.97; H, 8.87; N, 5.44.

3-Ethylquinolizidine hydrobromide (VIII·HBr) showed very weak absorption in the ultraviolet above 215 mμ. The infrared spectrum (solid, potassium bromide pellet) showed no evidence of unsaturation. The following bands were observed (cm.⁻¹): 3425; 2941(strong); 2700–2674(s); 2577-(s); 2551(s); 2359(weak); 1650(w); 1460(s); 1342; 1174–1168; 1053-1048; 1032; 1010-1006(w); 995; 970-(w); 945(w); 920(w).

3-Ethylquinolizidine Picrate (VIII·Picrate).—The hydrobromide VIII·HBr was dissolved in ethanol and treated with ethanolic picric acid solution under reflux for 10 minutes. The picrate was deposited in clusters of lemon yellow needles, m.p. 156–157.5°.

The m.p. was undepressed by an authentic specimen of 3-ethylquinolizidine picrate of Boekelheide and Rothchild.[7] The infrared spectra of both specimens were superposable and showed the following bands (cm.⁻¹; solid, potassium bromide pellet): 3440(weak); 3070(w); 2950(strong); 2750(s); 2600; 1625–1610(s); 1565–1560(s); 1515(s); 1506(s); 1472(s); 1462(shoulder); 1430(s); 1362(s); 1340–1316(s); 1265(s); 1207(w); 1160; 1078; 1052; 996(w); 972-(w); 943(shoulder); 936; 917(w); 907; 787; 744; 723-(shoulder); 708(s); 678(w); 667(w).

Thieno(3,2-b)quinolizinium Bromide (III·Br⁻).—Pyridine-2-aldehyde (23.5 g.) and 2-thenyl chloride[11] (29.1 g.) were kept for eight weeks at 20–30° in a stoppered flask in the dark. Most of the reaction mixture turned into a dark brown-red glassy mass. A small amount of dark brown-red viscous supernatant liquid was decanted, and the glassy solid was left under the same conditions for a further period of four weeks. Hydrobromic acid (100 ml., 48%) was added. The glassy solid dissolved overnight, leaving a slight black residue, which was filtered off. The acid solution was refluxed for 19 hr. and filtered. The hydrobromic acid was removed at 20 mm., leaving a black residue. The latter was extracted with hot water, leaving a considerable part undissolved. The aqueous extract was evaporated to dryness at 20 mm., and the black residue was extracted with ethanol, leaving a considerable part undissolved. The ethanolic extract was passed through a column of alumina, which was subsequently eluted with ethanol, from which dark greenish needles were deposited on concentration, m.p. 216° (2.7 g.). After five crystallizations from ethanol, light yellow needles of m.p. 216–217° (hot-stage) were obtained.

Anal. Calcd. for $C_{11}H_8NSBr$: C, 49.64; H, 3.03; N, 5.26; Br, 30.03; S, 12.05. Found: C, 49.66; H, 3.16; N, 5.37; Br, 30.33; S, 11.94.

The infrared spectrum of III·Br⁻ (solid, potassium bromide pellet) showed the following bands (cm.⁻¹): 3472-(strong), 3068(s); 2941; 2874; 2370(weak); 1626(s); 1582(w); 1560(w); 1479(w); 1447(s); 1412(s); 1380(s); 1360, 1340; 1300(s); 1260(w); 1217(w); 1160(s); 1097-(w); 1029; 948(w); 893–890; 865(s); 830(w); 804; 788; 755(s); 680(s).

The picrate (III· picrate) was precipitated from an ethanolic solution of the bromide III·Br⁻ and crystallized from nitromethane as fine felted light yellow needles, m.p. 210.5–211°.

Anal. Calcd. for $C_{17}H_{10}O_7N_4S$: C, 49.28; H, 2.43; N, 13.52. Found: C, 49.97; H, 2.51; N, 13.00.

JERUSALEM, ISRAEL

---

[9] E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

[10] R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

[11] K. B. Wiberg and H. F. McShane, *ibid.*, p. 157.